Journal of Gastroenterology and Hepatology

WILEY | JGHF Journal of Gastroenterology and Hepatology Foundation

ORIGINAL ARTICLE - HEPATOLOGY (CLINICAL)

Noninvasive Detection of MASH and Fibrotic Burden Using Ultrasound-Derived LIID and LSM in MASLD: A Multicenter Study

Feng Gao[1] | Yao Zhang[2] | Yang Ding[3] | Yiling Li[4] | Jie Li[5] | Yameng Sun[6] | Feng Xue[7,8] | Gaofeng Chen[9] | Lijun Chang[10] | Bihui Zhong[11] | Yongfeng Yang[12] | Chengwei Chen[13] | Qingchun Fu[13] | Lungen Lu[14] | Yun Xu[15] | Jiangao Fan[16] | Junping Shi[17] | Yongjian Zhou[18] | Xinhe Zhang[4] | Ming-Hua Zheng[19,20,21] | Lai Wei[8]

Correspondence: Ming-Hua Zheng (zhengmh@wmu.edu.cn) | Lai Wei (weelai@163.com)

Received: 20 December 2025 | **Revised:** 20 February 2026 | **Accepted:** 24 June 2026

Keywords: fibrosis | MASH | MASLD | noninvasive diagnosis | quantitative ultrasound

ABSTRACT

Background and Aims: Metabolic dysfunction-associated steatohepatitis (MASH), the progressive form of metabolic dysfunction-associated steatotic liver disease (MASLD), is associated with adverse hepatic and cardiometabolic outcomes. The study aimed to validate a novel quantitative ultrasound (QUS)-derived score, the LIID score, for noninvasive diagnosis of MASH, and to evaluate the performance of liver stiffness measurement (LSM) using the same ultrasound platform for detecting fibrotic burden in MASLD.

Methods: This multicenter study enrolled 438 participants with MASLD who underwent both *iLivTouch* examination and liver biopsy between November 2018 and December 2024 from 10 hospitals in China. After the exclusion criteria were applied, a total of 410 patients with biopsy-proven MASLD and successful QUS measurements were included to assess the performance of the LIID score.

Results: The LIID score demonstrated an area under the receiver operating characteristic curve (AUROC) of 0.71 (95% CI: 0.66–0.76) for detecting MASH. A rule-out threshold of 6.0 achieved high sensitivity (89.6%) and negative predictive value (78.2%), whereas a rule-in threshold of 7.8 provided high specificity (88.4%) and positive predictive value (70.5%). LSM showed excellent diagnostic performance for advanced fibrosis (AUROC: 0.86; 95% CI: 0.79–0.92) and acceptable accuracy for significant fibrosis (AUROC: 0.75; 95% CI: 0.69–0.79) and cirrhosis (AUROC: 0.78; 95% CI: 0.61–0.95).

Conclusions: The LIID score offers a noninvasive, ultrasound-based approach for identifying MASH. Combined with LSM, this strategy enables comprehensive, noninvasive assessment of hepatic inflammation and fibrosis in MASLD and may reduce the need for liver biopsy in clinical practice.

1 | Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as nonalcoholic fatty liver disease (NAFLD), has emerged as a global health concern, affecting approximately 30% of the adult population worldwide [1, 2]. MASLD encompasses a spectrum of liver diseases, ranging from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH) [3]. MASH is not only the most rapidly increasing indication for liver transplantation but also significantly associated with an elevated risk of

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; GGT, γ-glutamyltranspeptidase; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; LSM, liver stiffness measurement; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NAS-CRN, *NASH-Clinical Research Network*; NASH, nonalcoholic steatohepatitis; NPV, negative predictive value; PPV, positive predictive value; TC, total cholesterol; TE, transient elastography; TG, triglycerides; UAP, ultrasound attenuation parameter.

Article Guarantors: Lai Wei and Ming-Hua Zheng.

extrahepatic complications, including cardiovascular disease and chronic kidney disease [4–6]. Identifying patients at high risk of MASH is critical for making informed prognostic assessments and therapeutic decision-making.

Diagnosing MASH remains challenging due to its asymptomatic nature and the lack of reliable clinical or laboratory indicators [7]. Currently, liver biopsy serves as the gold standard for diagnosing and staging MASH in both clinical and research settings. However, it is invasive, costly, and associated with risks such as pain, bleeding, and sampling variability [8]. These limitations underscore the need for accurate, noninvasive, and accessible diagnostic alternatives for MASH.

Among various noninvasive techniques, quantitative ultrasound (QUS) has demonstrated a unique advantage in providing detailed insights into liver tissue composition through raw radiofrequency data [9, 10]. Building on this technology, we previously developed the Liver Inflammation and Injury Detection (LIID) score, a QUS-derived algorithm designed to detect MASH in patients with biopsy-proven MASLD [11]. While the LIID score showed promising results in an initial internal validation within a single-center retrospective study, further external validation using large, multicenter cohorts is necessary to confirm its broader applicability.

The primary aim of this study was to externally validate the diagnostic performance of the LIID score for identifying MASH in a multicenter cohort of patients with biopsy-proven MASLD. A secondary objective was to assess the accuracy of LSM, integrated into the same ultrasound platform, for detecting fibrotic burden in MASLD. A schematic illustration is shown in Figure 1.

2 | Methods

2.1 | Study Population and Design

This multicenter study initially enrolled 438 patients with MASLD who underwent both *iLivTouch* examination and liver biopsy between November 2018 and December 2024 across 10 hospitals in China. The geographic distribution of the different centers is shown in Figure 2. Twenty-eight patients were excluded from the cohort due to (i) invalid QUS measurements, (ii) incomplete biopsy data precluded calculation of the NAFLD activity score (NAS), or (iii) hepatic steatosis involving less than 5% of hepatocytes on histology. After exclusions, 410 patients were included in the cohort.

The study protocol was approved by the ethics committees of all participating centers. All procedures involving human participants were performed in accordance with the ethical standards outlined in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all participants.

2.2 | Clinical and Biochemical Data

Clinical and biochemical data were collected within 48 h of liver biopsy. Blood samples were drawn following an overnight fast. Body mass index (BMI) was calculated using the formula: weight (kg)/height (m^2). Severe obesity was defined as BMI $\geq$ 28 kg/m^2, consistent with criteria for the Asian population. Type 2 diabetes mellitus (T2DM) was diagnosed based on a self-reported history, a fasting glucose level $\geq$ 7.0 mmol/L, hemoglobin A1c $\geq$ 6.5% ($\geq$ 48 mmol/mol), or the use of any antihyperglycemic medications. Hypertension was defined as blood pressure $\geq$ 140/90 mmHg or the use of antihypertensive medications. The scores for AAR [12], FIB-4 [13], and acMASH [14, 15] were determined according to the previously established formulas in their respective original publications.

