WED-433-YI

Translating genetic information into clinical practice: Improved decision-making in advanced fibrosis assessment

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Background and aims: Genetic information is not yet used for the clinical diagnosis of advanced fibrosis in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). Here we investigated whether incorporating genetic information regarding *PNPLA3* and *TM6SF2* into existing non-invasive fibrosis scoring systems could enhance the predictive accuracy, particularly in terms of reducing indeterminate diagnostic zones.
Method: Data were collected from a cohort of 573 patients with biopsy-proven MASLD. All participants underwent liver stiffness measurement (LSM), serum marker analysis, and genotyping for *PNPLA3* (rs738409), *TM6SF2* (rs58542926), and other relevant SNPs. We evaluated the benefit of adding genetic information to existing non-invasive tests (NIT)—including the Agile 3+, Fibrosis-4 (FIB-4) index, and NAFLD fibrosis score (NFS). Decision curve analysis (DCA) was performed to determine the net benefit of adding genetic information, and we analyzed the impact on reducing indeterminate zones.
Results: Integration of *PNPLA3* and *TM6SF2* genotypes improved the predictive accuracy of existing models, particularly by reducing the indeterminate diagnostic zones Additionally, integrating genotype data into existing NIT significantly improved their performance, as demonstrated by higher net benefits compared to models without genetic information. The net benefit at a 30% threshold increased from 18.7 to 19.0 per 100 patients with genotypes for Agile 3+, increased from 12.7 to 13.7 for the NFS, and increased from 9.2 to 12.1 for FIB-4.
Conclusion: Incorporating genetic data into NIT for MASLD enhanced their predictive accuracy. Addition of genetic data particularly reduced indeterminate zones, thereby offering a more reliable tool for identifying patients at risk for advanced fibrosis. This approach may improve clinical decision-making and outcomes.

WED-434

Use of noninvasive tests (NITs) to diagnose and follow non-alcoholic steatohepatitis (NASH) with liver fibrosis patients treated with resmetirom

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Background and aims: MAESTRO-NASH (NCT03900429) is an ongoing 54-month, randomized, double-blind, placebo-controlled Phase 3 trial evaluating the efficacy of resmetirom in patients with biopsy-confirmed NASH and fibrosis. 966 patients with biopsy-confirmed NASH were randomized 1:1:1 to resmetirom 80 mg, resmetirom 100 mg, or placebo once daily. Dual primary endpoints at Week 52 were achieved with both resmetirom 80 mg and 100 mg: NASH resolution with no worsening of fibrosis (NR) or ≥1-stage improvement in fibrosis with no worsening of NAS (FI). Both Week 52 liver biopsy endpoints, NR and FI, were achieved. Resmetirom was recently approved for the treatment of adult patients with noncirrhotic NASH and liver fibrosis consistent with F2 to F3 stages. Expert guidances recommend treatment with resmetirom based on staging fibrosis using FibroScan VCTE. EASL recommends stratifying patients using FIB-4. Most guidelines recommend using VCTE cutoffs lower than 10≤15 kPa for treatment.
Method: We assessed results from baseline noninvasive tests (FIB-4, VCTE) against biopsy results in MAESTRO-NASH to measure how well they diagnosed noncirrhotic patients with NASH (consistent with F2–F3 stages at baseline). We assessed the utility of a lower VCTE cutoff (8.5 to <10 kPa) in capture of F2 and F3 patients who otherwise would be missed. Also evaluated was the addition of MRE/MRI-PDFF or ELF to FibroScan VCTE to assess diagnostic utility.
Results: FIB-4 poorly predicted patients in the non-cirrhotic fibrosis stages: F2 (60% patients fell into low-risk) and F3 (40% fell into low-risk). Including a lower cutoff of VCTE (8.5 to <10 kPa) captured F1B (34% 8.5≤10 kPa) and many F2 (25% 8.5≤10 kPa) and F3 patients (19% 8.5≤10 kPa). The addition of MRE/MRI-PDFF to FibroScan VCTE increased diagnostic accuracy for F2/F3 to 68% and F4 to 81%. The addition of the ELF to the FibroScan VCTE suggested that a low ELF result paired with high VCTE may warrant a VCTE repeat.
Conclusion: Identification of patients with NASH F2 to F3 was achieved with FibroScan and VCTE. F1B are F2 equivalent (F1B is moderate fibrosis on biopsy). Patients with fibrosis stage F4 were effectively ruled out. In addition to FibroScan VCTE, practitioners may consider expanded noninvasive criteria (ELF, MRE) to help refine fibrosis staging.

