OS026

Liver stiffness predicts incident severe liver disease in patients with chronic liver disease

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Background and aims: Prognosis in chronic liver disease is heterogenous, and fibrosis stage is the best predictor of liver-related events. Liver stiffness measurement (LSM) by Vibration-Controlled Transient Elastography (VCTE) is a non-invasive biomarker of fibrosis. It is uncertain if LSM can predict risk for future liver-related events. The aim was to investigate the prognostic ability of LSM.
Method: This was a Swedish multi-center cohort study including patients (n = 13, 170) with chronic liver disease who underwent LSM by VCTE between 2008 and 2019. Exclusion criteria were an unreliable LSM, congestive heart failure, and decompensated cirrhosis at baseline. Liver-related events were ascertained from Swedish national health registers. In patients without baseline cirrhosis, we investigated progression to "severe liver disease," defined as a diagnosis of cirrhosis, decompensated cirrhosis or hepatocellular carcinoma (HCC). In patients with baseline cirrhosis, we investigated progression to decompensation or HCC. Incidence rates and cumulative incidence at two and five years were calculated. Cox regression was used to evaluate the rate of outcomes for categories of LSM values.
Results: Patients (median age 46 years, 59% men) had a median LSM of 5.9 (interquartile range 4.6–8.0) kPa. Etiologies consisted of hepatitis C (n = 6849, 52.0%), hepatitis B (n = 3497, 26.6%), alcohol-related liver disease (n = 211, 1.6%), autoimmune liver disease (n = 624, 4.7%), non-alcoholic fatty liver disease (n = 699, 5.3%) and other or uncertain etiologies (n = 1290, 9.8%). Patients without baseline cirrhosis (n = 11, 883) had 333 (2.8%) events of severe liver disease during a median follow-up time of 2.9 years. Patients with cirrhosis at baseline (n = 1287) had 206 (16.0%) events of decompensation or HCC. In patients without cirrhosis, a LSM of 12–15 kPa was associated with a 42-fold higher rate of severe liver disease than a LSM of <6 kPa (Figure A). In patients with cirrhosis, a LSM >30 kPa was associated with a 5.4-fold higher rate of decompensation compared to a LSM of 15–17 kPa (Figure B). Incidence rates per 1000 person-years in severe liver disease ranged from 2.1 (95%CI 1.6–2.8) to 88.9 (95%CI 73.2–107.9) for LSM <6 kPa and 12–15 kPa, respectively. Incidence rates per 1000 person-years in decompensated cirrhosis ranged from 18.2 (95% CI 10.3–32.0) to 109.6 (95%CI 88.9–135.1) for LSM 15–17 kPa and >30 kPa, respectively. In patients without cirrhosis, the cumulative incidence at two years ranged from 0.4 (0.3–0.6)% to 19.1 (15.1–23-5)%, and at five years from 1.1 (0.8–1.6)% to 32.9 (26.9–38.9)%, respectively.
Conclusion: Increased LSM by VCTE is associated with higher rates of progression to cirrhosis and decompensation in a dose-response manner. The results can be used to guide follow-up and treatment decisions.

OS027

Linear slope of serial FIB-4 measurements predicts liver-related complications and correlates with cirrhosis-associated genetic variants among patients with ALT-based NAFLD phenotype

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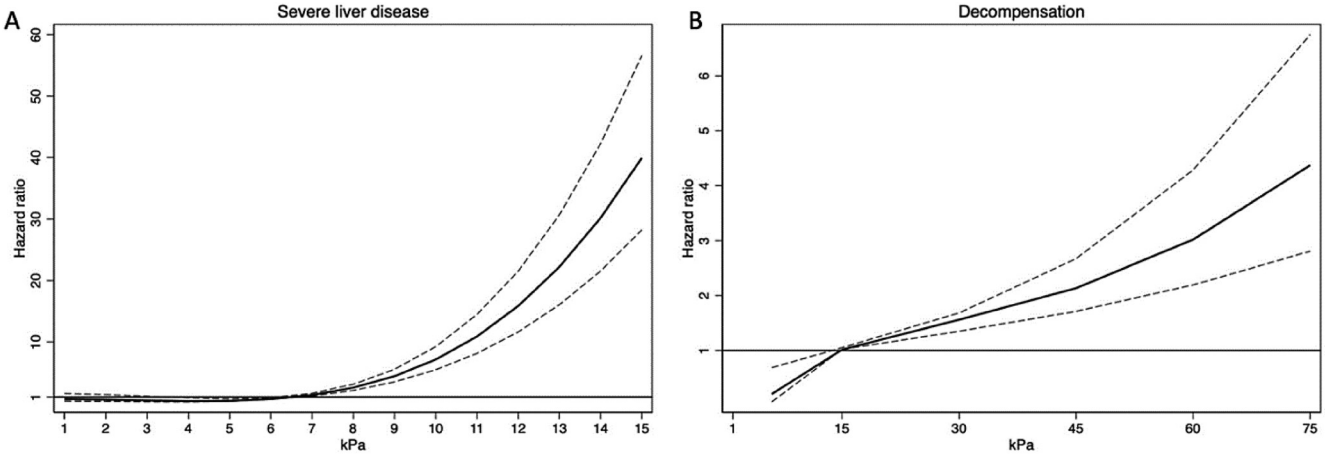

Figure: (abstract: OS026): A. Patients without cirrhosis at baseline. B. Patients with cirrhosis at baseline.

