High-Risk Coronary Plaque at Coronary CT Angiography Is Associated with Nonalcoholic Fatty Liver Disease, Independent of Coronary Plaque and Stenosis Burden: Results from the ROMICAT II Trial[1]

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Purpose: To determine the association between nonalcoholic fatty liver disease (NAFLD) and the presence of high-risk coronary atherosclerotic plaque as assessed with coronary computed tomographic (CT) angiography.

Materials and Methods: This study was approved by the local ethics committees; informed consent was obtained. Patients randomized to the coronary CT angiography arm of the Rule Out Myocardial Infarction using Computer Assisted Tomography, or ROMICAT, II trial who underwent both nonenhanced CT to assess calcium score and contrast material–enhanced coronary CT angiography were included. Readers assessed coronary CT angiography images for the presence of coronary plaque, significant stenosis (≥50%), and high-risk plaque features (positive remodeling, CT attenuation < 30 HU, napkin-ring sign, spotty calcium). NAFLD was defined as hepatic steatosis at nonenhanced CT (liver minus spleen CT attenuation < 1 HU) without evidence of clinical liver disease, liver cirrhosis, or alcohol abuse. To determine the association between high-risk plaque and NAFLD, univariable and multivariable logistic regression analyses were performed, with high-risk plaque as a dependent variable and NAFLD, traditional risk factors, and extent of coronary atherosclerosis as independent variables.

Results: Overall, 182 (40.9%) of 445 patients had CT evidence of NAFLD. High-risk plaque was more frequent in patients with NAFLD than in patients without NAFLD (59.3% vs 19.0%, respectively; $P < .001$). The association between NAFLD and high-risk plaque (odds ratio, 2.13; 95% confidence interval: 1.18, 3.85) persisted after adjusting for the extent and severity of coronary atherosclerosis and traditional risk factors.

Conclusion: NAFLD is associated with advanced high-risk coronary plaque, independent of traditional cardiovascular risk factors and the extent and severity of coronary artery disease.

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This article reflects the views of the authors and not necessarily those of the National Institutes of Health or the Department of Health and Human Services.

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Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease, with an estimated prevalence of 20%–30% in the general population (1,2). The histologic spectrum of NAFLD ranges from simple steatosis to steatohepatitis, fibrosis, and, ultimately, cirrhosis. Although the pathogenesis still remains partly unknown, various mechanisms have been identified, including increased oxidative stress, insulin resistance, lipotoxicity of fatty acids, and systemic inflammation by tumor necrosis factor α. Patients with NAFLD have a dysregulated secretion of pro- and antiinflammatory cytokines and often have multiple components of the metabolic syndrome, such as abdominal obesity, low serum high-density lipoprotein cholesterol levels, high serum triglyceride levels, and impaired glucose tolerance (3–5).

Biopsy confirms the histologic presence of hepatic steatosis and is the diagnostic reference standard for NAFLD; however, it is an invasive procedure. Computed tomography (CT) has been validated as an accurate imaging modality to detect and characterize hepatic steatosis by measuring the liver CT attenuation and the difference in liver and spleen CT attenuation values (6–8).

Several studies showed an association between NAFLD and coronary artery disease (CAD), suggesting a pathophysiological link between the two diseases (9–13). The association of NAFLD and subclinical atherosclerosis detected by means of intima media thickness and coronary artery wall calcification was independent of traditional cardiovascular risk factors and metabolic syndrome (14). While increased prevalence of CAD might reflect the overlap between components of metabolic syndrome and cardiovascular risk factors, NAFLD could also be seen as a causal mediator itself, triggering systemic inflammation beyond these classic established factors. Coronary CT angiography, in addition to providing assessment of obstructive CAD, also permits detection and characterization of coronary plaque. High-risk plaque features, such as positive remodeling, spotty calcium, plaque with a low CT attenuation, and the napkin-ring sign, are associated with acute coronary syndrome and future adverse cardiovascular events (15–17).

We hypothesized that NAFLD is associated with high-risk coronary plaque and that this association is independent of traditional cardiovascular risk factors and the extent and severity of CAD.

Accordingly, the purpose of this study was to determine the association between NAFLD and the presence of high-risk coronary atherosclerotic plaque as assessed with coronary CT angiography.

Advances in Knowledge

- Nonalcoholic fatty liver disease (NAFLD) increases the likelihood of the presence of high-risk coronary plaques by approximately six times (odds ratio [OR], 6.48; 95% confidence interval [CI]: 4.17, 10.06; $P < .001$).
- In multivariable logistic regression analysis, the association between NAFLD and high-risk plaque (OR, 2.13; 95% CI: 1.18, 3.85; $P = .012$) persists after adjustment for traditional cardiovascular risk factors (age, sex, body mass index, arterial hypertension, diabetes mellitus, dyslipidemia, current or former smoking) and the extent and severity of coronary artery disease (CAD) (significant CAD with stenosis ≥ 50%, number of segments with noncalcified plaque, coronary calcium score).

