

Association between higher pericoronary adipose tissue attenuation measured by coronary computed tomography angiography and nonalcoholic fatty liver disease

A matched case-control study

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is a risk factor for cardiac mortality. Pericoronary adipose tissue (PCAT) attenuation, expressed by the fat attenuation index on coronary computed tomography angiography, reflects pericoronary inflammation. We aimed to investigate the association between PCAT attenuation and NAFLD.

This is a single-center cohort study comprising of patients who underwent coronary computed tomography angiography for suspected stable coronary artery disease between January and December 2020. Patient characteristics and coronary computed tomography angiography findings were analyzed between patients with NAFLD (n=78) and a propensity score-matched cohort of patients without NAFLD (n=78). PCAT attenuation was assessed in Hounsfield units (HU) of proximal 40-mm segments of the left anterior descending artery (LAD) and right coronary artery.

The mean PCAT attenuation in LAD and right coronary artery were significantly higher in patients with NAFLD than those without NAFLD. When patients were divided into 2 groups using the median LAD-PCAT attenuation of -72.5 HU, the high PCAT attenuation group had more males (82% vs 67%, $P=.028$) and NAFLD patients (63% vs 37%, $P=.001$) compared to the low PCAT attenuation group. No differences in age, body mass index, conventional cardiovascular risk factors, or the presence of high-risk plaque were observed between the 2 groups. In the multivariate logistic analysis, NAFLD was independently associated with high PCAT attenuation (odds ratio 2.912, 95% confidence interval 1.386 to 6.118, $P=.005$).

NAFLD is associated with high PCAT attenuation on coronary computed tomography angiography. This finding suggests that pericoronary inflammation is involved in the increased cardiac mortality in NAFLD patients.

Abbreviations: CTA = computed tomography angiography, LAD = left anterior descending artery, NAFLD = nonalcoholic fatty liver disease, PCAT = pericoronary adipose tissue, RCA = right coronary artery.

Keywords: coronary computed tomography angiography, non-alcoholic fatty liver disease, perivascular coronary inflammation

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease, with an estimated prevalence of 15% to 30% in the general population.^[1] NAFLD is not only associated with increased liver-related mortality, but also with increased cardiac mobility and mortality.^[2,3] Earlier, we reported a significant association between NAFLD and the presence of high-risk plaques on coronary computed tomography angiography (CTA) that increase the likelihood of cardiovascular events.^[4] Emerging evidence demonstrated that NAFLD represented a chronic low-grade inflammatory state, characterized by elevated circulating levels of cytokines and activation of pro-inflammatory signaling pathways.^[5,6] However, the underlying mechanisms of the increased cardiac mortality in patients with NAFLD have not been fully understood.

Vascular inflammation is linked to the development of atherosclerosis and the pathogenesis of acute coronary syndrome.^[7] Recently, pericoronary adipose tissue (PCAT) attenuation on coronary CTA was introduced as a novel method to identify localized coronary inflammation.^[8] High PCAT attenuation was found to be associated with the progression of non-calcified plaque and total plaque volumes as determined with coronary CTA.^[9] In the Cardiovascular RISK Prediction using

Computed Tomography (CRISP-CT) study, high PCAT attenuation around the right coronary artery and left anterior descending artery (LAD) and the right coronary artery (RCA) was shown to be a significant risk factor for the increased cardiac mortality.^[10] To date, no study has been reported on the differences in pericoronary vascular inflammation between patients with and without NAFLD.

Therefore, the present study aimed to investigate the association between NAFLD and PCAT attenuation as quantified by coronary CTA.

2. Materials and methods

2.1. Study population

This case-control study was a sub-analysis of the prospective, single-center registry that evaluated the impact of NAFLD on the prognosis in patients with stable coronary artery disease (CAD) undergoing coronary CTA at Okayama University Hospital. Figure 1 shows the flow diagram of the study design. Three hundred seventy one Japanese outpatients without a history of CAD who underwent coronary CTA for suspected stable CAD from January to December 2020 were enrolled. Stable CAD was defined as angina with no changes in the frequency, duration, or intensity of anginal symptoms within 4 weeks before coronary CTA. The patients who consumed >20g of alcohol per day (n=42), with known liver disease (carriers of hepatitis B or C virus, n=15), who were currently using oral corticosteroids (n=10) were excluded from the study. Finally, 304 patients were included in the study, of which 78 were diagnosed with NAFLD by abdominal CT. Of the 226 non-NAFLD patients, 78 age- and sex-matched patients were selected as the non-NAFLD group. The study protocol was approved by the Institutional Review Board of Okayama University Hospital and the study was conducted in accordance with the principles of the Declaration of

Helsinki. All enrolled patients provided written informed consent.

