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ORIGINAL RESEARCH

Liver Fibrosis Scores and Coronary Artery Disease: Novel Findings in Patients with Metabolic Dysfunction-Associated Fatty Liver Disease

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Background: Metabolic dysfunction-associated fatty liver disease (MAFLD) is a recently proposed term as a more appropriate definition for nonalcoholic fatty liver disease (NAFLD). Previous studies have shown an association between liver fibrosis scores and cardiovascular disease (CVD) in patients with NAFLD. In this study, we aimed to investigate the relationship between liver fibrosis scores and coronary artery disease (CAD) severity in patients with MAFLD.

Methods: This study was conducted on 1346 patients with MAFLD at the Second Hospital of Dalian Medical University between January 2018 and December 2021. We calculated the liver fibrosis scores, including the fibrosis 4 (FIB-4) score, nonalcoholic fatty liver disease fibrosis score (NFS), and aspartate aminotransferase-to-platelet ratio index (APRI). We divided the participants into three groups based on the degree of coronary artery stenosis assessed using coronary computed tomography angiography (CCTA): CAD (≥50%), non-obstructive (1–49%), and normal (no stenosis).

Results: An increased FIB-4 score and NFS were significantly associated with CAD severity in patients with MAFLD. The percentage of patients with a high FIB-4 score was higher in the CAD group than in the other two groups (5.80%, 4.31%, and 2.24%, respectively; $p<0.001$), as was the percentage of patients with NFS (11.12%, 5.19%, and 0.93%, respectively; $p<0.001$). Carotid atherosclerosis, creatinine levels, and CAC scores were significant predictors of CAD. The FIB-4 score and NFS were independently associated with CAD even after adjusting for sex and well-known cardiovascular risk factors. The APRI was not a significant factor for CAD in any model. In the bivariate correlation analysis, the FIB-4 score and NFS were directly correlated with CAC scores.

Conclusion: Non-invasive liver fibrosis scores (FIB-4 and NFS) were significantly associated with the CAD severity and CAC scores in patients with MAFLD. Screening for CAD may be beneficial for subjects with high liver fibrosis risk MAFLD.

Keywords: metabolic dysfunction-associated fatty liver disease, coronary artery disease, liver fibrosis scores, coronary artery calcium scores, nonalcoholic fatty liver disease

Introduction

Fatty liver disease is a prevalent and significant health issue worldwide, and is characterized by the accumulation of excess fat in the liver. It has been recognized as the most rapidly increasing cause of liver-related mortality for several decades and affects nearly a quarter of the adults in the general population.[1–3]

The definition of nonalcoholic fatty liver disease (NAFLD) has been used for decades, excluding viral hepatitis, autoimmune diseases, and heavy drinking as the underlying cause of the disease. However, this definition does not accurately reflect the contribution of systemic metabolic dysregulation to liver diseases. To address this, an international panel of experts proposed a new definition in early 2020, called metabolic dysfunction-associated fatty liver disease (MAFLD).[4] The new definition emphasizes the importance of metabolic abnormalities in the development and progression of the disease. The diagnostic criteria for MAFLD are hepatic steatosis of ≥5%[5] and the presence of one of the following three conditions: type 2 diabetes mellitus (T2DM), overweight/obesity by body mass index (BMI) classifications, and metabolic risk abnormalities (Box 1).[4]

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Box 1 Metabolic Risk Abnormalities - 2 Out of 7

1. Waist circumference ≥102/88 cm in Caucasian men and women, (or≥90/80 cm in Asian men or women);
2. Blood pressure ≥130/85 mmHg or specific drug treatment;
3. Plasma triglycerides ≥150 mg/dL (≥1.70 mmol/L) or specific drug treatment;
4. Plasma HDL-C <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 (ie fasting glucose levels 100–125 mg/dL (5.6–6.9 mmol/L) or 2-hour post-load glucose levels 140–199 mg/dL (7.8–11.0 mmol/L) or HbA1c of 5.7–6.4% (39–47 mmol/mol);
6. Homeostasis model assessment of insulin resistance score ≥2.5;
7. Plasma high-sensitivity C-reactive protein level >2 mg/L.

Abbreviations: HDL-C, high-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin.

