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ORIGINAL RESEARCH—CLINICAL

A Noninvasive Scoring System for Liver Fibrosis in Patients With Metabolic Dysfunction-Associated Fatty Liver Disease

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BACKGROUND AND AIMS: Metabolic dysfunction-associated fatty liver disease (MAFLD) is diagnosed in patients with hepatic steatosis who meet at least one of the following criteria: body mass index >25, diabetes mellitus type 2, and metabolic dysfunction. Given about one-third of Americans meet the criteria for MAFLD, there is an unmet need for a score to noninvasively triage patients who need transient elastography and possible biopsy. We determined the risk factors for advanced fibrosis (F3+ on transient elastography) in a cohort of 2671 MAFLD patients and developed the MAFLD fibrosis-4 (FIB-4) score to help clinicians predict the risk of advanced fibrosis. **METHODS:** Multivariate logistic regression analysis and independent t-tests were used to evaluate the relationship between physical exam parameters, lab values, and interview responses and risk of advanced fibrosis. The most significant risk factors were used to build the MAFLD FIB-4 score, equivalent to −46.55 + (7.89*log[waist circumference]) + (1.25*log [fasting plasma glucose]) + (0.85*FIB-4 score). **RESULTS:** Risk factors for advanced fibrosis in MAFLD patients are elevated body mass index (odds ratio [OR] = 5.90; $P < .01$), waist circumference (OR = 3.53; $P < .01$), high fasting plasma glucose (OR = 2.45; $P < .01$), high homeostasis model assessment-estimated insulin resistance score (OR = 2.18; $P = .02$), high triglycerides (OR = 1.94; $P = .03$), positive hepatitis C RNA (OR = 14.92; $P = .02$), high ferritin (OR = 1.58; $P = .05$), and alanine transaminase > aspartate aminotransferase (OR = 1.54; $P = .04$). The MAFLD FIB-4 score has a specificity of 80%, sensitivity of 97%, and receiver operating characteristic of 0.85 (compared to the receiver operating characteristic of 0.60 for FIB-4 and 0.68 for nonalcoholic fatty liver disease existing scores) for the detection of advanced fibrosis in MAFLD patients. **CONCLUSION:** Clinicians can utilize the MAFLD FIB-4 score to noninvasively identify patients with advanced fibrosis risk for further evaluation and management.

Keywords: Liver Fibrosis; MAFLD; NAFLD; FIB-4

Introduction

The recently proposed metabolic dysfunction-associated fatty liver disease (MAFLD) offers advantages over nonalcoholic fatty liver disease (NAFLD), including patients with viral hepatitis and heavy alcohol use. MAFLD is diagnosed in patients with hepatic steatosis who meet at least 1 of 3 criteria: overweight or obesity, diabetes mellitus type 2, and metabolic dysfunction. Hepatic steatosis is defined as more than 5% of liver weight is from fat. It can be diagnosed histologically, radiologically, and via transient elastography (TE). Based on recent estimates, approximately one-third of Americans meet the criteria for MAFLD.[1] An estimated 10%–20% of MAFLD patients are known to have metabolic-associated steatohepatitis and are at risk of developing advanced liver fibrosis including cirrhosis.[2–4] Risk factors for advanced fibrosis in MAFLD patients are not known, and prior analyses investigating fatty liver disease have used the fibrosis-4 (FIB-4) index and not TE to predict the risk of advanced fibrosis. TE is the most accurate noninvasive method of scoring liver fibrosis, secondary only to liver biopsy. We investigated which metabolic conditions and comorbid factors carried the greatest risk of advanced fibrosis, defined by TE as F3 fibrosis or higher, in adults in the United States.

Given the high prevalence of MAFLD, there is an unmet need for a score to noninvasively triage patients who need TE and possible biopsy. Practitioners only have the available options of the FIB-4 index, initially developed to predict fibrosis in hepatitis patients, and the NAFLD score, developed to predict fibrosis in NAFLD patients. We further developed and validated the MAFLD FIB-4 (MFIB-4) score to help clinicians predict the risk of advanced fibrosis in MAFLD patients.