Materials and Methods

Patient Population

The study cohort consisted of subjects randomized to the coronary CT angiography arm of the Rule Out Myocardial Infarction using Computer Assisted Tomography (ROMICAT) II trial who underwent both coronary CT angiography and nonenhanced CT to assess the presence of coronary calcium (18). A detailed description of the patient population was reported recently (18). Briefly, between April 2010 and January 2012, 501 patients who were examined in the emergency department of nine hospitals in the United States and had chest pain and a clinical suspicion of acute coronary syndrome were enrolled (Fig 1). All study participants provided written consent for participation in the ROMICAT II trial. The local institutional review boards approved the study (ROMICAT II, *clinicaltrials.gov* no. NCT01084239).

Baseline clinical characteristics, medical history, and cardiovascular risk factors (arterial hypertension, hyperlipidemia, diabetes mellitus, and former or current smoking) were collected in

Implications for Patient Care

- The assessment of NAFLD could be performed more widely with nonenhanced cardiac CT scans.
- The additional assessment of NAFLD with CT could improve the risk stratification of patients suspected of having CAD.

Published online before print
10.1148/radiol.14140933 **Content codes:** CA CT

Radiology 2015; 274:693–701

Abbreviations:
BMI = body mass index
CAD = coronary artery disease
CI = confidence interval
NAFLD = nonalcoholic fatty liver disease
OR = odds ratio
ROMICAT = Rule Out Myocardial Infarction using Computer Assisted Tomography

Author contributions:
Guarantors of integrity of entire study, S.B.P., T.L., U.H., M.F.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, S.B.P., M.T.L., S.D.W., M.F.; clinical studies, S.B.P., M.T.L., T.L., B.B.G., J.L.F., U.H., M.F.; experimental studies, B.B.G., M.F.; statistical analysis, S.B.P., T.M., U.H., M.F.; and manuscript editing, S.B.P., M.T.L., T.L., A.P., B.B.G., Q.A.T., S.D.W., J.L.F., U.H., M.F.

Funding:
This research was supported by the National Institutes of Health (grant nos. U01HL092040, U01HL092022, 5T32 HL076136, 5K24HL113128, K23HL098370, L30HL093896, and 5T32 HL076136).

Conflicts of interest are listed at the end of this article.

Figure 1

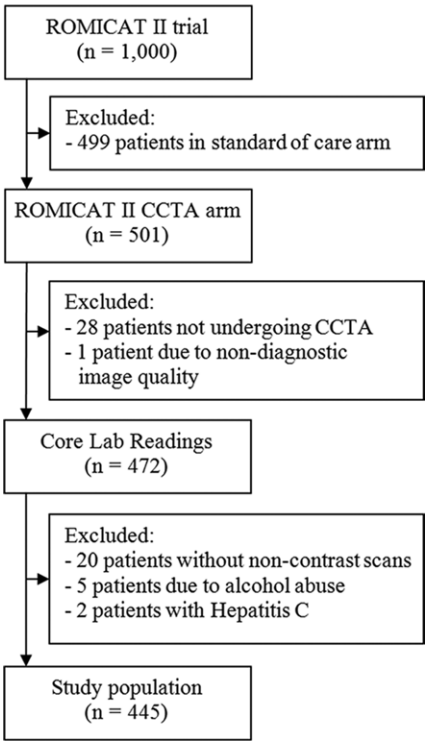

Figure 1: Flowchart demonstrates study population enrollment, both exclusion and inclusion. *CCTA* = coronary CT angiography.

the ROMICAT II trial (18). The medical records of all subjects were reviewed for a history of alcohol consumption, alcohol abuse, and liver disease. Body mass index (BMI) was calculated as body weight divided by the square of the participant's height.

Coronary CT Angiography Analysis and High-Risk Coronary Plaque Assessment

CT images were acquired by using a 64–detector row scanner or a more recent scanner with either retrospectively electrocardiographically gated or prospectively electrocardiographically triggered coronary CT angiography protocols. The protocol consisted of a nonenhanced calcium score scan, followed by a contrast material–enhanced coronary CT angiography scan. Three experienced core laboratory readers with at least 5 years of experience in cardiac CT and level III training (M.F., with 12 years of experience in cardiac CT; S.B.P., with 6 years of experience in cardiac CT; and T.L., with 6 years of experience in cardiac CT) performed the image analysis on a dedicated cardiac workstation (TeraRecon, San Mateo, Calif). The coronary CT angiography analysis was performed on a per–coronary segment basis by using the model of the Society of Cardiovascular Computed Tomography (19). For each coronary segment, the reader determined whether the image quality was sufficient to evaluate the presence of stenosis and coronary plaque with confidence. Coronary segments that were assessed as being nondiagnostic in image quality were treated as noninformative for the purpose of the analysis.