The new definition is not only a name change but also highlights the association of this common liver disease with metabolic risk and coexisting extrahepatic diseases.[6] NAFLD is known to be a significant risk factor for cardiovascular disease (CVD), which is the leading cause of death in patients with NAFLD.[7] There are several common risk factors shared by NAFLD and CVD, such as hypertension, T2DM, lipid abnormality, obesity, and smoking. Recently, the American Heart Association has recognized NAFLD as an underappreciated and independent risk factor for CVD.[8] However, the relationship between the newly redefined MAFLD and CVD has not been well investigated.

Liver fibrosis is a progressive condition that is associated with both NAFLD and MAFLD. Recent evidence indicates that liver fibrosis severity is related to an increased risk of fatal and non-fatal CVD events.[9] Several mechanisms contribute in liver fibrosis to CVD risk, such as hepatic insulin resistance, systemic low-grade inflammation, adhesion molecules, and endothelial dysfunction.[10] Although liver biopsy remains the gold standard for diagnosing liver fibrosis, several noninvasive liver fibrosis scores have been developed, such as the fibrosis 4 (FIB-4) score,[11] nonalcoholic fatty liver disease fibrosis score (NFS),[12] and aspartate aminotransferase to platelet ratio index (APRI),[13] which have been used to evaluate the degree of liver fibrosis. Studies have shown that liver fibrosis scores can predict the prognosis of CAD in patients with NAFLD.[14–16] We hypothesized that liver fibrosis scores could serve as feasible markers for assessing cardiovascular risk. In this cross-sectional study, we aimed to evaluate the association between liver fibrosis scores (FIB-4, NFS, and APRI) and CAD severity in MAFLD patients.

Methods

Study Population

We conducted a retrospective cross-sectional study of patients hospitalized at the Second Hospital of Dalian Medical University between January 2018 and December 2021. We included patients who met the diagnostic criteria for MAFLD, and assessed their degree of hepatic steatosis using ultrasonography. Among these patients, we included 1568 who underwent a coronary computed tomography angiography (CCTA) scan due to suspicion of CAD or for health checkups. We excluded patients who had pre-existing CAD or other severe diseases, including (1) previous history of CAD, structural heart disease, and heart failure; (2) severe hepatic or renal insufficiency; (3) hematological disease; (4) acute or chronic infectious disease; or (5) insufficient medical records. Finally, we analyzed 1346 participants in this study. All subjects enrolled in the study gave informed consent in writing. Our study complied with the Declaration of Helsinki and was approved by the local ethics committee of the Second Hospital of the Dalian Medical University.

Assessment

Professional clinicians collected clinical data, such as age, sex, hypertension, T2DM, and CAD. Weight and height were measured using a digital scale on the day of admission, and BMI was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured in the right arm after 20 minutes in the seated position using an electronic sphygmomanometer. Biochemical parameters were measured by automatic biochemical analyzer

(Siemens), including complete blood counts, lipid profiles (total cholesterol, triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C)), and aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting plasma glucose, glycosylated hemoglobin (HbA1c), uric acid (UA), and creatinine levels, were measured after overnight fasting blood tests. The estimated glomerular filtration rate (eGFR) was calculated according to the Modification of Diet in Renal Disease equation. The severity of hepatic steatosis was determined by ultrasonography.

We used the following formula to calculate NAFLD fibrosis scores, including the FIB-4 score, NFS, and APRI:[13,17] FIB-4= age (years)×AST (U/L)/platelet count ($\times 10^9$/L)×[square root of ALT(U/L)]; NFS=−1.675+0.037×age(years) +0.094×BMI(kg/m^2)+1.13×impaired fasting glucose/diabetes (yes=1, no=0)+0.99×AST/ALT ratio-0.013×platelet($\times 10^9$/L)-0.66×albumin (g/dL); APRI=[AST(U/L)/upper normal limit of AST(U/L)]/platelet count ($\times 10^9$/L) × 100.