Abbreviations used in this paper: **A1c, glycylated hemoglobin; ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; CI, confidence interval; CRP, C-reactive protein; FIB-4, fibrosis-4; HDL, high-density lipoprotein; HepB sAg, hepatitis B surface antigen; HepC RNA, hepatitis C ribonucleic acid; HOMA-IR, homeostasis model assessment-estimated insulin resistance; LSM, liver stiffness measurement; MAFLD, metabolic-associated fatty liver disease; MR, magnetic resonance; NAFLD, nonalcoholic fatty liver disease; NHANES, National Health and Nutrition Examination Survey; NPV, negative predictive value; OR, odds ratio; ROC, receiver operating characteristic; TE, transient elastography.**

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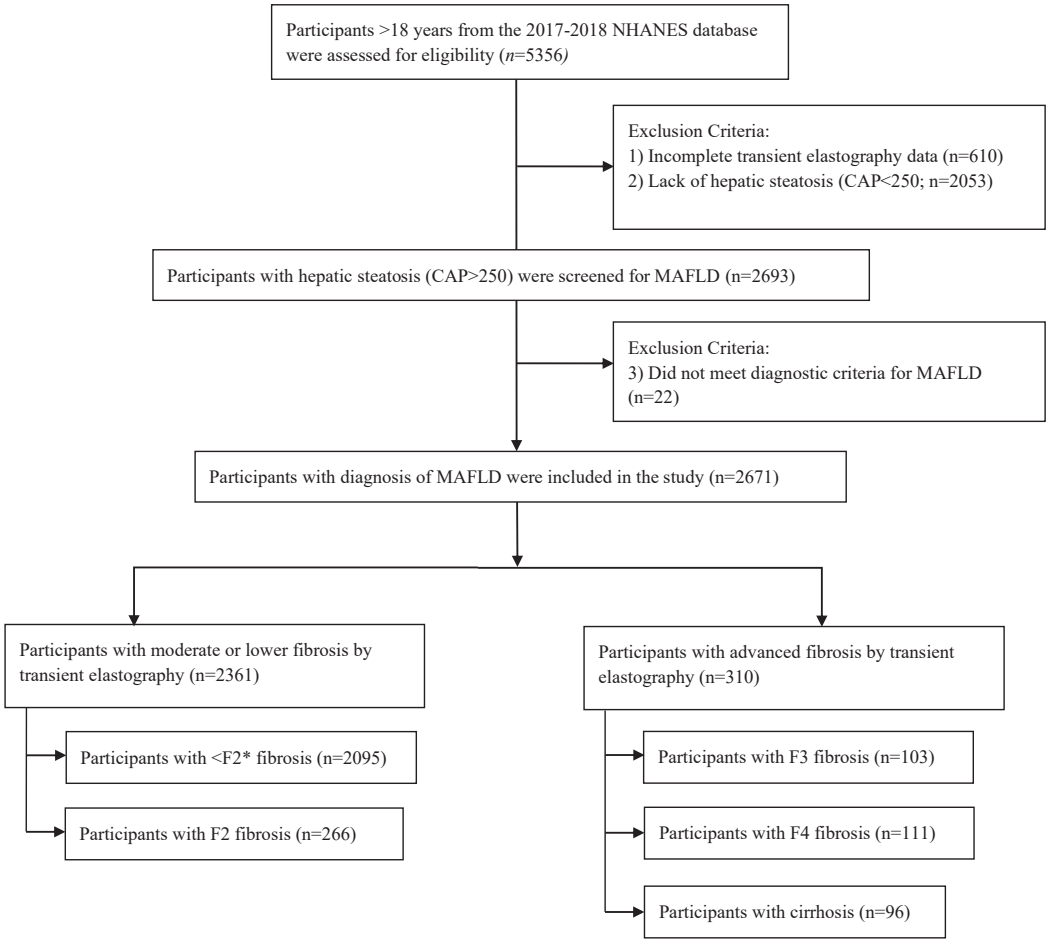

Figure 1. Study CONSORT flow diagram. CAP, controlled attenuation parameter; CONSORT, Consolidated Standards of Reporting Trials; LSM, liver stiffness measurement; MAFLD, metabolic-associated fatty liver disease; NHANES, National Health and Nutrition Examination Survey. *<F2 fibrosis defined as LSM < 7 kPA; F2 fibrosis as 7 kPA < LSM < 8.7 kPa; F3 fibrosis as 8.7 kPA < LSM < 10.3 kPa; F4 fibrosis as 10.3 kPA < LSM < 13.6 kPa; cirrhosis defined as LSM >13.6 kPa.

Methods

Study Population

The study data came from the National Health and Nutrition Examination Survey (NHANES) 2017–2018 conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention in the United States.[5] NHANES is a cross-sectional, periodic survey using a stratified, clustered probability sampling design to include participants representative of the general U.S. population. The methodology of the NHANES data collection is fully described elsewhere.[6] NHANES was approved by the National Center for Health Statistics Research Ethics Review Board, with written informed consent obtained from participants aged >18 years. The present analysis was deemed exempt by the institutional review board at our institution, as the data set used in the analysis was completely deidentified.