WED-435

Development of a novel model using machine learning algorithms to predict absence of metabolic associated steatotic liver disease in healthy and patient trial volunteers. A population screening tool

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Background and aims: Metabolic associated steatotic liver disease (MASLD) affects approximately one in four of the global adult population, and ranges in severity from benign fatty liver infiltration, to hepatitis, cirrhosis, hepatocellular carcinoma, and death. MASLD has important implications for clinical trial volunteers as an occult co-morbid condition – there is evidence that MASLD modulates drug metabolism, with studies suggesting that Grade 3–4 liver reactions are four times more common in healthy volunteers with probable MASLD than without. Halting promising potential new drug therapies in clinical development due to false positive liver safety signals. Additionally, the tool could be used to screen the population for those not exhibiting symptoms.
Method: An observational cross-sectional study of 1507 clinical trial volunteers was completed, collecting bioimpedance vector analysis (visceral fat%, total body fat% and skeletal muscle %), anthropometric measurement and laboratory bloods. A FibroScan is performed as a pragmatic gold standard 'outcome' for MASLD using >248 dB/m or >7.6 kPa as a positive. The data was divided into a training set of (75%) used to build the model, (25%) used to validate its predictive accuracy. Lasso Logistic Regression, Elastic Net Logistic Regression, Random Forest and XGBoost were then compared for model with highest performance. SHAP analysis was used to identify feature importance and remodelling with reduced features to simplify clinical data needed for the model was performed.

Results: All models achieved an AUROC 0.91 or better. Random Forest produced the highest performing model using all 18 features achieving AUROC 0.92, Accuracy 0.866, F1 score 0.705 and NPV 0.932. A reduced feature model developed with 7 features (Waist circumference, WHR, BMI, ALT, ALP, weight, age) achieving AUROC 0.91, Accuracy 0.879, F1 Score 0.714 and NPV 0.923.
Conclusion: The model developed produces a highly accuracy tool which using waist circumference, height, weight, ALT, ALP and Age – readily available in clinical settings. Allowing research teams to identify prospectively confirm enrolled volunteers with pre-clinical MASLD. This is a group where the effective detection of concomitant, occult fatty liver disease is possible and has significant implications for adverse drug reactions in first-in-human studies. Feasibility in the health screening setting is now starting for earlier identification and intervention.

