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Liver fibrosis scores and coronary artery ectasia

Background	Although scoring systems showing liver fibrosis using non-invasive methods have been accepted as effective tools for predicting cardiovascular risk, their role in predicting coronary ectasia (CAE) has not been evaluated. This study investigated whether aprison (APRI) and fibrosis-4 indices (FIB-4), which are indicators of fibrosis in nonalcoholic fatty liver disease (NAFLD), are associated with CAE.
Material and methods	A retrospective, cross-sectional study consisted of 215 patients, 108 with CAE and 107 without CAE, as diagnosed by angiography. The mean age of all patients was 61.8±9.9 yrs, and 171 (78.8%) were males. The relationships between APRI, FIB-4, NAFLD, and Bard scores and CAE were evaluated.
Results	APRI, FIB-4, NAFLD, and Bard scores were independent predictors of CAE. Fib 4, APRI, NAFLD, and Bard scores were higher in the CAE patients. There were a moderate, positive correlations for FIB-4, APRI, and NAFLD scores with coronary ectasia (r=0.55, p<0.001; r=0.52, p<0.001; r=0.51, p<0.001, respectively). A weak-moderate positive correlation was observed between the Bard score and CAE (r=0.34, p<0.001). Univariate and multivariate regression analysis showed that APRI score, low HDL, and Bard score were independent risk factors for CAE ectasia (p<0.001). Cut-off values to predict CAE as determined by ROC curve analysis were: FIB-4 index ≥1.43 (AUC=0.817, 95% confidence interval (CI): 0.762 to 0.873, p<0.001), APRI index ≥0.25 (AUC=0.804, 95% CI: 0.745 to 0.862, p<0.001), NAFLD score ≥–0.92 (AUC=0.798, 95% CI: 0.738 to 0.857.p<0.001), Bard score ≥2 (AUC=0.691, 95% CI: 0.621 to 0.761, p<0.001).
Conclusion	APRI, FIB-4, NAFLD, and Bard scores are associated with CAE.
Keywords	APRI index; FIB-4 index; coronary ectasia; Bard score; NAFLD score
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Introduction

Isolated coronary artery ectasia (CAE) is defined as non-obstructive coronary lesions, which may be diffuse or localized, and are characterized by lumen dilatation 1.5 times or more than the adjacent normal segment [1]. This anatomical abnormality can be seen in approximately 5% of patients undergoing coronary angiography [2].

The etiopathogenesis of CAE is not fully understood; however, atherosclerosis and inflammation appear to be key factors in the pathophysiology of this coronary dilation. The main cause of CAE is the degeneration of the media layer. Adiponectin, nitric oxide synthetase (NOS), and matrix metalloproteinase-3 have been found to be associated with CAE [3, 4]. Isolated CAE is a form of coronary atherosclerosis that is associated with risk of death and myocardial infarction equivalent to obstructive coronary artery disease (CAD).

Non-alcoholic fatty liver (NAFLD) is the hepatic reflection of obesity and metabolic syndrome, and it has been recognized as a marker of pathological accumulation of ectopic fat associated with a long-term, low-grade, inflammatory state. This low-grade chronic inflammation results in a variety of deleterious pathophysiological processes, such as abnormal glucose, increased oxidative stress, hypercoagulation, endothelial dysfunction, and progression of atherosclerosis.

In addition, the fact that most morbidity and mortality in NAFLD patients are cardiovascular rather than liver-related has caused NAFLD to gain importance as an independent cardiovascular risk factor [5]. Use of non-invasive markers and scoring systems is recommended to determine the risk of poor prognosis related to the liver. APRI and FIB-4 are two indices that are effective in predicting liver failure. These indices include liver enzymes and cardiometabolic risk factors. In addition, previous studies have shown that FIB-4 and APRI can predict all-cause mortality and are associated with subclinical coronary atherosclerosis in patients with and without NAFLD [5].

Compared with other examination methods, the FIB-4 and APRI scores and other scoring systems have the advantages of being inexpensive, noninvasive, and reproducible in a variety of populations. Therefore, we examined the relationship between FIB-4, APRI, other scoring systems and CAE.

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Material and methods

Study population

This study complied with the Declaration of Helsinki, and it was approved by the local ethics review board. Patients applying to our outpatient clinic between January 2020 and January 2022 and undergoing angiography procedures for any of the following reasons were included in the study: angina-like chest pain, positive treadmill exercise test, abnormal myocardial perfusion scintigraphy for myocardial ischemia, or clinically suspected coronary artery disease. Patients with chronic, total coronary occlusion, viral hepatitis, acute coronary syndrome, previous myocardial infarction, severe heart valve disease, immunological or inflammatory disease, hematological disorder, active local or systemic infection, or history of malignancy were excluded from the study. In addition, patients diagnosed with heart failure according to the European society of cardiology (ESC) guidelines were excluded from the study [6]. 215 patients were enrolled in the study, 108 patients with CAE and 107 without CAE.

