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MEFIB-Index and MAST-Score in the assessment of hepatic decompensation in Metabolic dysfunction-associated steatosis liver disease (MASLD)- Individual participant data meta-analyses

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Summary

Background & Aims: There are limited data regarding the longitudinal association between MEFIB-Index (MRE combined with FIB-4) versus MAST-Score (MRI-aspartate aminotransferase) and hepatic decompensation. We aimed to examine the longitudinal association between MEFIB-Index versus MAST-Score in predicting hepatic decompensation in patients with metabolic dysfunction-associated steatotic liver disease (MASLD).

Methods: This is a longitudinal, retrospective analysis of subjects from three countries (United States, Japan, and Turkey) who underwent a baseline MRE and MRI-PDFF and were followed for hepatic decompensation. Cox-proportional hazard analyses were used to assess the association

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AUTHOR CONTRIBUTIONS

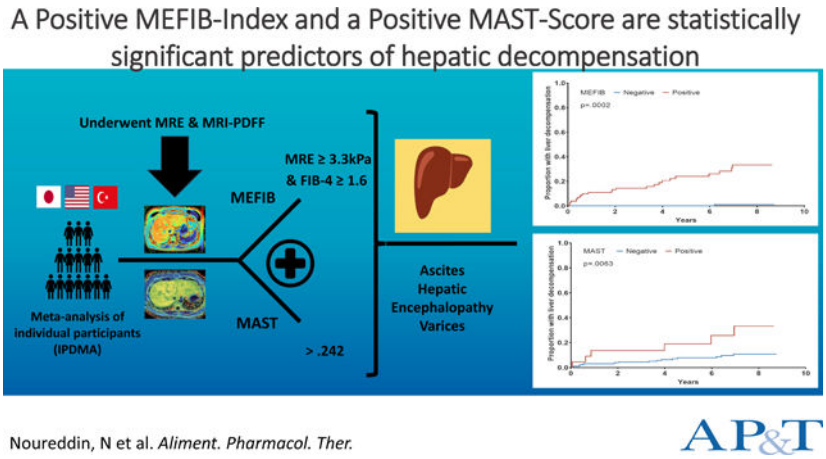
Study concept and design: RL; data acquisition: VA, NN, DL, AM, TN, NT, NI, AN, RI, MG, DK, AE, , RL; data analysis: JB, NN, VA drafting of the manuscript: NN; critical revision and approval of the final manuscript: all authors.

between MEFIB-Index versus MAST-Score with a composite ***primary outcome (hepatic decompensation)*** defined as ascites, hepatic encephalopathy, and varices needing treatment.

Results: This meta-analysis of individual participants (IPDMA) included 454 patients (58% women) with a mean (± SD) age of 56.0 (±13.5) years. The MEFIB-Index (MRE ≥ 3.3kPa + FIB 4 ≥ 1.6) and MAST-Score (>.242) were positive for 34% and 9% of the sample, respectively. At baseline, 23 cases met criteria for hepatic decompensation. Among 297 patients with available longitudinal data with a median (IQR) of 4.2 (5.0) years of follow-up, 25 incident cases met criteria for hepatic decompensation. A positive MEFIB-Index [HR=49.22 (95%CI: 6.23–388.64, p<0.001)], and a positive MAST-Score [HR=3.86 (95%CI: 1.46–10.17, p<0.001)] were statistically significant predictors of the incident hepatic decompensation. MEFIB-Index (c-statistic: 0.89, standard error(se)=0.02) was statistically superior to the MAST-Score (c-statistic: 0.81, se=0.03) (p<.0001) in predicting hepatic decompensation.

Conclusion: A combination of MRI-based biomarker and blood tests; MEFIB-Index and MAST-Score can predict risk of hepatic decompensation in MASLD patients.

Graphical abstract



Keywords

non-invasive biomarkers; ascites; hepatic encephalopathy; varices; hepatocellular carcinoma

INTRODUCTION

Globally, metabolic dysfunction-associated steatotic liver disease (MASLD) is a leading cause of chronic liver disease; one-fifth to one- quarter of adults in developed countries have MASLD (1, 2). Metabolic dysfunction-associated steatohepatitis (MASH) is the inflammatory form of MASLD, characterized by the presence of inflammation and cellular injury which may progress to advanced fibrosis (3, 4). MASH is the fastest growing indication for liver transplantation (5) and the most rapidly growing cause of hepatocellular carcinoma (HCC) in the United States (6–9). Progression of MASH to cirrhosis may lead to hepatic decompensation (ascites, hepatic encephalopathy, varices), HCC, and/or death(10, 11). The stage of fibrosis is associated with hepatic decompensation and mortality. Thus,

identifying those patients who at risk of developing advanced fibrosis is a major priority(12–15).