Definitions

The criterion for MAFLD utilizes the same standard for hepatic steatosis evidence as NAFLD. However, metabolic dysfunction factors must also be considered during the diagnosis. This requires meeting at least one of the following three criteria: T2DM, overweight/obesity by BMI, or two or more metabolic risk abnormalities, as listed in Box 1.[4]

Abdominal Ultrasonography

Abdominal ultrasonography was performed using LOGIQ 9 (GE Healthcare) scanner equipped with a 2.5–4.0 MHz linear matrix transducer by experienced radiologists at the Second Hospital of Dalian Medical University. They were blinded to the clinical and laboratory data. Hepatic steatosis was diagnosed by the following criteria: (1) parenchymal brightness; (2) liver to kidney contrast; (3) deep beam attenuation; and (4) vessel blurring.

Coronary Computed Tomography Angiography

We performed CCTA using a 256-multislice scanner (Philips Healthcare) in patients hospitalized at the Second Hospital of Dalian Medical University. In addition to evaluating the degree of coronary artery stenosis, we also calculated coronary artery calcium (CAC) scores using the method described by Agatston et al.[18] Three experienced physicians with at least five years of experience in cardiac CT read all images.

CAD severity was assessed based on CCTA imaging and CAC scores. CAD was defined as > 50% degree of coronary artery stenosis. Therefore, we divided the participants into three groups based on the degree of coronary artery stenosis: CAD (≥50%), non-obstructive (1–49%), and normal (no stenosis).

Statistical Analysis

We used the Statistical Package for the Social Sciences version 27.0 to perform all statistical analyses. Continuous variables were presented as mean ± standard deviation or median (Q1–Q3 quartiles), while categorical variables were summarized as frequencies and percentages. For normally distributed continuous variables, we compared the groups using a one-way analysis of variance with the Scheffe post-hoc test. For non-normally distributed continuous variables, we compared the groups using the Mann–Whitney *U*-test. We analyzed categorical variables using the chi-square test. We used Pearson or Spearman correlation analysis to assess the correlation of liver fibrosis scores with clinical parameters.

To evaluate the association between clinical characteristics and CAD, we used multivariate binary logistic regression analysis. We performed univariate and multivariate binary logistic regression analyses to identify the risk factors for CAD. In the multivariate analysis, we included statistically significant factors ($p<0.05$) and probably associated characteristics based on clinical experience as covariates. In the multivariable regression model, we adjusted the liver fibrosis scores for sex (model 1) and progressively added other statistically significant covariates (model 2 and model 3). Statistical significance was defined as $p<0.05$.

Results

Baseline Characteristics

Table 1 displays the baseline characteristics of the 1346 participants, with a mean age of 58.4± 11.2 years. Out of the participants, 662 were male (49.2%). Patients with CAD demonstrated significantly higher age, systolic pressure, fasting glucose, glycosylated hemoglobin, creatinine, FIB-4 score, NFS, CAC scores, percentage of T2DM, and carotid atherosclerosis compared to the normal and non-obstructive groups ($p<0.05$). However, no significant differences were observed in the BMI, diastolic pressure, platelet count, UA, AST, TB, TG, HDL-C, LDL-C, apolipoprotein B (Apo B), and APRI.

Sub-Analysis of Liver Fibrosis Risk and the Presence of CAD in MAFLD Patients

To analyze the correlation between liver fibrosis risk and the presence of CAD, we calculated the FIB-4 score with cut-offs of 1.30 and 2.67 for the low-, intermediate-, and high-risk categories, respectively. Similarly, the cutoff values for