Our cohort included 2671 participants aged ≥18 years with reliable TE exam data who had hepatic steatosis and met the diagnostic criteria for MAFLD in the 2017–2018 NHANES. Our cohort was randomly divided into two-third of participants for the estimation group (n = 1782) and one-third of participants for the validation group (n = 889). The estimation group was used for risk factor analysis and model building, and the validation group was used to compare receiver operating characteristic (ROC) and for validation testing across fibrosis scores.

The presence of liver steatosis was defined by a median controlled attenuation parameter (CAP) ≥250 dB/m, a cutoff that yielded 90% sensitivity in distinguishing steatosis.[7] The TE exam was deemed complete if at least 10 valid measurements were obtained with an interquartile range/median liver stiffness measurement (LSM) < 30% after a fasting time of at least 3 hours. Exclusion criteria include incomplete TE data (n = 610), lack of hepatic steatosis (CAP<250; n = 2053), and not meeting diagnostic criteria for MAFLD (n = 22). The presence of liver fibrosis was determined using the median LSM on TE, with advanced fibrosis defined as F3 and above, moderate fibrosis as F2, and low fibrosis defined as less than F1. F1 fibrosis is defined as LSM < 7 kPA, F2 fibrosis as 7 kPA ≤ LSM < 8.7 kPa, F3 fibrosis as 8.7 kPA ≤ LSM < 10.3 kPa, F4 fibrosis as 10.3 kPA ≤ LSM < 13.6 kPa, and cirrhosis defined as LSM ≥13.6 kPa.[8] Of the 2671 participants who met the criteria for MAFLD, 309 had advanced fibrosis. Figure 1 shows the study Consolidated Standards of Reporting Trials diagram, stratified by degree of fibrosis.

In terms of the diagnostic criteria for MAFLD, diagnosis of diabetes was based on a history of diabetes, the use of oral antidiabetic medications, or A1c >6.5%. Diagnosis of metabolic dysfunction is defined as the presence of 2 or more of the following conditions: (1) waist circumference >102 cm in men and 88 cm in women, (2) blood pressure ≥130/85 mmHg (given clinic setting) or specific drug treatment, (3) plasma triglycerides >150 mg/dL (>1.70 mmol/L) or specific drug treatment, (4) plasma high-density lipoprotein cholesterol <40 mg/dL (<1.0 mmol/L) for men and <50 mg/dL (<1.3 mmol/L) for women or specific drug treatment, (5) prediabetes (fasting glucose levels 100–125 mg/dL [5.6–6.9 mmol/L] or hemoglobin A1c 5.7%–6.4% [39–47 mmol/mol]), (6) homeostasis model assessment of insulin resistance (HOMA-IR) score > 2.5, and (7) plasma high-sensitivity C-reactive protein level >2 mg/L. Elevated fasting plasma glucose is defined as >126 mg/dL, and elevated A1c as >6.5%. Hepatitis C virus infection was indicated by positive viral DNA and/or a positive antibody test, and hepatitis B virus infection as a positive surface antigen test. Low iron is defined as <80 in males and <60 in females. High ferritin is defined as >336 mcg/dL in males and >307 mcg/dL in females. Alcohol consumption was estimated based on self-reported data on the amount and frequency of alcohol use within the previous year. The amount of alcohol consumed was reported in standard drinks. It was considered at-risk level if >2/d for men and >1/d for women.

Statistical Analysis

Variables of interest included physical exam parameters, lab values, and interview responses. One-tailed, independent, 2-sample t-tests were performed to compare variables of interest in MAFLD patients with and without advanced fibrosis, assuming unequal variances. Appropriate sampling weights were applied to all analyses to account for the complex survey design of NHANES. Data are expressed as weighted proportions (±standard error) for categorical variables and as weighted means ± standard error for continuous variables. Univariate and multivariate logistic regression analyses were performed to identify variables independently associated with presence or absence of advanced fibrosis. Only those variables with a P value <.05 by univariate analysis were included in the multivariate analysis.

