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ORIGINAL ARTICLE

Liver fibrosis scores and coronary atherosclerosis: novel findings in patients with stable coronary artery disease

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Abstract

Background Although non-invasive liver fibrosis scores (LFSs) have already been considered as effective tools for estimating cardiovascular risk, their roles in predicting disease severity and cardiovascular event (CVEs) in patients with stable coronary artery disease (CAD) are not comprehensively evaluated. The aim of the present study was to investigate whether non-alcoholic fatty liver disease fibrosis score (NAFLD-FS) and fibrosis-4 (FIB-4) are associated with CVEs in a large cohort with long-term follow-up.

Methods A cohort of 5143 patients with angiography-proven stable CAD were consecutively enrolled and followed up for CVEs. The degree of coronary severity was assessed using the number of diseased vessels, Gensini, Syntax, and Jeopardy scores. The predictive values of NAFLD-FS and FIB-4 scores to coronary severity, coronary calcification (CAC), and CVEs were assessed, respectively.

Results During a median follow-up of 7 years, 435 CVEs were recorded. Both NAFLD-FS and FIB-4 were predictors for the presence of CAC. The degree of coronary stenosis was significantly higher in high NAFLD-FS categories while FIB-4 was only positively associated with the number of diseased vessels and Gensini score. In Kaplan–Meier analysis, the patients with intermediate and high NAFLD-FS and FIB-4 had higher risk of CVEs and cardiovascular mortality. In multivariate Cox regression analysis, NAFLD-FS and FIB-4 were independently associated with CVEs [hazard ratio (95% confidence interval): 1.150 (1.063–1.244), $p < 0.001$ and 1.128 (1.026–1.240), $p = 0.012$].

Conclusion The current data first indicated that both NAFLD-FS and FIB-4 scores were not only significantly related to coronary severity but also associated with CAC and CVEs.

Clinical trials registration None.

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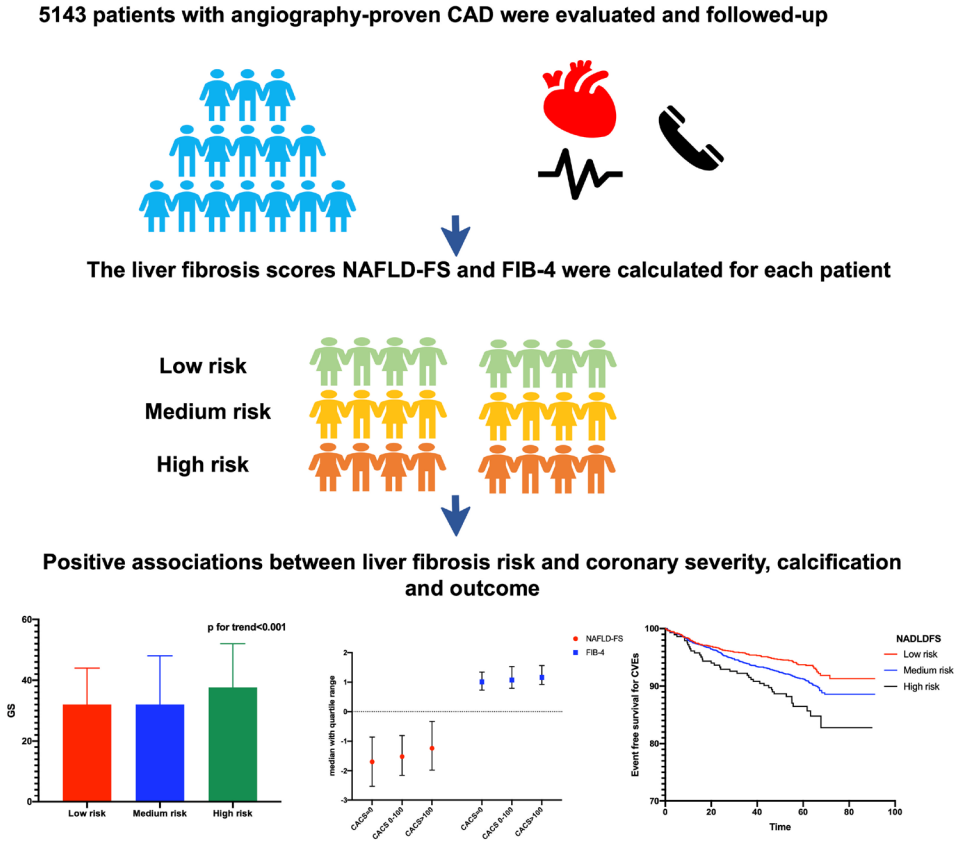
Graphic abstract



Keywords Liver fibrosis score · Stable coronary artery disease · Stenosis · Calcification · Outcome · Non-invasive · Cardiovascular event · Risk factor · Prognosis · Clinical study

Introduction

Coronary artery disease (CAD) is a major cause of human mortality throughout the world. Despite the updated strategies for the prevention and treatment of CAD, the current status remains unsatisfactory, which may indicate that the presence and progression of CAD are associated with multiple unknown reasons. In fact, patients with established CAD have been categorized as very high-risk population and often demonstrate a list of metabolic comorbidities including diabetes mellitus (DM), hypertension, and dyslipidemia. Clinically, the patients with these metabolic disorders had more cardiovascular events (CVEs) compared with those without [1, 2]. In addition, among patients with CAD who received optimal treatment and had well-managed traditional cardiometabolic risk factors, the CVEs rate remained high [3]. In our previous study, data showed that liver enzymes were independent predictors of cardiovascular outcome in patients with CAD and non-alcoholic fatty liver disease (NAFLD), indicating that the predictive value of liver-related metabolic dysfunction may be promising [4].

There is accumulating evidence showing the close relation between liver-related metabolic disorders and cardiovascular disease. In the current guidelines, using non-invasive markers and scoring systems in identifying risk of worse liver-related prognosis is highly recommended [5]. Among all the validated scoring systems, non-alcoholic fatty liver disease fibrosis scores (NAFLD-FS) and fibrosis-4 (FIB-4) are the two most efficient ones to identify those with high probability for having worse liver-related outcomes [6], both of which include liver enzymes and traditional cardiometabolic risk factors. Furthermore, previous studies had indicated that FIB-4 and NAFLD-FS could predict all-cause mortality and were related to subclinical coronary atherosclerosis in patients with and without NAFLD [2, 7]. Compared with other means of examinations, FIB-4 and NAFLD-FS scores were with advantages of cheap, non-invasive, and repeatable in diverse populations. Hence, we hypothesized that FIB-4 and NAFLD-FS might also

be useful for predicting not only disease severity but also adverse outcomes. To test this issue, we comprehensively investigated whether FIB-4 and NAFLD-FS were associated with coronary calcification (CAC), disease severity and CVEs using a large, prospective cohort with stable CAD.