Table 1 Baseline Characteristics of the Participants

Characteristic	Normal n=214	Non-Obstructive n=925	CAD n=207	p-value
Age (years)	50.91±11.53	59.01±10.61*	62.73±10.48*+	<0.001
Male	98(45.8%)	437(47.2%)	127(61.4%)*+	<0.001
BMI (kg/m^2)	27.71±3.26	27.61±3.31	27.52±2.87	0.661
Systolic pressure (mmHg)	135.44±19.55	140.02±19.67*	143.58±20.33*+	<0.001
Diastolic pressure (mmHg)	88.95±14.50	88.42±12.46	88.85±13.46	0.956
HTN	103(48.1%)	614(66.4%)*	151(72.9%)*	<0.001
T2DM	32(15.0%)	194(21.0%)	70(33.8%)*+	<0.001
Carotid atherosclerosis	52(24.3%)	389(42.1%)*	151(72.9%)*+	<0.001
Fasting glucose (mmol/L)	5.69(5.17, 6.61)	5.89(5.25, 7.25)	6.25(5.44, 8.06)*+	<0.001
HbA1c (100%)	5.7(5.5, 6.1)	5.9(5.6, 6.4)*	6.1(5.8, 6.8)*+	<0.001
Platelet (×109/L)	237.55±57.83	231.19±53.86	231.89±72.72	0.327
Creatinine (umol/L)	65.19±15.20	65.12±14.04	69.04±16.23*+	0.003
eGFR	107.26±21.43	103.93±20.62*	101.28±24.41*	0.021
UA (umo/L)	370.40±90.92	360.31±87.03	370.71±88.19	0.146
ALT (U/L)	29.11(19.47, 48.56)	26.59(19.65, 37.22)	25.46(17.77, 34.49)+	0.010
AST (U/L)	22.31(18.40, 31.14)	21.72(18.15, 27.22)	21.83(17.57, 27.83)	0.749
ALB (g/L)	43.85±3.16	43.23±3.36*	42.81±3.25*	0.029
TB (umol/L)	12.31(9.46, 16.17)	12.72(9.84, 16.54)	12.20(9.50, 15.47)	0.647
TC (mg/dl)	4.81±0.91	4.92±1.07	4.74±1.24 +	0.049
TG (mg/dl)	1.73(1.25, 2.36)	1.73(1.25, 2.40)	1.56(1.17, 2.28)	0.396
HDL-C (mg/dl)	1.12±0.24	1.14±0.27	1.11±0.25	0.273
LDL-C (mg/dl)	2.62±0.69	2.64±0.78	2.57±0.92	0.465
Apo A (mg/dl)	1.38±0.20	1.39±0.21	1.35±0.21 +	0.021
Apo B (mg/dl)	0.94±0.20	0.96±0.23	0.94±0.25	0.366
FIB-4 score	1.06±0.78	1.28±0.75*	1.45±0.89*+	<0.001
NFS	−1.92±1.24	−1.33±1.58*	−0.93±2.13*+	<0.001
APRI	0.23(0.19, 0.34)	0.24(0.19, 0.32)	0.24(0.19, 0.34)	0.883
CAC scores	0(0, 0)	0(0, 35.9)*	241.0(86.7, 510.0)*+	<0.001
0	212(99.1%)	463(50.1%)*	11(5.3%)*+	<0.001
0–100	1(0.5%)	338(36.5%)*	46(22.2%)*+	<0.001
>100	1(0.5%)	124(13.4%)*	150(72.5%)*+	<0.001

Notes: *p<0.05 vs Normal group; +p<0.05 vs Non-obstructive group.

Abbreviations: CAD, coronary artery disease; BMI, body mass index; HTN, hypertension; T2DM, type 2 diabetes mellitus; HbA1c, glycosylated hemoglobin; eGFR, estimated glomerular filtration rate; UA, uric acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; TB, total bilirubin; TC, total cholesterol, TG, triglyceride; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein; Apo A, apolipoproteins A; Apo B, apolipoproteins B; FIB-4, fibrosis 4; NFS, nonalcoholic fatty liver disease fibrosis score; APRI, aspartate aminotransferase-to-platelet ratio index; CAC scores, coronary artery calcium scores.

NFS were −1.455 and 0.676, respectively. Figures 1 and 2 displays the percentage of liver fibrosis risk divided by the FIB-4 score and NFS in the normal, non-obstructive, and CAD groups. The percentages of high FIB-4 score and NFS were significantly higher in the CAD group than in the other two groups. Statistical differences were observed between the groups, and statistical comparisons were performed using the Chi-square test.

Factors Associated with CAD in MAFLD Patients

Table 2 summarizes the results of logistic regression analysis studying the association of CAD with clinical parameters. The univariate binary logistic regression analysis identified 14 factors that were significantly associated with CAD.