Those variables with $P < .05$ by multivariate analysis were used to construct a scoring system to predict advanced fibrosis. The overall diagnostic accuracy of the scoring system was determined by calculating the area under the ROC curve (the c-statistic) and its 95% confidence intervals (CIs). Validation testing and ROC curve estimation were performed in both the validation data set (n = 889) and the full data set (n = 2671) for the MFIB-4 score and the existing FIB-4 and NAFLD fibrosis scores. The NAFLD fibrosis score is equivalent to −1.675 + (0.037*age [years]) + (0.094*body mass index [BMI] [kg/m^2]) + (1.13*IFG/diabetes [yes = 1, no = 0]) + (0.99*aspartate aminotransferase [AST]/alanine transaminase [ALT] ratio) – (0.013*platelet count [×10^9/L]) – (0.66*albumin [g/dL]). The FIB-4 score is equivalent to FIB-4 = age (years) × AST (U/L)/(Platelets [10^9/L] × ALT$^{1/2}$ [units/L]). Using the ROC curve for the final model, 2 cutoff points were selected, so that the negative predictive value (NPV) for advanced fibrosis was at least 90%, and specificity and sensitivity for advanced fibrosis at least 80%. All analyses were performed using StataSE version 15.1 (StataCorp, College Station, TX).

Results

Table 1 compares demographic, laboratory, and interview response data in MAFLD patients with and without advanced fibrosis. MAFLD patients with advanced fibrosis were on average older ($P < .01$), more commonly male ($P < .01$), had higher BMI and waist circumference ($P < .01$), were more commonly with metabolic dysfunction ($P < .01$), had higher ALT, AST, fasting plasma glucose, and lower platelets ($P < .01$) (Table 1). There was no statistically significant difference across ethnicity groups, blood pressure readings, alcohol use, A1c, and lipid panels between patients with and without advanced fibrosis (Table 1).

Table 2 displays the associated risk of advanced fibrosis with meeting 1 or more of MAFLD diagnostic criteria. A total of 2521 MAFLD patients met one criterion, 1397 met 2 or more criteria, and 309 met 3 criteria. Of the total, 94.8% with advanced fibrosis had a BMI ≥25 vs 87.8% without ($P = .00$; z = −3.63). Fifty-two percent of MALFD patients with advanced fibrosis had metabolic dysfunction vs 44.3% with F2 fibrosis and lower ($P < .01$; z = −2.60). There was no similar difference in those with diabetes mellitus or those who met all 3 diagnostic criteria. Of those meeting 2 or more criteria, the majority met the metabolic dysfunction and the overweight criteria. When a multivariate regression analysis was performed with all 3 MAFLD criteria in 1 model, BMI ≥25 was independently associated with advanced fibrosis (odds ratio [OR], 4.72; 95% CI, 2.30–9.87; $P < .00$/per unit BMI increase: r = 0.26; 95% CI, 0.16–0.36; $P < .00$), while diabetes, metabolic dysfunction, and meeting more than 1 criterion were not associated with advanced fibrosis.

Table 3 displays the risk factors associated with advanced fibrosis in the estimation group. In univariate analyses, elevated BMI (OR = 5.90; $P < .01$), waist circumference (OR = 3.53; $P < .01$), high fasting plasma glucose (OR = 2.45; $P < .01$), high HOMA-IR score (OR = 2.18; $P = .02$), high triglycerides (OR = 1.94; $P = .03$), positive hepatitis C RNA (OR = 14.92; $P = .02$), high ferritin (OR = 1.58; $P = .05$), and ALT > AST (OR = 1.54; $P = .04$) were associated with an increased risk of advanced fibrosis (Table 3). In multivariate analysis of these variables, elevated BMI, elevated waist circumference, elevated fasting plasma glucose, and positive hepatitis C RNA stayed significant with P values <.05. At-risk or ever alcohol use, other metabolic parameters, and the use of chronic medications were not associated with advanced fibrosis in MAFLD patients (Table 3).

Using the estimation group (n = 1782), we considered the 4 variables significantly associated with fibrosis in the multivariate analysis (Table 3) for our model-building process. We utilized fasting plasma glucose and waist circumference in our model and found that the addition of positive