Histology is the reference standard for assessment of fibrosis. However, liver biopsy is limited by sampling error, subjective assessments, and inter- and intra-observer variability(16, 17). Liver biopsy is also invasive and associated with complications, including infections, bleeding, and, rarely, death. Thus, multiple noninvasive tests (NITs), such as magnetic resonance elastography (MRE), vibration-controlled transient elastography (VCTE), and Fibrosis-4 (FIB4) score, have been developed and validated to detect fibrosis. Most NITs have good diagnostic accuracy for advanced stages of fibrosis, but some are limited in detecting earlier stages (18–20). Among the NITs, MRE has the highest diagnostic accuracy for detecting fibrosis, (21–23) and it is superior to VCTE in the non-invasive diagnosis of fibrosis stage among patients with MASLD(24). A combination of blood tests and magnetic resonance imaging (MRI)-based panels, such as MEFIB-Index (MRE combined with FIB-4) and MAST-Score (MRI-aspartate aminotransferase) have been useful for detecting “at risk” MASH, defined as ≥ stage 2 fibrosis with MASH(25, 26).

A recent systematic review and meta-analysis of adults with MASLD determined that liver stiffness assessed by MRE can detect hepatic decompensation, HCC, and death(27). However, the longitudinal association between MEFIB-Index (MRE ≥ 3.3 Kpa + FIB-4 ≥ 1.6) compared with MAST-Score (liver stiffness [LS] by MRE + liver fat by MRI-PDFF + AST) and hepatic decompensation has not been systematically assessed. Therefore, we aimed to compare these tests in the longitudinal prediction of hepatic decompensation in patients with MASLD.

METHODS

This collaborative systematic review and meta-analysis of individual participants (IPDMA) was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Institutional review board approval was obtained from each individual site, and the study was performed on de-identified data.

Search Strategy and Selection Criteria

An experienced medical librarian conducted a systematic literature search of several databases from inception to April 24th, 2023, to identify all relevant articles that evaluated liver stiffness on MRE and its association with hepatic decompensation in MASLD patients. We then asked experts in the field to identify additional published and unpublished primary studies. Inclusion criteria were (1) liver stiffness assessment by MRE, (2) liver fat by MRI-PDFF (3) completed assessment for hepatic decompensation or death, and (4) adult patients (≥ 18 years of age) with MASLD. MASLD was diagnosed based upon imaging and clinical criteria consistent with the American Association for the Study of Liver Diseases NAFLD Practice Guidance(3). The search strategy is provided in the supplemental material.

Covariates

The data obtained from each study were age at the time of MRI; sex; race/ethnicity; body mass index; metabolic comorbidities (hypertension, hyperlipidemia, and type 2 diabetes

mellitus); and biochemical tests (albumin, glucose, hemoglobin A1C, fasting lipid panel, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, platelets, sodium, creatinine, and international normalized ratio. FIB-4(28) and MELD-Na Score were calculated as described (29).

Magnetic Resonance Imaging

MRE uses a driver system to produce mechanical waves which propagate as shear waves within the liver tissue. A modified phase-contrast pulse sequence is used to image the micron-level cyclic displacements caused by the propagating shear waves to create a magnitude image, and a phase image. With postprocessing, these images are transformed into wave image and liver stiffness maps that are reported in kPa, also known as elastograms. We collected the mean liver stiffness values in kPa from the elastograms. MRI exploit the difference in resonance frequencies between water and fat proton signals to quantitatively measure the proton density fat fraction (PDFF) which refers to the proportion of mobile protons attributable to fat over the total proton density in the liver tissue

MEFIB-Index, MAST-Score, and Rationale for Choosing Cut Points

The MEFIB-Index, which is a combination of MRE and FIB-4, has identified a cut-point (defined as positive when MRE ≥ 3.3kPa and FIB-4 ≥ 1.6) that can identify patients with stage 2 fibrosis or higher, with a high positive predictive value of 91.0% to 97.1% (26, 27).

The MAST-Score uses a combination of AST, MRE, and MRI-PDFF(25). The MAST-Score has score cutoffs of 0.165 and 0.242, corresponding to 90% sensitivity and 90% specificity, respectively. A value of 0.242 identifies patients with stage 2 fibrosis or higher.

Both MRI based panels are included in the current AASLD guidelines as part of the modalities to identify “at-risk” MASH(3).

Outcome Measures and Follow up

A composite *primary outcome (hepatic decompensation),* defined as developing either ascites, hepatic encephalopathy, or varices that needed treatment was assessed by the local site investigator. This was captured at baseline within 7 days of the first MRI and followed longitudinally. Ascites was defined per the American Association for the Study of Liver Diseases guidance by imaging or physical examination(30). According to Association guidelines, hepatic encephalopathy was defined as brain dysfunction caused by liver dysfunction and/or portosystemic shunting(31). Varices needing treatment were defined as medium/large varices, small varices with high-risk stigmata, decompensated patients with small varices, or variceal hemorrhage per practice guidance(30).

Secondary outcomes were developing HCC, defined by histology or Liver Reporting and Data Systems (LI-RADS 5) for definite HCC, death, and liver transplant.