Each evaluable coronary segment was assessed for the presence of at least 50% stenosis and the presence of coronary atherosclerotic plaque. Noncalcified coronary plaque was defined as any discernible structure that could be assigned to the coronary artery wall, had a CT number below that of the contrast-enhanced coronary lumen but above that of the surrounding connective tissue, and could be identified in at least two independent planes (15). Calcified atherosclerotic plaque was defined as any structure with an attenuation of at least 130 HU that could be visualized separately from the contrast-enhanced coronary lumen, could be assigned to the coronary artery wall, and could be identified in at least two independent planes (15).

We performed qualitative evaluation for the presence of high-risk plaque features in each coronary segment with plaque. High-risk plaque features were defined as positive remodeling, plaque with a low CT number, napkin-ring sign, and spotty calcium (Fig 2). Positive remodeling was assessed visually on multiplanar reformatted images reconstructed in long-axis and short-axis views of the vessel. A threshold of 1.1 for the maximal diameter of the vessel at the plaque over the diameter of the proximal and distal normal vessel reference was used to define positive remodeling (20). If a low CT number (in Hounsfield units) was visually noted in noncalcified plaque, readers placed three regions of interest (approximately 0.5–1.0 mm^2) in the noncalcified low–CT number portion of the plaque. Plaque with a low CT number was defined as a mean CT number within these three regions of interest of less than 30 HU (21). The napkin-ring sign was defined as ringlike peripheral higher attenuation surrounding a central core of low attenuation of a noncalcified coronary plaque (22). Spotty calcium was defined by calcified plaque with a maximum diameter of less than 3 mm in any direction, length (extent in the longitudinal direction of the vessel) of the calcification of less than 1.5 times the vessel diameter, and width (extent of the calcification perpendicular to the longitudinal direction of the vessel) of the calcification of less than two-thirds of vessel diameter (23).

Coronary Artery Wall Calcification Analysis

Coronary artery wall calcification was quantified on nonenhanced scans by using established technique (24). An experienced reader with at least 5 years of experience in cardiac CT and level III training (S.B.P., with 6 years of experience in cardiac CT) performed coronary artery wall calcification measurements on a dedicated cardiac workstation (TeraRecon) and reported Agatston score.

CT Assessment of NAFLD

A reader with more than 5 years of experience in abdominal CT (M.T.L., with 7 years of experience in radiology) who was blinded to the results of coronary CT angiography performed measurement of hepatic and splenic CT attenuation on the nonenhanced CT scans, which were acquired for the coronary artery wall calcium quantification (Fig 3). The hepatic CT attenuation was measured by selecting three circular regions of interest with an area of at least 2 cm^2 on three cross-sections obtained at different hepatic levels. The largest possible region was selected by avoiding areas of hepatic vascular and biliary structures, as described previously (9). The hepatic CT attenuation was calculated as the mean of the three

Figure 2

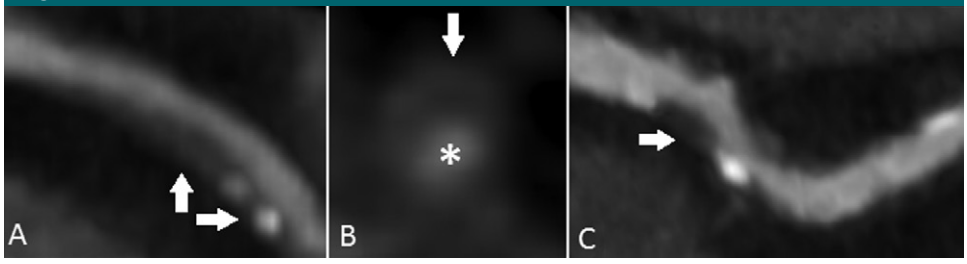

Figure 2: Coronary CT angiography images demonstrate examples of high-risk plaque features. *A*, Image was obtained in a 63-year-old man with partially calcified plaque, positive remodeling (vertical arrow), and spotty calcium (horizontal arrow). *B*, A cross-sectional view of a noncalcified plaque in a 65-year-old man demonstrates a napkin-ring sign with a central low-attenuation area, surrounded by a peripheral rim of higher attenuation (arrow) next to the lumen (*). *C*, Image in a 60-year-old woman with partially calcified plaque demonstrates a low CT number in the midportion (arrow).

