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Evaluating the efficacy of 8 non-invasive models in predicting MASLD and progression: a prospective study

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Abstract

Background Selecting the optimal non-invasive diagnostic model for MASLD (Metabolic Dysfunction-Associated Steatosis Liver Disease) and steatosis progression is a critical issue given the variety of available models. We aimed to compare the performance of eight clinical prediction models for diagnosing and predicting the progression of hepatic steatosis using MRI-PDFF (Magnetic Resonance Imaging-Derived Proton Density Fat Fraction), and validate the findings with FibroScan and histopathological results.

Methods In this study, 846 participants were initially enrolled, with 108 undergoing liver biopsy and 706 completing one-year follow-up, including 26 who underwent repeat biopsy. We calculated scores for eight clinical prediction models (FAST, KNAFLD, HSI, FLI, Liver Fat Score, Liver Fat Equation, BAAT, LAP) using collected clinical data and defined steatosis progression as a 30% relative increase in liver fat content (LFC) measured by MRI-PDFF. CAP(Controlled Attenuation Parameter) and LSM (Liver Stiffness Measurement) were obtained by Fibroscan. MRI-PDFF served as the reference standard for evaluating model accuracy, and sensitivity analyses were performed using liver biopsy and Fibroscan results.

Results Among the eight clinical models, NAS (nonalcoholic fatty liver disease activity score) showed higher correlation with the FAST and KNAFLD models (r: 0.62 and 0.52, respectively). Among the whole cohort ($N=846$), KNAFLD was the best model for predicting different degrees of hepatic steatosis (AUC = 0.84). When the KNAFLD score was above 2.935, LFC was significantly higher (4.4% vs. 19.7%, $P<0.001$). After 1 year of follow-up ($N=706$), FAST performed best in predicting MASLD progression (AUC = 0.84); with dFAST > -0.02, LFC increased (8.6–10.9%, $P<0.05$), mean LSM increased by 0.51 kPa, and with dFAST < -0.02, LFC significantly decreased (11.5–8.5%, $P<0.05$), mean LSM and NAS decreased by 0.87 kPa and 0.76, respectively (both $P<0.05$).

Conclusions Most models demonstrated good diagnostic and prognostic capabilities for hepatic steatosis, with FAST and KNAFLD showing particular promise as primary non-invasive tools in clinical practice.

Trail Registration Chinese Clinical Trial Registry NO: ChiCTR2100054743, Registered December 26, 2021.

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Key message

What is already known on this topic Numerous blood and imaging biomarkers have been developed to diagnose MASLD, which can progress to MASH, cirrhosis, and HCC. Early diagnosis and long-term follow-up using noninvasive methods are essential.

What this study adds Comparison of the accuracy of 8 noninvasive methods to predict liver steatosis and its progression based on MRI-PDFF in the 1-year prospective study revealed that most noninvasive techniques are correlated with LFC (Liver Fat Content) and have an acceptable accuracy to estimate the degree and progression of hepatic steatosis. KNAFLD has the best accuracy in predicting MASLD degree. FAST has the best accuracy in predicting steatosis progression.

How this study might affect research practice or policy KNAFLD performed best in predicting MASLD and discriminating different degrees of hepatic steatosis, which could be used as a reference in clinical diagnosis. For a long-term follow-up study in MASLD patients, the changes in FAST or KNAFLD scores might be a better method to predict the status of steatosis progression.

Keywords Metabolic dysfunction -associated steatohepatitis (MASH), Metabolic dysfunction associated steatotic liver disease (MASLD), Prospective study, Magnetic resonance imaging-derived proton density fat fraction (MRI-PDFF), Clinical model

Introduction

Nonalcoholic fatty liver disease (NAFLD) affects approximately one in four individuals globally, can progress to NASH and cirrhosis and is a major cause of liver-related morbidity and mortality; it is the fastest growing cause of hepatocellular carcinoma [1, 2]. In recent years, there has been a trend towards adopting updated terminology, such as metabolic dysfunction-associated steatosis liver disease (MASLD) and its subcategories, like metabolic dysfunction-associated steatohepatitis (MASH). These terms aim to better reflect the underlying pathophysiology and metabolic aspects of the disease [3]. Obesity, insulin resistance, and type 2 diabetes mellitus (T2DM) are prevalent risk factors for progressive liver disease in MASLD. The risk of progression in MASLD patients is notable, with approximately 3% potentially developing cirrhosis within a 15-year period [4]. However, it's important to clarify that this statement does not suggest a consistent progression rate for all MASLD individuals, as the disease trajectory can significantly differ among patients.

MASLD encompasses a spectrum from simple steatosis to MASH, which may advance to cirrhosis and HCC [5]. As biopsy procedures are invasive and infrequent for assessing MASLD progression, noninvasive markers tested annually or biannually may serve as central indicators. Various noninvasive tests, such as imaging markers (FibroScan and MRI-PDFF, Magnetic resonance imaging-derived proton density fat fraction) and blood markers (CK18, FGF21, IL-6, and clinical models), have been developed [6]. Many clinical models, incorporating easily obtained clinical data such as BMI, waist circumference, age, ALT, and AST, have demonstrated reliability and higher accuracy compared to individual blood biomarkers [7], Clinicians face challenges in selecting the appropriate model for evaluating patient status or determining MASLD progression or improvement compared to previous assessments. Hepatic steatosis, as the initial stage of MASLD, is linked to adverse outcomes [8, 9]. Recent study had revealed changes on MRI-PDFF (≥30% decline relative to baseline) are associated with NAS improvement and fibrosis regression [10]. Moreover, various blood-based biomarkers have been developed, including predictive models like the NAFLD fibrosis score, FIB-4 index, and BARD score, as well as markers of inflammation (e.g., circulating keratin 18 fragments), fibrosis (e.g., FibroTest, ELFTM, or Pro-C3 tests), and steatosis (e.g., FLI, HSI, and KNAFLD score) [11]. Despite recent advancements, many existing predictive models were developed using biopsy or ultrasound examination data, lacking validation against MRI-PDFF in prospective studies. Consequently, clinicians may face uncertainty when selecting suitable tests and models to accurately predict disease progression in various clinical scenarios.

This study aimed to compare the performance of eight clinical prediction models for diagnosing and predicting the progression of hepatic steatosis using MRI-PDFF, and validate the findings with FibroScan and histopathological results.

Method

Study design

To elucidate the natural progression of MASLD over a one-year period, participants were equipped with lifestyle education at the time of enrollment and during each subsequent follow-up visit. Notably, the study design excluded pharmacological interventions for MASLD itself; however, medications for comorbid conditions such as hypertension, diabetes, and hyperlipidemia were permitted. Participants were recruited through

online and printed advertisements and provided written informed consent.

The study included adults (age 18–75) previously diagnosed with fatty liver based on imaging examinations (ultrasound, CT, MRI) dating back to the 1990s. Exclusion criteria encompassed contraindicated for MRI examination, excessive alcohol consumption (>60 g/d or 50 g/d for male and female), concurrent viral hepatitis, drug-induced hepatitis, autoimmune hepatitis, history of liver transplantation or planned liver transplantation during the study period, prior bariatric surgery or planned bariatric surgery during the study, or other factors leading to fatty liver diseases, tumors, or cardiovascular events, severe systemic diseases unrelated to MASLD.