Patient Follow-Up

Charts were reviewed retrospectively for follow-up assessment. The time of the first MRI was taken as the start of the follow-up time. The median follow-up was calculated based on

time from the initial MRE scan. Participants (N=297) with recorded follow-up time were followed until death or the last clinical encounter. Twenty-three patients had at least one of the hepatic decompensation events at baseline. No longitudinal follow-up was found recorded for a subset of patients (N=134) of the total cohort for whom only hepatic decompensation at baseline could be assessed.

Statistical Analysis

Patient characteristics, including demographic, laboratory, imaging, and outcome data were summarized as mean (SD) or median (IQR) for continuous variables and N (%) for categorical variables and compared using t-tests, Kruskal-Wallis, and Chi-square tests. Logistic regression was used to evaluate the association between hepatic decompensation at baseline and demographics, biochemical factors, and NITs. Cox-proportional hazard analyses were used to evaluate the association between all outcomes and demographics, biochemical factors, and NITs with specific focus on MEFIB-Index positive indicator (MRE ≥ 3.3 kPa and FIB-4 ≥ 1.6) and MAST-Score positive indicator (MAST ≥ .242). Concordance statistics(32) were used to compare the predictive accuracy of MEFIB-Index and MAST-Score for the primary outcome (32). All models included adjustments for age, sex, race, and clinical site. All statistical analyses were performed with SAS 9.4; a p-value of < .05 was considered statistically significant.

Results

Study selection and Characteristics

Two published studies were identified by using our primary search strategy and met our inclusion criteria (33, 34) and two studies were identified by experts in the field (one published (35) and one remains unpublished). After contacting the primary or corresponding authors, we obtained individual participant data from all four studies. The study identification and selection process flow chart is shown in supplementary figure 1. All studies were retrospective.

Patient Characteristics

Patients' clinical, demographic, and imaging characteristics are presented in Table 1. This IPDMA included 454 patients (58% women). The mean (± SD) age was 56.0 ±13.5 years, and BMI was 30.9± 6.4 kg/m^2. A total of 166 (37%) were White, 153 (34%) were Asian, and 119 (26%) were Hispanic. The patients were from 3 distinctly different geographic areas: 142 (31%) from Japan, 80 (18%) from Turkey, and 232 (51%) from the United States.

Biochemical profile and NIT results

The median (IQR) for NITs scores were FIB-4 1.45 (1.85), and MELD Score 7.0 (2.0). The mean MRE (kPa) for 454 patients was 3.80 (SD 1.91) and the mean MRI-PDFF was 12.27 (SD 7.91). The MEFIB-Index (MRE ≥ 3.3kPa & FIB-4 ≥ 1.6) and MAST-Score (>.242) were positive for 34% and 9% of the sample, respectively. Patients who had positive MEFIB-Index were significantly older than those who had negative MEFIB-Index, (64.5 ± 8.1 years vs 51.7 ± 13.7; p 0.0001) whereas the age difference in patients who had positive

or negative MAST-Score did not reach statistical significance (59.6 ± 12.1 vs 55.7 ± 13.6 years; p 0.08).

Hepatic decompensation at baseline

At baseline (within 7-days of the date of MRI), 23 (5%) patients had hepatic decompensation at baseline [total events 46, ascites (n=18), hepatic encephalopathy (n=14), or varices needing treatment (n=14)] (Supplementary Table 1). A positive MEFIB-Index [OR=13.95 (95%CI: 11.73–16.59)], and a positive MAST-Score [OR=17.81 (95%CI: 10.70–29.63)] were both associated with increased risk for hepatic decompensation at baseline. Other factors associated with increased risk of hepatic decompensation were AST (per 5-unit increase) [OR=1.08 (95%CI: 1.04–1.12)], MELD score (per 1-unit increase) [OR=1.59 (95%CI: 1.48–1.70)]. Higher albumin [OR=0.07 (95%CI: 0.02–0.24)], and higher platelet count (per10-unit increase) [OR=0.84 (95%CI: 0.81–0.88)] were associated with lower chance of developing hepatic decompensation at baseline. (Table 2).

Primary and secondary outcomes

Among 297 patients with available longitudinal data who had a median (IQR) of 4.2 (5.0) years of follow-up, 25 patients developed the primary outcomes of hepatic decompensation [total events 44, ascites (n=18), hepatic encephalopathy (n=12), or varices needing treatment (n=14] (Table 3). Clinical, demographic, and imaging characteristics for patients with the primary outcome summarized in supplementary table 2. Both a positive MEFIB-Index [HR=49.22 (95%CI: 6.23–388.64, p<0.001)], and a positive MAST-Score [HR=3.86 (95%CI: 1.46–10.17, p<0.001)] were statistically significant predictors of hepatic decompensation (Figure 1). The median time to decompensation was 1.9 (3.9) years. The 1- and 3-year risk of the primary outcome were 11% vs 0% and 14% vs 0% for positive MEFIB-Index vs negative MEFIB-Index (p<0.0001 for both). The 1- and 3-year risk of the primary outcome were 14% vs 3% (p=0.01). and 14% and 4% (p=0.04) for positive MAST-Score vs negative MAST-Score.