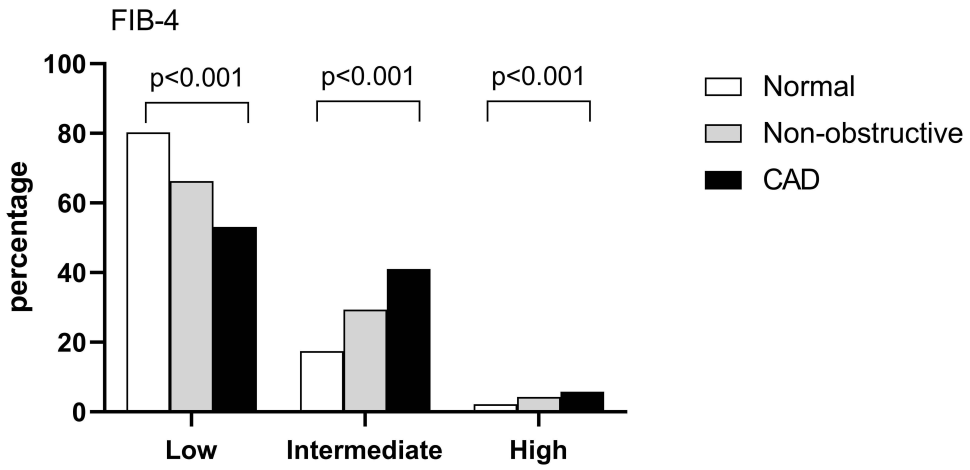

Figure 1 The percentage of liver fibrosis risk divided by the FIB-4 score in the normal, non-obstructive, and CAD groups. The percentage of high FIB-4 score were significantly higher in the CAD group than in the other two groups ($p<0.01$).
Abbreviations: FIB-4, fibrosis 4; CAD, coronary artery disease.

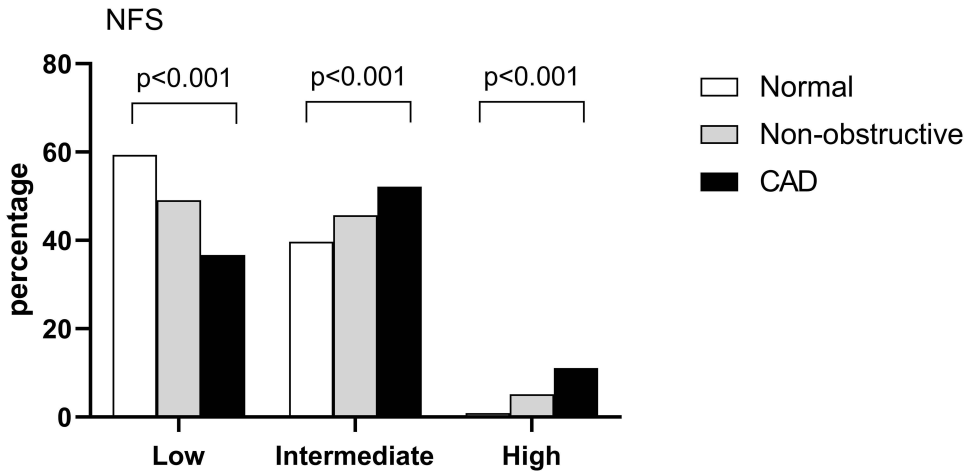

Figure 2 The percentage of liver fibrosis risk divided by the NFS in the normal, non-obstructive, and CAD groups. The percentage of high NFS were significantly higher in the CAD group than in the other two groups ($p<0.01$).
Abbreviations: NFS, nonalcoholic fatty liver disease fibrosis score; CAD, coronary artery disease.