This prospective study commenced in January 2020, enrolling an average of 20 new participants per month until Jun 2024, resulting in a total of 846 participants at the Phase I Clinical Center of the First Hospital of Jilin University (Fig. 1). 706 completed two follow-up visits one year apart. Additionally, 108 participants underwent liver biopsy, with 26 undergoing repeat biopsies after one year, the nonalcoholic fatty liver disease activity score (NAS) was assessed. Participants were included on the day they provided informed consent, completed questionnaires, underwent hematological examinations, and FibroScan assessments. The MRI-PDFF scans were completed within seven days of enrollment. Liver biopsies were performed within a fortnight of the enrollment date. Demographic and anthropometric data, including age, sex, weight, height, waist circumference, and BMI, along with medical history, smoking and alcohol habits, were gathered. Haematology and biochemical analyses were conducted by the laboratory at the First Hospital of Jilin University on blood samples obtained after an 8-hour fasting period. Biochemical analyses were carried out on blood samples collected within 7 days of MRI-PDFF and FibroScan examinations [12]. Based on MRI-PDFF findings, samples were classified into four groups: Control, and mild, moderate, and Severe Steatosis-MASLD groups, with corresponding LFC cutoffs of <5.1%, 5.2–14.1%, 14.2–28%, and >28%, respectively [13]. Metabolic syndrome was defined as the presence of ≥3 components of metabolic abnormalities(NCEP ATP III definition) [14]. Diabetes was defined as a self-reported diagnosis [15] or fasting plasma glucose≥7.0 mmol/L [16]. MASLD was diagnosed according to the new criteria [3], one patient, identified with fatty liver by MRI-PDFF but not meeting MASLD diagnostic criteria, was excluded from the analysis. MASH was diagnosed based on histopathological findings (NAS≥4, with ≥1 point for steatosis, ballooning, and lobular inflammation) in accordance with the most recent guidelines [17]. The clinical study was registered under the number ChiCTR2100054743 (Chinese Clinical Trial Registry, registration date: December 26, 2021, https://www.chictr.org.cn). Ethics approval was granted by the First Hospital of Jilin University (Ethical Approval Number: 19K096001).

Statistical analysis

Disease progression/improvement was determined by a 30% relative increase/decrease in LFC in one year [18], while those below this threshold were classified as Stable.

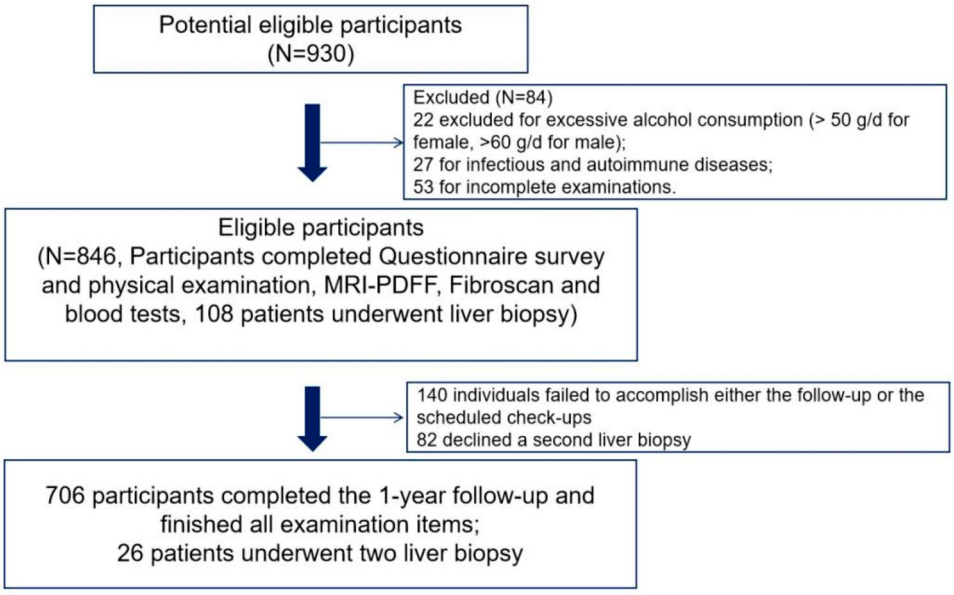

Fig. 1 Flowchart of Cohort Participants in Fatty Liver Disease Study. The flowchart illustrates the progression of participants through the fatty liver disease cohort study. At baseline, 846 individuals were enrolled, of whom 108 underwent liver biopsy. One year later, 706 participants returned for a second visit, and among them, 26 agreed to a second liver biopsy

Z: Set at 1.96;p: The expected event occurrence rate. The occurrence rate of fibrosis progression is 36.1%, and the occurrence rate of fibrosis improvement is 20.8%;E: Represents the estimation error, set at 5%;In this study, both the progression group and the improvement group were observed. We calculated the sample sizes for the progression group and the improvement group separately to get the total sample size, considering the dropout rate, the estimated sample size for fatty liver is set at 800. The Shapiro-Wilk test was employed to assess normality, and differences in non-normally distributed variables were evaluated using the Kruskal test. continuous data were described as median(IQR) and compared using Wilcox method, categorical variables were presented as proportions and compared using $\chi 2$ analysis. Pairwise comparisons were conducted via one-way ANOVA. Eight predictive models (FAST, HSI, FLI, KNAFLD, BAAT, LAP, Liver Fat Score, Liver Fat Equation) were computed based on previous research (supplementary Table 1) [19–25]. Model performance was compared using the area under the receiver-operating characteristic curve (AUC). Optimal cutoff values were determined and evaluated using the Youden index. Spearman's rank correlation test was employed to assess correlations. In the cross-sectional analysis, to ensure the control group's sample size was matched, 40% were randomly selected from each MASLD group using the tidyfst package. Since the incidence of NA (Not Available) was less than 2% in this cohort, they were substituted with the median value using the gtools package. Statistical analyses were conducted using R 4.2.3.

To evaluate the discriminative ability of eight non-invasive clinical prediction models across different degrees of fatty liver disease, the NAS obtained through liver biopsy and LSM values acquired via FibroScan were compared using Spearman's rank correlation coefficient. This analysis aimed to assess the consistency between the non-invasive model scores and the gold-standard NAS and LSM results. To further evaluate the predictive capacity of these models for MASLD progression over one year, we employed linear mixed-effects models [26]. These models were used to validate the thresholds of changes in model scores in relation to changes in LFC, LSM and NAS.

Results

Clinical characteristics at the baseline

This study enrolled subjects with a history of fatty liver, due to the extended period between diagnosis and enrollment, MRI-PDFF assessments indicated that some participants no longer had evidence of fatty liver at the time of entry into the study ($N=146$). Table 1 summarizes the demographics and characteristics of each of the included cohorts separated by different degrees of steatosis, which were assessed by MRI-PDFF (Control: $N=146$, 17.3%; Mild Steatosis-MASLD: $N=400$, 47.3%; Moderate Steatosis-MASLD: $N=257$, 30.4%; Severe Steatosis-MASLD: $N=43$, 5%). Sex was compared between the four groups, and the median age across the cohorts ranged from 34 to 43 years and was significantly lower in the more-severe MASLD group. The rate of metabolic syndrome was higher in the severe MASLD group than in the less-severe MASLD group (32%, 42%, 56%, 47%, in the Control, Mild, Moderate and Severe group respectively, $P<0.001$), and the less-severe MASLD group showed lower BMI (27.0 kg/m^2, 28.0 kg/m^2, 28.9 kg/m^2, 29.1 kg/m^2, $P<0.001$).