Materials and methods

Study design and populations

Our study complied with the Declaration of Helsinki and was approved by the local ethical review board. Informed written consents were obtained from all patients enrolled in this study.

As described in the flowchart (Supplemental Figure S1), from March 2011 to February 2015, 6811 patients were recruited from 3 medical centers and scheduled for coronary angiography because of angina-like chest pain and/or positive treadmill exercise test or clinically suspected CAD. The patients received blood tests before admission and those with viral hepatitis were excluded at the beginning. Among these patients, 569 were excluded because they were not angiography-proven CAD (coronary stenosis ≥ 50% of at least one coronary artery). Other patients were excluded for reasons as the flowchart indicated. Most importantly, prior or current excessive alcohol consumption was one of the exclusion criteria. Excessive alcohol consumption was defined as > 21 drinks/week in male and > 14 drinks/week in women. One drink contains 12 g of alcohol. Current smoking was defined as having at least one piece of cigarette per day for 1 year or more.

DM was diagnosed by fasting plasma glucose (FPG) ≥ 7.0 mmol/L or the 2-h plasma glucose of the oral glucose tolerance test ≥ 11.1 mmol/L, hemoglobin A1c (HbA1c) level ≥ 6.5% or currently using anti-diabetic drugs or insulin. Hypertension was diagnosed as medical history of hypertension, currently receiving antihypertensive drugs or hospital-recorded systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg for three or more consecutive times. The body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Baseline medications (medications before admission) and other baseline parameters were collected by interviewing or from hospital-recorded medical history.

Laboratory analysis

Fasting blood samples were obtained from each patient after 12-h fasting once upon admission. Plasma concentrations of aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were measured by automatic biochemistry analyzer (Hitachi 7150, Tokyo, Japan) in an enzymatic assay. HbA1c was measured using Tosoh Automated Glycohemoglobin Analyser (HLC-723G8, Tokyo, Japan).

Liver fibrosis score

The FIB-4 score was calculated with following equation, with the cut-offs of 1.30 and 2.67 as for low, intermediate and high-risk categories: FIB-4 = age[years] × AST [IU/L]/(platelet [$\times 10^9$/L] × ALT[IU/L]$^{1/2}$). The NAFLD-FS was calculated by the following formula: NFS = − 1.675 + 0.037 × age [years] + 0.094 × BMI [kg/m^2] + 1.13 × hyperglycemia/diabetes [yes = 1, no = 0] + 0.99 × (AST [IU/L]/ALT [IU/L]) − 0.013 × platelet count [× 109/L] − 0.66 × ALB [g/dL], with two cut-offs at − 1.455 and 0.676 for low, intermediate and high-risk categories. The BARD score: BMI ≥ 28 = 1 point, AST to ALT ratio ≥ 0.8 = 2 points; DM = 1 point, ranged from 0 to 4. AST to platelet ratio index (APRI) was calculated as: APRI = AST (IU/L)/AST (the upper limit of normal, ULN) × 100/platelet count (109/L), with cut-offs at 0.5 and 1.5. Forns score was calculated as: 7.811–3.131 log (platelet count [109/L]) + 0.781 log(GGT [IU/L]) + 3.467 log(age [year]) – 0.014 total cholesterol (mg/dl), with cut-offs being set at 4.2 and 6.9.

Evaluation of CAD severity

Angiographic data were collected from catheter laboratory records. The severity of CAD was assessed according to the SYNTAX, Gensini, and Jeopardy scoring systems. The procedure was performed by three experienced interventional physicians as previously reported. The syntax score was calculated using an online calculator (http://www.syntaxscore.com). Gensini score was calculated. The precise method of calculating GS was introduced by Gensini GG in 1983[8]. We also evaluated the patients with the Jeopardy scoring system [9].

Evaluation of coronary calcification

Among individuals studied, 1262 of them received computed tomography and were also evaluated for degree of CAC. A 64-slice scanner (Light Speed VCT, GE Healthcare, Milwaukee, Wisconsin) with a rotation time of 0.35 s and a pitch of 0.16–0.22 was used to obtain coronary calcium score (CACS). At least three contiguous pixels present, and a CT threshold of 130 HU was defined as calcium. The CACS of each lesion was calculated by multiplying lesion area by a density factor as developed by Agatston et al. Furthermore,

CAC severity was categorized into three groups according to scores of 0, 0–100 and > 100.

Follow-up

Patients were followed up at 6 months' intervals by means of interviewing directly or using telephone. Trained nurses or physicians who were blinded to the clinical data fulfilled the interview. CVEs were defined as cardiovascular mortality, non-fatal myocardial infarction (MI) and stroke. Non-fatal myocardial infarction was diagnosed as positive cardiac troponins along with typical chest pain or typical electrocardiogram serial changes. Stroke was diagnosed by the presence of typical symptoms and imaging.

Statistical analysis

The values for the continuous variables and the categorical variables were presented as the mean ± SD, median (Q1–Q3 quartiles) or number (percentage). The Kolmogorov–Smirnov test was used to test the distribution pattern. The differences of variables among groups were analyzed using Student's t test, analysis of variance, or nonparametric test where appropriate. The Kaplan–Meier method was used to estimate the event-free survival rates among groups. The log-rank test was used to test the statistical significance. The hazard ratios (HRs) and 95% confidence intervals (CI) were calculated by univariate and multivariate Cox regression analyses. In multivariate Cox regression models, traditional risk factors including sex, body mass index, current smoking, diabetes, hypertension, family history of CAD, left ventricular ejection fraction, creatinine, TG, LDL-C, HDL-C, and baseline statin use were used as adjustments. The variables in the score formula were not enrolled in the model. In addition, sensitivity and subgroup analyses were performed to better clarify the association of LFSs with cardiovascular risk, which were mentioned in the online supplemental material. Univariate and Multivariate Cox regression analysis was also performed for patients ≥ 65 years using new cut-off previously reported by McPherson et al. [10]. A p value < 0.05 was considered statistically significant. The statistical analyses were performed with SPSS version 21.0 software (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

As was presented in Table 1, higher proportions of patients were categorized as high risk by both NAFLD-FS and FIB-4 in CVEs group than control group (all $p < 0.001$). Patients with CVEs also showed higher FPG, HbA1c, AST/ALT ratio, creatinine, Gensini score, Syntax score and Jeopardy score, higher percentages of hypertension and DM and lower left ventricle ejection fraction (all $p < 0.05$). There were no significant differences in TC, HDL-C, LDL-C, the percentages of patients who smoked cigarettes, who drank or who had family history of CAD (all $p > 0.05$). Lower proportions of patients received statins at baseline in CVEs group, but no difference was found regarding other medications and statins at discharge.