2.2. CT assessment of nonalcoholic fatty liver disease

An abdominal non-contrast CT scan was performed just before the cardiac scan on the same day, as previously described.^[2,11] Hepatic and splenic Hounsfield attenuations were measured in the largest possible regions. The regions of interest included 2 areas that were aligned to the anterior-posterior dimension of the right liver lobe and one that was aligned to the spleen. The hepatic-to-spleen attenuation ratio was calculated using the mean Hounsfield unit (HU) measurements of the 2 right liver lobe regions of interest. A hepatic-to-spleen attenuation ratio of <1.0 was defined as the cutoff for a positive diagnosis of hepatic steatosis.

2.3. Acquisition and analyses of coronary computed tomography angiography images

CT scans were performed using a 128-slice CT scanner (SOMATOM Definition Flash; Siemens Medical Solutions, Erlangen, Germany) as previously described.^[12] Coronary CTA findings were interpreted by 2 experienced cardiovascular imagers (K.I. and T.M.) who were blinded to clinical and CT data. Plaque characteristics were defined in accordance with the Society of Cardiovascular CT.^[13] Significant coronary artery stenosis was defined by a cross-sectional narrowing of >50%. The vascular remodeling index was calculated by dividing the cross-sectional lesion vessel area by the proximal reference vessel area. Positive remodeling was defined as a remodeling index >1.1. Plaques with a CT attenuation number of <50 HU were defined as low-density plaques. Spotty calcification was defined as a calcium burden length <1.5 times the vessel diameter and a width less than two-thirds of the vessel diameter. High-risk plaques were defined when 2 or more plaque characteristics,

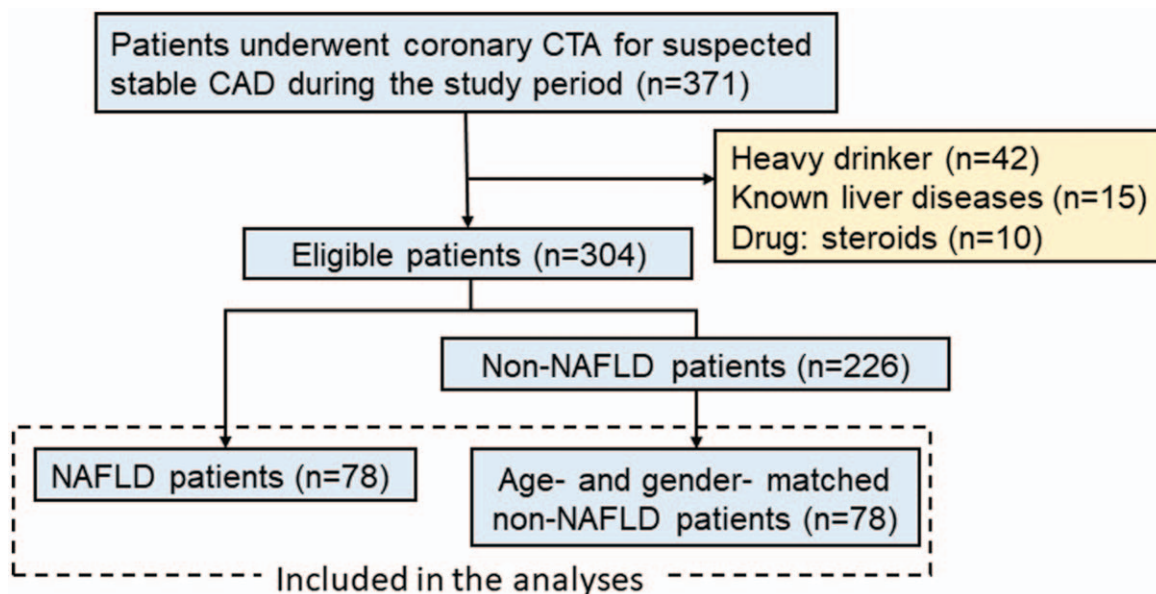


Figure 1. Flowchart showing the study design. Among 371 Japanese outpatients without a history of CAD who underwent coronary CTA for suspected stable CAD, those who consumed >20g of alcohol per day, with known liver disease (carriers of hepatitis B or C virus), and who were currently using oral corticosteroids were excluded. A total of 78 patients were diagnosed with NAFLD, and 78 age- and sex- matched patients were selected as the non-NAFLD group from the remaining 226 non-NAFLD patients. CAD = coronary artery disease, CTA = computed tomography angiography, NAFLD = non-alcoholic fatty liver disease.