The predictive power of the MEFIB-Index (c=.89) was statistically superior that of the MAST-Score (c-statistic: 81) (p<.0001). Sensitivity, specificity, positive predict value and negative predictive value was higher for MEFIB-Index vs MAST-score (supplementary table 3). Other NIT's predictive power were also assessed; a c-statistic comparison between FIB-4, MAST-Score, MEFIB-Index, and MELD is shown in supplementary figure 3.

Other factors associated with increased risk of developing the primary outcome were FIB-4 (per 1-unit increase) [HR=1.52 (95%CI: 1.34–1.74)], MELD score (per 1-unit increase) [HR=1.28 (95%CI: 1.14–1.43)]. Higher albumin [HR=0.13 (95%CI: 0.06–0.26)] and higher platelet count (per 10-unit increase) [HR=0.78 (95%CI: 0.71–0.84)] were associated with lower chance of developing the primary outcome on follow up (Table 4).

In terms of secondary outcomes, 18 patients developed HCC, 1 patient underwent liver transplantation, and 16 died. Both a positive MEFIB-Index [HR=18.86 (95%CI: 2.24, 158.69)], and a positive MAST-Score [HR=6.48 (95%CI: 2.13, 19.73)] were associated with increased risk of developing HCC.

Other factors associated with higher risk of HCC were FIB-4 (per 1-unit increase) [HR=1.41 (95%CI: 1.21, 1.64)], and MELD score (per 1-unit increase) [HR=1.38 (95%CI: 1.16, 1.64))]. Higher albumin [HR=0.19 (95%CI: 0.07, 0.52)], and higher platelet count [HR=0.80 (95%CI: 0.71, 0.89)] were protective and associated with decreased risk of developing HCC. (Supplementary Table 4).

Discussion

This individual patient data meta-analysis of 454 patients from four centers in three countries determined the clinical utility of MRI-based panels in the prediction of hepatic decompensation in patients with MASLD. MRI-based panels, i.e., MEFIB-Index and MAST-Score, were statistically significant predictors of hepatic decompensation. We compared the predictive power of the only two MRI-based panels known to date in the literature to detect patients “at risk” of MASH (≥ stage 2 fibrosis) and found that MEFIB-Index had significantly higher discrimination for hepatic decompensation than the MAST-Score. In practice, both the MRI-based panels may be used to identify high-risk patients who require intensive monitoring and modification of risk factors for hepatic decompensation.

Our study builds on previous efforts to use NITs to predict hepatic decompensation and help risk-stratify MASH patients using MRI-based panels. FIB-4, based on serum markers to identify liver fibrosis in patients with MASLD, have predicted hepatic decompensation; however, the predictive ability was modest and best in patients followed for relatively short times(36). This was found in a large Swedish study that evaluated the ability of various NITs scores (FIB-4 included) to identify individuals at risk for severe liver disease, which was defined as the diagnosis of cirrhosis, liver failure, HCC, liver transplantation, or decompensated liver disease (captured by ICD codes).

VCTE studies have investigated the association between liver stiffness measurements (LSM) and hepatic decompensation and death. In a multicenter retrospective analysis of 1039 MASLD patients with a histologic diagnosis of F3–F4 fibrosis and/or LSMs >10 kPa followed for at least 6 months, changes in LSM were independently associated with hepatic decompensation, HCC, and mortality, including liver-related mortality(37). Recently, analysis of four large, prospective, international, multicenter, randomized placebo-controlled trials of participants with MASH and biopsy-proven advanced fibrosis (F3–F4), found that progression of clinical disease was associated with higher liver stiffness identified by VCTE at baseline. The optimal baseline liver stiffness thresholds were ≥16.6 kPa for predicting progression to cirrhosis, and ≥30.7 kPa for predicting liver-related events. The study also found that a≥5 kPa (and ≥20%) increase in liver stiffness was associated with progression to cirrhosis among participants with bridging fibrosis at baseline(38).

In MRE-based studies, per the original MEFIB development paper, MEFIB outperformed MRE alone in detecting at-risk MASH, when the optimal cut-point for MRE alone was used (area under the receiver operating curve 0.90 versus 0.87), and this difference was statistically significant. A multicenter retrospective study of 320 MASLD patients who underwent MRE found that specific MRE cut-offs are predictive of individual hepatic decompensation. Gidener et al, in a retrospective cohort study of 829 MASLD patients

with a follow-up period of 4 years, found that LSM measured by MRE is a predictor of the development of cirrhosis [HR = 2.93 (95% CI, 1.86–4.62, p <.0001) per 1 kPa increment](39). In a meta-analysis for diagnosing fibrosis stages (including cirrhosis) in 14,609 patients across 82 studies (53 VCTE, 11 MRE, 12 shear wave elastography, and 4 two-dimensional shear wave elastography studies), the authors found that the AUC for diagnosis of cirrhosis were 0.89 for VCTE, 0.90 for MRE, 0.90 for shear wave elastography, and 0.88 for two-dimensional shear wave elastography (40). Recently, our group showed that LSM measured by MRE is associated with hepatic decompensation; HR for hepatic decompensation was 11.0 (95%CI: 7.03–17.1, P < .001) for MRE between 5–8 kPa and 15.9 (95%CI:9.32–27.2, P < .001) for MRE ≥ 8 kPa. The study also found that the 3-year risk of incident HCC was 0.35% for MRE<5 kPa, 5.25% for 5–8 Pa, and 5.66% for MRE≥8 kPa(27).