In this MASLD cohort, the concentrations of liver injury biomarkers, glucose metabolism and lipid metabolism were significantly higher in patients with more-severe fatty liver. The equations of the models used in the study are presented in Suppl Table 1. All models were significantly different between the 4 groups, and most were positively correlated with MASLD severity. The lower Liver Fat Equation was found in severe MASLD, which was presumably due to the relatively low rate of diabetes and MetS in this group (as the presence of MetS and diabetes was a significant factor for the model).

Among the 108 individuals who underwent liver biopsy, there were no significant differences in age, sex ratio, or BMI between the no MASH ($N=44$, Table 2) and MASH ($N=64$) groups. However, compared to the no MASH group, the MASH group exhibited significantly higher levels of ALT, AST, GGT, glucose, insulin, triglycerides, and total cholesterol, along with lower HDL levels, suggesting a distinct biochemical profile associated with MASH. Imaging assessments, including LSM, CAP and LFC), revealed more severe steatosis and fibrosis in the MASH group compared to the no MASH group. Most clinical prediction models, except for LAP, showed significant differences between the MASH and non-MASH groups.

The performance of clinical models in predicting MASLD

To explore the correlation between pathological findings (NAS) and model scores, we conducted Spearman correlation analyses in 108 individuals who underwent liver biopsy. The results revealed the following correlation coefficients between the NAS and various clinical prediction models: the strongest correlation was observed with FAST ($r=0.62$, Supplementary Fig. 1), followed by KNAFLD ($r=0.52$), Liver Fat Equation ($r=0.49$), Liver Fat Score ($r=0.43$), BAAT ($r=0.38$), HSI ($r=0.36$), and FLI ($r=0.30$). The weakest correlation was noted with LAP ($r=0.21$). Similarly, within the whole cohort ($N=846$), the correlation analysis revealed that LFC was most strongly correlated with KNAFLD ($r=0.56$, $P<0.01$, Supplementary Fig. 2), and other clinical models (FAST, Liver Fat

Table 1 Characteristics of the clinical variables and scoring systems grouped by MRI-PDFF examination at the baseline

	Control (*N* = 146)	Mild Steatosis-MASLD (*N* = 400)	Moderate Steatosis-MASLD (*N* = 257)	Severe Steatosis-MASLD (*N* = 43)	*p*
basic information					
Age (years), median (IQR)	43 (10)	41 (16)	37 (18)	34 (9)	< 0.0001
WC (cm), median (IQR)	94.6 (10.75)	97.9 (10.55)	99.3 (9.9)	100 (12.2)	< 0.0001
Male, N (%)	109 (75%)	273 (68%)	180 (70%)	27 (63%)	0.38
Diabetes, N (%)	59 (40%)	183 (46%)	136 (53%)	17 (40%)	0.0617
Mets, N (%)	46 (32%)	169 (42%)	144 (56%)	20 (47%)	< 0.0001
BMI, kg/m2, median (IQR)	27.0 (3.15)	28.0 (4.7)	28.9 (4.4)	29.1 (3.7)	< 0.0001
SBP (mmHg), median (IQR)	124 (17.75)	130 (19)	132 (17)	131 (15.5)	< 0.001
DBP (mmHg), median (IQR)	81.5 (16)	83 (14)	84 (14)	84 (10.5)	0.0229
blood test					
ALT (U/L), median (IQR)	25.9 (15)	41.5 (31.15)	59.3 (41.4)	85.8 (51.65)	< 0.0001
AST (U/L), median (IQR)	24 (8.8)	29 (14.33)	36.6 (18.7)	44.5 (21.95)	< 0.0001
GGT (U/L), median (IQR)	34.8 (33.75)	41.9 (37)	51.8 (37.1)	57.3 (56.9)	< 0.0001
Glucose(mmol/L), median(IQR)	5.46 (1)	5.62 (1.13)	5.76 (1.11)	5.8 (0.95)	0.0174
Insulin(pmol/ml), median (IQR)	72.1 (55.74)	115.65 (82.32)	140.3 (91.8)	148.9 (140.87)	< 0.0001
TG (mmol/L), median (IQR)	1.58 (1.11)	2.08 (1.35)	2.43 (2.07)	2.45 (1.77)	< 0.0001
LDL (mmol/L), median (IQR)	3.12 (1.08)	3.3 (1.16)	3.3 (0.97)	3.34 (1.14)	0.0882
HDL (mmol/L), median (IQR)	1.14 (0.31)	1.1 (0.28)	1.1 (0.3)	1.1 (0.3)	0.1732
score system					
FAST, median (IQR)	0.07 (0.07)	0.12 (0.12)	0.19 (0.17)	0.26 (0.17)	< 0.0001
HSI, median (IQR)	37.4 (5.31)	41.2 (7.29)	43.3 (6.67)	45.1 (6.62)	< 0.0001
FLI, median (IQR)	12.6 (21.34)	23.0(32.17)	36.4 (36.18)	40.4 (43.15)	< 0.0001
KNAFLD, median (IQR)	-0.06 (2.68)	2.43 (4.26)	5.31 (5.31)	7.82 (3.36)	< 0.0001
BAAT, median (IQR)	1 (1)	2 (1)	2 (1)	2 (1)	< 0.0001
LAP, median (IQR)	50.2 (37.08)	69.1 (50.15)	89.0 (72.27)	88.8 (97.98)	< 0.0001
Liver Fat Score, median (IQR)	-0.61 (2.17)	1.02 (2.6)	2.38 (3.05)	2.57 (3.93)	< 0.0001
Liver Fat Equation, median (IQR)	5.12 (91.82)	12.12 (167.81)	13.82 (287.31)	11.06 (344.42)	< 0.0001
imaging results					
LFC (%), median (IQR)	3.6 (1.6)	9.3 (4.62)	18.4 (5.9)	31.3 (5.05)	< 0.0001
CAP (db/m), median (IQR)	256 (43.5)	289 (53)	332 (42)	351 (30)	< 0.0001
LSM (kPa), median (IQR)	4.8 (1.27)	5.7 (2.1)	6.4 (2.5)	6.4 (1.95)	< 0.0001

Note WC (waist circumference) BMI (body mass index) SBP (systolic blood pressure) DBP (diastolic blood pressure) ALT (alanine aminotransferase) AST (aspartate aminotransferase) GGT (gamma-glutamyl transferase) TG (triglycerides) LDL (low-density lipoprotein cholesterol) HDL (high-density lipoprotein cholesterol) LFC (liver fat content) CAP (controlled attenuation parameter) LSM (liver stiffness measurement),IQR (interquartile range)

Score, BAAT, HSI, FLI, LAP, Liver Fat Equation) also showed significantly positive correlations with LFC (correlation coefficients: 0.48, 0.48, 0.45, 0.43, 0.38, 0.35, 0.33, respectively; $P<0.05$ for all).