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Background and aims: FIB-4 is a clinically relevant marker to track fibrosis in patients with chronic liver disease including NAFLD/NASH. Here, we first defined Fib-4 trajectory by linear slope of serial FIB-4 measurements as a measure of fibrosis progression, then examined its correlation with liver-related complications and genetic associations with a non-invasive ALT-based proxy NAFLD phenotype recently defined among participants in the VA's Million Veteran Program (MVP) with available clinical and genetic data (Serper et al, PLOS ONE 2020).
Method: Individual FIB-4 slopes were estimated via linear regression for MVP participants with greater than 4 outpatient FIB-4 values who met criteria for proxy NAFLD phenotype based on previously validated algorithm for chronic ALT elevation without other known causes of chronic liver disease. Linear models were constructed excluding outliers at >2 Cook's distances from predicted. Patients whose initial FIB-4 values exceeded the 90% percentile (baseline advanced fibrosis) were assigned slopes equivalent to the 99th percentile of the sample. The AUROCs for the coefficient of FIB-4 slope for predicting development of cirrhosis, hepatocellular carcinoma, ascites and death were generated. MFIB4 was then used as a quantitative phenotype in a genome-wide association analysis using REGENIE software. Variants were restricted to MAF >0.01 and INFO >0.30. Three distinct racial/ethnic groups were defined for the cohort (European, African, and Hispanic ancestry) and analyzed separately; a trans-ancestry meta-analysis was performed with METAL software.
Results: FIB-4 slopes were obtained from 61, 689 subjects (10, 594 African, 46, 137 European, and 4, 958 Hispanic ancestry subjects). AUROC of FIB-4 slope for prediction of cirrhosis, hepatocellular carcinoma or ascites were 0.75–0.76. Among European ancestry subjects, FIB-4 slope was associated with 6 genome-wide significant loci (p value $<5 \times 10^{-8}$) including 3 with previously known associations to NAFLD and hepatic fibrosis (GCKR, HSD17B13, and PNPLA3). The GWAS of African and Hispanic ancestry did not return any significant results, however, the trans-ancestry meta-analysis identified an additional signal.
Conclusion: Fibrosis progression based on FIB-4 trajectory correlated with clinically meaningful complications of liver disease progression, as well as known markers of cirrhosis among patients with non-invasive ALT-based NAFLD phenotype. Further work is ongoing to define the use of FIB-4 trajectory and genetic risk factors as predictors for long term outcome of chronic liver disease.

OS028

Machine learned histological fibrosis score empowers characterization of baseline gene signatures associated with fibrosis progression or regression in a NASH F3/F4 clinical trial

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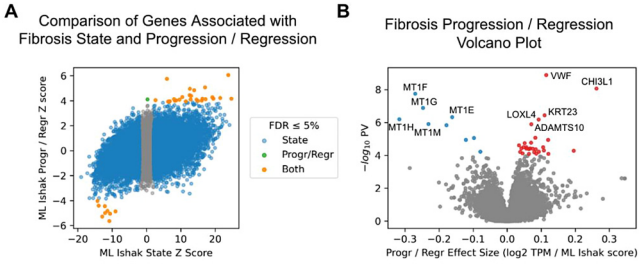
Background and aims: We characterized disease severity with a machine learning (ML) analysis of liver biopsy images, and used it to identify baseline gene signatures that are predictive of fibrosis progression or regression in NASH.
Method: Bulk RNA-seq, HandE stained biopsy images, and pathologist Ishak fibrosis scores are curated from screening and week 48 visits in the STELLAR 3 and STELLAR 4 clinical trials (n = 1097 patients with all end points). A continuous score for fibrosis was extracted using convolutional neural networks (CNN) trained to predict pathologist scores from HandE-stained biopsies (Casale et al, EASL 2020). We identify genes associated with fibrosis state by testing for associations between baseline expression and baseline fibrosis scores, controlling for age and sex. Fibrosis progression/regression genes are identified by testing for associations between baseline expression and the difference between baseline and followup fibrosis scores after controlling for both ML and pathologist baseline fibrosis scores, age, sex, and treatment.
Results: The continuous ML fibrosis scores are highly correlated with pathologist Ishak scores (correlation = 0.88). Variation of the ML fibrosis score within Ishak scores exhibits similar transcriptomic associations as variation in Ishak scores (correlation of z scores = 0.88), suggesting that the ML score identifies intra-score variability consistent with pathologist assessed fibrosis. We identify 12, 862 genes associated with ML fibrosis state (likely driven in part by changes in cell type composition) and 37 genes associated with ML fibrosis progression/regression (A, B). Using the same covariates, analysis of the ML score identifies a superset of the progression/regression genes identified with the pathologist score (37 vs 3 genes). Notably, the progression/regression-associated genes are not the top state-associated genes. Progression associated genes include expected extracellular matrix and cytoskeletal function-related genes. Lipid metabolism genes identified include the progression associated gene AKR1B10 (involved in hepatic carcinogenesis) and the regression associated gene AKR1D1 (involved in resistance to oxidative stress). Other regression associated genes identified include metallothionein genes, involved in the protection against oxidative stress, and CLEC4M, a liver sinusoidal endothelial cell-specific gene.
Conclusion: ML assessment of liver biopsies and the statistical inference framework introduced herein produced insights on baseline gene expression signatures that are predictive of and potential drivers for NASH fibrosis progression or regression.



Genes associated with fibrosis state and progression / regression. A) Scatter plot of z scores from differential expression analysis of ML fibrosis state and progression / regression. B) ML fibrosis progression / regression differential expression volcano plot.

OS029

Fibroscan-AST (FAST) score predicts liver-related outcomes in 1683 HIV-infected patients at risk for NAFLD

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) affects 35% of people living with HIV (PWH) in absence of viral