Most recently, an MRE-based multivariable model to predict hepatic decompensations was developed and validated based on an international multi-center cohort study of MASLD patients. The model included age, MRE, albumin, AST, and platelets; and it showed outstanding discrimination for the 3- and 5- year risk of hepatic decompensations (c-statistic 0.912 and 0.891 respectively, in the training cohort and 0.871 and 0.876 in the valuation cohort)(41).

There are still limited data comparing the MRI-based panels for prediction of hepatic decompensation. The outperformance of the MEFIB-Index compared with the MAST-Score might be due to the inclusion of liver fat measurement in the MAST-Score, which may decrease with more advanced disease and thus impact predictive power for liver-related outcomes.

Strengths and limitations

This study is novel as it examines the comparative utility of MEFIB-Index versus MAST-Score to detect hepatic decompensation. The strengths of the study include availability of individual patient data for MRE and MRI-PDFF, diverse patient cohort derived from United States, Turkey and Japan, and longitudinal follow-up. However, this study is limited due to the retrospective nature of meta-analyses and the utilization of potentially different protocols of MRE and MRI-PDFF between centers. Our study is also limited by the low number of events for the primary outcome. Therefore, prospective longitudinal studies to compare NITs in predicting risk for hepatic decompensation are needed, this should also include studying the optimal cutoff of MAST-Score to predict hepatic decompensation. Further studies are also needed to investigate the cost-effectiveness among different NITs in predicting risk for hepatic decompensation. We acknowledge that MRI-based scores are more expensive and may not be widely available, especially in resource-limited settings. Further studies are required to compare the cost-effectiveness of MRI-based scores, compared to conventional NITs in predicting liver-related outcomes.

Implications for clinical practice and future research

In this work, we have documented that a combination of MRI-based biomarkers and blood tests such as MEFIB-Index and MAST-Score predict risk of hepatic decompensation. These

MRI-based panels might be an alternative to liver biopsy, with its well-known drawbacks(16, 17), in predicting progression of disease and clinical outcomes. Patients with negative MEFIB-Index and negative MAST-Score have low risk of hepatic decompensation for an average of 5 years from the time of the index MRI. This assurance might mean less need for close surveillance of patients with a negative MEFIB-Index and MAST-Score, which will reduce in the economic burden on the healthcare system (fewer clinic visits and invasive interventions, such as endoscopic surveillance for esophageal varices, and decreased exposure of patients to risks of these procedures). The findings of this study will also help in early identification of patients who are at the risk of developing hepatic decompensation. These findings will also help identify MASH patients who should be prioritized for clinical trials or receive treatment once newer agents become available. Prospective studies to assess MRE and MRI-based panels in ethnically and geographically diverse patient cohorts will be needed to validate these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Potential conflict of interests:

RL serves as a consultant to Aardvark Therapeutics, Altimmune, Anylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Bristol-Myer Squibb, CohBar, Eli Lilly, Galmed, Gilead, Glympse bio, Hightide, Inipharma, Intercept, Inventiva, Ionis, Janssen Inc., Madrigal, Metacrine, Inc., NGM Biopharmaceuticals, Novartis, Novo Nordisk, Merck, Pfizer, Sagimet, Theratechnologies, 89 bio, Terns Pharmaceuticals and Viking Therapeutics. In addition his institutions received research grants from Arrowhead Pharmaceuticals, Astrazeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Galectin Therapeutics, Galmed Pharmaceuticals, Gilead, Intercept, Hanmi, Intercept, Inventiva, Ionis, Janssen, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, Novo Nordisk, Merck, Pfizer, Sonic Incytes and Terns Pharmaceuticals. Co-founder of LipoNexus Inc.