including positive remodeling, low-density plaques, and spotty calcification were present, as previously described.^[2]

2.4. Analysis of pericoronary adipose tissue attenuation

In all patients, PCAT attenuation was measured using a dedicated workstation (Aquarius iNuition Edition version 4.4.13; TeraRecon Inc., Foster City, CA, USA). The semi-automated software used in this study had been validated with respect to repeatability before, showing a very good intra-observer and interobserver agreement for the PCAT attenuation (intraclass correlation coefficient 0.987 [$P < .0001$] and 0.980 [$P < .0001$], respectively).^[10] The standard measurements of PCAT attenuation around the proximal LAD and the proximal RCA are the excellent surrogates of the background vascular inflammation of the entire coronary tree.^[14] As shown in Figure 2A–F, the proximal 40 mm segments of the LAD and proximal 10 to 50 mm segment of the RCA were traced in an automated manner with the additional manual adjustments to the automatic delineation of the coronary vessel wall. PCAT was defined as the adipose tissue located within a radial distance from the outer vessel wall equal to the diameter of the coronary vessel, as described and validated previously.^[8,15] Adipose tissue was defined as all voxels with an attenuation between -190 HU and -30 HU, and the PCAT attenuation was automatically calculated as the mean CT attenuation value of PCAT. PCAT attenuation analysis was performed by 2 investigators (T.M. and K.O.) who were blinded to clinical and CT data. We measured the LAD-PCAT attenuation in all patients ($n = 156$)

and the RCA-PCAT attenuation in 138 patients (88%) due to hypoplasia of the RCA. Thus, in the present study, PCAT attenuation surrounding the LAD was used for further analysis.

2.5. Statistical analysis

Continuous variables are expressed as mean \pm standard deviation or median with interquartile range. Dichotomous variables are expressed as numbers (proportion). Differences in continuous variables between the 2 groups were analyzed by the paired Student t test or the Mann–Whitney U test, as appropriate. Categorical data were compared by Chi-Squared analysis or Fisher exact test, based on the category cell size. Univariable and multivariable logistic regression analyses were performed to evaluate the association between NAFLD and high PCAT attenuation. In multivariable logistic regression analysis, the associations were adjusted for the variables. All reported P values were two-sided and $P < .05$ was considered statistically significant. Statistical analyses were performed using SPSS software (version 24; IBM Corp., Armonk, NY).

3. Results

3.1. Patient characteristics and coronary computed tomography angiography findings according to nonalcoholic fatty liver disease status

The mean age of the study population was 62 years, and 75% were males. The baseline characteristics of patients with and without NAFLD are shown in Table 1. Patients with NAFLD had