2.3 | iLivTouch Parameter Measurement

LSM and ultrasound attenuation parameter (UAP) were measured using the *iLivTouch* system (Wuxi Hisky Medical Technologies Co. Ltd., China), operated by trained technicians who were blinded to the clinical and histological data of participants [16]. The procedure involved placing the probe below the right seventh, eighth, or ninth ribs between the anterior and mid-axillary lines to assess liver stiffness. Ten valid measurements were required, and the median value was used for analysis. Validity criteria included an interquartile range (IQR) to median ratio of less than 30% and a success rate of $\geq$ 60%.

According to measurement results and radiofrequency data acquired from *iLivTouch*, a total of 18 ultrasonographic features were obtained with different time gain compensation and named as P1–P18 based on the intensity, attenuation, and scattering characteristics of the ultrasound signals, including LSM (P3) and UAP (P1). P2–P10 are mainly related to intensity, whereas P11–P18 are mainly related to scattering. The LIID score was derived from the QUS data, including information on the intensity, frequency, scattering, and attenuation characteristics of the ultrasound signals. The formula of the LIID score was as follows: $LIID = 0.063 * P7 + 0.019 * P13$.

In the raw RF data, P7 is mainly related to intensity, and P13 is mainly related to scattering. These features were utilized to assess the likelihood of MASH, as previously described [11].

2.4 | VCTE-Based LSM Measurement

A subset of 56 patients from the WMU cohort have both *iLivTouch*-derived LSM and VCTE-based LSM. VCTE-based LSM were measured by two experienced operators, using vibration-controlled transient elastography technology (Fibroscan; Echosens, Paris, France), according to the manufacturer's recommendations. Patients underwent FibroScan examination within 2 weeks of liver biopsy, and they were asked to fast at least 3 h before the examination. Each LSM measurement was considered adequate when including at least 10 valid measurements for each patient, with a success rate > 60% and variability of measurements (IQR/M) < 30% of the median.

2.5 | Liver Histology

Percutaneous liver biopsy was performed under ultrasound guidance. Liver histopathological assessment was carried out

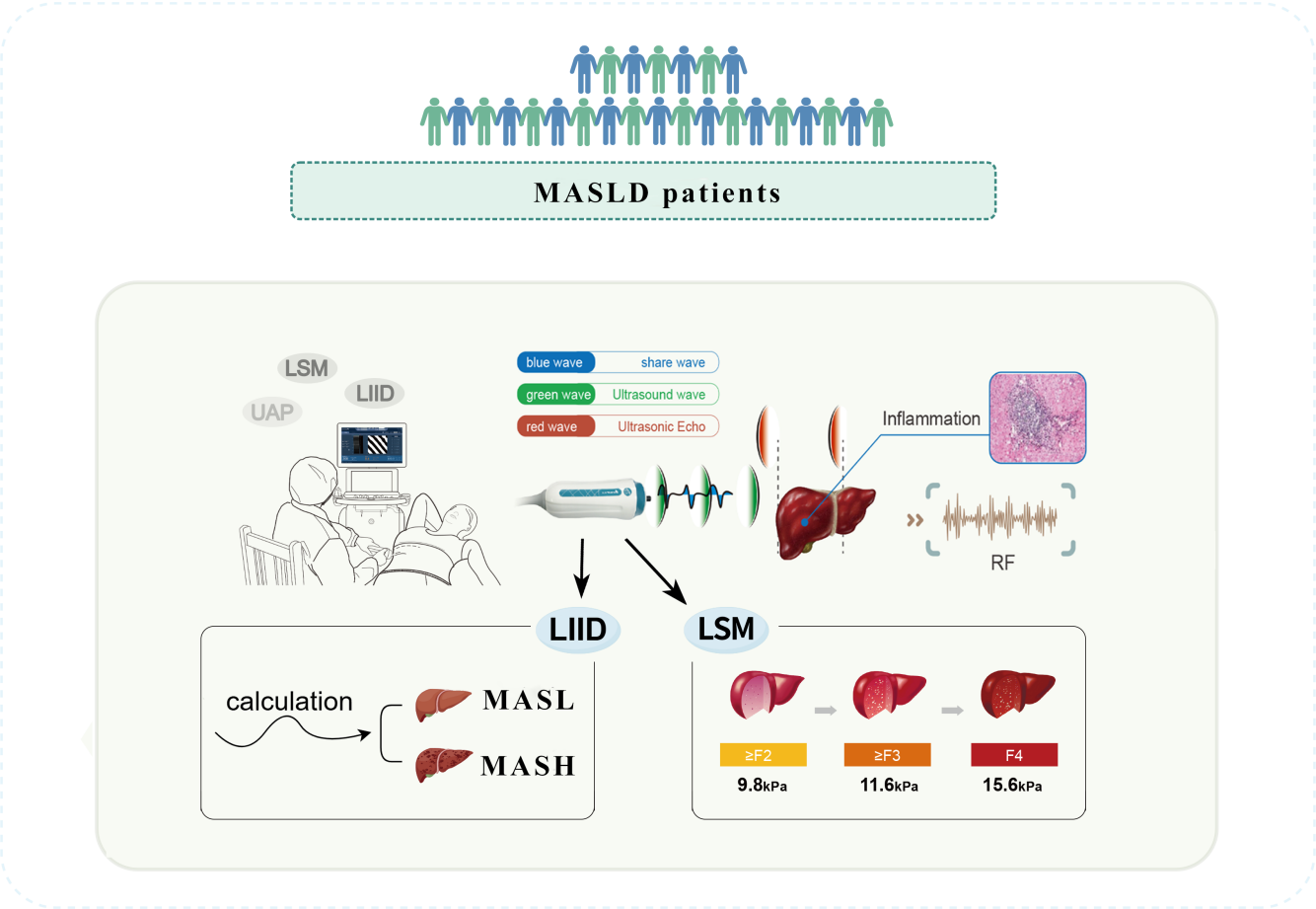

FIGURE 1 | Schematic illustration of the LIID score to differentiate MASH from MASL.

by experienced pathologists blinded to the clinical data of participants, following the NASH-Clinical Research Network (CRN) Scoring System [17, 18]. At each center, slides were independently reviewed by two pathologists, and in cases of disagreement, a third pathologist was consulted to reach consensus.