Diabetes mellitus was defined as a fasting plasma glucose of >126 mg/dl or any value at any time >200 mg/dl or the use of any antidiabetic drug or insulin. Hypertension was defined as systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg on repeat measurements, or use of any antihypertensive drug. Body mass index (BMI) was calculated by dividing weight (kg) by height (m) squared. A record of essential, pre-hospitalization drugs was made from the medical history recorded at admission.

Assessment of coronary angiography

Coronary angiography was performed using radial or femoral artery access site with the Judkins technique with routine standard projections using appropriate catheters after informed consent. Each vessel was visualized in at least two different projections. The coronary angiograms were interpreted by two independent cardiologists who were blinded to the patients' status. An arterial segment with a diameter ≥1.5 times the diameter of the adjacent normal segment was considered to have segmental CAE. Dilated lesions involving≥1/3 of the coronary artery were classified as CAE, and those with < 1/3 affected artery were classified as focal CAE. In the absence of an identifiable adjacent normal segment, the mean diameter of the corresponding coronary segment in the control group was taken as the normal value. The severity of CAE was determined according to the Markis classification [7]. In order of decreasing severity, CAE was classified as follows: Type 1, diffuse ectasia in two or three vessels; Type 2, diffuse ectasia in one vessel and localized ectasia in the other vessel; Type 3, diffuse ectasia in only one vessel; Type 4 localized segmental ectasia [8].

Laboratory data

Peripheral venous blood samples were obtained at admission to the hospital. Initial lipid panels, fasting glucose, creatinine, urea, alanine transferase (ALT), aspartate transferase (AST), serum albumin, total bilirubin, indirect bilirubin, and CRP were measured by chemiluminescence on an autoanalyzer. All blood samples were obtained after a 12-hr fast. Blood samples were collected into tubes containing dipotassium ethylenedinitrotetraacetic acid (EDTA) to measure hemoglobin and white blood cell and platelet counts. Samples were analyzed on a Beckman Coulter device. Estimated glomerular filtration rate (eGFR) was determined by a modified modification of diet in renal disease equation (MDRD) [9]:

$$eGFR = 186 \times (\text{serum creatinine} \times 0.011) - 1.154 \times (\text{age}) - 0.203 \times (0.742 \text{ if female}) \times 1.233 \text{ [10]}.$$

The FIB-4 score was calculated with the following formula, with cut-off values of 1.30 and 2.67 for the low and high risk categories:

$$\text{FIB-4} = \text{age [yrs]} \times \text{AST [IU/l]} / (\text{platelets [} \times 10^9/\text{l]} \times \text{ALT [IU/l] } 1/2) \text{ [11]}.$$

NAFLD score was calculated with the following formula:

$$\text{NALFD score} = -1.675 + 0.037 \times \text{age [yrs]} + 0.094 \times \text{BMI [kg/m}^2\text{]} + 1.13 \times \text{hyperglycemia/diabetes [1 if yes, 0 if no]} + 0.99 \times (\text{AST [IU/L]/ALT [IU/L]}) - 0.013 \times \text{platelet count [} \times 10^9/\text{l]} - 0.66 \times \text{albumin [g/dl]} \text{ [12]}$$

For the low- and high-risk categories, the cut-off points were –1.455 and 0.676.

The BARD score ranges from 0 to 4 points. Scoring was made according to the following criteria. Body mass index (BMI)≥28=1 point, AST/ALT ratio≥0.8=2 points; Diabetes mellitus (DM)=1 point [13]. The APRI index (AST – platelet ratio index) was calculated as: AST concentration (IU/l)/upper limit of normal AST (IU/l) × 100/platelet count (109/l). The cut-off values for the groups were as follows: below 0.5 is low risk, over 1.5 is high risk evaluated as [14].

Statistical analysis

All data were analyzed by using SPSS 22.0 statistical Package program for Windows (SPSS Inc, Chicago, IL, USA). We evaluated whether the data were normally distributed with the Kolmogorov–Smirnov test. Descriptive statistics for continuous variables are presented as mean±SD for normally distributed data or as median (interquartile range (25^{th} – 75^{th} percentile) for non-normally distributed data.