To compare the performances of models in predicting fatty liver, MRI-PDFF was used as the standard in predicting the degree of steatosis. Given that the ratio of cases to controls (control vs. MASLD) was 146/700, after 40% of the samples were randomly extracted from the mild, moderate and Severe Steatosis-MASLD groups, the ratio was nearly 1:2 (146/279), and 8 models performed well in discriminating MASLD and Control subjects. The AUC values of the models (KNAFLD, Liver Fat Score, FAST, BAAT) in predicting MASLD were 0.84, 0.82, 0.77 and 0.78, respectively (Fig. 2a). KNAFLD was reported to have the strongest LFC association within the 425 samples ($r=0.55$, $P<0.01$), and the Liver Fat Score, FAST and BAAT were weaker ($r=0.49$, $r=0.44$, $r=0.49$, all $P<0.01$). The cut-offs of these models were as follows: 0.94, 0.72, 0.168 and 2 (Table 3). The boxplots (Fig. 3a-c) intuitively showed significantly higher LFC (%) when scores (KNAFLD, Liver Fat Score, FAST) were above the cut-off: the median LFC was 4.3% and 12.2% (below/above the cut-off of KNAFLD); 4.8% vs. 13% (below/above the cut-off of Liver Fat Score) and 5.7% vs. 14.5% (below/above the cut-off of FAST). The P values were below 0.001 for all comparisons.

For predicting Mild Steatosis-MASLD or Control, KNAFLD had the greatest AUC (AUC=0.77, Fig. 2b), followed by Liver Fat Score (AUC=0.75), BAAT (AUC=0.72), and HSI (AUC=0.72). KNAFLD and BAAT showed the strongest correlation with LFC (both $r=0.4$, $P<0.01$), followed by HSI ($r=0.36$, $P<0.01$) and Liver Fat Score ($r=0.33$, $P<0.01$). Their cut-off values were 0.94, -0.501, 2 and 39.06, respectively. When the cohort was classified by the cut-off of BAAT, KNAFLD and Liver Fast

Table 2 Characteristics of the clinical variables and scoring systems grouped by biopsy results at the baseline

Variables	not-MASH (*n* = 44)	MASH (*n* = 64)	*p*
basic information			
Male, N(%)	22 (50%)	37 (58%)	0.5454
Age (years), median(IQR)	45 (17.5)	41 (16.25)	0.4342
WC(cm) median(IQR)	100.2 (8.15)	98.4 (9.55)	0.3324
BMI (kg/m2), median(IQR)	29.85 (4.15)	29.95 (5.4)	0.8292
Mets, N(%)	13 (30%)	24 (38%)	0.516
Diabetes, N(%)	8 (18%)	23 (36%)	0.0738
blood test			
ALT (U/L), median (IQR)	26.5 (21.5)	58.5 (46.98)	< 0.0001
AST (U/L), median (IQR)	24.0 (11.32)	36.5 (25.37)	< 0.0001
GGT (U/L), median (IQR)	28.5 (36.23)	58.1 (56.35)	< 0.0001
Glucose (mmol/L), median (IQR)	5.3 (1.21)	6.0 (1.08)	0.0061
Insulin (pmol/ml), median (IQR)	107.4 (91.74)	142.4 (116.43)	0.0354
TC (mmol/L), median (IQR)	5.17 (1.49)	5.38 (1.44)	0.9501
TG (mmol/L), median (IQR)	1.6 (1.25)	2.0 (2.29)	0.025
LDL (mmol/L), median (IQR)	3.24 (1.48)	3.33 (1.03)	0.861
HDL (mmol/L), median (IQR)	1.21 (0.34)	1.14 (0.25)	0.0332
score system			
FAST, median (IQR)	0.15 (0.22)	0.43 (0.31)	< 0.0001
HSI, median (IQR)	40.62 (6.5)	43.99 (8.69)	0.0035
FLI, median (IQR)	75.99 (26.62)	80.65 (23.36)	0.0325
KNAFLD, median (IQR)	0.73 (2.7)	3.48 (4.06)	< 0.0001
BAAT, median (IQR)	2 (1)	2 (1.25)	0.025
LAP, median (IQR)	60.64 (45.62)	82.89 (79.56)	0.0975
Liver.Fat.Score, median (IQR)	-0.01 (2.48)	2.05 (3.53)	0.0002
Liver.Fat.Equation, median (IQR)	4.5 (4.49)	8.8 (9.25)	< 0.0001
imaging results			
LFC (%), median (IQR)	6.4 (5.48)	15.4 (9.32)	< 0.0001
CAP (db/m), median (IQR)	290.5 (56)	322.5 (53.5)	0.0006
LSM (kPa), median (IQR)	5.7 (1.7)	7 (3.4)	0.0003
histopathology results			
Steatosis, median (IQR)	1 (0.25)	2 (1)	< 0.0001
Inflammation, median (IQR)	0 (1)	2 (1)	< 0.0001
Ballooning, median (IQR)	0 (1)	1 (0)	< 0.0001
Fibrosis, median (IQR)	0 (0)	0 (1)	< 0.0001
NAS, median (IQR)	1.5 (2)	5 (1)	< 0.0001

Note WC (waist circumference) BMI (body mass index) ALT (alanine aminotransferase) AST (aspartate aminotransferase) GGT (gamma-glutamyl transferase) TG (triglycerides) LDL (low-density lipoprotein cholesterol) HDL (high-density lipoprotein cholesterol) LFC (liver fat content) CAP (controlled attenuation parameter) LSM (liver stiffness measurement),IQR (interquartile range), NAS (Nonalcoholic fatty liver disease activity score)

Score, significantly higher LFCs were also found (supplementary Fig. 3a-c): 5.4% vs. 9.3% (below/above cut-off of KNAFLD, $P<0.001$), 4.8% vs. 9.0% (below/above cut-off of Liver Fat Score, $P<0.001$) and 7.1% vs. 10.0% (below/above cut-off of BAAT, $P<0.001$).

When attempting to discriminate Control and moderate-severe patients, KNAFLD, Liver Fat Score and FAST were found to have the top 3 highest accuracies (AUC: 0.90, 0.87 and 0.84, respectively. Figure 2c), and the correlation analysis showed similar results ($r=0.58$, $r=0.51$, $r=0.49$, respectively; all $P<0.01$). Their cut-off values were 2.935, 0.804 and 0.141, respectively (Table 3). When the cohort was classified by the cut-off of FAST, KNAFLD and Liver Fat Score, significantly higher LFCs were found when the score was above the cut-off (grouped by KNAFLD cut-off: 4.4% vs. 19.7%; Liver Fat Score: 14.8% vs. 19.6%; FAST: 4.8% vs. 19.3%; all $P<0.001$).

The KNAFLD score was also found to perform best in differentiating mild and moderate-severe subjects (AUC=0.72, cut-off =4.13, Fig. 2d; Table 3), followed by FAST (AUC=0.69, cut-off =0.18), Liver Fat Score (AUC=0.67, cut-off =1.97) and BAAT (AUC=0.64, cut-off =2). KNAFLD was most strongly related to the LFC ($r=0.4$, $P<0.01$), FAST and BAAT were weaker ($r=0.32$ and 0.28, respectively, both $P<0.01$), and values above the cut-off of those models predicted higher LFC (supplementary Fig. 4a-c): 10.9% vs. 15.8% (below/above cut-off of KNAFLD, $P<0.001$), 10.4% vs. 16.0% (below/above cut-off of Liver Fat Score, $P<0.001$) and 11.1% vs. 15.6% (below/above cut-off of FAST, $P<0.001$).

Clinical characteristics of the follow-up study

When decreased/increased by 30% from baseline were classified as the Improve/Progression group, those who did not meet this change threshold were designated as the Stable group, and the results of a 1-year follow-up from 706 samples were categorized (Improve group: $N=150$, 21.2%; Stable group: $N=381$, 53.9%; Progression group: $N=175$, 24.7%; Supplementary Table 2) to verify that the changes in score systems (FAST, HSI, FLI, KNAFLD, BAAT, LAP, Liver Fat Score, Liver Fat Equation) from baseline were sensitive enough to predict the progression of liver steatosis.