The NAS score was calculated as the sum of the scores for liver steatosis (0–3), ballooning (0–2), and lobular inflammation (0–3). Liver fibrosis was staged according to Brunt's histologic criteria, ranging from F0 (no fibrosis) to F4 (cirrhosis) [17, 18]. MASLD was defined by hepatic steatosis in $>5\%$ of hepatocytes combined with the presence of at least 1 of 5 cardiometabolic risk factors [2]. MASH was defined as the presence of hepatic steatosis, lobular inflammation, and ballooning with NAS ≥ 5. Significant fibrosis was defined as fibrosis stage ≥ 2 ($F \geq 2$) [19]. Advanced fibrosis was classified as F3 or F4, and cirrhosis was classified as F4 [20].

2.6 | Statistical Analysis

Continuous variables were expressed as means ± standard deviation (SD) or medians with IQR, and comparisons between groups were performed using the unpaired Student's *t*-test or the Mann–Whitney *U* test, as appropriate. Categorical variables were expressed as frequencies (percentages) and compared using the chi-square test or Fisher's exact test. Comparisons between groups were performed using the Kruskal–Wallis test, a nonparametric method suitable for evaluating differences in continuous outcomes across three or more independent ordinal groups.

The diagnostic accuracy of the LIID score was evaluated using the area under the receiver operating characteristic curve (AUROC). Pairwise comparisons of AUROC values were conducted using the DeLong test. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), likelihood ratio, and diagnostic odds ratio were calculated at different cutoff values. The dual cutoffs for the LIID score, corresponding to the 90% sensitivity and 90% specificity thresholds for detecting MASH, were calculated. The optimal cutoff value was determined by maximizing the Youden Index (sensitivity + specificity − 1) derived from the ROC analysis. The point corresponding to the maximum Youden Index was selected as the optimal threshold to balance sensitivity and specificity. Violin plots were chosen to depict both the probability density and the central tendency (median and IQR) of values within each subgroup. The association between increasing the LIID score (as exposure measures) and the presence of MASH (as the outcome measure) was assessed by binary logistic regression analysis. The concordance between LSM obtained by *iLivTouch* and VCTE was evaluated using Spearman's rank correlation coefficient (ρ), which is appropriate for assessing

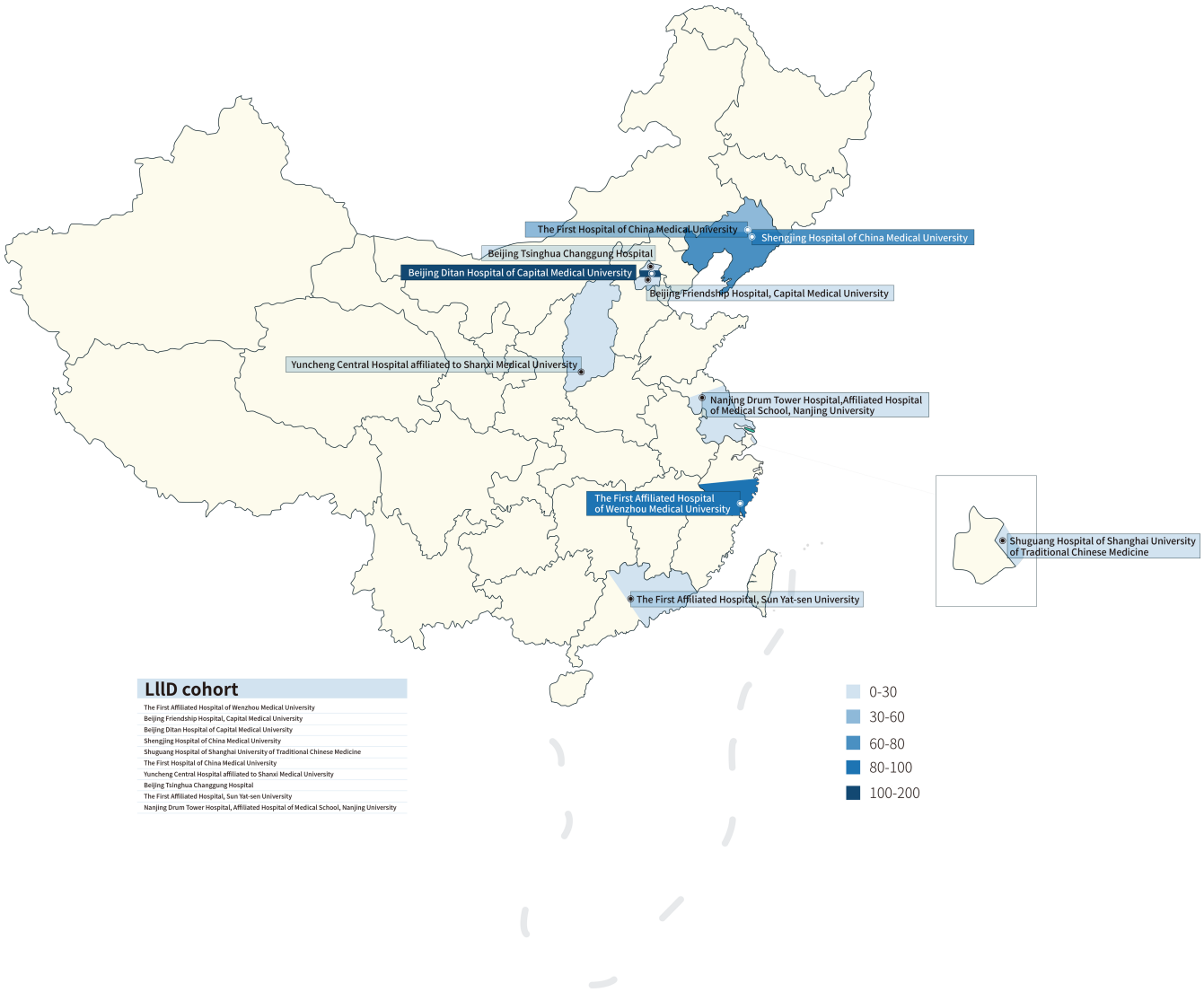

FIGURE 2 | The geographic distribution of the different centers.

the strength and direction of the monotonic relationship between two continuous variables. A ρ value of ≥ 0.70 was considered indicative of strong concordance. Statistical analyses were performed using R (Version 3.3.1; R Foundation for Statistical Computing, Vienna, Austria), and a two-sided p-value < 0.05 was considered statistically significant.