Table 1. Characteristics of the Patient Population by Fibrosis Status

Variable	All patients with MAFLD (n = 2671)	MAFLD patients without advanced fibrosis (n = 2362)	MAFLD patients with advanced fibrosis (n = 309)	*P* value[a]
Age (y)[b]	52.47 (16.88)	52.10 (16.98)	55.40 (15.78)	<.01
Gender (male, %)[c]	53.21 (0.12)	52.59 (0.13)	60.70 (0.22)	<.01
Ethnicity				
Hispanic (%)	26.84 (0.86)	26.42 (0.91)	30.10 (2.61)	.09
Non-Hispanic White (%)	34.33 (0.92)	34.08 (0.98)	36.25 (2.73)	.23
Non-Hispanic Black (%)	19.69 (0.77)	19.94 (0.82)	17.80 (0.22)	.58
Non-Hispanic Asian (%)	13.92 (0.67)	14.48 (0.72)	9.71 (1.68)	.78
Other (%)	5.20 (0.43)	5.08 (0.45)	6.15 (1.37)	.23
BMI (kg/m^2)	31.99 (7.61)	31.26 (6.87)	37.52 (10.28)	<.01
Waist circumference (cm)	102.99 (25.44)	101.99 (23.53)	110.61 (36.01)	<.01
Diabetes (%)	24.41 (0.15)	24.51 (0.17)	23.62 (0.23)	.63
Metabolic dysfunction (%)	45.18 (0.11)	44.28 (0.18)	52.10 (0.35)	<.01
Systolic blood pressure (mmHg)	116.65 (24.38)	116.64 (24.61)	116.78 (22.67)	.46
Diastolic blood pressure (mmHg)	66.55 (15.38)	66.27 (15.49)	67.63 (14.64)	.09
Hypertension %	85.23 (0.15)	84.80 (0.12)	88.08 (0.34)	.17
A1c (%)	5.80 (1.09)	5.80 (1.09)	5.78 (1.11)	.61
ALT (IU/L)	21.80 (14.60)	20.84 (11.65)	29.19 (27.27)	<.01
AST (IU/L)	24.22 (18.46)	23.11 (16.04)	32.63 (30.03)	<.01
Albumin (g/dL)	3.86 (0.90)	3.87 (0.90)	3.78 (0.92)	.06
Platelets ($\times 10^9$/L)	238.61 (75.86)	240.39 (75.22)	225.03 (79.47)	<.01
CRP (mg/L)	3.60 (7.62)	3.60 (7.57)	3.47 (7.93)	.60
HOMA-IR score	2.74 (6.11)	2.66 (6.05)	3.49 (6.56)	.09
Fasting plasma glucose (mg/dL)	121.79 (43.23)	119.82 (41.19)	139.87 (55.80)	<.01
LDL cholesterol (mg/dL)	112.24 (36.42)	113.05 (36.11)	104.79 (38.56)	.64
Triglycerides (mg/dL)	162.06 (136.97)	160.57 (136.51)	173.38 (140.14)	.07
Positive HepC RNA (%)	0.63 (0.16)	0.49 (0.15)	1.69 (0.75)	.06
Positive HepB sAg (%)	7.43 (0.52)	7.39 (0.55)	7.77 (1.56)	.59
At risk alcohol use (%)	31.57 (0.80)	31.64 (0.85)	31.04 (2.32)	.40
Ever binge alcohol use (%)	26.48 (0.85)	27.06 (0.91)	22.08 (2.36)	.97
Number of alcoholic drinks/d	1.69 (2.23)	1.68 (2.22)	1.69 (2.29)	.52

A1c, glycylated hemoglobin; CRP, C-reactive protein; HepB sAg, hepatitis B surface antigen; HepC RNA, hepatitis C ribonucleic acid.
[a]One-tailed independent 2-sample t-tests were performed to compare variables in MAFLD patients with and without advanced fibrosis assuming unequal variances.
[b]Continuous variables reported as mean (standard deviation).
[c]Categorical variables reported as percentage (standard deviation).

hepatitis C RNA and elevated BMI did not improve the ROC of our analysis. Using risk regression analysis on the estimation group, we built the MFIB-4 score as equivalent to the following equation: −46.55 + (7.89*log[waist circumference, cm]) + (1.25*log[fasting plasma glucose, g/dL]) + (0.85*FIB-4 score).

Using the validation group (n = 889), we compared the ROC curves of the MFIB-4 score to the ROC curves of the FIB-4 score and NAFLD fibrosis score in predicting advanced fibrosis. In the validation group, the ROC of the MFIB-4 score is 0.85 (±0.02; CI, 0.79–0.91), compared to the ROC of the FIB-4 score at 0.60 (±0.03; CI, 0.54–0.67) and NAFLD fibrosis score at 0.68 (±0.03; CI, 0.62–0.74). Figure 2A–C compares the ROC curves of the 3 scores on the validation group (n = 889) and on the entire cohort (n = 2671). Using the low cutoff point of −2.08 and the high cutoff point of −0.50, the MFIB-4 score has a specificity of 80%, sensitivity of 97%, positive predictive value of 55%, and NPV of 96% for the detection of advanced fibrosis.