As we took no intervention measures other than oral education, unexpectedly significantly higher LFCs at baseline were found in the Improve group (median LFC at baseline: 13.7% vs. 11.9% vs. 7.0% in the Improve, Stable, and Progress groups, respectively; $P<0.001$). Other variables that had strongly positive correlations with LFC were also found to be significantly different between the three groups (ALT, AST, CAP, etc.).

The performances of clinical models in predicting disease progression/improvement

Similar results were found in describing the changes in markers from baseline to 1 year (supplementary Table 3). After 1 year of follow-up, the changes in BMI and WC were significantly different between the Improvement, Stable and Progression groups (-0.8 kg/m2, 0 kg/m2 and 0.5 kg/m2; -2 cm, -0.5 cm and 0.4 cm, respectively; $P=0.003$). For biomarkers related to liver injury (change

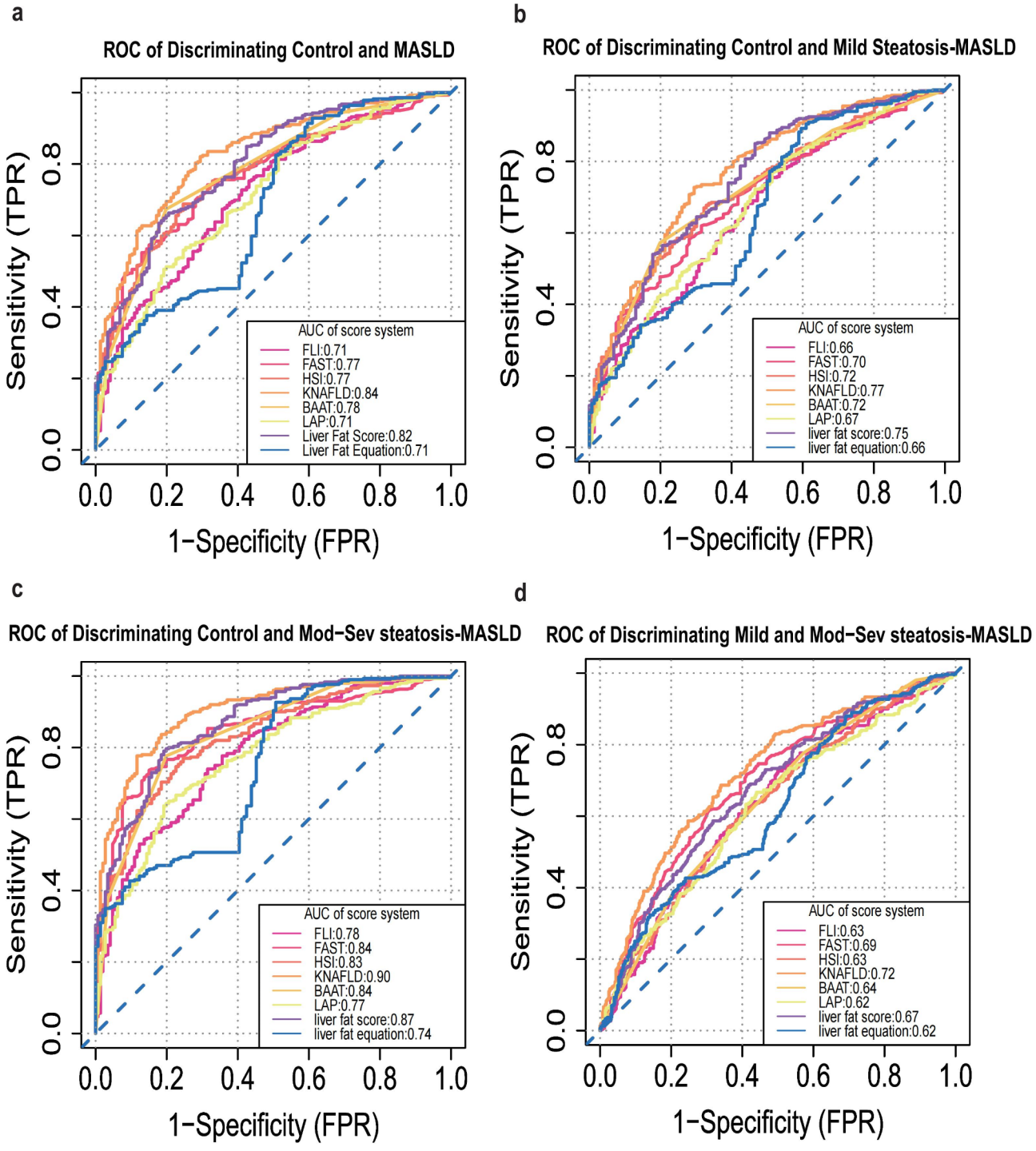

Fig. 2 ROC plots for clinical models in predicting different degree of MASLD or Control. Figures abcd compare the ability of models (FAST, KNAFLD, HSI, FLI, liver fat score, Liver Fat Equation, BAAT, LAP) to distinguish varying degrees of hepatic steatosis. The colored curves represent the ROC curves for different models, with the AUC of each ROC curve displayed in the bottom right corner of the images

in ALT: -16.5 U/L, -3.8 U/L and 5.3 U/L; change in AST: -7.1 U/L, -1.3 U/L and 3.2 U/L; change in GGT: -12.1 U/L, -1.3 U/L and 3.2 U/L, respectively; all $P<0.001$) and lipid metabolism (TG: -0.19 mmol/L, -0.02 mmol/L, 0 mmol/L; $P<0.001$), most changes were also significantly different between the three groups. Among those biomarkers, the changes in 8 formulas were all significantly different between the three groups: changes in KNAFLD (-1.67 vs. -0.2 vs. 0.98), HSI (-3.3 vs. 0.1 vs. 0.9), FLI (-10.5 vs. -1.2 vs. 5.3), FAST (-0.14 vs. -0.01 vs. 0.06) and Liver

Table 3 Models discriminating health and different degrees of MASLD

No MASLD vs. MASLD					**No MASLD vs. Mod-Sev**				
Clinical models	**Value**	**FPR**	**TPR**	**Cutoff**	**Clinical models**	**Value**	**FPR**	**TPR**	**Cutoff**
FLI	0.311	0.37	0.681	18.822	FLI	0.425	0.315	0.74	21.815
FAST	0.409	0.082	0.491	0.168	FAST	0.586	0.151	0.737	0.141
HSI	0.431	0.247	0.677	40.035	HSI	0.523	0.247	0.77	40.023
KNAFLD	0.559	0.295	0.853	0.943	KNAFLD	0.66	0.116	0.776	2.935
BAAT	0.472	0.199	0.67	2	BAAT	0.578	0.199	0.776	2
LAP	0.319	0.466	0.785	51.975	LAP	0.445	0.192	0.637	77.468
Liver Fat Score	0.504	0.205	0.71	0.72	Liver Fat Score	0.598	0.192	0.79	0.804
Liver Fat Equation	0.361	0.521	0.882	4.499	Liver Fat Equation	0.42	0.507	0.927	4.574
No MASLD vs.Mild					Mild MASLD vs. Mod-Sev				
Clinical models	value	FPR	TPR	cutoff	Clinical models	value	FPR	TPR	cutoff
FLI	0.25	0.5	0.75	12.348	FLI	0.23	0.5	0.73	22.84
FAST	0.3	0.315	0.62	0.094	FAST	0.31	0.31	0.62	0.18
HSI	0.34	0.329	0.6775	39.061	HSI	0.22	0.4	0.62	42.39
KNAFLD	0.43	0.294	0.7275	0.943	KNAFLD	0.35	0.34	0.69	4.13
BAAT	0.373	0.199	0.5725	2	BAAT	0.2	0.57	0.78	2
LAP	0.262	0.548	0.81	45.15	LAP	0.23	0.44	0.67	74.23
Liver Fat Score	0.384	0.466	0.85	-0.501	Liver Fat Score	0.27	0.32	0.59	1.97
Liver Fat Equation	0.297	0.596	0.8925	3.495	Liver Fat Equation	0.19	0.69	0.88	5.35