NAFLD-FS and FIB-4 categories and coronary severity

As shown in Fig. 1a and b, significantly higher proportions of patients were with multivessel disease in high NAFLD-FS and FIB-4 subgroups than low NAFLD-FS and FIB-4 subgroups. The associations of NAFLD-FS and FIB-4 categories with Gensini, Syntax, and Jeopardy scores were depicted in Fig. 1c–h. Gensini, Syntax, and Jeopardy scores were significantly higher in intermediate and high NAFLD-FS categories (p for trend all < 0.001). Gensini score but not Syntax or Jeopardy scores was positively associated with FIB-4. As shown in supplemental Figure S2, APRI was positively associated with Gensini score but not Syntax, or Jeopardy scores. Both BARD and Forns risk scores were not associated with coronary severity.

Relationship between NAFLD-FS and FIB-4 with coronary calcification

Among 1262 patients who received computed tomography 853 patients (67.6%) had CAC scores of 0, whereas 209 (16.6%) had CAC scores of 1–100 and 200 (15.8%) had CAC scores > 100. Highest NAFLD-FS and FIB-4 were observed in those with CAC scores > 100 ($p < 0.001$, Fig. 2). Furthermore, univariate and multivariate logistic regression analysis showed that both NAFLD-FS and FIB-4 were independently associated with presence of CAC [NAFLD-FS: intermediate risk: odds ratio(OR) 1.911, 95% CI 1.502–2.602, $p < 0.001$, high risk: OR 3.069, 95% CI 1.169–5.569, $p = 0.001$; FIB-4: intermediate risk: OR 1.536, 95% CI 1.186–1.989, $p < 0.001$, high risk: OR 2.420, 95% CI 1.323–4.428, $p = 0.004$, Supplemental Table S1].

NAFLD-FS, FIB-4 and cardiovascular outcomes

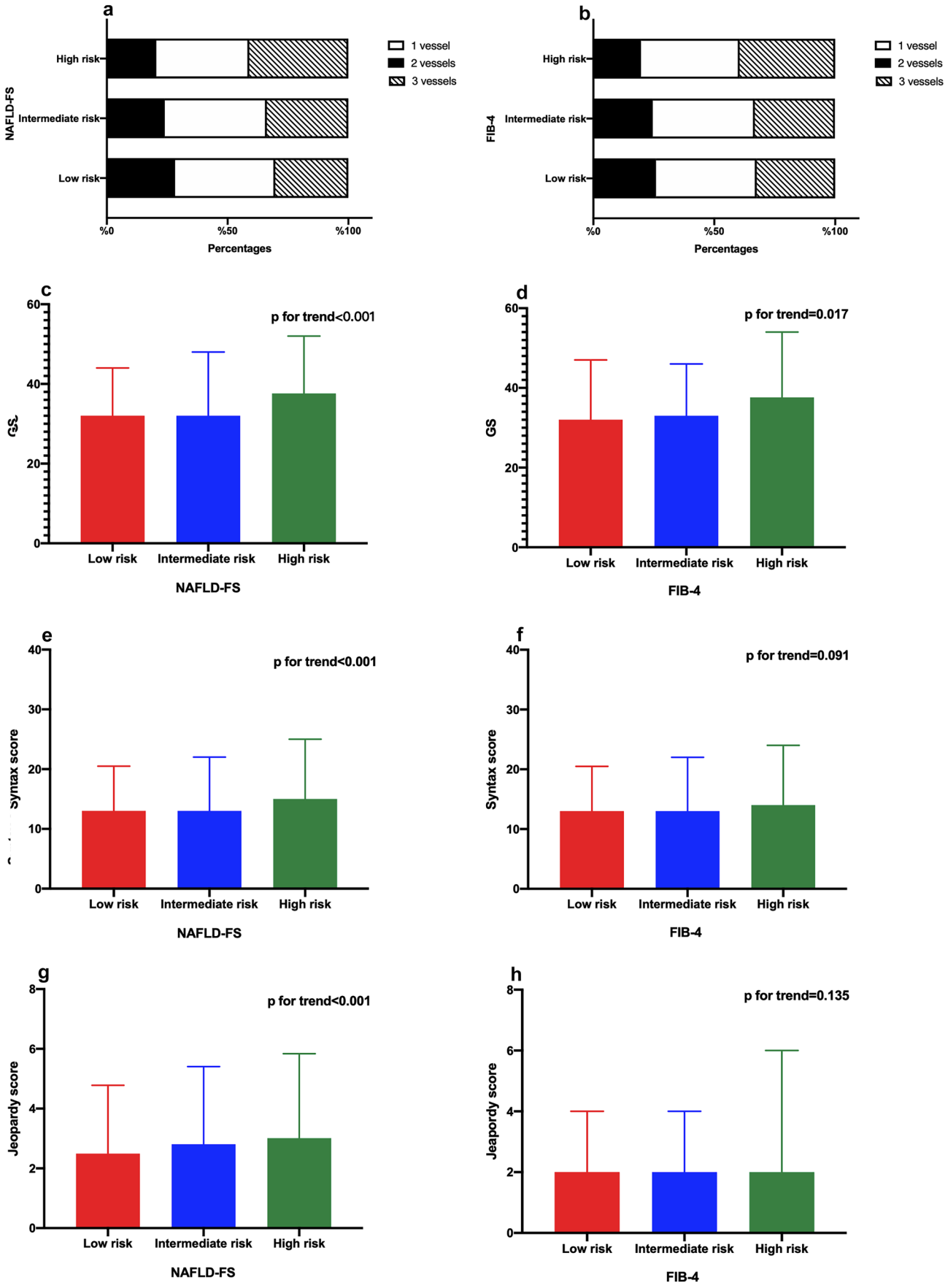
In Kaplan–Meier analysis (Fig. 3a, b), patients in intermediate and high NAFLD-FS and FIB-4 subgroups had lower event-free survival rate for CVEs than those in the low NAFLD-FS and FIB-4 subgroups (log rank $p < 0.05$). We further compared the event-free survival rate among NAFLD-FS and FIB-4 low to high categories for cardiovascular mortality (Fig. 3c, d). Similarly, intermediate and