Discussion

Our data suggest an increased risk of advanced fibrosis in MAFLD patients diagnosed based on abnormal BMI, compared to the other 2 criteria (diabetes and metabolic dysfunction). Given that the majority of patients with hepatic steatosis met the criteria for MAFLD (2671/2693), we sought to initially stratify risk based on the diagnostic criteria met. Patients who specifically met the abnormal BMI

Table 2. Association Between MAFLD Criteria and Advanced Fibrosis in a Logistic Regression Model Among Patients With MAFLD (N = 2671)

	Univariate analysis		Multivariate analysis	
MAFLD criteria[a]	OR (95% CI)	*P* value	OR (95% CI)	*P* value
BMI ≥25	4.76 (2.30–9.87)	<.01	4.72 (2.30–9.87)	<.01
Diabetes	0.93 (0.60–1.45)	.74	0.88 (0.55–1.41)	.58
Metabolic dysfunction	1.27 (0.78–2.06)	.29	1.25 (0.77–2.04)	.34
At least 2 of the above	1.34 (0.89–1.99)	.14		
All 3 of the above	1.19 (0.68–2.09)	.51		

[a]Diagnosis of diabetes was based on a history of diabetes, use of oral antidiabetic medications, or A1c>6.5%. Metabolic dysfunction defined as the presence of 2 or more of the following: (1) waist circumference >102/88 cm in men and women, respectively; (2) blood pressure ≥130/85 mmHg (given clinic setting) or specific drug treatment, (3) plasma triglycerides >150 mg/dL (>1.70 mmol/L) or specific drug treatment, (4) plasma high-density lipoprotein cholesterol <40 mg/dL (<1.0 mmol/L) for men and <50 mg/dL (<1.3 mmol/L) for women or specific drug treatment, (5) prediabetes (fasting glucose levels 100–125 mg/dL [5.6–6.9 mmol/L] or hemoglobin A1c 5.7%–6.4% [39–47 mmol/mol]), (6) homeostasis model assessment of insulin resistance (HOMA-IR) score >2.5, and (7) plasma high-sensitivity C-reactive protein level >2 mg/L.

Table 3. Characteristics Associated With Advanced Fibrosis in a Logistic Regression Model Among Patients in the Estimation Group (n = 1782)

	Univariate analysis		Multivariate analysis	
Predictor	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Lab parameters[c]				
Metabolic dysfunction[d]	1.18 (0.72–1.91)	.49		
BMI ≥25	5.90 (2.42–14.42)	<.01	2.93 (1.23–6.99)	.04
BMI ≥30	3.71 (2.36–5.82)	<.01	[a]	
Elevated waist circumference	3.53 (1.31–9.53)	.01	3.39 (2.25–5.12)	<.01
Elevated plasma glucose	2.45 (1.22–4.89)	<.01	1.93 (1.22–3.08)	.01
Elevated A1c	0.72 (0.36–1.44)	.33		
Elevated HOMA-IR score	2.18 (1.17–4.07)	.02	[b]	
Elevated fasting insulin	1.44 (0.71–2.93)	.29		
Low HDL	0.97 (0.49–1.91)	.21		
Elevated triglycerides	1.94 (1.08–3.48)	.03	1.23 (0.85–3.35)	.50
Positive HepC RNA	14.92 (2.15–103.62)	.02	1.73 (1.03–2.89)	.04
Positive HepB sAg	1.76 (0.52–5.92)	.34		
Elevated ferritin	1.58 (1.00–2.67)	.05	1.08 (0.77–1.61)	.68
ALT>AST	1.54 (1.03–2.31)	.04	1.82 (0.83–3.96)	.12
Interview parameters[e]				
On cholesterol medication	1.08 (0.66–1.74)	.75		
On hypertension medication	2.71 (0.65–11.35)	.16		
On oral diabetes medication	1.25 (0.37–3.98)	.73		
At-risk alcohol use	1.41 (0.81–2.46)	.21		
Ever binge alcohol use	1.07 (0.63–1.80)	.79		
On antiacid medication	1.78 (0.90–3.53)	.09		