Note Value: Youden index, FPR: False Positive Rate; TPR: True Negative Rate. The optimal cut-off values were determined by the Youden index

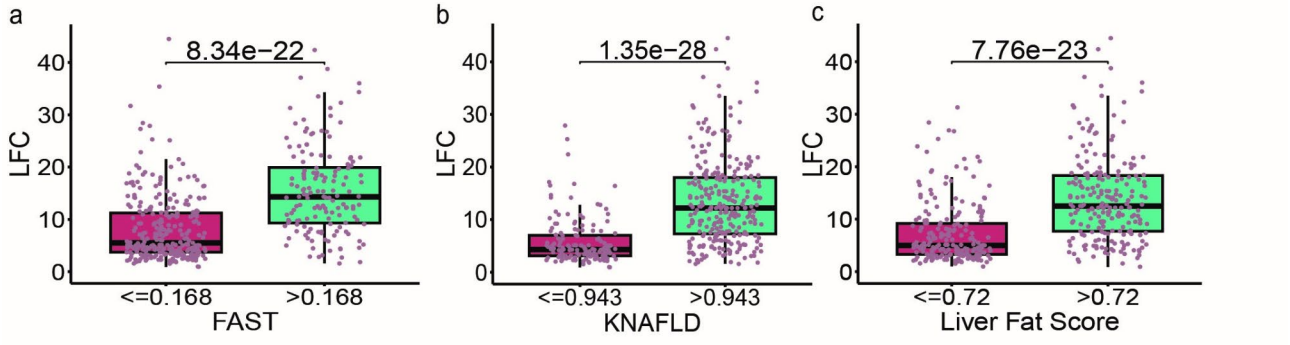

Fig. 3 Comparison of LFCs between two groups in the Control or MASLD population. Figures abc compare hepatic steatosis based on scores from different models. The y-axis represents liver fat content, while the x-axis indicates grouping based on model thresholds. Differences with $p < 0.05$ are considered statistically significant

Fat Score (-1.1 vs. 0.13 vs. 0.48); all $P<0.01$. The results shown above inspired us to explore the optimal cut-off for discriminating disease progression or improvement in future clinical practice.

Correlation analysis showed that the association between the changes in FAST and LFC was the strongest ($r=0.52$, $P<0.01$), followed by KNAFLD ($r=0.49$, $P<0.01$) and BAAT ($r=0.42$, $P<0.01$); others showed weaker correlations (range from 0.25 to 0.52). In predicting the status of disease progression (progression or improvement, Fig. 4), the AUCs of FAST and KNAFLD were the top 2 highest (AUC: 0.87 and 0.84, respectively), and FLI, Liver Fat Equation and Liver Fat Score also performed well (AUC: 0.83, 0.80 and 0.78, respectively). Similarly, the optimal changing cut-offs in those models were calculated (Table 4, the changing thresholds of FAST, KNAFLD and FLI were −0.02, 0.09 and 0.46, respectively).

To verify our results, the changes in scores were cut by their thresholds (the cohort grouped by above/below the cut-off). As the plot depicted (Supplementary Fig. 5a-h), When the change in FAST from baseline was lower than −0.02, the degree of liver steatosis decreased from 14.1 to 11.1% (average decrease of 2%), and when the change was higher than −0.02, steatosis increased from 10.4 to 12.4% (average increase of 3.1%). Similar results were observed for changes in KNAFLD and FLI (changes in KNAFLD below 0.09: LFC decreased from 13.1 to 11.1%, average decrease of 1.9%; above 0.36: LFC increased from 10.6 to 12.8%, average increase of 2.2%; changes in FLI below 0.484: LFC decreased from 13.1 to 11.1%, average decrease of 2.1; above 0.484: LFC increased from 10.9

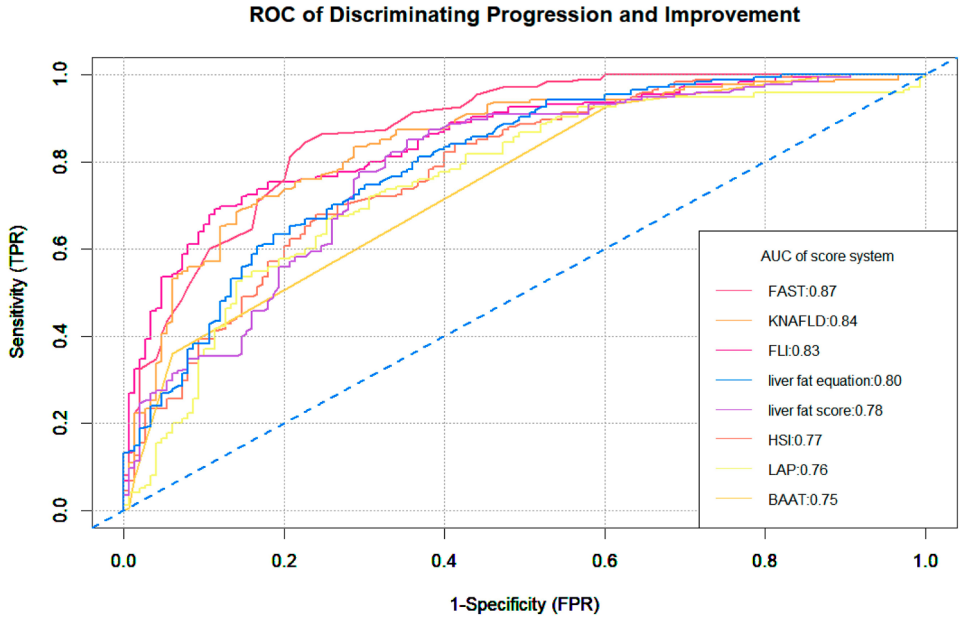

Fig. 4 ROC plots for clinical models in predicting progression or improvement. Legend: Different models' predictive abilities (FAST, KNAFLD, HSI, FLI, Liver Fat Score, Liver Fat Equation, BAAT, LAP) for disease progression are depicted by ROC curves in various colors. The area under the curve (AUC) for each model is displayed in the bottom right corner

Table 4 Models discriminating the progression or improvement in the follow-up study

Score	Value	FPR	TPR	cutoff	AUC
dFAST	0.62	0.23	0.85	-0.021	0.87
dKNAFLD	0.58	0.17	0.71	0.09	0.84
dFLI	0.55	0.11	0.69	0.46	0.83
dLiver Fat Score	0.50	0.35	0.85	0.59	0.78
dLiver Fat Equation	0.45	0.30	0.75	-0.66	0.80
dHSI	0.44	0.24	0.68	-0.49	0.77
dLAP	0.42	0.25	0.67	-0.62	0.76
dBAAT	0.32	0.61	0.93	0	0.75

Note Value: Youden index, FPR: False Positive Rate; TPR: True Negative Rate; AUC: area under roc curve. The optimal cut-off values were determined by the Youden index. Model prefixes denoted by 'd' represent the change in the model over one year

to 12.7%, average increase of 1.7%). The specific thresholds of other clinical models also accurately predicted the trends in LFC changes over one year. The impact of other model changes on LFC changes is detailed in Supplementary Table 4.