Table 2 Factors Associated with CAD in Subjects with MAFLD: Logistic Regression

Variable	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (years)	1.047 (1.032–1.062)	<0.001		
Male	0.558 (0.412–0.755)	<0.001		
BMI (kg/m^2)	0.986 (0.941–1.033)	0.555		
Systolic pressure (mmHg)	1.011 (1.004–1.018)	0.003		
Diastolic pressure (mmHg)	1.001 (0.989–1.012)	0.897		
HTN	1.587 (1.142–2.206)	0.006		
T2DM	2.064 (1.495–2.850)	<0.001		
Carotid atherosclerosis	4.268 (3.071–5.931)	<0.001	2.058 (1.350–3.138)	<0.001
Fasting glucose (mmol/L)	1.071 (1.022–1.123)	0.004		
HbA1c (100%)	1.255 (1.131–1.393)	<0.001		
Platelet (×109/L)	0.999 (0.997–1.002)	0.568		
Creatinine (umol/L)	1.017 (1.007–1.027)	<0.001	1.020 (1.005–1.035)	0.010
eGFR	0.993 (0.986–1.000)	0.058		
UA (umol/L)	1.001 (0.999–1.003)	0.299		
ALB (g/L)	0.961 (0.919–1.005)	0.083		
TB (umol/L)	0.997 (0.973–1.022)	0.810		
TC (mg/dl)	0.864 (0.750–0.994)	0.041		
TG (mg/dl)	0.945 (0.848–1.053)	0.305		
HDL-C (mg/dl)	0.680 (0.384–1.204)	0.186		
LDL-C (mg/dl)	0.890 (0.735–1.077)	0.229		
Apo A (mg/dl)	0.387 (0.184–0.813)	0.012		
Apo B (mg/dl)	0.726 (0.374–1.410)	0.344		
FIB-4 score	1.345 (1.142–1.583)	<0.001		
NFS	1.191 (1.080–1.313)	<0.001		
APRI	1.471 (0.936–2.311)	0.094		
CAC scores	1.007 (1.006–1.009)	<0.001	1.007 (1.005–1.008)	<0.001

Abbreviations: CAD, coronary artery disease; MAFLD, metabolic dysfunction-associated fatty liver disease; BMI, body mass index; HTN, hypertension; T2DM, type 2 diabetes mellitus; HbA1c, glycosylated hemoglobin; eGFR, estimated glomerular filtration rate; UA, uric acid; ALB, albumin; TB, total bilirubin; TC, total cholesterol, TG, triglyceride; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein; Apo A, apolipoproteins A; Apo B, apolipoproteins B; FIB-4, fibrosis 4; NFS, nonalcoholic fatty liver disease fibrosis score; APRI, aspartate aminotransferase-to-platelet ratio index; CAC scores, coronary artery calcium scores; OR, odds ratio; CI, confidential interval.

Including these factors, the multivariate binary logistic regression analysis revealed that the presence of carotid atherosclerosis, creatinine, and CAC scores were significant factors for predicting CAD (p<0.001, p=0.010, and p<0.001, respectively) (Table 2).

Associations of Noninvasive Fibrosis Scores with CAD in Subjects with MAFLD

To assess the association between NFS, FIB-4 score, and CAD, a multivariate analysis adjusted for potential confounders was subsequently performed. The FIB-4 score (OR 1.345, 95% CI 1.142–1.583) and NFS (OR 1.191, 95% CI 1.080–1.313) were independently associated with CAD in the base model. In model 1, which was adjusted for sex, the FIB-4 score and NFS were significant predictive factors for CAD. In addition, adjustments for the presence of hypertension, DM, and carotid atherosclerosis, total cholesterol, creatinine, FIB-4 score, and NFS were also significant predictive factors for CAD (model 2 and model 3) (Table 3). Unlike the other two noninvasive fibrosis markers, the APRI was not a significant factor for CAD in each model.

Correlation of Liver Fibrosis Scores with Clinical Parameters

In bivariate correlation analysis (Pearson or Spearman correlation) performed on the whole population, the FIB-4 score and NFS were inversely correlated with diastolic pressure, TC, TG, LDL-C, and directly correlated with CAC scores (Table 4).

Table 3 Associations of Noninvasive Fibrosis Scores with CAD in Subjects with MAFLD: Logistic Regression

Variable	OR (95% CI)	p-value
FIB-4 score		
Unadjusted	1.345 (1.142–1.583)	<0.001
Model 1	1.388 (1.176–1.639)	<0.001
Model 2	1.238 (1.042–1.471)	0.015
Model 3	1.229 (1.031–1.464)	0.021
NFS		
Unadjusted	1.191 (1.080–1.313)	<0.001
Model 1	1.218 (1.101–1.348)	<0.001
Model 2	1.114 (1.023–1.214)	0.013
Model 3	1.108 (1.018–1.207)	0.018

Notes: Model 1: adjusted for gender; Model 2: adjusted for gender and presence of hypertension, DM, and carotid atherosclerosis; Model 3: adjusted items in Model 2 plus for total cholesterol and creatinine.
Abbreviations: CAD, coronary artery disease; MAFLD, metabolic dysfunction-associated fatty liver disease; FIB-4, fibrosis 4; NFS, nonalcoholic fatty liver disease fibrosis score; OR, odds ratio; CI, confidential interval.