A1c, glycylated hemoglobin; CRP, C-reactive protein; HDL, high-density lipoprotein; HepB sAg, hepatitis B surface antigen; HepC RNA, hepatitis C ribonucleic acid.
[a]Predictor "BMI ≥30" excluded in multivariate analysis due to overlap with "BMI ≥25".
[b]Predictor "HOMA-IR" excluded in multivariate analysis due to overlap with "elevated plasma glucose."
[c]Elevated waist circumference defined as >88 cm in women and >102 cm in men. Elevated fasting plasma glucose defined as >126 mg/dL. Elevated A1c defined as >6.5%. Elevated HOMA-IR score defined as >2.5. Low HDL defined as <40 mg/dL for men and <50 mg/dL for women. Elevated triglycerides defined as >200 mg/dL. Elevated ferritin defined as >336 mcg/dL in males and >307 mcg/dL in females.
[d]Metabolic dysfunction defined in Table 2.
[e]Medication defined as current use of lipid-lowering, hypertension, and oral diabetes medications. At-risk alcohol use defined as >2 drinks/d in men and >1 drink/d in women. Ever binge alcohol use defined as >5 drinks/d in men and 4 drinks/d in women. Antiacid medications defined as current use of over-the-counter antiacids and prescribed proton pump inhibitors.

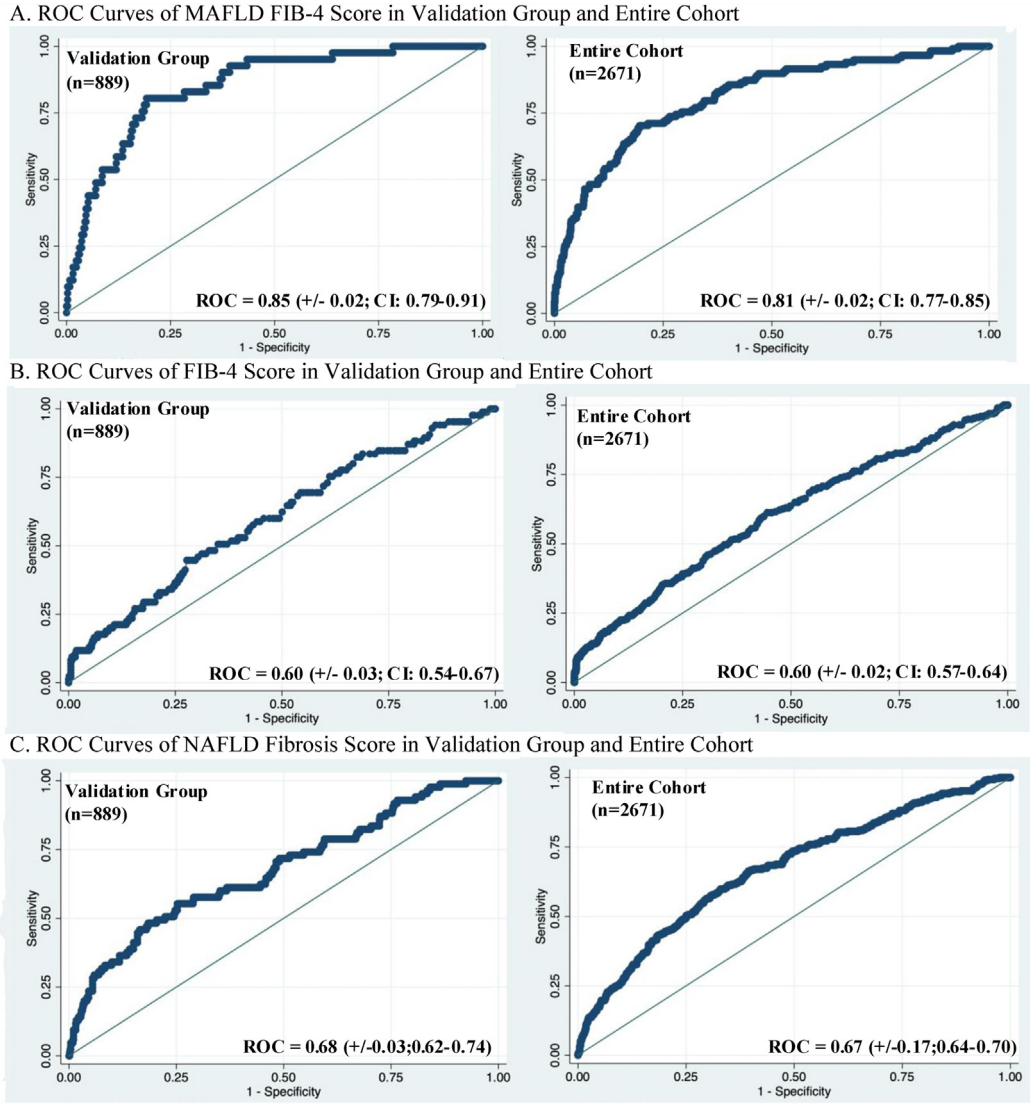

Figure 2. Comparing ROC of fibrosis scores in predicting advanced fibrosis. (A) ROC curves of MAFLD FIB-4 score in the validation group and entire cohort. (B) ROC curves of FIB-4 score in the validation group and entire cohort. (C) ROC curves of NAFLD fibrosis score in the validation group and entire cohort. CI, confidence interval; FIB-4, fibrosis-4; MAFLD, metabolic-associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease; ROC, receiver operative characteristics.