Table 1 Baseline characteristics

Variables	Events $n=435$	Non-events $n=4708$	p
Clinical characteristics			
Age, years	61.9 ± 10.5	57.7 ± 10.3	< 0.001
Male, *n* (%)	304(69.9)	3420(72.6)	0.218
BMI (kg/m^2)	25.4 ± 3.2	25.8 ± 3.1	0.026
Hypertension, *n* (%)	294(67.6)	2954(62.7)	0.045
DM, *n* (%)	240(55.2)	1965(41.7)	0.001
Family history of CAD, *n* (%)	59(13.6)	684(14.5)	0.584
Prior stroke, *n* (%)	36(8.3)	323(6.9)	0.268
Atrial fibrillation, *n* (%)	26(6.0)	214(4.5)	0.176
Current smoker, *n* (%)	228(52.4)	2582(54.8)	0.330
Drinking, *n* (%)	106(33.2)	1337(34.1)	0.073
Laboratory findings			
FPG (mmol/L)	5.9 ± 2.0	5.7 ± 1.7	0.010
HbA1c (%)	6.6 ± 1.3	6.4 ± 1.1	< 0.001
Creatinine (μmol)	80.9 ± 20.0	75.6 ± 16.4	< 0.001
AST (U/L)	19(15–24)	18(15–22)	0.412
ALT (U/L)	22(16–34)	23(17–34)	0.117
AST/ALT	0.84(0.59–1.07)	0.76(0.58–1.00)	0.006
NAFLD-FS risk category			< 0.001
Low	116(26.7)	1683(35.7)	
Intermediate	280(64.4)	2781(59.1)	
High	39(9.0)	244(5.2)	
FIB-4 risk category			< 0.001
Low	227(52.2)	3120(66.3)	
Intermediate	187(43.0)	1452(30.8)	
High	21(4.8)	136(2.9)	
GGT (U/L)	27(19–42)	38(20–43)	0.810
TC (mmol/L)	4.20 ± 1.26	4.13 ± 1.12	0.197
HDL-C (mmol/L)	1.06 ± 0.30	1.05 ± 0.28	0.284
LDL-C (mmol/L)	2.53 ± 1.10	2.52 ± 1.01	0.941
TG (mmol/L)	1.48(1.05–2.07)	1.52(1.13–2.10)	< 0.001
LVEF (%)	60.0 ± 10.6	63.5 ± 8.1	< 0.001
Gensini score	37(18–76)	27(12–50)	0.047
Syntax score	20(10–30)	15(8–23)	< 0.001
Jeopardy score	4(2–6)	2(2–4)	0.001
Medications			
Statins at baseline, *n* (%)	294(67.6)	3504(74.4)	0.002
Statins at discharge, *n* (%)	425(98.2)	4637(98.5)	0.583
Aspirin at baseline, *n* (%)	263(60.4)	2806(59.6)	0.727
Aspirin at discharge, *n* (%)	415(95.4)	4435(94.2)	0.301
ACEIs/ARBs at baseline, *n* (%)	120(27.6)	1328(28.2)	0.783
ACEIs/ARBs at discharge, *n* (%)	(84.2)	4007(85.1)	0.586
β-blockers at baseline, *n* (%)	235(54.1)	2458(52.2)	0.469
β-blockers at discharge, *n* (%)	54(87.5)	4058(86.2)	0.419

Data were expressed as mean ± SD, median with 25th and 75th percentile or *n* (%)

BMI body mass index, *DM* diabete mellitus, *HbA1c* haemoglobin A1c, *TC* total cholesterol, *TG* triglyceride, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *LVEF* left ventricular ejection fraction, *GS* gensini score, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *GGT* γ-glutamyl transpeptidase, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker


a
High risk
Intermediate risk
Low risk
NAFLD-FS
1 vessel
2 vessels
3 vessels
%0
%50
%100
Percentages
b
High risk
Intermediate risk
Low risk
FIB-4
1 vessel
2 vessels
3 vessels
%0
%50
%100
Percentages
c
p for trend<0.001
GS
Low risk
Intermediate risk
High risk
NAFLD-FS
d
p for trend=0.017
GS
Low risk
Intermediate risk
High risk
FIB-4
e
p for trend<0.001
Syntax score
Low risk
Intermediate risk
High risk
NAFLD-FS
f
p for trend=0.091
Syntax score
Low risk
Intermediate risk
High risk
FIB-4
g
p for trend<0.001
Jeopardy score
Low risk
Intermediate risk
High risk
NAFLD-FS
h
p for trend=0.135
Jeapordy score
Low risk
Intermediate risk
High risk
FIB-4

◂**Fig. 1 a–h** Coronary severity score Gensini score, Syntax score, Jeopardy score and diseased vessels) according to different risk categories of NAFLD-FS and FIB-4

high NAFLD-FS and FIB-4 categories had higher CVEs and mortality rates than the reference group (low NAFLD-FS and FIB-4 subgroups, log rank $p < 0.001$).

As presented in Table 2 and Supplemental Table S2, univariate Cox regression analyses showed that continuous NAFLD-FS and FIB-4 were positively associated with CVEs and cardiovascular mortality [hazard ratio (HR) for CVEs: NAFLD-FS 1.210, 95% CI 1.102–1.308, $p < 0.001$, FiB-4: HR 1.201, 95% CI 1.102–1.308, $p = 0.002$; HR for cardiovascular mortality: NAFLD-FS: 1.520, 95% CI 1.344–1.718, $p < 0.001$, FiB-4: HR 1.322, 95% CI 1.187–1.473, $p < 0.001$]. Such associations did not change after adjustment of confounders (adjusted HR for CVEs: NAFLD-FS: 1.150, 95% CI 1.063–1.244, $p < 0.001$; FiB-4: HR 1.128, 95% CI 1.026–1.240, $p = 0.012$, adjusted HR for cardiovascular mortality: NAFLD-FS: 1.433, 95% CI 1.256–1.634, $p < 0.001$, FiB-4: HR 1.217, 95% CI 1.072–1.382, $p = 0.002$). The significant associations remained unchanged in sensitivity analyses including patients with the highest probability of having liver steatosis (Supplemental Table S3). However, no such association was observed for APRI and Forns risk scores with cardiovascular risk. Only BARD risk score was associated with cardiovascular mortality (HR 1.272, 95% CI 1.084–1.494, $p = 0.003$, Supplemental Table S4).