Categorical variables (given as percentages) were compared with Chi-square or Fisher's exact tests. Normally distributed, continuous variables were compared with Student's t-tests, and nonparametric variables were compared with Mann-Whitney U tests. A p-value less than 0.05 was considered statistically significant. ROC analysis was performed to determine the optimum cut-off value of the FIB-4 index, APRI

Table 1. Baseline demographic and clinical characteristics of patients without and with CAE.

Variable	CAE (-) (n=107)	CAE (+) (n=108)	All patients (n=215)	p value
		Demographic Data		
Age (yrs)	61.3±10.1	62.4± 9.7	61.8±9.9	0.440**
Gender (male)	83 (76.1)	88 (81.5)	171(78.8)	0.407*
Diabetes mellitus	26 (23.9)	23 (21.3)	49 (22.6)	0.746*
Hypertension	56 (51.4)	60 (55.6)	116 (53.5)	0.587*
Hyperlipidemia	23 (21.3)	16 (14.8)	39 (18.1)	0.288*
Current smoking	12 (30)	31 (28.7)	43 (29.1)	0.990*
BMİ (kg/m^2)	29±4.4	27.1±3.05	28.05±3.7	< 0.001**
Fib 4 index	1.1 (0.8-1.51)	2 (1.34-2.95)	1.45 (1.01-2.27)	< 0.001 γ
APRI index	0.19 (0.15-0.25)	0.37 (0.25-0.57)	0.25 (0.17-0.4)	<0.001 γ
NAFLD score	-1.66 (-2.48)-0.89)	-0.02 (-1.00)-0.97)	-0.92 (-2.01)-0.19)	< 0.001 γ
Bard score	2 (2-3)	3 (2-4)	3 (2-3)	<0.001 γ
		Laboratory and Echocardiographic Data		
EF (%)	56.2±9.2	54.3±8.3	60±8.7	0.142**
LVDD (mm)	49.2±5.5	48.9±4.3	48±4.9	0.645**
GFR(ml/min)	84.9±17	81.4±18.4	83.1±17.8	0.151**
Glucose (mg/dl)	123.8±41.8	152.4±75.6	138.4±63	0.001**
Creatine (mg/dl)	1.11±1.3	0.96±0.25	1±1	0.246**
Total bilirubin (mg/dl)	0.74±0.43	0.73±0.45	0.74±0.44	0.832**
Indirect bilirubin (mg/dl)	0.61±0.39	0.59±0.41	0.6±0.4	0.807**
WBC (10^3/μl)	8.38±2.78	9.7±7.3	9.2±6.1	0.084**
Hemoglobin (mg/dl)	14.1±1.7	14.4±1.7	14.3±1.7	0.162**
Platelet (10^3/μl)	261±62	206±57	233±65	<0.001**
CRP (mg/dl)	12.8±29	13.4±29	13.1±29.3	0.891**
Total cholesterol (mg/dl)	205.7±42.9	213.5±50.2	209.7±46.8	0.234**
LDL (mg/dl)	129±32.7	140±43.2	133.3±38.9	0.031**
HDL (mg/dl)	46.6±12	42.6±9.5	44.4±11.5	0.009**
Triglyceride (mg/dl)	125 (95-178)	143 (105-209)	137 (102-201)	0.065 γ
AST (IU/l)	23 (21-28)	26 (22-31)	24 (20-39)	0.012 γ
ALT (IU/l)	21.5 (16-33)	22 (18-28)	22 (16-40)	0.990 γ
CAE types				
Type 1 CAE	27 (25.0)			
Type 2 CAE	30 (27.8)			
Type 3 CAE	17 (15.7)			
Type 4 CAE	34 (31.5)			

Data are number (percentage), mean±SD, or as median and interquartile range (25th–75th percentile). *Chi square test. **Independent samples t-test. γ Mann-Whitney U test. OAD, oral antidiabetic drugs; ACE-I, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BMI, body mass index; LDL, low-density lipoprotein cholesterol; HDL, high- density lipoprotein cholesterol; LVDD, left ventricular end-diastolic diameter; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

score, NAFLD score, and Bard score for CAE. Univariate and multivariate logistic regression analysis was performed to identify independent predictors of CAE. Spearman correlation tests was used to determine the relationships between CAE and FIB-4 index, APRI, NAFLD score, and Bard score.

Results

The demographic characteristics of the patients are presented in Table 1. The mean age of the 215 patients was 61.8±9.9 yrs, and 171 (78.8%) of the patients were males. Patients without and with CAE were similar in terms of demographic characteristics including age, gender, diabetes, smoking, hypertension, and hyperlipidemia. The FIB-4 index, APRI, NAFLD, and Bard scores were higher in the CAE patients.