Figure 3

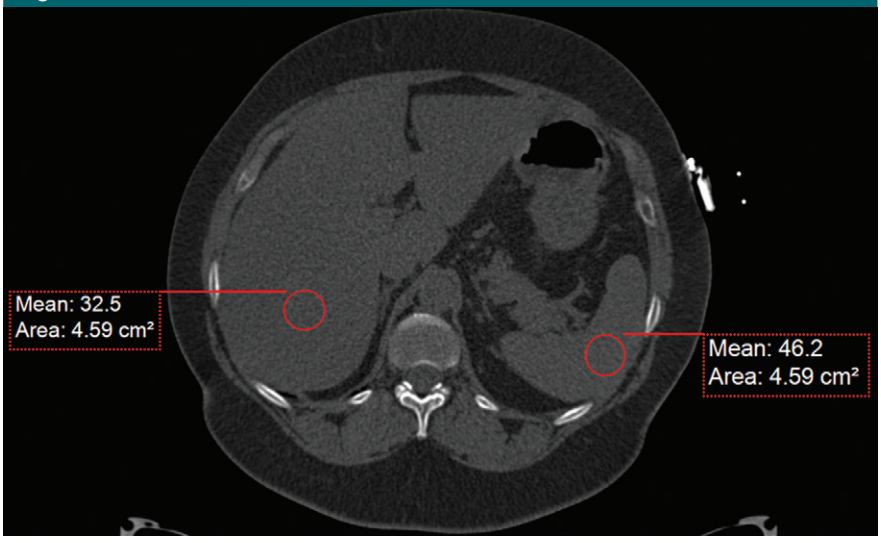

Figure 3: Axial nonenhanced CT image in a 62-year-old man demonstrates attenuation measurements of the liver and spleen. Image shows a diffuse fat accumulation in the liver, with a mean liver attenuation of 32.5 HU and a mean spleen attenuation of 46.2 HU.

measurements. The splenic CT attenuation was calculated in a similar fashion. CT numbers were measured in three different regions of interest in the spleen. The splenic CT attenuation was calculated as the mean of the three measurements.

CT Definition of NAFLD

The presence of NAFLD was defined as CT evidence of hepatic steatosis and absence of any evidence of clinical liver disease, liver cirrhosis, and reported alcohol abuse. CT steatosis was defined as hepatic CT attenuation minus splenic CT attenuation of less than 1 HU, which has previously been demonstrated to correlate with the presence of steatosis at liver biopsy and was shown to be very specific for the presence of steatosis (6). We also used an alternative definition of hepatic steatosis: the mean CT number ratio of liver-to-spleen parenchyma of less than 1 HU (7).

Definition and Adjudication of Acute Coronary Syndrome

The outcome of acute coronary syndrome during the index hospitalization was determined in the ROMICAT II trial. Acute coronary syndrome was defined as acute myocardial infarction or unstable angina pectoris according to the American College of Cardiology and American Heart Association Guidelines (18). The end point was predefined and adjudicated by an external, independent clinical events committee.

Statistical Analysis

All statistical analyses were performed by using Stata 13.1 software (StataCorp LP, College Station, Tex). Continuous data are presented as means ± standard deviations. Comparisons between groups were performed with the use of an independent sample *t* test for continuous variables, the Fisher exact test for categorical variables, and the Wilcoxon rank sum test for ordinal variables.

To determine the association between high-risk plaque features and NAFLD, we performed univariable (ie, unadjusted) and multivariable (ie, adjusted) logistic regression analyses. We used multilevel mixed-effects models that included sites (hospitals) as a random effect and therefore controlled for possible clustering effects within sites. The models included the presence of high-risk plaque as the dependent variable and the presence of NAFLD, traditional cardiovascular risk factors (age, sex, BMI, arterial hypertension, diabetes mellitus, dyslipidemia, current or former smoking) and extent of CAD (significant CAD with stenosis ≥ 50%, number of segments with noncalcified plaque, and coronary calcium score

categories [0, 1–100, 101–300, >300]) as independent variables.

