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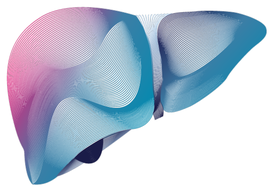
NAFLD: Diagnostics and non-invasive assessment



A mass-spectrometry serum test for identifying liver fibrosis and at-risk NASH enabling cost-effective population screening

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METASIGHT

Introduction

- Accurate non-invasive diagnostic test for liver fibrosis and non-alcoholic steatohepatitis (NASH) is of major unmet need, for patient referral to hepatology care and for the identification of patients to be treated with the upcoming NASH drugs.
- Considering the underdiagnosis among high-risk non-alcoholic fatty liver disease (NAFLD) patients, having large portion of patients within FIB-4 indecisive-zone, there is a growing need for cost-effective methods to screen large patient populations.
- We developed a novel diagnostic method for liver fibrosis and at-risk NASH based on high-throughput mass-spectrometric analysis of serum samples, outperforming existing clinical scores, and applicable for wide population screening.
- This method extends upon our previous NASH-cirrhosis signature, which appears online in the conference abstracts.

Aim

- To develop and validate a cost-effective blood-based diagnostic signature to identify patients with liver fibrosis and at-risk NASH, using a proprietary high-throughput multi-OMICS technology.

Method

- **Discovery cohort –** Serum samples collected from 357 biopsy-proven NAFLD patients from two different hospital in Spain (Puerta de Hierro Hospital – Madrid and Marqués de Valdecilla Hospital – Cantabria). Significant fibrosis, advance fibrosis, and cirrhosis cases were defined as patients with F ≥ 2, F ≥ 3 and F = 4, respectively. At-risk NASH cases were defined as having biopsy confirmed NASH, a NAFLD activity score (NAS) ≥ 4 with at least 1 point in each one of the components, and F ≥ 2.
- **Validation cohort –** Serum samples from ~500,000 subjects were collected as part of standard clinical routine by a central Israeli health organization, within the ongoing Israeli multi-OMICS Serum Screening (IMOSS-500K) study. De-identified electronic health records (EHR) were used to identify 135 samples from patients diagnosed with probable NASH cirrhosis[1], which were then manually validated, and 313 control samples from NAFLD patients.
- **MetaSight's multi-OMICS platform –** All samples were analyzed with a proprietary robust high-throughput liquid-chromatography mass-spectrometry (LC-MS) based metabolomics, lipidomics, proteomics, detecting tens of thousands of biomarker ions per sample (RSD < 30%). Biomarker intensities were normalized based on repeated injection of a biological QC sample.
- **Statistical analysis –** The discovery cohort was randomly split to train and test sets. A cross-validated L2 regularized logistic regression was used to identify a serum molecular signature in the train set, that achieves best area under the receiver operating characteristic curve (AUROC) for fibrosis stage and at-risk NASH detection. The 95% confidence intervals (CI) for the AUROCs were estimated using Delong method.

1. Gastroenterology 2020;159:422–427

Conclusions

- MetaSight liver fibrosis score (MS-LFS) is a novel serum test for identifying fibrosis stage and at-risk NASH patients.
- Early data suggests that it outperforms commonly used clinical scores, FIB-4, BARD and NFS, and achieves similar diagnostic performance to Fibroscan, FAST, Agile 3+ and Agile 4.
- MS-LFS synergizes with FIB-4, improving diagnosis of fibrosis and at-risk NASH in patients with intermediate FIB-4 values.
- Using proprietary high-throughput mass-spectrometry enables a cost-effective analysis applicable for wide population screening.
- The potential of using MS-LFS in population screening was demonstrated with samples from IMOSS-500K study, identifying high-risk NAFLD patients as having probable NASH cirrhosis, in real-world primary care screening setting

FIB-4: Fibrosis-4 (FIB-4) score; BARD: body-mass index, aspartate aminotransferase/alanine aminotransferase ratio and diabetes; NFS: NAFLD Fibrosis Score; FAST: FibroScan-AST

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Results

Discovery Cohort Analysis

- 357 samples from patients with biopsy-confirmed NAFLD (Table 1).
- High-throughput LC-MS based multi-OMICS analysis (several min/sample), revealed a novel signature, MetaSight Liver Fibrosis Score (MS-LFS), with 3 biomarkers; all previously associated with liver physiology; and significantly correlated with fibrotic stage (Fig. 1).