ABBREVIATIONS

MRE	Magnetic resonance elastography
IPDMA	individual participant data pooled meta-analysis
NAFLD	nonalcoholic fatty liver disease
MASLD	Metabolic dysfunction-associated steatotic liver disease
BMI	body mass index
AASLD	American Association for the Study of Liver Diseases
LI-RADS	Liver Reporting and Data Systems
LSM	liver stiffness measurement
SD	standard deviation

IQR	interquartile range
MELD	model for end-stage liver disease
HCC	hepatocellular carcinoma

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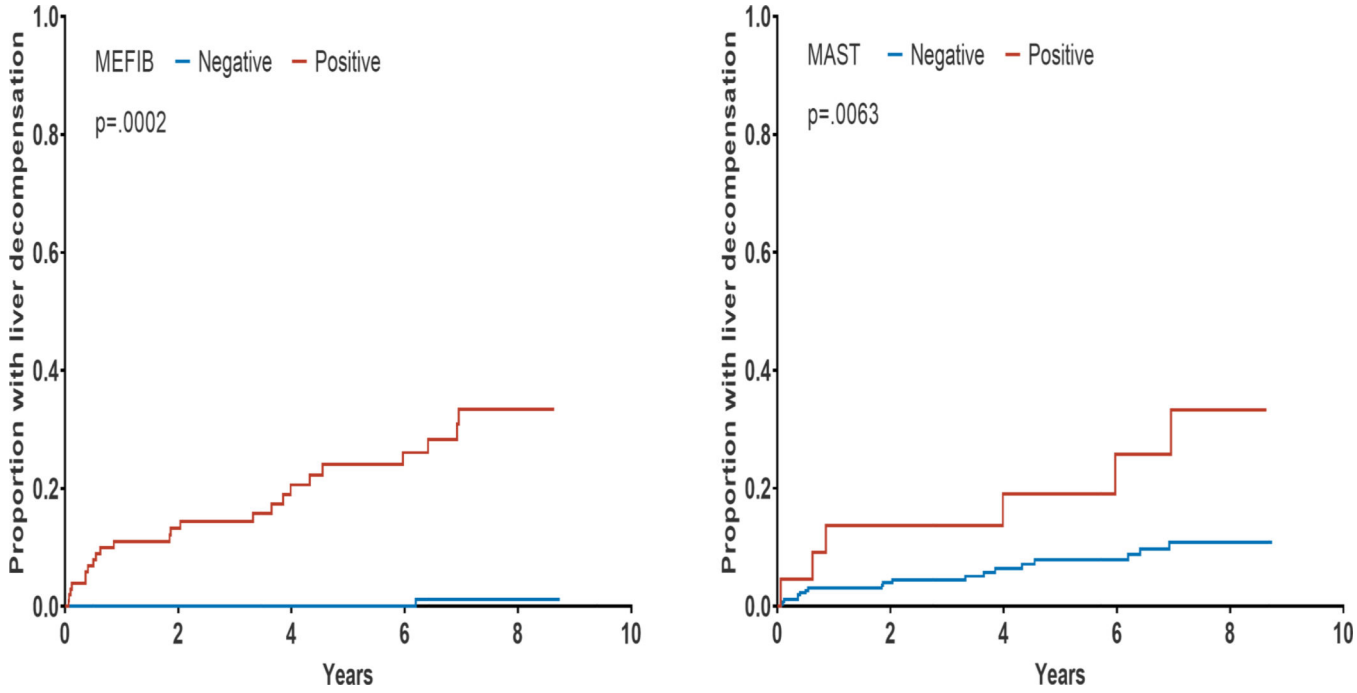

Figure 1: Cumulative incidence of hepatic decompensation for MEFIB-Index and MAST-Score

Footnote: Cumulative incidence plots for the primary outcome (ascites, hepatic encephalopathy, and varices needing treatment) for MEFIB-Index (Left) and MAST-Score (Right). Blue represents a negative value, and red represents a positive value. Positive MEFIB-Index is defined as MRE ≥ 3.3kPa & FIB-4 ≥ 1.6; negative MEFIB-Index is defined as MRE < 3.3kPa or FIB-4 < 1.6. (p= .0002). Positive MAST-Score defined as MAST > .242 and negative defined as MAST ≤.242 (p=.0063)

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Table 1.