3 | Results

3.1 | Baseline Characteristics

A total of 410 individuals with biopsy-proven MASLD were enrolled in the "LIID cohort." The mean age of participants was 44.7 years, and 46.6% of them were men. Their mean value of BMI was 27.0 kg/m^2, and 138 subjects (33.7%) had severe obesity. Their median value of the NAS score was 5 (IQR: 3–6). MASH was histologically diagnosed in 211 subjects (51.5%). Histological assessment showed that 328 participants (80.0%) had fibrosis (stage F ≥ 1). Significant fibrosis (stage F ≥ 2) was present in 160 participants (39.0%), advanced fibrosis (stage F ≥ 3) in 55 participants (13.4%), and cirrhosis in 15 participants (3.7%). More detailed baseline demographic, clinical, and histological characteristics of the study participants are summarized in Tables 1 and S1.

3.2 | Diagnostic Performance of the LIID Score for MASH

In this study, the LIID score demonstrated acceptable diagnostic accuracy for identifying histological MASH. The AUROC was 0.71 (95% CI: 0.66–0.76) (Figure 3A). Two clinically actionable cutoffs were identified: a rule-out threshold of 6.0 and a rule-in threshold of 7.8. At the lower cutoff, the LIID score achieved a sensitivity of 89.6%, specificity of 39.7%, and NPV of 78.2%. At the higher cutoff, specificity increased to 88.4% with a PPV of 70.5%, although sensitivity decreased to 26.1% (Table 2). The diagnostic odds ratios for the two thresholds were 5.7 and 2.7, respectively.

Notably, LIID scores increased in parallel with histological disease activity, as assessed by the NAS score. A significant positive association was observed between the LIID score and NAS score (p < 0.01), supporting the ability of LIID to reflect histological

TABLE 1 | Baseline characteristics of LIID cohort participants stratified by study center.

Variables	Youyi cohort ($n=11$)	Ditan cohort ($n=151$)	Gulou cohort ($n=19$)	Shengjin cohort ($n=67$)	WMU cohort ($n=100$)	CMU cohort ($n=29$)	Changgeng cohort ($n=11$)	The other cohort[a] ($n=22$)
Age, years	55.9 ± 7.2	45.7 ± 12.9	40.6 ± 11.2	44.0 ± 12.9	41.5 ± 13.3	47.8 ± 11.7	50.1 ± 12.2	44.7 ± 16.4
Men, *n* (%)	1 (9.1)	56 (37.1)	11 (57.9)	27 (40.3)	74 (74.0)	6 (20.7)	5 (45.5)	11 (50.0)
BMI, kg/m^2	28.4 ± 2.8	26.7 ± 3.8	28.8 ± 4.4	27.4 ± 4.4	26.9 ± 3.0	26.2 ± 3.9	27.2 ± 4.2	27.2 ± 3.5
Hypertension, *n* (%)	1 (9.1)	NA	10 (52.6)	19 (28.4)	53 (53.0)	17 (58.6)	1 (9.1)	9 (40.9)
Diabetes, *n* (%)	4 (36.4)	NA	4 (21.1)	12 (17.9)	45 (45.0)	4 (13.8)	2 (18.2)	6 (27.3)
Severe obesity, *n* (%)	5 (45.5)	54 (35.8)	9 (47.4)	24 (35.8)	30 (30.0)	6 (20.7)	4 (36.4)	6 (27.3)
UAP, dB/m^2	276 ± 49	291 ± 45	314 ± 28	289 ± 38	314 ± 22	290 ± 25	292 ± 20	288 ± 22
LSM, kPa	10.6 (7.5, 17.6)	10.2 (7.4, 14.9)	11.2 (9.7, 12.7)	8.6 (6.5, 11.6)	9.00 (7.5, 11.4)	9.60 (6.9, 11.5)	13.1 (10.4, 15.3)	10.5 (7.2, 16.0)
LIID score	6.54 ± 1.08	6.83 ± 1.12	7.82 ± 1.17	7.12 ± 1.23	6.62 ± 1.02	6.82 ± 1.20	7.00 ± 1.01	6.91 ± 1.09
Steatosis grade, *n* (%)								
S1	9 (81.)	62 (41.1)	1 (5.3)	17 (25.4)	51 (51.0)	8 (27.6)	5 (45.5)	8 (36.4)
S2	2 (18.2)	54 (35.7)	6 (31.6)	36 (53.7)	33 (33.0)	15 (51.7)	4 (36.3)	7 (31.8)
S3	0 (0.00)	35 (23.2)	12 (63.1)	14 (20.9)	16 (16.0)	6 (20.7)	2 (18.2)	7 (31.8)
Ballooning grade, *n* (%)								
B0	1 (9.0)	0 (0.00)	12 (63.2)	13 (19.4)	8 (8.0)	0 (0.0)	2 (18.2)	4 (18.2)
B1	5 (45.5)	85 (56.3)	7 (36.8)	43 (64.2)	48 (48.0)	24 (82.8)	6 (54.55)	11 (50.0)
B2	5 (45.5)	66 (43.7)	0 (0.0)	11 (16.4)	44 (44.0)	5 (17.2)	3 (27.3)	7 (31.8)
Lobular inflammation grade, *n* (%)								
L0	0 (0.0)	0 (0.0)	1 (5.3)	9 (13.4)	8 (8.0)	0 (0.0)	0 (0.0)	1 (4.6)
L1	7 (63.6)	45 (29.8)	17 (89.5)	42 (62.7)	49 (49.0)	17 (58.6)	5 (45.5)	9 (40.9)
L2	4 (36.4)	84 (55.6)	1 (5.3)	14 (20.9)	42 (42.0)	11 (37.9)	6 (54.5)	6 (27.3)
L3	0 (0.00)	22 (14.6)	0 (0.0)	2 (3.0)	1 (1.0)	1 (3.5)	0 (0.0)	6 (27.3)

(Continues)

TABLE 1 | (Continued)