Table 4 Correlation of Liver Fibrosis Scores with Clinical Parameters: Correlation Analysis

Variables	FIB-4 Score		NFS	
	r	P	r	P
BMI	−0.141	<0.01	0.087	<0.01
Systolic pressure	−0.007	0.801	0.013	0.645
Diastolic pressure	−0.167	<0.01	−0.157	<0.01
Fasting glucose	0.013	0.621	0.406	<0.01
HbA1c	0.086	0.002	0.345	<0.01
TC	−0.071	0.009	−0.119	<0.01
TG	−0.131	<0.01	−0.113	<0.01
HDL-C	0.063	0.020	0.029	0.281
LDL-C	−0.089	<0.01	−0.109	<0.01
CAC scores	0.285	<0.01	0.245	<0.01

Abbreviations: FIB-4, fibrosis 4; NFS, nonalcoholic fatty liver disease fibrosis score; BMI, body mass index; HbA1c, glycosylated hemoglobin; TC, total cholesterol, TG, triglyceride; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein; CAC scores, coronary artery calcium scores.

Discussion

The primary finding of our study was a significant positive correlation between FIB-4 score and NFS and CAD severity in patients with MAFLD. Among the MAFLD patients enrolled in this study, those with combined CAD had a significantly higher risk of liver fibrosis, as calculated using the FIB-4 score and NFS. Additionally, we found an association between the FIB-4 score and NFS and several clinical parameters, particularly CAC scores, which are recognized as essential predictors of CAD prognosis. Furthermore, even after adjusting for sex and other metabolic variables, the risk of CAD was independently associated with the FIB-4 score and NFS. Therefore, non-invasive liver fibrosis scores, such as the FIB-4 score and NFS, can be used to assess the risk of CAD in patients with MAFLD.

The relationship between fatty liver disease and cardiovascular disease has attracted considerable attention globally due to the increasing number of patients with fatty liver disease. There is growing evidence that NAFLD is a multi-system disease that increases the risk of early carotid atherosclerosis, cardiovascular disease, chronic kidney disease, and T2DM.[7,19,20] Targher et al suggested that NAFLD is strongly associated with early carotid atherosclerosis, independent

of classical risk factors such as insulin resistance.[21] A retrospective observational study of a nationwide population-based cohort in Sweden conducted by Shang et al found that NAFLD was associated with a higher risk of nonfatal cardiovascular disease, and NAFLD patients had a lower life expectancy than the general population.[22] Alon L et al also observed similar results, where the risk of myocardial infarction, ischemic stroke, atrial fibrillation, and heart failure increased in patients with NAFLD.[23]

Although the underlying mechanism by which fatty liver disease increases the risk of cardiovascular disease remains unclear, several possibilities have been suggested. First, impaired endothelial dysfunction is considered to be the early stage of atherosclerosis,[24] and hence is crucial in CVD development. This pathophysiological process is triggered by oxidative stress and chronic inflammation, which play an important role in fatty liver disease progression.[25–27] Therefore, endothelial dysfunction is considered a link between fatty liver disease and CVD risk. Second, the liver plays a central role in lipid and glucose metabolisms.[28] Fatty liver disease is associated with abnormal lipid metabolism, increased levels of TG and LDL-C, and decreased levels of HDL-C, which have been proven to be risk factors for CVD. Diabetes mellitus and insulin resistance are also recognized as basic components of cardiometabolic diseases. Patients with fatty liver disease had a higher prevalence of diabetes and dyslipidemia, which is consistent with the results of our study. Fatty liver disease may be linked to CVD because they share common metabolic dysfunction.[29]

Nonalcoholic steatohepatitis (NASH) is a progressive form of NAFLD characterized by liver damage and fibrosis. The incidence of progression of NASH was > 20%.[30] Previous studies have shown that NASH and CAD share many pathophysiological mechanisms, including endothelial dysfunction, oxidative stress, lipid metabolism, and chronic inflammation.[31] The progression of both liver fibrosis and arteriosclerosis may be induced by these common mechanisms.[32] Thus, CAD and liver fatty disease are the clinical consequences of metabolic disorders in different organs. Various biomarkers that assess liver fibrosis are considered useful for predicting the risk of CAD. Although liver biopsy remains the gold standard for assessing the fibrosis stage, non-invasive fibrosis scoring systems, including the FIB-4 score, NFS, and APRI, are widely used for their non-invasiveness.