The adjusted HRs and 95% CIs of CVEs and mortality according to categories of NAFLD-FS and FIB-4 in patients in different age groups are shown in Supplemental Table S5. In the univariate Cox analysis, among patients < 65 years, the risks of CVEs and mortality were significantly increased for intermediate and high score groups of NAFLD-FS and FIB-4 compared with those in the low score group (NAFLD-FS:CVEs: intermediate: HR 1.295; 95% CI 1.006–1.668, high: HR 2.646; 95% CI 1.445–4.843; mortality: intermediate: HR 1.841; 95% CI 1.081–3.137, high: HR 3.424; 95% CI 1.013–11.570; FIB-4: CVEs: intermediate: HR 2.051; 95% CI 1.609–2.614, high: HR 3.228; 95% CI 1.755–5.939; mortality: intermediate: HR 1.884; 95% CI 1.143–3.104, high: HR 3.452; 95% CI 1.071–11.126). Additional adjustment for other potential covariates did not change this association. For patients ≥ 65 years, using new cut-off previously reported by McPherson et al. [10], the predictive value of each FIB-4 risk category stayed the same while high but not intermediate NAFLD-FS could predict cardiovascular mortality (intermediate: HR 1.291; 95% CI 0.660–2.254, $p > 0.05$ and high: HR 2.083; 95% CI 1.057–4.102, $p < 0.05$, Supplemental Table S5).

Discussion

In this prospective study on angiography-proven stable CAD patients, we tried to fully investigate the association of two guidelines recommended liver fibrosis scoring systems (NAFLD-FS and FIB-4) with the disease severity, coronary calcification and clinical outcomes in a large Chinese Han cohort with long-term follow-up. One of the main novel findings was that the patients with high-risk categories of NAFLD-FS and FIB-4 had more severe stenosis assessed by the number of diseased vessels, Gensini, Syntax, and Jeopardy scores. Interestingly, data first showed that NAFLD-FS and FIB-4 were independently associated with the presence of CAC in a large cohort with stable CAD. More importantly, consistent with previous studies, NAFLD-FS and FIB-4 were associated with risk of incident CVEs and cardiovascular mortality even after adjustment for other cardiovascular risk factors in stable CAD patients with long-term follow-up. Clinically, the present study provided the novel insights and supported the notion that liver fibrosis screening by NAFLD-FS and FIB-4 score were useful predictive tools for the disease severity, coronary calcification and worse outcomes in CAD patients whose status is stable.

Recent studies have focused on the relation of liver disease to CVD. Approximately 60% of CAD patients were combined with NAFLD [11]. In fact, NAFLD share some similar pathogenic pathways as CAD, including insulin resistance, lipid disorder, and inflammation [12]. In previous studies, NAFLD was independently predictive of long-term risk for cardiovascular disease [13, 14]. However, whether there is a sensitive and efficient screening tool for identifying NAFLD-associated cardiovascular risk in CAD patients remains an unsolved question. According to previous studies, the performance of ultrasound for evaluating the degree of steatosis of NAFLD is a strategy with poor sensitivity [15, 16]. Liver biopsy is invasive and not suitable in primary detection for CAD. Besides, identifying the CVEs risk for those with high risk for NAFLD but not diagnosed NAFLD is also crucial. For these reasons, non-invasive scoring systems have been proposed for detecting the advanced fibrosis and predicting liver-related complications. For example, the 2012 practice guideline of the American Gastroenterological Association recommended the usefulness of NAFLD-FS for identifying NAFLD patients with higher likelihood of having bridging fibrosis and/or cirrhosis [5]. In the past few years, several studies have demonstrated that liver fibrosis scores (LFSs) have significant prognostic value on liver-related outcomes, cardiovascular mortality and all-cause mortality in both NAFLD population and general population [2, 7, 17]. Although the association between LFSs and cardiovascular

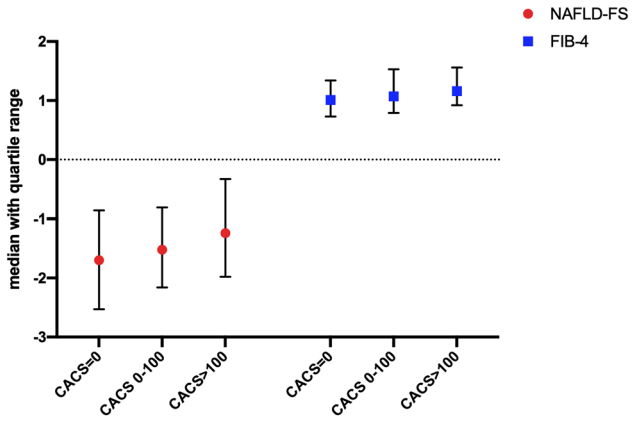


Fig. 2 Relationship between liver fibrosis score and coronary calcification

outcome has been validated by many prospective studies in diverse populations, no systematic study regarding the relationship of LFSs to coronary severity, CAC and CVEs has yet been found.

Previous studies have shown that the degree of liver fibrosis is related to the development of atherosclerosis [18–21]. In the study by Chen, et al. enrolling 2550 participants with ultrasound confirmed NAFLD, they found that those with NAFLD-FS > 0.676 presented 1.98-folds increased risk for elevated carotid intima-media thickness (CIMT), 2.28-folds increased risk for present carotid plaque and 2.68-folds increased risk for arterial stiffness [18]. Another study by Xin, et al. showed that LFSs including NAFLD-FS, fibrosis-4 score (FIB-4) and aspartate aminotransferase to platelet ratio index (APRI) were associated with arterial stiffness but was not related to CIMT [19]. However, all these studies had focused on the atherosclerosis of peripheral vessels. Very limited number of studies is currently available about the relationship between LFSs and atherosclerosis of coronary arteries. In a small-sample study on 109 CAD patients, the complexity of CAD evaluated by the SYNTAX score was independently associated with NAFLD-FS [20]. Additionally, Lee and his colleague reported that there was a significant association between NAFLD-FS and non-calcified plaque but not significant stenosis in 5121 consecutive asymptomatic individuals with no prior history of CAD [21]. In their study, less than 10% of study population was with significant stenosis and the coronary severity was assessed by CT. In our present study, we enrolled 5143 patients with