Variables	Youyi cohort ($n=11$)	Ditan cohort ($n=151$)	Gulou cohort ($n=19$)	Shengjin cohort ($n=67$)	WMU cohort ($n=100$)	CMU cohort ($n=29$)	Changgeng cohort ($n=11$)	The other cohort[a] ($n=22$)
MASH, *n* (%)	2 (18.2)	104 (68.9)	7 (36.8)	26 (38.8)	42 (42.0)	14 (48.3)	5 (45.5)	11 (50.0)
Fibrosis stage, *n* (%)								
F0	0 (0.0)	6 (4.0)	2 (10.5)	26 (38.8)	26 (26.0)	19 (65.5)	3 (27.3)	0 (0.0)
F1	3 (27.3)	70 (46.4)	10 (52.6)	20 (29.8)	47 (47.0)	8 (27.5)	4 (36.4)	6 (27.3)
F2	3 (27.3)	43 (28.5)	7 (36.9)	15 (22.4)	25 (25.0)	1 (3.5)	1 (9.1)	10 (45.5)
F3	2 (18.2)	27 (17.9)	0 (0.0)	2 (3.0)	2 (2.0)	1 (3.5)	3 (27.3)	3 (13.6)
F4	3 (27.2)	5 (3.3)	0 (0.0)	4 (6.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (13.6)

Abbreviations: BMI, body mass index; LSM, liver stiffness measurement; MASH, metabolic dysfunction-associated steatohepatitis; UAP, ultrasound attenuation parameter.
[a]The "other" cohort comprised the Shuguang cohort ($n=10$), Yuncheng cohort ($n=9$), and Zhongshan cohort ($n=3$).

inflammation and hepatocellular injury (Figure 4A). In the logistic regression analyses, each 1-unit increase in the LIID score was associated with a 94% increase in the risk of MASH (unadjusted-OR: 1.94, 95% CI: 1.59–2.36). Notably, the association between the LIID score and the presence of MASH remained significant even after adjusting for LSM (adjusted-OR: 1.93, 95% CI: 1.57–2.38).

3.3 | Comparison With Established Noninvasive Scores

Among the 251 patients with complete biochemical data, we performed additional comparative analyses evaluating the diagnostic performance of the LIID score against other commonly used noninvasive scores (acMASH, AAR, and FIB-4). As shown in Figure S1, the LIID score demonstrated an AUROC of 0.75 (95% CI: 0.69–0.80), compared with 0.54 (95% CI: 0.48–0.60) for FIB-4, 0.58 (95% CI: 0.52–0.64) for AAR, and 0.71 (95% CI: 0.65–0.77) for acMASH. The AUROC of the LIID score was significantly higher than that of FIB-4 and AAR (DeLong test, both $p<0.05$). Although no statistically significant differences were observed, the LIID score consistently demonstrated a numerically higher AUROC value compared with acMASH.

3.4 | Diagnostic Performance of Liver Stiffness Measurement (LSM)

LSM measured by *iLivTouch* showed high diagnostic accuracy for detecting significant fibrosis (≥F2), with an AUROC of 0.75 (95% CI: 0.69–0.79) (Figure 3B), advanced fibrosis (≥F3), with an AUROC of 0.86 (95% CI: 0.79–0.92) (Figure 3C), and cirrhosis (F4), with an AUROC of 0.78 (95% CI: 0.61–0.95) (Figure 3D).

The optimal cutoffs were 9.8 kPa for significant fibrosis, 11.6 kPa for advanced fibrosis, and 15.6 kPa for cirrhosis. At these thresholds, sensitivity and specificity were 73.1% and 64.0% for significant fibrosis, 87.3% and 74.4% for advanced fibrosis, and 73.3% and 86.8% for cirrhosis, respectively. LSM achieved high NPVs across fibrosis stages, with NPV of 78.8% for significant fibrosis, 97.4% for advanced fibrosis, and 98.8% for cirrhosis (Table 3).

In addition, LSM values correlated positively with histological fibrosis stage (F0–F4), with a statistically significant trend ($p<0.01$), further validating the utility of LSM for fibrosis staging (Figure 4B).

3.5 | Concordance Between iLivTouch-Derived LSM and VCTE-Based LSM

There are 56 patients from the WMU cohort who have both *iLivTouch*-derived LSM and VCTE-based LSM. Spearman's rank correlation analysis was performed to assess the relationship. The results showed a significant positive correlation between the two methods ($\rho=0.75$, $p<0.01$), indicating a strong concordance. This suggests that *iLivTouch*-derived LSM is in good agreement with VCTE-based LSM, supporting the clinical applicability of *iLivTouch* in assessing liver stiffness.