Additionally, we validated the predictive ability of these thresholds for changes in liver fibrosis through LSM changes (N=706). The Spearman correlation coefficients between changes in LSM and changes in various clinical prediction models over one year were as follows (Supplementary Fig. 6a-h): dFAST showed the highest correlation (r=0.47), followed by dKNAFLD (r=0.36), dFLI (r=0.28), and dLiver Fat Score (r=0.25). The correlation was slightly lower for dHSI (r=0.21) and dLiver Fat Equation (r=0.24). For dLAP, the coefficient was 0.18, and for dBAAT, it was 0.19. Linear mixed-effects models revealed that when the change in FAST didn't exceed a threshold of -0.02, the mean LSM decreased by 0.87. When the changes in KNAFLD and FLI did not exceed their respective thresholds of 0.09 and 0.46, the mean LSM decreased by 0.38 and 0.46, respectively. Conversely, when the changes in FAST, KNAFLD, and FLI exceeded their thresholds, the mean LSM increased by 0.51, 0.25, and 0.27, respectively. All results had p-values less than 0.05 (Fig. 5a-h). The predictive abilities of the remaining five models for changes in LSM are summarized in Table 5.

To evaluate the models' predictive power for disease progression using biopsy as the gold standard for diagnosis, we analyzed 26 subjects who underwent two biopsies separated by one year (Supplementary Fig. 7a-h). When the changes in the clinical models were below their respective thresholds, the mean changes±SD in NAS were as follows (Supplementary Table 5): dFAST ≤ -0.02 (dNAS: −0.76±0.38), dKNAFLD≤0.09 (−0.58±0.32), dFLI≤0.46 (−0.83±0.29), dLiver Fat Score≤0.59 (−0.52±0.28), dLiver Fat Equation ≤ -0.66 (−0.92±0.01), dHSI ≤ -0.49 (−0.88±0.29), dLAP ≤ -0.62 (−1±0.35), and dBAAT≤0 (−0.53±0.32). These results suggest that decreases in model scores below the specified thresholds were associated with improvements in NAS scores.

Discussion

In this study, employing MRI-PDFF, which offers improved prediction of MASLD [27], we compared the performance of eight models in predicting both the degree of steatosis and its progression. Due to the efficacy of these well-performing models, in our cross-sectional

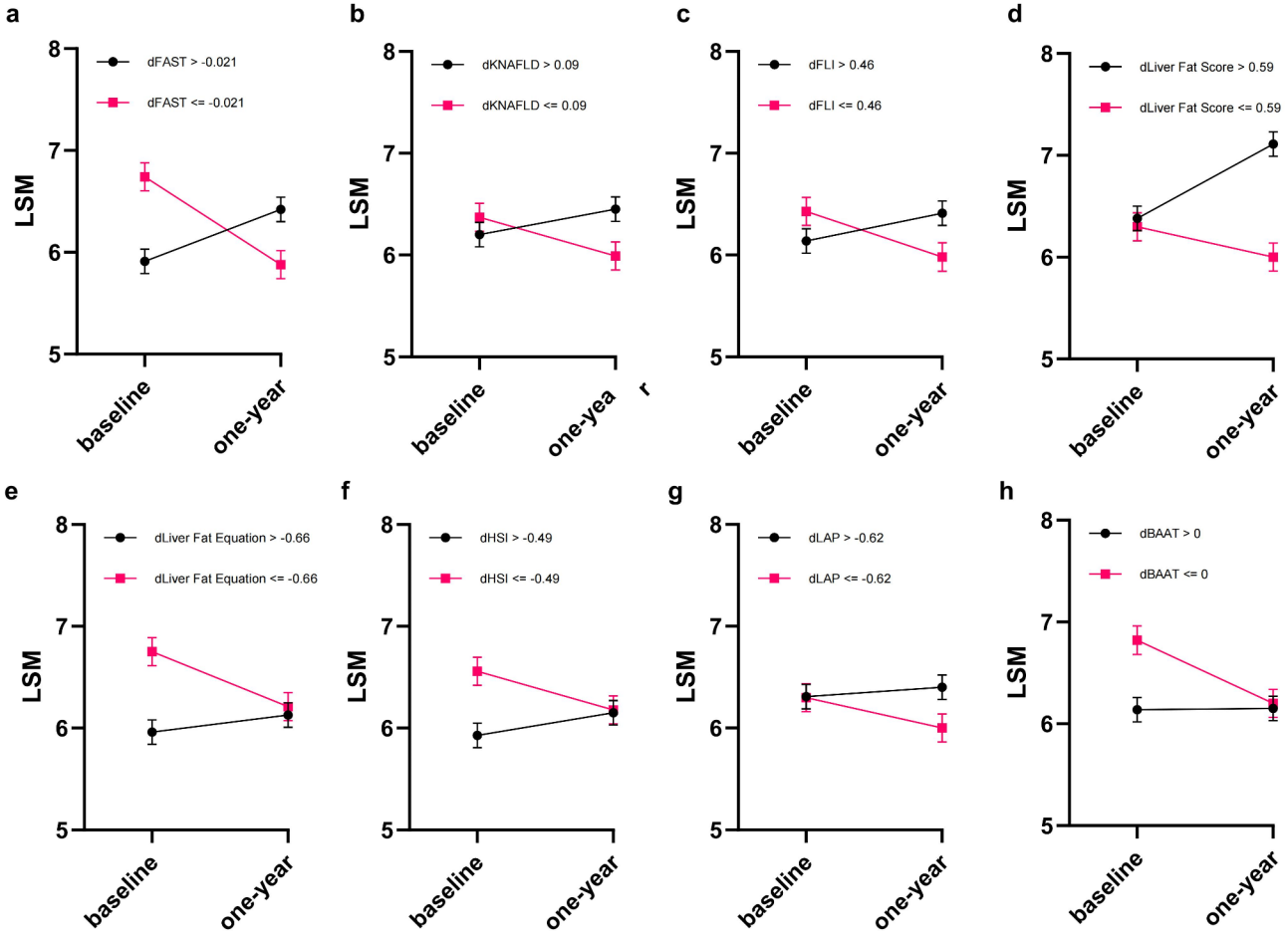

Fig. 5 Changes in LSM Over Time Predicted by the Eight Clinical Models Legend: Time course of LSM changes over one year, predicted by eight clinical models: KNAFLD, Liver Fat Equation, Liver Fat Score, BAAT, FAST, HSI, FLI, and LAP. Each panel represents a different model, with LSM changes depicted at baseline and one year later. Different colors distinguish participants with LSM values above or below the model-specific threshold. The average LSM values at each time point are represented by squares or circles, respectively

Table 5 Noninvasive Model scores Predicting LSM change in MASLD Cohort over one year