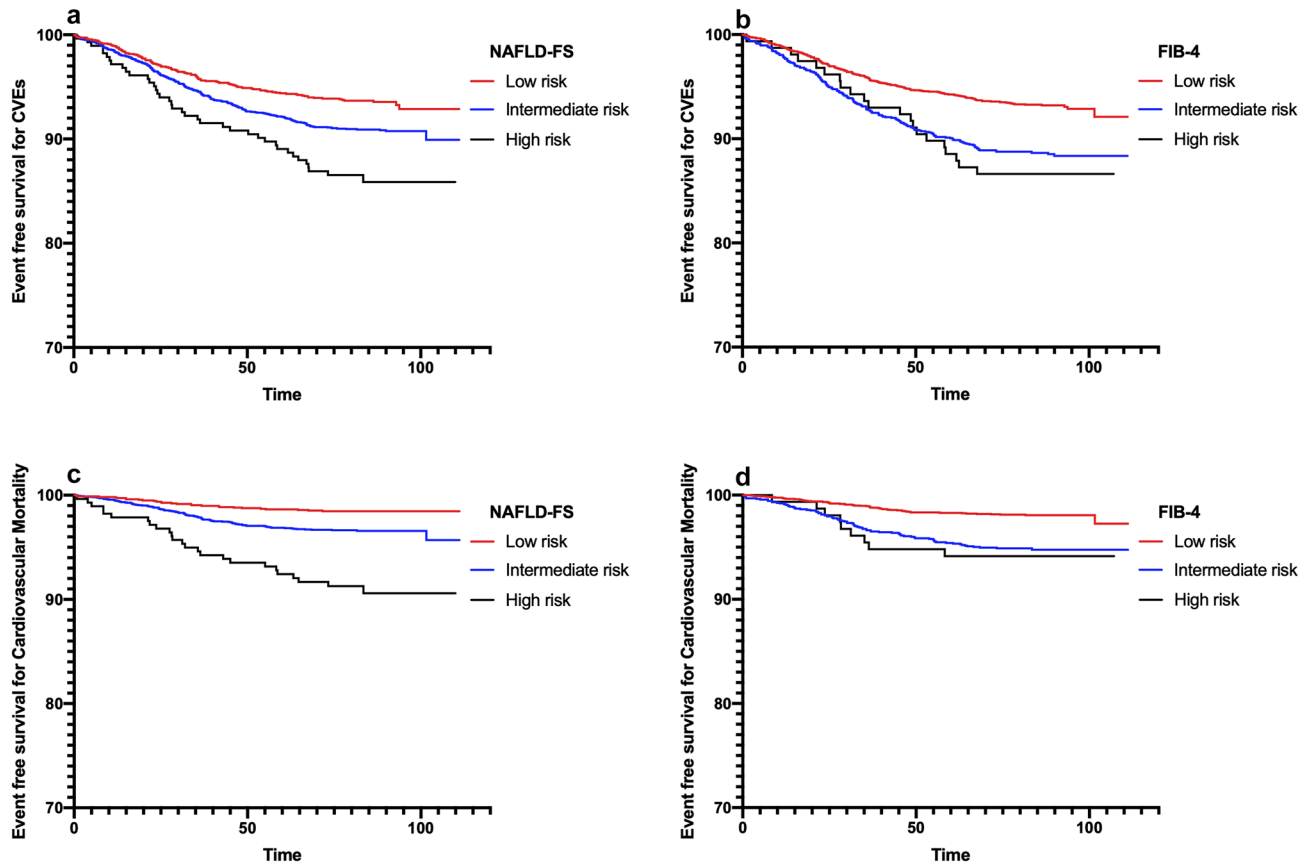


Fig. 3 Kaplan–Meier analysis of different risk categories of NAFLD-FS and FIB-4 and cardiovascular events (**a**, **b**) or cardiovascular mortality (**c**, **d**)

Table 2 Cox regression analysis of liver fibrosis score and CVEs

Variables	Univariate Cox regression		Multivariate Cox regression	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age	1.039(1.029–1.049)	< 0.001	–	–
Female sex	1.143(0.579–1.214)	0.351	–	–
BMI	0.966(0.937–0.996)	0.027	–	–
LVEF	0.966(0.958–0.975)	< 0.001	–	–
Hypertension	1.231(1.007–1.504)	0.043	–	–
DM	1.361(1.126–1.644)	0.001	–	–
Smoking	0.909(0.753–1.098)	0.322	–	–
FH	1.084(0.824–1.426)	0.566	–	–
Creatinine	1.014(1.010–1.018)	< 0.001	–	–
TG	0.986(0.908–1.071)	0.743	–	–
HDL-C	1.190(0.850–1.666)	0.312	–	–
LDL-C	1.006(0.916–1.104)	0.906	–	–
GS	1.009(1.007–1.012)	< 0.001	–	–
Baseline statin use	0.737(0.603–0.901)	0.003	–	–
NAFLD-FS	1.210(1.121–1.307)	< 0.001	1.150(1.063–1.244)	< 0.001
Low	Ref		Ref	
Intermediate	1.434(1.155–1.781)	0.001	1.422(1.141–1.774)	0.002
High	2.207(1.536–3.173)	< 0.001	2.191(1.516–3.167)	< 0.001
FIB-4	1.201(1.102–1.308)	< 0.001	1.128(1.026–1.240)	0.012
Low	Ref		Ref	
Intermediate	1.726(1.422–2.094)	< 0.001	1.710(1.402–2.085)	< 0.001
High	2.020(1.292–3.159)	0.002	2.007(1.323–3.259)	0.001

Adjusted for sex, body mass index, current smoking, diabetes, hypertension, family history of CAD, left ventricular ejection fraction, creatinine, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and baseline statin use, other than the variables included in the score formula and variables for stratification

stable CAD who was diagnosed by coronary angiography, the golden choice for the CAD evaluation and the most reliable tool in the assessment of lesion severity. The results indicated that both NAFLD-FS and FIB-4 were associated with coronary severity assessed by different means (numbers of diseased vessels, Gensini, Syntax, and Jeopardy scores) and provided solid evidence for the relationship between LFSs and the severity of coronary atherosclerosis.