Clinical, demographic, and imaging characteristics by MEFIB and MAST

	N	Total N=454	Positive MEFIB N=153	Negative MEFIB N=301	p	Positive MAST N=39	Negative MAST N=415	p
Demographic								
Age in years, mean (SD)	454	56.0 (13.5)	64.5 (8.1)	51.7 (13.7)	**<.0001**	59.6 (12.1)	55.7 (13.6)	.0832
Female, n (%)	454	264 (58%)	89 (58%)	64 (42%)	.9950	20 (51%)	244 (58%)	.3632
BMI (kg/m^2), mean (SD)	410	30.9 (6.4)	30.6 (6.6)	31.1 (6.3)	.5021	32.4 (7.9)	30.8 (6.2)	.2423
Race	454				.2724			.0873
White, n (%)		166 (37%)	50 (33%)	116 (39%)		7 (18%)	159 (38%)	
Hispanic, n (%)		119 (26%)	42 (27%)	77 (26%)		14 (36%)	105 (25%)	
Asian, n (%)		153 (34%)	58 (38%)	95 (32%)		16 (41%)	137 (33%)	
Other, n (%)		16 (4%)	3 (2%)	13 (4%)		2 (5%)	14 (3%)	
Site	454				.5811			.0130
Ankara		80 (18%)	27 (18%)	53 (18%)		1 (3%)	79 (19%)	
Cedars Sinai		114 (25%)	36 (24%)	78 (26%)		7 (18%)	107 (26%)	
UC San Diego		118 (26%)	36 (24%)	82 (27%)		16 (41%)	102 (25%)	
Yokohama		142 (31%)	54 (35%)	88 (29%)		15 (38%)	127 (31%)	
Diabetes, n (%)	453	237 (52%)	113 (74%)	124 (41%)	**<.0001**	30 (77%)	207 (50%)	.0013
Hypertension, n (%)	454	179 (39%)	80 (52%)	99 (33%)	**<.0001**	22 (56%)	157 (38%)	.0232
Hyperlipidemia, n (%)	452	210 (46%)	75 (49%)	135 (45%)	.4351	20 (51%)	190 (46%)	.5276
Biochemical profile								
HbA1c (%), median (IQR)	376	6.1 (1.3)	6.4 (1.7)	6.0 (0.8)	.0004	6.9 (1.6)	6.1 (1.2)	.0093
AST (U/l), median (IQR)	454	32.0 (25.0)	46.0 (36.0)	28.0 (19.0)	**<.0001**	88.0 (40.0)	31.0 (22.0)	**<.0001**
ALT (U/l), median (IQR)	454	39.0 (35.0)	41.0 (35.0)	39.0 (34.0)	.2556	72.0 (97.0)	36.0 (31.0)	**<.0001**
Alkaline Phosphatase (U/l), median (IQR)	454	102.0 (207.0)	123.0 (216.0)	96.0 (197.0)	**.0031**	138.0 (334.0)	99.0 (205.0)	**.0006**
Total bilirubin (mg/dl), median (IQR)	454	0.50 (0.50)	0.60 (0.60)	0.44 (0.40)	**<.0001**	0.60 (0.70)	0.50 (0.46)	.2385
Albumin (g/dl), median (IQR)	454	4.4 (0.4)	4.2 (0.5)	4.5 (0.4)	**<.0001**	4.2 (0.6)	4.4 (0.4)	**.0003**
Triglycerides (mg/dl), median (IQR)	435	152.0 (100.0)	145.0 (100.0)	154.0 (99.5)	.2521	148.5 (101.0)	152.0 (99.0)	.9795
HDL (mg/dl), median (IQR)	433	47.0 (15.0)	45.6 (18.0)	48.0 (14.0)	.1046	45.0 (14.0)	48.0 (15.0)	.1999

	N	Total N=454	Positive MEFIB N=153	Negative MEFIB N=301	p	Positive MAST N=39	Negative MAST N=415	p
LDL (mg/dl), median (IQR)	427	119.0 (45.0)	105.0 (45.0)	124.0 (42.0)	**<.0001**	112.0 (40.0)	120.0 (45.0)	.6161
Platelet count (10^9/L), median (IQR)	450	215.0 (110.0)	150.0 (83.0)	250.0 (86.0)	**<.0001**	155.0 (108.0)	221.0 (105.0)	**<.0001**
INR, median (IQR)	380	1.0 (0.1)	1.1 (0.2)	1.0 (0.1)	**<.0001**	1.1 (0.3)	1.0 (0.1)	**.0001**
Clinical scores								
FIB-4, median (IQR)	450	1.45 (1.85)	3.09 (2.20)	1.05 (0.72)	**<.0001**	3.98 (2.28)	1.37 (1.31)	**<.0001**
MELD Score, median (IQR)	379	7.0 (2.0)	7.0 (2.0)	6.0 (1.0)	**<.0001**	8.0 (4.0)	7.0 (1.0)	**.0008**
Imaging								
MRE (kPa), mean (SD)	454	3.80 (1.91)	5.66 (1.89)	2.85 (1.02)	**<.0001**	7.30 (2.34)	3.47 (1.49)	**<.0001**
MRI-PDFF, mean (SD)	454	12.27 (7.91)	9.52 (6.43)	13.68 (8.22)	**<.0001**	11.16 (8.91)	12.38 (7.81)	.3590

Abbreviations: HbA1c, Hemoglobin A1c; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; BMI, Body mass index; HDL, high-density lipoprotein; INR, International normalized ratio; IQR, interquartile range; LDL, low-density lipoprotein; FIB-4, Fibrosis index based on the 4 factor; MRE, Magnetic resonance elastography; SD, Standard deviation. ANOVA performed on continuous variables presented as mean (SD), Kruskal-Wallis performed on all other continuous variables. Chi-square or Fisher's exact test as appropriate on all categorical variables

Table 2.