AST, glucose, and LDL were higher in the ectasia group, while BMI, platelet, and HDL levels were higher in patients

Table 2. Correlation analysis of FİB-4 Index, APRI Index, NAFLD Score and Bard score with coronary artery ectasia.

Variable	r value	p value
FİB-4 index	0.55	<0.001
APRI index	0.52	<0.001
NAFLD score	0.51	<0.001
Bard score	0.34	<0.001

Spearman correlation analysis was used.

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Table 3. Univariate and Multivariate regression analysis of independent parameters in predicting CAE

Variable	Univariate analysis			Multivariable analysis		
	OR	95% CI	p value	HR	95% CI	p value
Age	1.013	0.986-1.042	0.342	–	–	–
Gender (male)	1.375	0.710-2.664	0.345	–	–	–
Glucose	1.009	1.003-1.015	0.002	1.002	0.995-1.009	0.615
AST	1.009	0.967-1.053	0.664	–	–	–
LDL	1.006	0.999-1.014	0.089	–	–	–
HDL	0.962	0.937-0.988	0.004	0.963	0.930-0.997	0.032
Platelets	0.982	0.976-0.988	<0.001	0.998	0.988-1.008	0.699
FİB-4 index	4.391	2.671-7.220	<0.001	1.421	0.553-3.655	0.465
APRI index	1.963	1.447-2.616	<0.001	7.3	1.269-42.68	0.038
NAFLD score	2.322	1.798-2.997	<0.001	1.132	0.653-1.963	0.659
Bard score	2.223	1.627-3.037	<0.001	1.675	1.019-2.754	0.042
BMİ	1.152	1.062-1.250	0.001	1.019	0.890-1.167	0.505

without ectasia. The Spearman correlation analysis (Table 2) demonstrated moderate, positive correlations of FIB-4 index, APRI index, and NAFLD score, with CAE (r=0.55, p<0.001; r=0.52, p<0.001; r=0.51, p<0.001, respectively). A weak, – moderate, positive correlation was observed between Bard score and CAE (r=0.34, p<0.001). Univariate and multivariate regression analysis (Table 3) showed that the APRI score, low HDL and Bard score were independent risk factors for CAE (p<0.001 for all). The ROC curve analysis (Table 4) showed that FIB-4, APRI score ≥0.25, NAFLD score ≥–0.92, and Bard score ≥2 were significant, independent predictor of CAE.

Discussion

In this retrospective study on patients with angiography-proven ectasia, we investigated the relationship between liver fibrosis scoring systems and CAE. One of the new findings was that patients with high-risk APRI and FIB-4 categories had CAE. Clinically, this study provided new insights and supported the idea that APRI and FIB-4 scores and screening for liver fibrosis are associated with CAE.

CAE is an anatomical abnormality with pathophysiological effects on the myocardium [15]. The pathogenesis of CAE has not been fully elucidated; however, atherosclerosis and inflammation-induced abnormal vascular remodeling appear to be the main pathophysiological mechanisms for CAE [16]. More importantly, patients with CAE have a significantly increased risk for cardiovascular events, including acute myocardial infarction [17].

Recent studies have focused on the association of liver disease with cardiovascular diseases (CVD). NAFLD shares some pathogenic pathways similar to coronary artery disease (CAD), including insulin resistance, lipid dysfunction, and inflammation [18]. In previous studies, NAFLD was an independent predictor of long-term risk for CVD [19]. However, whether NAFLD is a sensitive and effective screening tool to determine the cardiovascular risk in patients with CAD remains an unresolved question. According to previous studies, ultrasound performance and sensitivity is a poor strategy for assessing the degree of steatosis of NAFLD [20]. Liver biopsy is invasive and not suitable for primary detection of CAD. For these reasons, non-invasive scoring systems have been proposed to detect advanced fibrosis and predict liver-related complications. Over the past few years, several studies have demonstrated that liver fibrosis scores (LFSs) have significant prognostic value for liver outcomes, cardiovascular mortality, and all-cause mortality in both the NAFLD population and the general population [9]. Although the association between LFSs and cardiovascular

Table 4. ROC of independent predictors in patients with CAE.

Variable	AUC (95%)	Cut off value	p-value	Sensitivity %	Specificity %
FİB-4 index	0.817 (0.762-0.873)	≥1.43	<0.001	71.3	71.4
APRI index	0.804 (0.745-0.862)	≥0.25	<0.001	75	75.2
NAFLD score	0.798 (0.738-0.857)	≥-0.92	<0.001	72.2	72.4
Bard score	0.691 (0.621-0.761)	≥2	<0.001	66.7	59

outcome has been confirmed by many prospective studies in various populations, no studies have been conducted on the association of LFSs with CAE.