CAC is a marker of coronary atherosclerosis with high specificity [22]. In patients with stable CAD, those with higher CAC were identified as having significantly increased risk for subsequent severe cardiac events [23]. Hence, in patients with stable CAD, identifying markers in relation with CAC may be clinically important. It was previously indicated that NAFLD was significantly associated with the development of CAC independent of other cardiometabolic risk factors [14, 24]. As for the relationship between LFSs and CAC, inconsistent results were reported in several studies. In general population without known history of CAD, NAFLD-FS was not related to calcified plaque [21]. In two studies about Korean ($n = 665$) and Japanese patients ($n = 94$) with NAFLD, FIB-4 was a useful marker of CAC [25]. It was obvious that previous studies mostly concentrated on non-CAD and NAFLD patients and some of them were with small sample size. Therefore, we analyzed the relationship of CAC and two LFSs (NAFLD-FS and FIB-4) in a subgroup of 1662 patients who received CT scan to evaluate CACS. Our study validated the association of LFSs and CAC in a relatively large cohort of Chinese patients with angiography-proven CAD. This finding further stressed the importance of regarding LFSs as important risk markers.

Recently, a great deal of evidence suggested that the prognostic utility of LFSs on worse outcome was not limited in NAFLD population and high LFSs were not only predictive of liver-relative complications but also associated with CVEs and cardiovascular mortality. Findings from a Japanese Multicenter Registry indicated that FIB-4 was independently associated with risks of cardiovascular events and all-cause mortality in patients with atrial fibrillation [26]. In the study by De Vincentis et al. NAFLD-FS and FIB-4 could predict cardiovascular and all-cause mortality in older people while other LFSs could only predict overall mortality [27]. More importantly, a recent study by Chen et al. indicated that the higher LFS scores including NAFLD-FS,

FIB-4, APRI, gamma-glutamyl transferase to platelet ratio (GPR), and Forns score were associated with all-cause and cardiovascular mortality among 3263 patients with either ACS or Stable CAD who were followed up for 7.56 years [2]. Our study enrolled a larger sample size of 5143 patients with stable CAD and reported that NAFLD-FS and FIB-4 were more significantly associated with cardiovascular risk than APRI, Forns and BARD scores. Compared with previous studies, this is a systematic study regarding the relationship of LFSs to coronary severity, CAC and CVEs, which makes our results more reliable.

NAFLD-FS and FIB-4 are two LFSs with diagnostic accuracy of both sensitivity and specificity to discriminate patients with advanced fibrosis recommended by guidelines [6]. In a prospective study of patients over 65 years, NAFLD-FS and FIB-4 trumped other LFSs in predicting cardiovascular mortality [27]. Although previous studies might show positive results of multiple LFSs, the original importance of using LFSs in accurately identifying the risk of liver complications should not be neglected. As was shown in the previous study by Chen et al., increment in five LF scores was associated with increment in risk of all-cause and CVD mortality after adjusting for conventional risk factors [2]. Our study verified part of their findings and extended the study by indicating that NAFLD-FS and FIB-4 score were significantly related to CAC and coronary severity. As was shown in the univariate model, the well-known factors including DM, Age, GS, and LVEF were predictive of CVEs. Using LFSs, the composite risk scores including both traditional risk factors and liver-related parameters, had better performance in predicting outcome. It is reasonable to use these two recommended LFSs to accurately reflect the risk of NASH and worse cardiovascular outcome in CAD patients. Hence, in this large Chinese cohort of stable CAD patients with long-term follow-up, we mostly concentrated on the association of NAFLD-FS and FIB-4 to CAC, coronary severity and CVEs. LFSs were composed of liver-related parameters and traditional risk factors. As previously indicated, non-invasive LFSs can effectively detect advanced fibrosis with the C-statistic approximately 0.80 [28]. Besides, many liver-related factors may interact with traditional cardiovascular risk factors promoting a vicious circle leading to bad prognosis. Hence, we aimed at taking liver-related risk into consideration in prognosis of CAD patients.

In fact, the exact mechanisms underlying the connection between LFSs and CAD are currently unclear. One possible pathway is that increased hepatic production of multiple prothrombogenic factors like fetuin-A, which promotes atherosclerotic plaque formation and accelerates vascular calcium deposition in patients with liver fibrosis [29, 30]. Of note, patients who have high tendency to develop NAFLD were often combined with increased inflammatory state, endothelial dysfunction, insulin resistance and lipid metabolism, which may also promote vascular atherosclerosis [12]. Further studies are necessary to elucidate the exact mechanisms, which may also provide useful information for developing new LFSs for more accurately predicting both liver-related and cardiovascular outcome.

Some potential limitations existed in our present study. First, although we have excluded patients with alcoholic liver disease, excessive alcohol consumption or other known severe liver diseases, the confounding effect of undiagnosed liver diseases was inevitable. Second, we only calculated the baseline NAFLD-FS and FIB-4, the change of these scores during follow-up may change the risk categories of patients. Third, not all patients received standard abdominal ultrasound due to the baseline feature of the study population. Identifying those with NAFLD may help make further risk assessment.

In conclusion, the present study, for the first time, demonstrated that NAFLD-FS and FIB-4 scores were significantly related to CAC and coronary severity by different scoring systems and independently predictive of CVEs and cardiovascular mortality in patients with stable CAD. These findings may support the notion that LFSs are useful tools for predicting cardiovascular outcomes and further studies are clinically warranted.

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Data availability The datasets used and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (FuWai Hospital and National Center for Cardiovascular Diseases, Beijing, China) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent to participate was obtained from all individual participants included in the study. Informed consent to publish was obtained from all individual participants included in the study.