Model	dLSM (*N* = 706, kPa)	*P*	Model	dLSM (*N* = 706, kPa)	*P*
dFAST <= -0.02	-0.87 ± 0.09	< 0.001	dFAST > -0.02	0.51 ± 0.08	< 0.001
dKNAFLD < = 0.09	-0.38 ± 0.08	< 0.001	dKNAFLD > 0.09	0.25 ± 0.1	< 0.001
dFLI < = 0.46	-0.46 ± 0.09	< 0.001	dFLI > 0.46	0.27 ± 0.10	0.0065
dLiver Fat Score < = 0.59	-0.28 ± 0.07	0.001	dLiver Fat Score > 0.59	0.72 ± 0.18	< 0.001
dLiver Fat Equation <= -0.66	-0.54 ± 0.10	< 0.001	dLiver Fat Equation > -0.66	0.17 ± 0.09	0.0535
dHSI <= -0.49	-0.39 ± 0.08	< 0.001	dHSI > -0.49	0.22 ± 0.1	0.03
dLAP <= -0.62	-0.34 ± 0.09	0.002	dLAP > -0.62	0.09 ± 0.10	0.36
dBAAT < = 0	-0.62 ± 0.1	< 0.001	dBAAT > 0	0.01 ± 0.08	0.89

Note data were showed as estimate ± Standard error, Estimate was Estimated Marginal Means calculated by emmeans packge, P values are corrected by the FDR method. Model prefixes denoted by 'd' represent the change in the model over one year. dLSM: absolute change of LSM

study assessing diagnostic performance, the scores of the eight models exhibited significant differences across the four groups. Additionally, correlation and regression analyses demonstrated their effectiveness in diagnosing MASLD, with AUC values ranging from 0.70 to 0.90. We utilized the Youden index to determine the optimal cutoff values of the eight models for predicting Control and varying degrees of MASLD within our cohort. Although slight variations in cutoff values were observed compared to other studies, potentially attributable to differences in steatosis evaluation methods or participant demographics, our cutoff values effectively discriminated between

different levels of liver steatosis, a novel finding not previously reported. Notably, the KNAFLD model, computed using sex, waist circumference, triglycerides, and systolic blood pressure, excelled in distinguishing between control and MASLD cases and predicting MASLD severity, possibly due to the homogeneity of the subjects' racial background [22], likely due to the homogeneity of the subjects' racial background. Pathology, as the gold standard for fatty liver evaluation, confirmed good correlations between the eight clinical prediction models and histopathological diagnoses in 108 liver biopsy patients. The FAST model, calculated with CAP, LSM, and AST, showed strongest correlation with the NAS score (r: 0.62), suggesting its utility in assessing disease severity.

The progression of the disease does not necessarily occur in individuals with severe cases, who may pay more attention than less severe patients to disease management and thus engage in preventative measures, for example, exercise and diet intervention as more significant weight loss were found in the improvement group. In predicting MASLD progression or improvement over one year using clinical models, regression and correlation analyses revealed that the change in FAST, was the most accurate predictor. This may be attributed to CAP's superior correlation with MRI-PDFF than other biomarkers, as demonstrated in our previous study [12]. Other models also exhibited acceptable performance in predicting progression status, with AUC values ranging from 0.61 to 0.84. It's important to note that the FAST score was specifically optimized for predicting progression, with its main purpose being the identification and stratification of NASH patients at high risk of disease advancement [19]. Conversely, the KNAFLD scoring system was tailored to detect MASLD and highlight metabolic risks and insulin resistance [22]. In our study, the superior diagnostic capability of KNAFLD for hepatic steatosis compared to FAST may stem from its specific design. KNAFLD focuses on metabolic parameters closely associated with hepatic steatosis, rendering it a more sensitive tool for detecting fatty liver. Conversely, FAST's ability to outperform KNAFLD in predicting disease progression can be attributed to its incorporation of liver stiffness measurement, a well-established surrogate marker of liver fibrosis. Given fibrosis's direct correlation with disease progression in MASLD patients, the FAST score emerges as a more effective tool for this purpose.

In the analysis of NAS score and model score changes in 26 patients with paired liver biopsies, we confirmed a correlation between model changes and histopathological outcomes. Given the small sample size and the majority of patients (17 out of 26) experiencing no increase in NAS, the models, notably FAST, KNAFLD, and FLI, showed a decrease in NAS score in those below the predefined model change threshold, particularly in those who improved. Additionally, in the population undergoing two Fibroscan examinations (N=706), we explored the reliability of the predefined thresholds. Regardless of whether the values were below or above the model thresholds, we found a strong correlation between changes in LSM and most of the models. This supports the significant association between model changes and liver fat content, fibrosis, and pathological outcomes. Future assessments can leverage these clinically accessible measures to calculate model scores and evaluate the severity and progression of fatty liver disease.

The present study has several limitations. Firstly, it was a single-center prospective study conducted on a predominantly Han Chinese population, potentially introducing bias related to race and sample homogeneity, the absence of an external validation cohort, which limits our ability to confirm the accuracy of the estimated cutoffs for each score. This omission underscores the need for future research to externally validate the findings in diverse populations. Secondly, the case-control ratio was imbalanced, leading to the utilization of simple random sampling for selecting MASLD subjects to adjust the ratio, which unavoidably introduced selection bias. Thirdly, while MRI-PDFF has proven useful in predicting disease progression, the true validation of the models would ideally be conducted using liver biopsy, the gold standard. Our study is limited by the relatively small number of liver biopsy samples (N=108), and future studies with larger cohorts are needed to further validate the predictive capabilities of these models.

This study evaluated eight clinical prediction models for MASLD using MRI-PDFF, validating them with LSM and histopathological results. KNAFLD and FAST emerged as superior tools for assessing MASLD severity and progression, making them valuable assets in managing MASLD patients.

Abbreviations

AC	Abdominal circumference
ALT	Alanine transaminase
AST	Aspartate aminotransferase
AUC	Area under curve
BMI	Body mass index
CAP	Controlled attenuation parameter
CK18	Cytokeratin 18
DBP	Diastolic blood pressure
FAST	FibroScan-AST
FLI	Fatty liver index
GGT	Gamma-glutamyl transferase
HC	Hip circumference
HCC	Hepatocellular carcinoma
HDL-C	High-density lipoprotein cholesterol
HSI	Hepatocyte steatosis index
IL-6	Interleukin-6
IR	Insulin resistance
LDL-C	Low-density lipoprotein cholesterol
LFC	Liver fat content
LSM	Liver stiffness measurement
MASLD	Metabolic dysfunction-associated steatosis liver disease
MASH	Metabolic dysfunction-associated steatohepatitis

MetS	Metabolic syndrome
MRI-PDFF	Magnetic resonance imaging-derived proton density fat fraction
NA	Not Available
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NAS	Nonalcoholic fatty liver disease activity score
SBP	Systolic blood pressure
T2DM	Type 2 Diabetes mellitus
TG	Triglyceride
UA	Uric acid
WC	Waist circumference

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-024-03449-8.

Supplementary Material 1

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Author contributions

A.Y., G.L., Y.D. and N.J. contributed to study design; A.Y. and X.Z contributed to the Control education and informed consent; A.Y., Z.L., D.Z., M.J. and Z.H contribute to the examination and reports of MRI-PDFF; Y.Z. contribute to the examination and reports of Fibroscan; A.Y contributed to the collect and analysis of data and wrote the manuscript; Y.D. reviewed the manuscript; Y.D., X.L. and A.Y. obtained the funding.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Competing interests

The authors declare no competing interests.

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