Results

Study Population

Of 501 subjects who were randomized to the coronary CT angiography arm of the ROMICAT II trial, both contrast-enhanced and nonenhanced scans were available in 452 subjects. After review of the medical records, we excluded seven patients with a history of alcohol abuse (n = 5) or liver disease (n = 2) (Fig 1). Baseline characteristics of the study population are shown in Table 1. NAFLD was detected in 182 patients (40.9%) with the primary CT-based definition by using the difference between liver and spleen CT attenuation of less than 1 HU. The prevalence of NAFLD was similar (n = 175, 39.3%) when the liver-to-spleen CT attenuation ratio of less than 1 was used for the definition of NAFLD. Patients with NAFLD were older and less likely to be women, had higher BMI, and had a higher prevalence of cardiovascular risk factors, such as hypertension, diabetes mellitus, and dyslipidemia.

CAD Characteristics as Detected with Coronary CT Angiography

CAD, defined as the presence of any coronary plaque, was detected in 248 patients (55.7%). Of these patients, 42 had significant CAD, defined by at least 50% stenosis, and 206 had nonobstructive CAD, with a stenosis of 1%–49%. Calcified plaques were present in 205 patients (46.1%) and noncalcified plaques in 190 patients (42.7%). At least one high-risk plaque feature was present in 158 patients (35.5%). The most common high-risk plaque feature was spotty calcium, which was present in 145 patients (32.6%). Positive remodeling was present in 49 patients (11.0%), plaque with a low CT number was present in 37 patients (8.3%), and the napkin-ring sign was present in 22 patients (4.9%). At least two high-risk plaque features were present in 51 patients (11.5%), and at least three high-risk plaque features were present in 31 patients (7.0%).

Table 1

Clinical Characteristics of Study Patients Stratified according to the Presence of NAFLD at CT

Characteristic	Total (n = 445)	NAFLD (n = 182)	No NAFLD (n = 263)	P Value
Age (y)*	53.9 ± 8.0	56.2 ± 8.0	52.2 ± 7.7	<.001
No. of women	208 (46.7)	62 (34.1)	146 (55.5)	<.001
BMI (kg/m^2)*	29.4 ± 5.1	30.3 ± 4.8	28.8 ± 5.2	.002
Cardiovascular risk factors				
Arterial hypertension	242 (54.4)	123 (67.6)	119 (45.2)	<.001
Diabetes mellitus	73 (16.4)	46 (25.3)	27 (10.3)	<.001
Dyslipidemia	203 (45.6)	110 (60.4)	93 (35.4)	<.001
Former or current smoker	222 (49.9)	99 (54.4)	123 (46.8)	.123

Note.—Unless otherwise indicated, data are numbers of patients, with percentages in parentheses. Distribution of patients was as follows: 27% at hospital 1, 22% at hospital 2, 16% at hospital 3, 13% at hospital 4, 9% at hospital 5, 6% at hospital 6, 5% at hospital 7, 1% at hospital 8, and 0% at hospital 9.

* Data are means ± standard deviations.

Table 2

Coronary CT Angiography Characteristics of Patients Stratified according to Presence of NAFLD

Characteristic	Total (n = 445)	NAFLD (n = 182)	No NAFLD (n = 263)	P Value
CAD category				
No CAD	197 (44.3)	17 (9.3)	180 (68.4)	<.001
Nonobstructive CAD (1%–49% stenosis)	206 (46.3)	136 (74.7)	70 (26.6)	<.001
Significant CAD (≥50% stenosis)	42 (9.4)	29 (15.9)	13 (4.9)	<.001
Coronary plaque				
Calcified plaque	205 (46.1)	142 (78.0)	63 (24.0)	<.001
Noncalcified plaque	190 (42.7)	125 (68.7)	65 (24.7)	<.001
Any high-risk plaque	158 (35.5)	108 (59.3)	50 (19.0)	<.001
Calcium score				<.001
0	239 (53.7)	46 (25.3)	193 (73.4)	…
1–100	127 (28.5)	73 (40.1)	54 (20.5)	…
101–300	41 (9.2)	32 (17.6)	9 (3.4)	…
>300	38 (8.5)	31 (17.0)	7 (2.7)	…

Note.—Data are numbers of patients with percentages in parentheses, unless indicated otherwise.

Association between Coronary CT Angiography Characteristics of CAD and NAFLD

The results of coronary CT angiography analysis in patients with and those without NAFLD are summarized in Table 2. Both significant and nonobstructive CAD were more often seen in patients with NAFLD as compared with those without NAFLD. Less than 10% of patients with NAFLD were free of coronary atherosclerosis. Conversely, more than two-thirds of patients without NAFLD had no evidence of coronary atherosclerosis at coronary CT angiography. Coronary artery wall calcification scores were also higher in patients with NAFLD.

The prevalence of high-risk plaque features was significantly higher in patients with NAFLD than in those without NAFLD. The difference in the prevalence of high-risk plaque was observed for individual high-risk plaque features (spotty calcium, plaque with a low CT number, and positive remodeling) (Fig 4).