References

1. Olesen KKW, Madsen M, Gyldenkerne C, Thrane PG, Würtz M, Thim T, et al. Diabetes mellitus is associated with increased risk of ischemic stroke in patients with and without coronary artery disease. Stroke 2019;50(12):3347–3354
2. Chen Q, Li Q, Li D, Chen X, Liu Z, Hu G, et al. Association between liver fibrosis scores and the risk of mortality among patients with coronary artery disease. Atherosclerosis 2020;299:45–52
3. Presta V, Figliuzzi I, Miceli F, Coluccia R, Fogacci F, Cicero AFG, et al. Achievement of low density lipoprotein (LDL) cholesterol targets in primary and secondary prevention: analysis of a large real practice database in Italy. Atherosclerosis 2019;285:40–48
4. Liu HH, Cao YX, Sun D, Jin JL, Guo YL, Wu NQ, et al. Impact of non-alcoholic fatty liver disease on cardiovascular outcomes in patients with stable coronary artery disease: a matched case-control study. Clin Transl Gastroenterol 2019;10(2):e00011
5. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. Gastroenterology 2012;142(7):1592–1609
6. Vilar-Gomez E, Chalasani N. Non-invasive assessment of non-alcoholic fatty liver disease: clinical prediction rules and blood-based biomarkers. J Hepatol 2018;68(2):305–315
7. Kim D, Kim WR, Kim HJ, Therneau TM. Association between noninvasive fibrosis markers and mortality among adults with nonalcoholic fatty liver disease in the United States. Hepatology 2013;57(4):1357–1365
8. Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. Am J Cardiol 1983;51(3):606
9. Califf RM, Phillips HR 3rd, Hindman MC, Mark DB, Lee KL, Behar VS, et al. Prognostic value of a coronary artery jeopardy score. J Am Coll Cardiol 1985;5(5):1055–1063
10. McPherson S, Hardy T, Dufour JF, Petta S, Romero-Gomez M, Allison M, et al. Age as a confounding factor for the accurate non-invasive diagnosis of advanced NAFLD fibrosis. Am J Gastroenterol 2017;112(5):740–751
11. Wong VW, Wong GL, Yeung JC, Fung CY, Chan JK, Chang ZH, et al. Long-term clinical outcomes after fatty liver screening in patients undergoing coronary angiogram: a prospective cohort study. Hepatology 2016;63(3):754–763
12. Lonardo A, Nascimbeni F, Mantovani A, Targher G. Hypertension, diabetes, atherosclerosis and NASH: Cause or consequence? J Hepatol 2018;68(2):335–352
13. Wild SH, Walker JJ, Morling JR, McAllister DA, Colhoun HM, Farran B, et al. Cardiovascular disease, cancer, and mortality among people with type 2 diabetes and alcoholic or nonalcoholic fatty liver disease hospital admission. Diabetes Care 2018;41(2):341–347
14. Chang Y, Ryu S, Sung KC, Cho YK, Sung E, Kim HN, et al. Alcoholic and non-alcoholic fatty liver disease and associations with coronary artery calcification: evidence from the Kangbuk Samsung Health Study. Gut 2019;68(9):1667–1675
15. Garg H, Aggarwal S, Shalimar YR, Shalimar YR, Datta Gupta S, Agarwal L, et al. Utility of transient elastography (fibroscan) and impact of bariatric surgery on nonalcoholic fatty liver disease (NAFLD) in morbidly obese patients. Surg Obes Relat Dis 2018;14(1):81–91
16. Schwenzer NF, Springer F, Schraml C, Stefan N, Machann J, Schick F. Non-invasive assessment and quantification of liver steatosis by ultrasound, computed tomography and magnetic resonance. J Hepatol 2009;51(3):433–445
17. Angulo P, Bugianesi E, Bjornsson ES, Charatcharoenwitthaya P, Mills PR, Barrera F, et al. Simple noninvasive systems predict long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 2013;145(4):782–789 (**e4**)
18. Chen Y, Xu M, Wang T, Sun J, Sun W, Xu B, et al. Advanced fibrosis associates with atherosclerosis in subjects with nonalcoholic fatty liver disease. Atherosclerosis 2015;241(1):145–150
19. Xin Z, Zhu Y, Wang S, Liu S, Xu M, Wang T, et al. Associations of subclinical atherosclerosis with nonalcoholic fatty liver disease and fibrosis assessed by non-invasive score. Liver Int 2020;40(4):806–814
20. Turan Y. The nonalcoholic fatty liver disease fibrosis score is related to epicardial fat thickness and complexity of coronary artery disease. Angiology 2020;71(1):77–82
21. Lee SB, Park GM, Lee JY, Lee BU, Park JH, Kim BG, et al. Association between non-alcoholic fatty liver disease and subclinical coronary atherosclerosis: an observational cohort study. J Hepatol 2018;68(5):1018–1024
22. Rumberger JA, Simons DB, Fitzpatrick LA, Sheedy PF, Schwartz RS. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study. Circulation 1995;92(8):2157–2162
23. Uebleis C, Becker A, Griesshammer I, Cumming P, Becker C, Schmidt M, et al. Stable coronary artery disease: prognostic value of myocardial perfusion SPECT in relation to coronary calcium scoring–long-term follow-up. Radiology 2009;252(3):682–690
24. Sinn DH, Kang D, Chang Y, Ryu S, Gu S, Kim H, et al. Non-alcoholic fatty liver disease and progression of coronary artery calcium score: a retrospective cohort study. Gut 2017;66(2):323–329
25. Song DS, Chang UI, Kang SG, Song SW, Yang JM. Noninvasive serum fibrosis markers are associated with coronary artery calcification in patients with nonalcoholic fatty liver disease. Gut Liver 2019;13(6):658–668
26. Saito Y, Okumura Y, Nagashima K, Fukamachi D, Yokoyama K, Matsumoto N, et al. Impact of the Fibrosis-4 Index on Risk Stratification of Cardiovascular Events and Mortality in Patients with Atrial Fibrillation: Findings from a Japanese Multicenter Registry. J Clin Med 2020;9(2)
27. De Vincentis A, Costanzo L, Vespasiani-Gentilucci U, Picardi A, Bandinelli S, Ferrucci L, et al. Association between non-invasive liver fibrosis scores and occurrence of health adverse outcomes in older people. Dig Liver Dis 2019;51(9):1330–1336
28. Siddiqui MS, Yamada G, Vuppalanchi R, Van Natta M, Loomba R, Guy C, et al. Diagnostic accuracy of noninvasive fibrosis models to detect change in fibrosis stage. Clin Gastroenterol Hepatol 2019;17(9):1877–1885 (**e5**)
29. Sato M, Kamada Y, Takeda Y, Kida S, Ohara Y, Fujii H, et al. Fetuin-A negatively correlates with liver and vascular fibrosis in nonalcoholic fatty liver disease subjects. Liver Int 2015;35(3):925–935
30. Eleftheriadou I, Grigoropoulou P, Kokkinos A, Mourouzis I, Perrea D, Katsilambros N, et al. Association of plasma fetuin-a levels with peripheral arterial disease and lower extremity arterial calcification in subjects with type 2 diabetes mellitus. J Diabetes Complic 2017;31(3):599–604