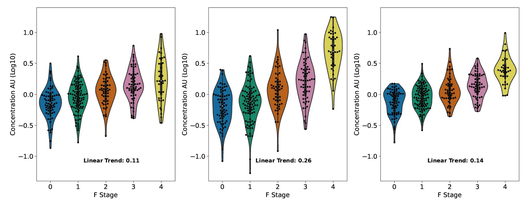

Fig. 1. Dependency of MS-LFS feature on fibrosis stage

	Discovery Cohort					Validation Cohort	
	F0	F1	F2	F3	F4	NAFLD controls	Probable NASH Cirrhosis cases
Demographic							
n	78	118	55	66	40	313	135
Female (n)	27	54	22	36	17	139	65
Male (n)	51	64	33	30	23	174	70
Age avg (std)	52.3 (10.3)	52.4 (11)	54.4 (8.2)	59.2 (9.7)	60.2 (6.3)	68.9 (9.9)	68.7 (10.7)
Clinical characteristics							
T2DM (%)	18	28	40	61	55	56	60
BMI avg (std)	34.0 (10.1)	34.7 (6.2)	34.9 (6.1)	33.8 (6.2)	34.2 (5.1)	29.9 (5.1)	30.1 (5.3)
Dyslipidemia (%)	46	46	49	62	55	77	75
Hypertension (%)	12	6	7	18	20	61	64
FIB-4 avg (std)	1.12 (0.5)	1.51 (1.8)	1.53 (0.7)	2.1 (1.4)	3.57 (2.0)	1.72 (0.9)	3.71 (3.7)
HbA1C avg (std)	5.8 (0.7)	6.1 (1.2)	7.1 (7.6)	6.4 (1.1)	6.4 (1.2)	6.2 (1.0)	6.2 (1.2)
LSM avg (std)	10.9 (12.5)	10.8 (5.1)	13.1 (7.0)	14.3 (7.7)	28.8 (15.1)	NA	NA
CAP avg (std)	312.2 (61.8)	323.8 (4.7)	337.4 (39.6)	328.8 (47.5)	314.9 (61.8)	NA	NA
Histology							
NAS avg (std)	3.1 (1.5)	4.1 (1.5)	4.5 (1.4)	4.7 (1.4)	4.3 (1.4)	NA	NA

Table 1. Patient characteristics of biopsy-confirmed Discovery cohort (n = 357) and real-world patient validation cohort (n = 448). T2D, type 2 diabetes mellitus; ,BMI, body-mass index; HbA1c, hemoglobin A1c. In the validation cohort: NAFLD defined based on ICD-9 and with documented history of abdominal imaging test. Probable NASH cirrhosis defined based on ICD-9 diagnosis ± 6 months blood collection, no evidence for a competing etiology and at least 2 coexisting or history of metabolic comorbidities[1]

MS-LFS Diagnostic Performance

- MS-LFS shows high diagnostic performance for significant and advanced fibrosis, cirrhosis and at-risk NASH (AUROC of 0.837, 0.847, 0.924, 0.8, respectively), significantly outperforming clinical scores FIB-4, BARD and NFS (Fig. 2, Fig. 3a).
- The advantage of MS-LFS is further emphasized when focusing on patients with indecisive fibrosis stage, having an intermediate FIB-4 score (1.30 < FIB-4 < 2.67; Fig. 3b).
- MS-LFS performs similarly / better to Fibroscan-based tests, with / without additional clinical parameters (FAST, Agile 3+ and Agile 4) (Fig. 3a).

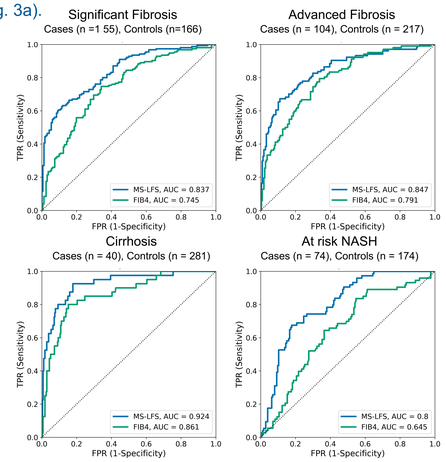

Fig. 2. MS-LFS diagnostic performance for significant and advanced fibrosis, cirrhosis and at-risk NASH in the discovery cohort, focusing on subjects with FIB-4 measurement for comparison

Real-world Primary Care Patient Validation Cohort

- Cost-effective analysis of samples collected during a routine blood test from 135 probable NASH cirrhosis patients diagnosed with cirrhosis from the IMOSS-500K study; ~20% of newly diagnosed cirrhosis cases in Israel on 2021-2022.
- Higher diagnostic performance of probable NASH cirrhosis for MS-LFS vs. FIB-4, BARD and NFS (Fig 3b, Fig. 5).
- The high diagnostic performance remains also when focusing on patients with intermediate FIB-4 subpopulation (Fig. 4b).

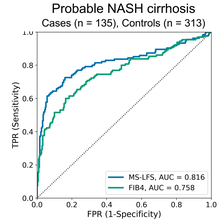

Fig. 5. MS-LFS diagnostic performance for probable NASH cirrhosis in a real-world validation cohort

MS-LFS Outperforms Existing Clinical Scores and Performs Similarly to Fibroscan – Discovery and Validation Cohorts

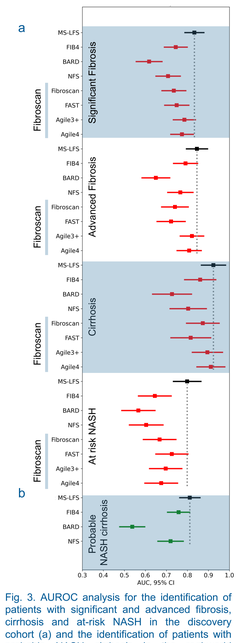

Fig. 3. AUROC analysis for the identification of patients with significant and advanced fibrosis, cirrhosis and at-risk NASH in the discovery cohort (a) and the identification of patients with probable NASH cirrhosis in the real-world validation cohort (b)

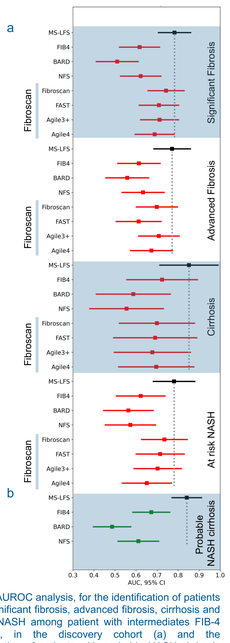

Fig. 4. AUROC analysis, for the identification of patients with significant fibrosis, advanced fibrosis, cirrhosis and at-risk NASH among patient with intermediates FIB-4 patients, in the discovery cohort (a) and the identification of patients with probable NASH cirrhosis in the real-world validation cohort (b)