Previous studies have shown that the degree of liver fibrosis correlates with the development of atherosclerosis [21]. Xin et al. showed that LFSs, including FIB-4 and aspartate aminotransferase/platelet ratio index (APRI), were associated with arterial stiffness but not with carotid intima-media thickness [22]. However, all these studies focused on atherosclerosis of peripheral vessels. There are currently very limited studies on the relationship between LFSs and atherosclerosis of the coronary arteries. In one study, the association of FIB-4 with atherosclerosis severity was evaluated using different scoring systems (Gensini, Syntax, and Jeopardy scores), and provided solid evidence for the relationship between LFSs and severity of coronary atherosclerosis. CAE is considered a variant of CAD and the main cause of CAE is atherosclerosis [21]. Several studies have shown that CAE is an independent predictor of mortality. The overall 5-year survival in patients with CAE is only 71% [23]. Increased cardiac morbidity and mortality are caused by slow coronary blood flow, coronary vasospasm, dissection, and thrombus formation [24].

The pathological mechanism underlying CAE is still not fully understood. However, increased cytokine expression as a result of chronic inflammatory conditions and endothelial dysfunction have received much attention in recent years [25]. Mediators of the inflammatory process such as cytokines, proteolytic agents, growth factors, cellular adhesion molecules, and inflammatory mediators are involved in the pathogenesis of CAE [25]. Kocaman et al. showed that patients with isolated CAE had significantly higher levels of leukocytes, monocytes, and neutrophils than patients with obstructive CAD and non-obstructive coronary artery disease (NCA) [26]. Kalaycioglu et al. reported that increased neutrophil-to-lymphocyte ratio was independently associated with the presence and severity of isolated CAE [27]. Similarly, Kundi et al. suggested that the platelet-lymphocyte ratio was significantly higher in patients with isolated CAE than in patients with NCA or obstructive CAD [28].

It has been previously noted that NAFLD is significantly associated with the development of CAE independent of other cardiometabolic risk factors [5]. The NAFLD score and FIB-4 index were useful predictors of CAE and coronary artery calcification (CAC) in a Japanese study involving 698 patients [29]. The association between LFSs, CAE, and CAC was confirmed in a study in China involving 1173 patients [30].

Findings from a Japanese Multicenter Registry demonstrated that FIB-4 is independently associated with risk of cardiovascular events and all-cause mortality in patients with atrial fibrillation [31]. More importantly, in a study with 7.56 years of patient follow-up, Chen et al. noted that higher LFS scores were associated with all-cause and cardiovascular mortality among 3263 patients with acute coronary syndromes (ACS) or stable CAD [32].

In fact, the exact mechanisms underlying the link between LFS and CAD are currently unclear. One possible pathway may be increased hepatic production of multiple prothrombogenic factors such as fetuin-A, which promotes atherosclerotic plaque formation and accelerates vascular calcium deposition in patients with liver fibrosis [33]. Patients with a high tendency to develop NAFLD often have an increased inflammatory state, endothelial dysfunction, insulin resistance, and lipid metabolism disorder, which may also support vascular atherosclerosis [34]. Further studies are required to elucidate the precise mechanisms that may provide useful information for developing new LFSs to more accurately predict both hepatic and cardiovascular outcome.

Limitations

This study has several limitations. First, although we excluded patients with alcoholic liver disease, excessive alcohol consumption, or other known serious liver diseases, the confounding effect of undiagnosed liver disease was unavoidable. Second, we only calculated NAFLD and FIB-4 and other scoring at baseline, changes in these scores during follow-up may have changed the risk categories of the patients. Third, not all patients underwent standard abdominal ultrasound due to the characteristics of the study population. Identifying those with NAFLD can help further risk assessment. Our study included a small group of patients. Therefore, randomized, controlled, prospective, larger sample size studies are needed.

Conclusion

This study showed for the first time that the APRI score and FIB-4 index were significantly associated with different scoring systems in patients with CAE. Patients with high-risk APRI and FIB-4 indices had CAE. Clinically, this study provided new insights and supported the idea that APRI and FIB-4 scores and screening for liver fibrosis are associated with CAE. These findings support the idea that LFSs are useful tools for predicting cardiovascular outcomes, but more extensive, multicenter, randomized, controlled, prospective clinical studies are needed.

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No conflict of interest is reported.

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