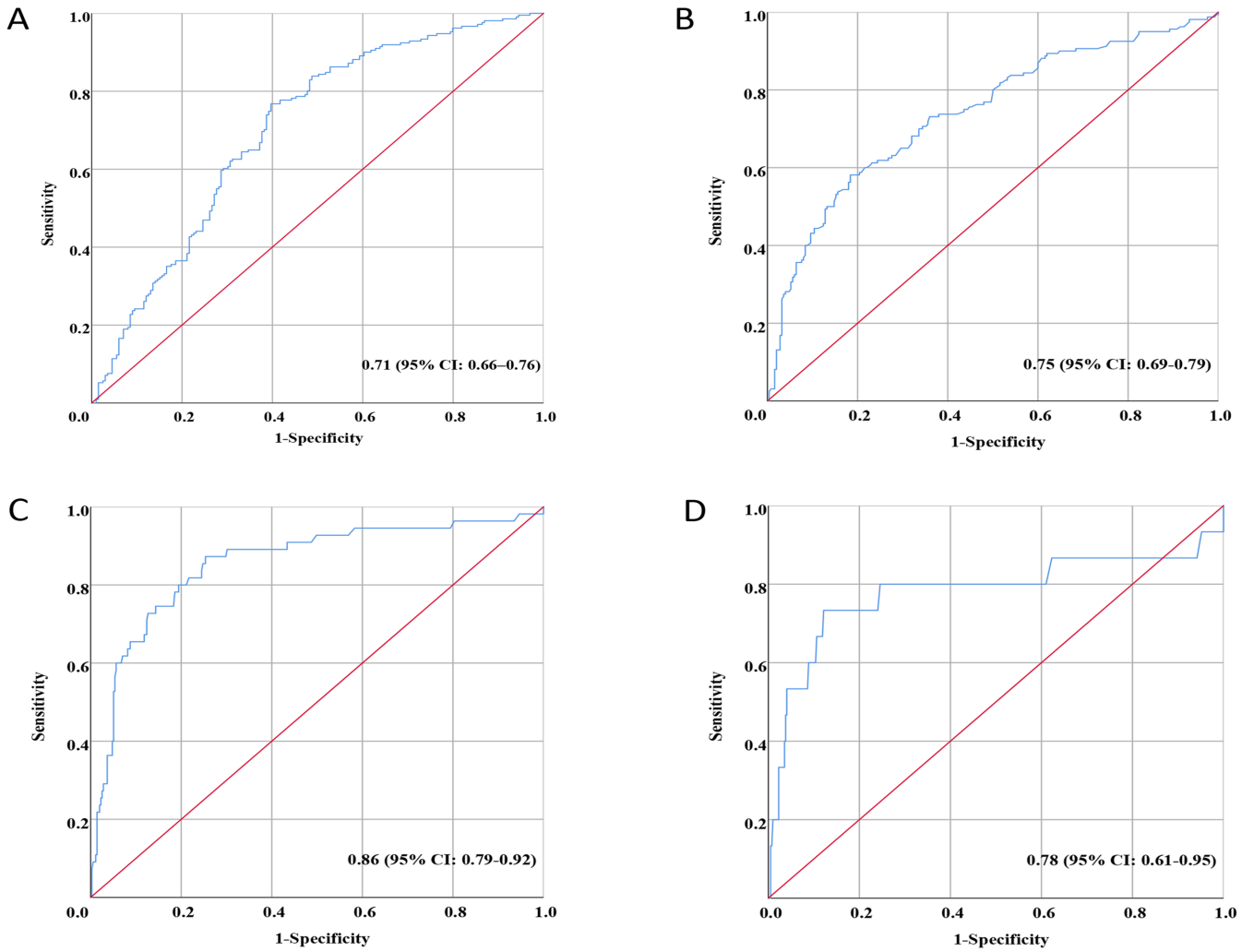

FIGURE 3 | (A) AUROC of the LIID score for the diagnosis of MASH; (B) AUROC of the LSM for the diagnosis of significant fibrosis (≥F2); (C) AUROC of the LSM for the diagnosis of advanced fibrosis (≥F3); (D) AUROC of the LSM for the diagnosis of cirrhosis (F4).

TABLE 2 | Operating characteristics for the two selected cutoffs of the LIID score.

	LIID score	
Cutoff	6.0	7.8
Sensitivity, % (*n*/*N*)	**89.6% (189/211)**	26.1% (55/211)
Specificity, % (*n*/*N*)	39.7% (79/199)	**88.4% (176/199)**
PPV, % (*n*/*N*)	61.2% (189/309)	**70.5% (55/78)**
NPV, % (*n*/*N*)	**78.2% (79/101)**	53.0% (176/332)
LR+	1.49	**2.25**
LR−	**0.26**	0.84
Diagnostic odds ratio	5.7	2.7

Abbreviations: LR−, negative likelihood ratio; LR+, positive likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

4 | Discussion

In this multicenter, biopsy-proven cohort of patients with MASLD, we demonstrated that a novel QUS-based score (LIID) can noninvasively identify patients with MASH, and that LSM by the same ultrasound platform can accurately assess fibrotic burden. To our knowledge, this is the first multicenter study assessing LIID in biopsy-confirmed MASLD patients across tertiary centers in China, using histology as the reference standard.

The LIID score, derived from raw radiofrequency analysis, achieved an AUROC of 0.71 for detecting histological MASH. Importantly, unlike serum- or MR-based indices, LIID relies solely on QUS technology integrated into conventional ultrasound platforms, enabling broader accessibility, especially in primary care or under-resourced settings [21–23]. The dual-threshold strategy employed (cutoffs of 6.0 and 7.8) facilitates flexible implementation: Lower thresholds yield high sensitivity and NPV, ideal for screening, whereas upper thresholds optimize specificity for diagnostic confirmation or clinical trial inclusion. A significant association between the LIID score and histological NAFLD activity score (NAS) further supports the biological plausibility of this tool. The QUS-derived features, such as signal attenuation, scatter, and spectral shifts, may reflect microarchitectural disorganization due to steatosis, ballooning, and inflammation hallmarks of MASH pathology [16]. Compared with existing scores for MASH, such as FAST (which combines FibroScan-derived liver stiffness, controlled-attenuation parameter [CAP], and serum AST),

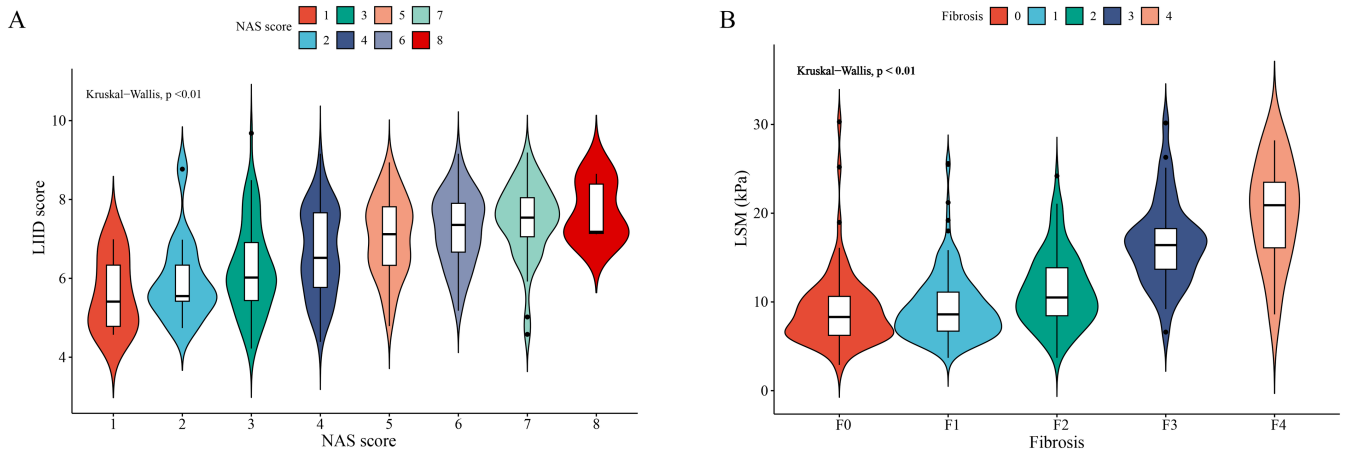

FIGURE 4 | (A) Violin plot of the LIID score versus histopathological severity; (B) violin plot of LSM versus fibrosis stage.

TABLE 3 | Operating characteristics for the optimal cutoff of the LSM.