Factors Associated with the Primary Outcome (Hepatic decompensation defined as Ascites, Hepatic Encephalopathy or Varices Needing Treatment) at Baseline on Logistic Regression (N=454)

	Liver-Related Outcomes OR (95% CI)	P-value
Demographic & Biochemical		
Age in years, mean (SD) (per 1 year increase)	1.04 (1.02–1.07)	**<.0001**
Female, n (%)	1.37 (0.90–2.08)	0.4823
BMI (kg/m^2) (per 1-unit increase) *	1.00 (0.98–1.03)	.9750
HbA1c (%) (per 1-unit increase) *	0.98 (0.77–1.24)	.8545
AST (U/l) (per 5-unit increase) *	1.08 (1.04–1.12)	**<.0001**
ALT (U/l) (per 5-unit increase) *	1.00 (0.98–1.03)	.7754
Alkaline Phosphatase (U/l) (per 5-unit increase) *	1.05 (1.02–1.09)	.0029
Total bilirubin (mg/dl) (per 1-unit increase) *	1.01 (0.98–1.04)	.4283
Albumin (g/dl) (per 1-unit increase) *	0.07 (0.02–0.24)	**<.0001**
Platelet count (10^9/L) (per 10-unit increase) *	0.84 (0.81–0.88)	**<.0001**
Clinical Score		
FIB-4 (per 1-unit increase) *	1.59 (1.15–2.20)	.0045
MELD score (per 1-unit increase) *	1.59 (1.48–1.70)	**<.0001**
Positive MEFIB *	13.95 (11.73–16.59)	**<.0001**
Positive MAST *	17.81 (10.70–29.63)	**<.0001**

Abbreviations: HbA1c, Hemoglobin A1c; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; BMI, Body mass index; HDL, high-density lipoprotein; INR, International normalized ratio; LDL, low-density lipoprotein; FIB-4, Fibrosis index based on the 4 factors; MRE, Magnetic resonance elastography.

* Models adjusted for age, gender, race, and clinical site

Table 3.

Incidence of hepatic decompensation and secondary outcomes

		MEFIB		MAST	
	Total # Incidents N= 297	**Positive MRE ≥ 3.3kPa & FIB-4 ≥ 1.6 N=103 (35%)**	**Negative MRE < 3.3kPa or FIB-4 < 1.6 N=194 (65%)**	**Positive > .242N=22 (7%)**	**Negative ≤ .242N=275 (93%)**
Any Primary Outcome Incident	25 (8%)	24 (23%)	1 (1%)	6 (27%)	19 (7%)
Ascites, N (%)	18 (6%)	18 (17%)	0 (0%)	4 (18%)	14 (5%)
Hepatic encephalopathy, N (%)	12 (4%)	12 (12%)	0 (0%)	2 (9%)	10 (4%)
Varices needing treatment, N (%)	14 (5%)	13 (13%)	1 (1%)	4 (18%)	10 (4%)
Hepatocellular carcinoma– N (%)	18 (6%)	15 (15%)	3 (2%)	5 (23%)	13 (5%)
Liver transplant– N (%)	1 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Death– N (%)	16 (5%)	13 (35%)	3 (2%)	2 (9%)	14 (5%)

Table 4.

Factors Associated with Incident Primary Outcome (Hepatic decompensation defined as Ascites, Hepatic Encephalopathy or Varices Needing Treatment) on Cox-Proportional Hazards Regression (N=297)

	Liver-Related Outcomes Hazard Ratios (95% CI)	P-value
Demographic & Biochemical		
Age in years, mean (SD) (per 1 year increase)	1.06 (1.02–1.10)	**.0026**
Female, n (%)	1.04 (0.47–2.32)	.9237
BMI (kg/m^2) (per 1-unit increase) *	0.98 (0.89–1.08)	.6961
HbA1c (%)(per 1-unit increase) *	1.19 (0.77–1.82)	.4374
AST (U/l) (per 5-unit increase) *	1.07 (1.01–1.14)	.0206
ALT (U/l) (per 5-unit increase) *	1.02 (0.96–1.08)	.5618
Alkaline Phosphatase (U/l) (per 5-unit increase) *	1.00 (1.00–1.01)	.0396
Total bilirubin (mg/dl) (per 1-unit increase) *	2.52 (1.48–4.28)	**.0007**
Albumin (g/dl) (per 1-unit increase) *	0.13 (0.06–0.26)	**<.0001**
Platelet count (10^9/L) (per 10-unit increase) *	0.78 (0.71–0.84)	**<.0001**
Clinical Score		
FIB-4 *	1.52 (1.34–1.74)	**<.0001**
MELD score (per 1-unit increase) *	1.28 (1.14–1.43)	**<.0001**
Positive MAST *	3.86 (1.46–10.17)	**.0063**
Positive MEFIB *	49.22 (6.23–388.64)	**.0002**

Abbreviations: HbA1c– Hemoglobin A1c; AST– Aspartate aminotransferase; ALT– Alanine aminotransferase; BMI– Body mass index; HDL– high-density lipoprotein; INR– International normalized ratio; LDL– low-density lipoprotein; FIB-4– Fibrosis index based on the 4 factors

* Models adjusted for age, gender, race, and clinical site.