Figure 4

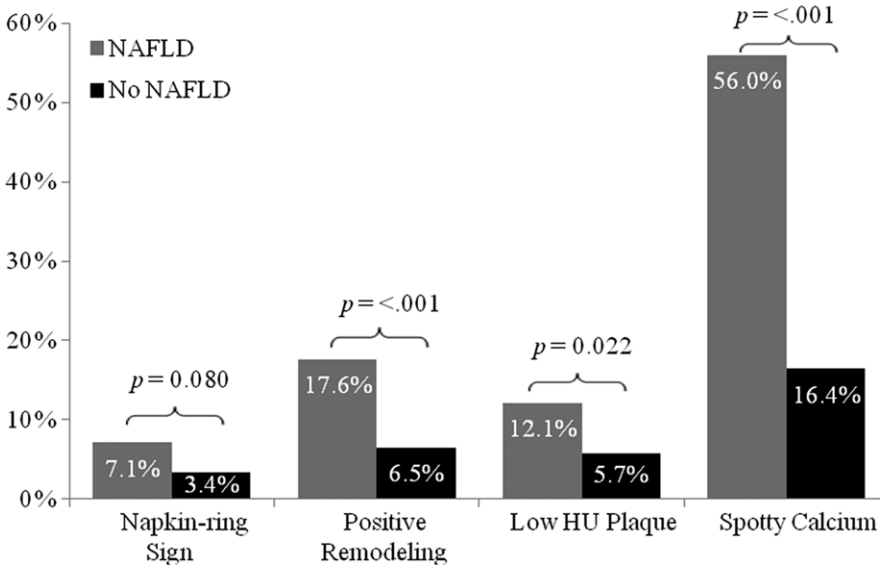

Figure 4: Bar graph demonstrates high-risk plaque features stratified according to presence or absence of NAFLD.

We performed multivariable logistic regression analyses to determine whether the association between NAFLD and high-risk plaque is independent of cardiovascular risk factors and other CAD characteristics. In univariable analysis, NAFLD was strongly associated with the presence of high-risk plaque. Patients with NAFLD were almost six times more likely to have at least one high-risk plaque feature present. Other variables significantly associated with the presence of high-risk plaque in the univariable analysis are summarized in Table 3. In the multivariable regression analysis, NAFLD remained significantly associated with the presence of high-risk plaque (adjusted odds ratio [OR], 2.13; 95% confidence interval [CI]: 1.18, 3.85) after adjusting for traditional cardiovascular risk factors and the extent and severity of CAD. The results of the univariable and multivariable analyses were similar when NAFLD was defined as the liver-to-spleen CT attenuation ratio of less than 1 (data not shown).

Traditional cardiovascular risk factors, such as age (OR, 1.07; 95% CI: 1.02, 1.12) and female sex (OR, 0.28; 95% CI: 0.12, 0.62), were significant predictors of significant CAD (≥50% stenosis) in the multivariable model. NAFLD was a significant predictor of significant CAD (≥50% stenosis) in the univariable analysis (OR, 3.65; 95% CI: 1.84, 7.23; $P < .001$) However, the association between NAFLD and CAD was attenuated after adjusting for traditional cardiovascular risk factors (OR, 2.04; 95% CI: 0.96, 4.29; $P = .062$).

Association of NAFLD with Acute Coronary Syndrome during the Index Hospitalization

Acute coronary syndrome during the index hospitalization occurred in 36 of 445 patients (8.1%; myocardial infarction, $n = 4$; unstable angina, $n = 32$). The rate of acute coronary syndrome in patients with NAFLD was 15.4%; in patients without NAFLD, the rate was 3.0% ($P < .001$). The presence of NAFLD was associated with an approximately six times higher risk of having acute coronary syndrome (OR, 5.84; 95% CI: 2.58, 13.22; $P < .001$).

Discussion

Our study demonstrated the association of NAFLD with the presence of high-risk coronary plaque. Furthermore, we found that the association between NAFLD and high-risk plaque is independent of the traditional cardiovascular risk factors and the extent and severity of CAD.

NAFLD is a common liver disease, with an estimated prevalence of 20%–30% in the general population (1,2). The prevalence in our study population was approximately 40%, most likely due to the fact that we included patients with acute presentation of symptoms who were examined in the emergency department and who had higher prevalence of risk factors for both CAD and NAFLD.

NAFLD is often associated with other disorders of metabolism, including visceral-type obesity, insulin resistance, diabetes mellitus, and dyslipidemia, which are main features of the metabolic syndrome. There is a strong overlap of the metabolic risk factors for NAFLD and traditional cardiovascular risk factors.