Fibrosis stage	F ≥ 2 (*n* = 160)	F ≥ 3 (*n* = 55)	F = 4 (*n* = 15)
AUROC	0.75 (0.69–0.79)	0.86 (0.79–0.92)	0.78 (0.61–0.95)
Optimal cutoff	9.8 kPa	11.6 kPa	15.6 kPa
Youden's index	0.37	0.62	0.60
Sensitivity	0.73 (117/160)	0.87 (48/55)	0.73 (11/15)
Specificity	0.64 (160/250)	0.74 (264/355)	0.87 (343/395)
PPV	0.57 (117/207)	0.35 (48/139)	0.17 (11/63)
NPV	0.79 (160/203)	0.97 (264/271)	0.99 (343/347)

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

acMASH, and MACK-3 (a serum-based panel incorporating AST, HOMA-IR, and CK-18), LIID is derived solely from QUS radiofrequency data without requiring blood tests, making it more accessible and less dependent on laboratory infrastructure [21, 24].

LSM showed robust diagnostic performance across fibrosis stages in this study. Notably, LSM achieved high NPVs, with 78.8% for significant fibrosis, 97.4% for advanced fibrosis, and 98.8% for cirrhosis. These results suggest that LSM can be confidently used to exclude advanced disease and minimize unnecessary liver biopsies. Conversely, high-specificity thresholds may help identify patients suitable for therapeutic enrollment or specialist referral. In line with prior studies, LSM values increased progressively with histological fibrosis stages, reinforcing its biological validity as a surrogate marker of fibrotic burden [25]. Mechanistically, increased stiffness is driven by collagen deposition, matrix crosslinking, vascular remodeling, and parenchymal distortion, which may be well captured by elastography [26].

The LIID score provides an effective, noninvasive method for identifying MASH, whereas LSM accurately assesses the degree of liver fibrosis. The integration of both LIID and LSM within a single ultrasound platform enables simultaneous evaluation of hepatic inflammation and fibrosis, offering a comprehensive, efficient, and patient-friendly diagnostic approach. Traditionally, the diagnostic workup for MASH and liver fibrosis has relied on separate modalities or invasive liver biopsy, which are resource-intensive and carry procedural risks [27, 28]. The co-implementation of LIID and LSM in a unified device streamlines the diagnostic workflow, reduces patient burden, and improves accessibility, particularly in primary care or resource-limited settings. This integrated approach represents a major step toward practical, scalable solutions for the early detection and staging of disease in patients with MASLD.

Nonetheless, certain limitations should be acknowledged. First, the LIID score's diagnostic performance, while promising, remains modest compared to imaging-based composite scores and requires further optimization. Second, the study population was drawn exclusively from Chinese tertiary centers, potentially limiting generalizability to other ethnic or community-based populations.

In conclusion, the combination of LIID and LSM in a single ultrasound device provides a noninvasive, efficient solution for diagnosing MASH and staging liver fibrosis in MASLD patients. This integration can streamline diagnostic workflows and reduce the need for liver biopsy, offering a cost-effective and accessible option for patient management.

Affiliations

[1]Department of Gastroenterology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China | [2]Department of Ultrasound, Beijing Ditan Hospital of Capital Medical University, Beijing, China | [3]Department of Infectious Disease, Shengjing Hospital of China Medical University, Shenyang, China | [4]Department of Gastroenterology, The First Hospital of China Medical University, Shenyang, China | [5]Department of Infectious Disease, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, China | [6]Liver Research Center, Beijing Friendship Hospital, Capital Medical University, State Key Lab of Digestive Health, National Clinical Research Center of Digestive Diseases, Beijing Key Laboratory of Translational Medicine on Liver Cirrhosis, Beijing, China | [7]Department of Gastroenterology, Binzhou Medical University Hospital, Binzhou, China | [8]Hepatopancreatobiliary Center, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China | [9]Institute of Liver Diseases, Shuguang Hospital of Shanghai University of Traditional Chinese Medicine, Shanghai, China | [10]Department of Infectious Disease, Yuncheng Central Hospital Affiliated to Shanxi Medical University, Yuncheng, China | [11]Department of Gastroenterology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China | [12]Department of Hepatology, The Second Hospital of Nanjing, Nanjing, China | [13]Liver Diseases Center, 905th Hospital of PLA Navy, Shanghai, China | [14]Department of Gastroenterology, Shanghai General Hospital of Shanghai Jiaotong University Medical School, Shanghai, China | [15]Department of Gastroenterology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China | [16]Department of Gastroenterology, Xinhua Hospital of Shanghai Jiaotong University Medical School, Shanghai, China | [17]Department of Hepatology, The Affiliated Hospital of Hangzhou Normal University, Hangzhou, China | [18]Department of Gastroenterology and Hepatology, Guangzhou Key Laboratory of Digestive Diseases, Guangzhou Digestive Disease Center, Guangzhou First People's Hospital, School of Medicine, South China University of Technology, Guangzhou, China | [19]MAFLD Research Center, Department of Hepatology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China | [20]Institute of Hepatology, Wenzhou Medical University, Wenzhou, China | [21]Key Laboratory of Diagnosis and Treatment for The Development of Chronic Liver Disease in Zhejiang Province, Wenzhou, China

Acknowledgments

The authors have nothing to report.

Funding

This work was supported by grants from the National Natural Science Foundation of China (82070588 and 82370577).

Ethics Statement

Ethical approval for the study was obtained from the ethics committees of all participating centers. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. G. Feng, Y. Yilmaz, L. Valenti, et al., "Global Burden of Major Chronic Liver Diseases in 2021," *Liver International: Official Journal of the International Association for the Study of the Liver* 45 (2021): e70058.

2. M. E. Rinella, J. V. Lazarus, V. Ratziu, et al., "A Multisociety Delphi Consensus Statement on New Fatty Liver Disease Nomenclature," *Journal of Hepatology* 79 (2023): 1542–1556.

3. EASL-EASD-EASO Clinical Practice Guidelines on the Management of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)," *Journal of Hepatology* 81 (2024): 492–542.

4. A. K. Singal, D. Panneerselvam, J. P. Arab, G. Im, and Y. F. Kuo, "Delisting From Liver Transplant List for Improvement and Recompensation Among Decompensated Patients at One Year," *American Journal of Gastroenterology* 120 (2024): 2086–2092.

5. T. Y. Wang, R. F. Wang, Z. Y. Bu, et al., "Association of Metabolic Dysfunction-Associated Fatty Liver Disease With Kidney Disease," *Nature Reviews. Nephrology* 18 (2022): 259–268.

6. N. Theodorakis and M. Nikolaou, "From Cardiovascular-Kidney-Metabolic Syndrome to Cardiovascular-Renal-Hepatic-Metabolic Syndrome: Proposing an Expanded Framework," *Biomolecules* 15 (2025): 213.