Non-invasive liver fibrosis scores have also recently been suggested to have a predictive value for adverse outcomes in patients with cardiovascular diseases.[33] For example, Liu et al found that high liver fibrosis scores might be useful for predicting adverse prognosis in patients with CAD following percutaneous coronary intervention (PCI).[34] In a cohort of 5143 patients with CAD, Jin et al suggested that the FIB-4 score and NFS were significantly related to CAD severity, coronary artery calcium (CAC) scores, and cardiovascular events.[14] Chen et al reported similar results; higher liver fibrosis scores were associated with increased risks of all-cause and cardiovascular mortality among patients with CAD. In addition, in other groups, such as T2DM, subclinical atherosclerosis, and NAFLD, non-invasive liver fibrosis scores have also been shown to have predictive and diagnostic values for CAD.[35–37] Our study revealed that CAD severity was associated with FIB-4 score and NFS, even after adjusting for sex and relatively well-known cardiovascular risk factors.

Previous cross-sectional studies and meta-analyses have reported that CAC scores reflect CAD severity and are associated with adverse cardiovascular outcomes.[38–40] Park et al also reported a significant association between liver fibrosis and coronary artery calcification development.[15] Therefore, we conducted further analysis and found that FIB-4 score and NFS were directly correlated with CAC scores, consistent with a previous study.

Notably, previous studies have been conducted in the field of NAFLD. Since the introduction of the term "metabolic dysfunction-associated fatty liver disease", there have been key areas in which the superiority of MAFLD over traditional NAFLD terminology has been demonstrated.[41–43] The application of the new term MAFLD has shown advantages in assessing the risk of liver and extrahepatic mortality, as well as identifying high-risk individuals.[44–46] Our study extended these previous observations to a new concept and discovered significant results regarding the predictive value of non-invasive liver fibrosis scores for CAD in patients with MAFLD. Risk screening for this population is necessary, considering the risk of extrahepatic comorbidity in MAFLD. Furthermore, we found that the percentage of patients with CAD in MAFLD was higher, especially those with a high liver fibrosis risk assessed using non-invasive liver fibrosis scores, which is consistent with our study. This novel finding suggests that calculating noninvasive liver fibrosis scores among MAFLD patients is necessary to identify individuals at a high risk of CAD. Although routine screening for CAD in patients with pre-existing MAFLD is not currently recommended, CCTA examination is a good recommendation for patients with a high risk of liver fibrosis, according to our study.

Several potential limitations existed in our present study. First, it was a retrospective cross-sectional study with a relatively small sample size, and the results should not be used to draw causal conclusions. Second, we used ultrasonography and noninvasive liver fibrosis scores to diagnose and stratify the severity of MAFLD instead of liver biopsy, which is regarded as the "gold standard." Third, a follow-up was not performed in our study. Further long-term follow-up studies are warranted to evaluate CAD progression and cardiovascular events.

Conclusion

In conclusion, our study suggests that noninvasive liver fibrosis scores (FIB-4 score and NFS) are significantly related to the severity of CAD and CAC scores in patients with MAFLD. This noninvasive index may be a useful risk assessment tool for CAD and can be widely used owing to its non-invasiveness and convenience. Therefore, subjects with a high liver fibrosis risk in MAFLD may benefit from screening for coronary artery disease at an early stage.

Abbreviations

ALT, alanine aminotransferase; Apo B, apolipoprotein B; APRI, aminotransferase to platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; CAC, coronary artery calcium; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis 4; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NFS, nonalcoholic fatty liver disease fibrosis score; MAFLD, metabolic dysfunction-associated fatty liver disease; PCI, percutaneous coronary intervention; T2DM, type 2 diabetes mellitus; TB, total bilirubin; TG, triglyceride; UA, uric acid.

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Disclosure

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