The studies of relationship between NAFLD and coronary atherosclerosis suggested that both NAFLD and coronary atherosclerosis are related to metabolic syndrome (25,26). Additionally, fatty infiltration of the liver is associated with visceral adiposity, which is also a known cardiovascular risk factor (27). However, it remains unclear whether the association between NAFLD and coronary atherosclerosis merely reflects the existence of underlying metabolic syndrome features that also promote the development of coronary atherosclerosis or whether NAFLD is an independent risk factor for the development of high-risk coronary atherosclerosis. Research has suggested the possible contribution of both mechanisms. Multiple studies showed an association of NAFLD with coronary artery wall calcification, CAD, and atherosclerosis in the carotid arteries (11,25,28). Coronary artery wall calcification was associated with NAFLD, independent of cardiovascular risk factors and visceral adiposity (28). In another study, the association of NAFLD and coronary artery wall calcification was independent of age, sex, and diabetes mellitus.

Table 3

Unadjusted and Adjusted Associations between Demographic and Clinical Risk Factors, High-Risk Plaque Features, and NAFLD

	Univariable Analysis		Multivariable Analysis					
			Model 1: Traditional Risk Factors		Model 2: Extent of Coronary Atherosclerosis		Model 3: All Risk Factors	
Independent Variable	Unadjusted OR	*P* Value	Adjusted OR	*P* Value	Adjusted OR	*P* Value	Adjusted OR	*P* Value
NAFLD	6.48 (4.17, 10.06)	<.001	4.06 (2.49, 6.63)	<.001	2.50 (1.42, 4.41)	.001	2.13 (1.18, 3.85)	.012
Age	1.08 (1.05, 1.11)	<.001	1.09 (1.06, 1.13)	<.001	…	…	1.04 (1.00, 1.08)	.078
Women	0.32 (0.21, 0.48)	<.001	0.27 (0.16, 0.45)	<.001	…	…	0.43 (0.23, 0.79)	.007
BMI	1.04 (1.00, 1.08)	.054	1.04 (0.99, 1.09)	.131	…	…	1.05 (0.99, 1.11)	.095
Arterial hypertension	1.91 (1.27, 2.88)	.002	1.10 (0.64, 1.90)	.732	…	…	0.87 (0.45, 1.68)	.686
Diabetes mellitus	1.88 (1.12, 3.15)	.016	1.23 (0.64, 2.39)	.537	…	…	0.80 (0.35, 1.81)	.586
Dyslipidemia	1.94 (1.30, 2.90)	.001	0.98 (0.58, 1.65)	.930	…	…	1.12 (0.61, 2.06)	.716
Former or current smoker	1.84 (1.22, 2.78)	.004	1.83 (1.13, 2.97)	.014	…	…	1.41 (0.80, 2.49)	.240
Significant CAD (≥50% stenosis)	31.38 (9.48, 103.9)	<.001	…	…	2.44 (0.55, 10.88)	.243	2.49 (0.52, 11.85)	.251
No. of segments with noncalcified plaque	2.35 (1.98, 2.78)	<.001	…	…	1.91 (1.50, 2.42)	<.001	1.93 (1.50, 2.48)	<.001
Coronary calcium score (categorized)	5.34 (3.82, 7.45)	<.001	…	…	2.83 (1.98, 4.04)	<.001	2.39 (1.62, 3.53)	<.001

Note.—The summary is based on all 445 observations. Numbers in parentheses are 95% CIs.

Oni et al extensively reviewed available literature and concluded that the association between NAFLD and subclinical atherosclerosis is independent of traditional cardiovascular risk factors and metabolic syndrome (14). In addition to association with subclinical atherosclerosis, NAFLD was also associated with more severe CAD at invasive coronary angiography by controlling for age, sex, waist circumference, and obesity (29).

Our findings confirmed the association of NAFLD with traditional cardiovascular risk factors and higher BMI.