WED-436
Identifying risk factors linked to metabolic-associated steatotic hepatitis in people living with HIV in Newark, New Jersey
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Background and aims: People living with HIV (PLWH) have a high incidence of comorbid conditions increasing their risk for metabolic-associated steatotic hepatitis (MASH). Limited data exists on risk factors that contribute to the highest risk for MASH, particularly among PLWH. In this study, we analyze several possible demographic and metabolic risk factors to better understand their contribution to MASH risk in this population.
Method: A cross-sectional study was conducted at two HIV clinics in Newark, NJ, USA between July 2024 and October 2024. Liver elastography was used to measure the controlled attenuation parameter (CAP) in PLWH attending these clinics. Eligible participants were over 18 years old, fasting for at least two hours prior to testing, and had an HIV viral load <200 c/ml. Individuals with chronic hepatitis B or C or excessive alcohol consumption (AUDIT score >5) were excluded. Participants were categorized into two groups based on CAP values: Group 1 (CAP consistent with S0-S1) and Group 2 (CAP consistent with S2-S3). Epidemiologic data, anthropometric measurements, comorbid conditions, and current medications were collected, and visceral adiposity index (VAI) was calculated. Risk factors for MASH were analysed using bivariate and multivariate methods.
Results: A total of 222 patients underwent liver elastography, with 143 patients categorized into Group 1 and 79 into Group 2. Descriptive results indicate a higher proportion of males in both groups, with Group 1 having 69.2% and Group 2 at 59.5%. Blacks are the majority race (60.1% in Group 1, 53.2% in Group 2). Hispanic and non-Hispanic representation is consistent across groups (32.2%–32.9% and 67.1%–67.8%, respectively). Older participants (>50 years) are more prevalent in Group 2 (82.3%) compared to Group 1 (63.4%). No statistically significant differences were found between the groups in gender, race, ethnicity, use of tenofovir alafenamide, second-generation integrase inhibitors, diabetes mellitus, or concurrent statin use ($p \geq 0.05$). Significant differences were identified in age ($p = 0.0086$), BMI ($p = 0.0001$), waist-hip ratio ($p = 0.0012$), and visceral adiposity index (VAI) ($p = 0.0004$). High cholesterol (total cholesterol >200 mg/dL) showed a weak association with MASH ($p = 0.04$). Additionally, results indicated Black PLWH had a 36% prevalence of excessive fat accumulation in the liver.
Conclusion: The strongest predictors of MASH were VAI, waist-hip ratio, BMI, and age. Refining MASH screening recommendations for PLWH involves prioritizing high-risk individuals based on specific metabolic indicators, integrating non-invasive tools into routine HIV care, and addressing health disparities through resource allocation and tailored guidelines. These efforts can improve early detection, intervention, and overall outcomes for this vulnerable population.

WED-437
suPAR levels independently discriminate patients with at-risk MASLD
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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a leading global cause of liver fibrosis. Early identification of patients at risk for significant fibrosis, which can progress to cirrhosis and other liver-related complications, relies heavily on non-invasive tests. The soluble urokinase plasminogen activator receptor (suPAR), an inflammatory biomarker linked to adverse outcome in various chronic conditions, has shown promise in liver disease and may offer added value in identifying MASLD at risk. This study aimed to assess the predictive value of suPAR for significant fibrosis in patients with MASLD and to compare its performance with other well-established non-invasive fibrosis scores, including FIB-4, APRI, NFS, and FAST. Finally, we explored whether suPAR adds predictive value or enhances current at-risk prediction models.
Method: From 2020 to 2021, we prospectively enrolled 259 patients with MASLD at the Department of Gastroenterology and Hepatology, Charité, Berlin, Germany. Each patient's epidemiological, medical, and laboratory data were systematically collected. At enrollment, all patients underwent a vibration-controlled transient elastography (by FibroScan®), routine laboratory work-up, as well as measurement of suPAR levels. Using non-invasive fibrosis assessments (FibroScan®, ultrasound, and various scoring models), we stratified patients into two groups based on their risk for at least significant fibrosis (≥8.0 kPa or sonographic signs of significant fibrosis). We then compared suPAR levels between the low- and high-risk groups and analyzed each scoring system's AUROC for fibrosis detection.
Results: In total, 66.41% (n = 172) patients were grouped in the low-risk group and 33.59% (n = 87) in the high-risk group. suPAR showed a good predictive value for significant fibrosis, still, its AUROC (0.813) was significantly inferior to the FAST and FIB-4 scores (0.865; $p = 0.012$ and 0.874; $p = 0.036$, respectively). suPAR performed non-inferior to the APRI and NFS scores. In both univariate and multivariate regression analyses, suPAR demonstrated the highest discriminatory power (OR: 1.787; $p < 0.001$ and OR: 1.263; $p = 0.013$) among all single laboratory and epidemiological parameters assessed for identifying higher stages of fibrosis (at-risk MASLD).
Conclusion: suPAR shows a good predictive power in the detection of significant stages of fibrosis compared to other, well-established scores, only FIB-4 and FAST performed better in our cohort. Still, its high discriminatory power on at-risk MASLD warrants the ability for suPAR in enhancing prognostic scores on fibrosis detection in the future.