7. K. Stefanakis, J. George, and C. S. Mantzoros, "Non-Invasive Diagnosis and Prognosis of MASH With Fibrosis F2-F3: In Need for a Tailored, Accessible, and Affordable Solution for the 21st Century Public Health Epidemic," *Metabolism, Clinical and Experimental* 169 (2025): 156296.

8. S. A. Harrison and J. Dubourg, "Liver Biopsy Evaluation in MASH Drug Development: Think Thrice, Act Wise," *Journal of Hepatology* 81 (2024): 886–894.

9. R. Cannella, F. Agnello, G. Porrello, et al., "Performance of Ultrasound-Guided Attenuation Parameter and 2D Shear Wave Elastography in Patients With Metabolic Dysfunction-Associated Steatotic Liver Disease," *European Radiology* 35 (2025): 2339–2350.

10. H. Kwon, M. G. Kim, S. Oh, et al., "Application of Quantitative Ultrasonography and Artificial Intelligence for Assessing Severity of Fatty Liver: A Pilot Study," *Diagnostics (Basel, Switzerland)* 14, no. 12 (2024): 1237.

11. F. Gao, Q. He, G. Li, et al., "A Novel Quantitative Ultrasound Technique for Identifying Non-Alcoholic Steatohepatitis," *Liver International: Official Journal of the International Association for the Study of the Liver* 42 (2022): 80–91.

12. A. L. Williams and J. H. Hoofnagle, "Ratio of Serum Aspartate to Alanine Aminotransferase in Chronic Hepatitis. Relationship to Cirrhosis," *Gastroenterology* 95 (1988): 734–739.

13. R. K. Sterling, E. Lissen, N. Clumeck, et al., "Development of a Simple Noninvasive Index to Predict Significant Fibrosis in Patients With HIV/HCV Coinfection," *Hepatology (Baltimore, Md.)* 43 (2006): 1317–1325.

14. X. X. Wu, K. I. Zheng, J. Boursier, et al., "acNASH Index to Diagnose Nonalcoholic Steatohepatitis: A Prospective Derivation and Global Validation Study," *EClinicalMedicine* 41 (2021): 101145.

15. G. Feng, F. E. Mózes, D. Ji, et al., "acFibroMASH Index for the Diagnosis of Fibrotic MASH and Prediction of Liver-Related Events: An International Multicenter Study," *Clinical Gastroenterology and Hepatology: The Official Clinical Practice Journal of the American Gastroenterological Association* 23 (2025): 785–796.

16. S. Man, Y. Deng, Y. Ma, et al., "Prevalence of Liver Steatosis and Fibrosis in the General Population and Various High-Risk Populations: A Nationwide Study With 5.7 Million Adults in China," *Gastroenterology* 165 (2023): 1025–1040.

17. D. E. Kleiner, E. M. Brunt, M. Van Natta, et al., "Design and Validation of a Histological Scoring System for Nonalcoholic Fatty Liver Disease," *Hepatology* 41 (2005): 1313–1321.

18. E. M. Brunt, D. E. Kleiner, L. A. Wilson, P. Belt, and B. A. Neuschwander-Tetri, "Nonalcoholic Fatty Liver Disease (NAFLD) Activity Score and the Histopathologic Diagnosis in NAFLD: Distinct Clinicopathologic Meanings," *Hepatology* 53 (2011): 810–820.

19. F. Gao, J. F. Huang, K. I. Zheng, et al., "Development and Validation of a Novel Non-Invasive Test for Diagnosing Fibrotic Non-Alcoholic Steatohepatitis in Patients With Biopsy-Proven Non-Alcoholic Fatty Liver Disease," *Journal of Gastroenterology and Hepatology* 35 (2020): 1804–1812.

20. A. J. Sanyal, J. Foucquier, Z. M. Younossi, et al., "Enhanced Diagnosis of Advanced Fibrosis and Cirrhosis in Individuals With NAFLD Using FibroScan-Based Agile Scores," *Journal of Hepatology* 78 (2023): 247–259.

21. J. Boursier, R. Anty, L. Vonghia, et al., "Screening for Therapeutic Trials and Treatment Indication in Clinical Practice: MACK-3, a New Blood Test for the Diagnosis of Fibrotic NASH," *Alimentary Pharmacology & Therapeutics* 47 (2018): 1387–1396.

22. M. Noureddin, E. Truong, J. A. Gornbein, et al., "MRI-Based (MAST) Score Accurately Identifies Patients With NASH and Significant Fibrosis," *Journal of Hepatology* 76 (2022): 781–787.

23. J. Jung, R. R. Loomba, K. Imajo, et al., "MRE Combined With FIB-4 (MEFIB) Index in Detection of Candidates for Pharmacological Treatment of NASH-Related Fibrosis," *Gut* 70 (2021): 1946–1953.

24. P. N. Newsome, M. Sasso, J. J. Deeks, et al., "FibroScan-AST (FAST) Score for the Non-Invasive Identification of Patients With Non-Alcoholic Steatohepatitis With Significant Activity and Fibrosis: A Prospective Derivation and Global Validation Study," *Lancet Gastroenterology & Hepatology* 5 (2020): 362–373.

25. Y. Qu, Y. Y. Song, C. W. Chen, et al., "Diagnostic Performance of FibroTouch Ultrasound Attenuation Parameter and Liver Stiffness Measurement in Assessing Hepatic Steatosis and Fibrosis in Patients With Nonalcoholic Fatty Liver Disease," *Clinical and Translational Gastroenterology* 12 (2021): e00323.

26. M. Menon, J. Langdon, and S. McAleavey, "Minimization of Displacement Estimation Bias due to High Amplitude-Reflections Using Envelope-Weighted Normalization," *Ultrasonic Imaging* 32 (2010): 65–80.

27. F. E. Mózes, J. A. Lee, E. A. Selvaraj, et al., "Diagnostic Accuracy of Non-Invasive Tests for Advanced Fibrosis in Patients With NAFLD: An Individual Patient Data Meta-Analysis," *Gut* 71 (2022): 1006–1019.

28. A. E. Feldstein, A. Wieckowska, A. R. Lopez, Y. C. Liu, N. N. Zein, and A. J. McCullough, "Cytokeratin-18 Fragment Levels as Noninvasive Biomarkers for Nonalcoholic Steatohepatitis: A Multicenter Validation Study," *Hepatology* 50 (2009): 1072–1078.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Comparison of the diagnostic performance of the LIID score and established noninvasive scores for MASH. **Table S1:** Baseline characteristics of LIID cohort participants with metabolic dysfunction-associated steatotic liver (MASL) and metabolic dysfunction-associated steatohepatitis (MASH) subgroups.