The pathologic links between NAFLD and advanced coronary atherosclerosis are complex and are present at many levels. The histologic severity of NAFLD has been shown to be strongly associated with increased risk of cardiovascular disease and atherogenic lipid profile (30). Several investigators reported a relationship between NAFLD and increased serum activity of liver enzymes, such as alanine aminotransferase and γ-glutamyltransferase, which have also been reported to be independent predictors of cardiovascular events (31). Further, insulin resistance was associated with NAFLD and also with atherosclerosis and endothelial dysfunction. Dyslipidemia—defined as an increase of low-density lipoprotein cholesterol, triglycerides, and apolipoprotein B and a decrease of high-density lipoprotein cholesterol—was also associated with both NAFLD and increased risk of cardiovascular disease (1). Inflammation and oxidative stress are suggested to play a key role in the pathogenesis of both NAFLD and cardiovascular disease. Early studies showed a significant association of inflammatory markers, such as C-reactive protein and atherosclerosis, whereas other, more recent studies suggested a tight relationship of inflammatory markers, including high-sensitivity C-reactive protein, with the presence and prediction of NAFLD (32,33). Fat is considered to be a metabolically active endocrine organ that produces proinflammatory cytokines, including tumor necrosis factor α, interleukin 6, and interleukin 8. Dysregulated secretion of pro- and antiinflammatory cytokines alongside increased oxidative stress, lipotoxicity of fatty acids, and systemic inflammation also plays a role in the development of liver steatosis (3–5). Furthermore, several investigators reported an association of oxidative stress and inflammatory markers with the presence of high-risk atherosclerotic plaques (34). The metabolic abnormalities and associated changes in secretion of cytokines, increased oxidative stress, and systemic inflammation may provide a pathophysiologic link for the association of NAFLD and advanced coronary atherosclerosis beyond the traditional cardiovascular risk factors.

Histologic studies in victims of sudden cardiac death demonstrated that culprit plaques often had a large necrotic core, positive remodeling, speckled calcium, and thin fibrous cap (35). Similar morphologic features were observed with intravascular imaging techniques and, more recently, with coronary CT angiography. Investigators from several single-center studies reported an association of high-risk plaque features, including positive remodeling, spotty calcium, napkin-ring sign, and plaque with a low CT number, with acute coronary syndrome (16).

Although there is an established association of NAFLD with coronary atherosclerosis, there are limited data regarding the relationship of NAFLD with more advanced coronary plaque, as characterized with coronary CT angiography. Patients with NAFLD had noncalcified plaques and positive remodeling more often, rather than

significant coronary stenosis (9,10). In 298 patients suspected of having coronary stenosis who were referred to undergo coronary CT angiography, Akabame et al found severe stenosis in 176 (59%). Patients with NAFLD had more coronary plaque with high-risk plaque features, such as plaque with a low CT number and positive remodeling. The association persisted after controlling for age, sex, BMI, smoking status, and alcohol consumption (10). However, no adjustment was performed for the presence of coronary stenosis and the extent of coronary atherosclerosis. In our study, we performed a more extensive evaluation of high-risk plaques, including the presence of spotty calcium and napkin-ring sign. We also found that NAFLD was associated with high-risk plaque. This association persisted after adjusting for cardiovascular risk factors, BMI, presence of significant CAD (≥50% stenosis), and extent of coronary atherosclerosis. Patients with NAFLD were approximately twice as likely to have high-risk plaque features. Our observation provides an interesting insight into the relationship between NAFLD and coronary atherosclerosis. It raises a possibility that patients with NAFLD are not only more prone to develop CAD, but they are specifically more likely to develop high-risk coronary plaques.

Our study had several limitations. First, this study was performed in patients with acute chest pain who were examined in the emergency department. The prevalence of cardiovascular risk factors, metabolic syndrome, and NAFLD were likely higher than in the general population. However, 44% of our patients had no evidence of coronary atherosclerosis, and only 9% of patients had significant CAD (≥50% stenosis). The burden of CAD was significantly lower compared with some other studies in which the association of CAD and NAFLD was explored. We were not able to quantify the amount of abdominal visceral fat. The data on alcohol consumption and history of liver disease were obtained from medical records rather than a validated questionnaire. Thus, the amount of alcohol consumption might have been underreported.

In conclusion, we demonstrated that the presence of NAFLD is associated with high-risk coronary plaque, independent of cardiovascular risk factors, BMI, and the extent and severity of CAD. Our observation supports a relationship between NAFLD and advanced high-risk coronary atherosclerosis, possibly related to dysregulated secretion of cytokines, increased oxidative stress, and systemic inflammation.

Disclosures of Conflicts of Interest: S.B.P. disclosed no relevant relationships. **M.T.L.** disclosed no relevant relationships. **T.M.** disclosed no relevant relationships. **T.L.** disclosed no relevant relationships. **A.P.** disclosed no relevant relationships. **B.B.G.** Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: author received payment from Siemens Healthcare for a valve imaging lecture. Other relationships: disclosed no relevant relationships. **Q.A.T.** Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: author received a grant from St. Jude Medical. Other relationships: disclosed no relevant relationships. **S.D.W.** disclosed no relevant relationships. **J.L.F.** disclosed no relevant relationships. **U.H.** disclosed no relevant relationships. **M.F.** disclosed no relevant relationships.

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