criteria are at a higher risk of advanced fibrosis. Although metabolic dysfunction was not associated with increased fibrosis risk in logistic regression analysis, a higher proportion of patients with advanced fibrosis met the criteria for metabolic dysfunction than those with moderate and lower fibrosis. Notably, meeting more than 1 diagnostic criterion or diagnosis of diabetes was not associated with increased fibrosis risk. This suggests that upon initial diagnosis of MAFLD, clinicians may easily stratify patients at increased risk by whether they met the BMI criterion. Furthermore, given the recent emphasis on screening for liver disease, patients with a BMI in the overweight and above category may be candidates for hepatic steatosis screening.

Additional risk factors for advanced fibrosis in MAFLD patients are high waist circumference, high plasma fasting glucose, HOMA-IR score, high triglycerides, positive hepatitis C RNA, high ferritin, and ALT $>$ AST. We utilized these determined risk factors to build an accurate MFIB-4 score to noninvasively assess fibrosis risk. Given that the FIB-4 score incorporated the same variables of age, AST, ALT, and platelets we determined to be significant in MAFLD patients with fibrosis (Table 2) and given the current familiarity that clinicians have with the existing FIB-4 score, we chose to utilize the FIB-4 score in our MFIB-4 score.

The ROC of the MFIB-4 score is 0.85 in the validation group, superior to the ROC of the FIB-4 score at 0.60 and the ROC of the NAFLD fibrosis score at 0.68 in predicting advanced fibrosis. The MFIB-4 score has a specificity of 80%, sensitivity of 97%, positive predictive value of 55%, and NPV of 96% for the detection of advanced fibrosis. If the MFIB-4 score of patients is <-2.08, there is a low risk of

advanced fibrosis, and lifestyle modifications are recommended. If the MFIB-4 score of patients is >-0.50, there is a high risk of advanced fibrosis, and referral to gastrointestinal for further evaluation is recommended. If patients fall between these cutoffs, there is a moderate risk of advanced fibrosis, and routine monitoring is recommended.

Huang et al studied fibrosis risk in MAFLD patients using the FIB-4 and NAFLD fibrosis scores to measure fibrosis in patients from 1988 to 1994.[9] In contrast to our finding that BMI had the greatest association with fibrosis risk out of the 3 MAFLD criteria, Huang et al found that diabetes had the greatest association with fibrosis risk. This difference can be explained by Huang et al's use of noninvasive fibrosis scores as opposed to the preferred vibration-controlled TE data in measuring the outcome of liver fibrosis. Similar to their report, we found insulin resistance to be correlated with liver fibrosis.

Ciardullo et al studied steatosis in MAFLD adolescent patients younger than 18 years and similarly found BMI and waist circumference to be associated with S3 steatosis and fibrosis and hypertension not associated with advanced fibrosis.[10] Similar to our findings, Harris et al and Huh et al found obesity as the greatest single independent risk factor, over metabolic markers, diabetes, or alcohol use, for liver fibrosis in adults without a known prior liver disease.[11,12]

Limitations of our study include retrospective data on participants and lack of liver biopsy data, which is the gold standard for confirming liver fibrosis although less suited for large studies. There is a lack of standardized cutoffs for steatosis (CAP) and fibrosis stages (LSM) although we used peer-reviewed cutoff criteria. Lastly, there is speculation that TE may be less accurate than magnetic resonance (MR) elastography in patients with truncal obesity secondary to excess adipose tissue as opposed to innate liver fibrosis.[13] In a prospective study, Chen et al found that in obese patients, both MR elastography (ROC = 0.93) and TE (ROC = 0.91) had accurate diagnostic performance for assessing hepatic fibrosis.[14] Although MR elastography is more technically reliable than TE due to higher interobserver reliability, our study excluded all unreliable TE examinations. For further validation of our results, a large, prospective study using MR elastography data, although MR elastography is more expensive than TE elastography, would be useful.

Given the financial and logistic barriers in using TE for all patients who meet criteria for MAFLD, we anticipate a large role for the MFIB-4 score in noninvasively triaging patients for further evaluation due to fibrosis risk.

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The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

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Data, analytic methods, and study materials for other researchers are available upon request to the first author.