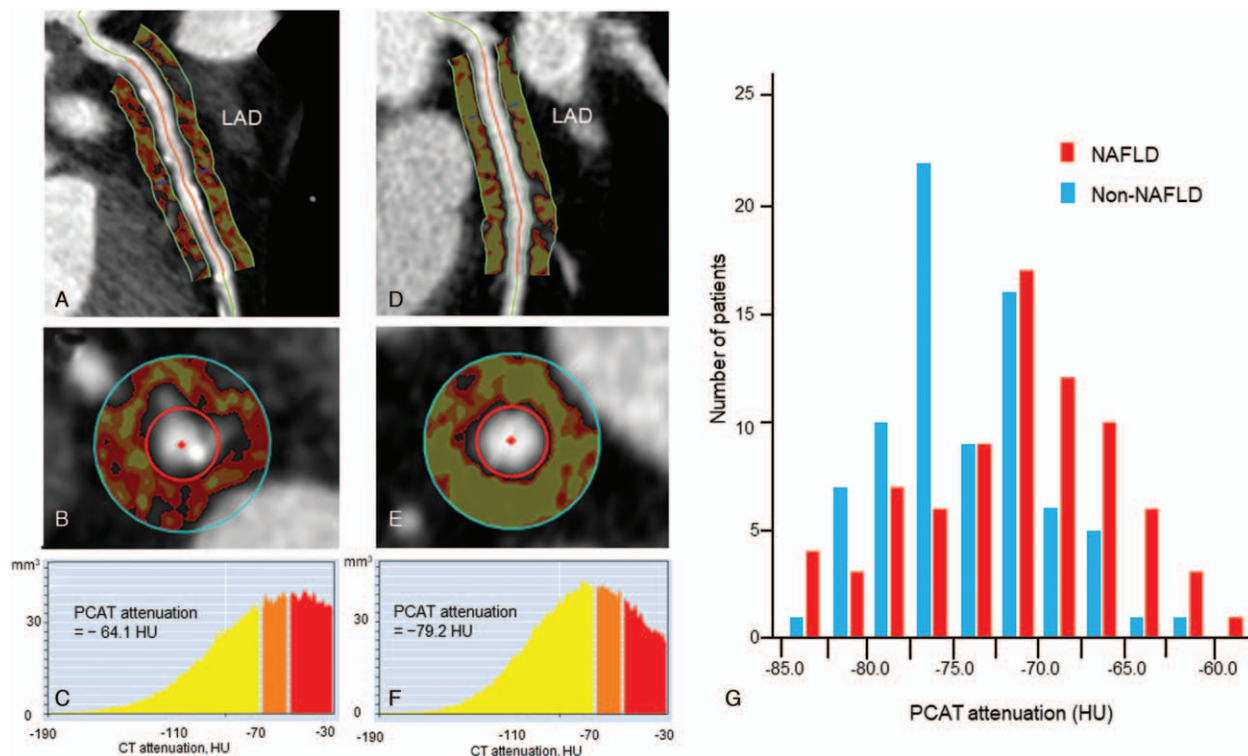


Figure 2. PCAT using coronary CT angiography. Representative images of PCAT attenuation in patients with NAFLD (A–C) and without NAFLD (D–F). Semi-automated software measurements showing color coded PCAT attenuation in axial view (A and C) and longitudinal view (B and D) around the proximal 40 mm of the LAD. PCAT attenuation was defined as the mean CT attenuation value (-190 to -30 HU) within a radial distance equal to the diameter of the vessel. Histograms demonstrated that the PCAT attenuation in the LAD was -64.1 HU and -79.2 HU in patients with and without NAFLD, respectively (C and F). The numbers of patients with NAFLD (red bar) and without NAFLD (blue bar) are shown in the histograms (G). CT = computed tomography, HU = Hounsfield unit, LAD = left anterior descending artery, NAFLD = non-alcoholic fatty liver disease, PCAT = pericoronary adipose tissue attenuation.

Table 1
Patient characteristics according to the presence or absence of NAFLD.

	All	NAFLD		* P value
		Present	Absent	
N	156	78	78	
Age, yrs	62±11	62±12	63±11	.801
Males	116 (74)	58 (74)	58 (74)	1.000
Body mass index, kg/m ²	26±4	27±3	25±3	<.001
Hypertension	94 (60)	58 (74)	36 (46)	<.001
Diabetes mellitus	54 (35)	34 (44)	20 (26)	.018
Dyslipidemia	88 (56)	47 (60)	41 (53)	.333
Current smoker	44 (28)	24 (31)	20 (26)	.477
†Obesity	82 (53)	54 (69)	28 (36)	<.001
β blocker	34 (22)	19 (24)	15 (19)	.438
Calcium channel blocker	57 (37)	37 (47)	20 (26)	.005
ACE-I or ARB	67 (43)	42 (54)	25 (32)	.006
Statin	48 (31)	31 (40)	17 (22)	.015
LAD-PCAT attenuation, HU	-72.9±5.5	-71.3±5.9	-74.5±4.6	<.001
High-risk plaques in LAD	41 (26)	28 (36)	13 (17)	.006
Significant stenosis in LAD	41 (26)	24 (31)	17 (22)	.203

Data are presented as mean ± standard deviation or number (%).

* Comparisons between patients with and without NAFLD.

† Obesity was defined as body mass index ≥ 25 kg/m².

ACE-I = angiotensin-converting enzyme inhibitor, ARB = angiotensin-receptor blocker, HU = Hounsfield units, LAD = left anterior descending artery, NAFLD = non-alcoholic fatty liver disease, PCAT = pericoronary adipose tissue.

a greater body mass index and a higher prevalence of hypertension, diabetes mellitus, and obesity. Patients with NAFLD also had higher levels of aspartate aminotransferase ($P=.002$), alanine aminotransferase ($P<.001$), and glycated hemoglobin A1c ($P=.005$) and lower levels of high-density lipoprotein ($P=.017$) than those without NAFLD.

The mean PCAT attenuation in LAD and RCA was -72.9 HU and -70.6 HU, respectively. The mean PCAT attenuation in patients with NAFLD was significantly higher than that in patients without NAFLD (LAD; -71.3 ± 5.9 HU and -74.5 ± 4.6 HU, $P<.001$, RCA; -69.6 ± 6.3 HU and -71.6 ± 5.2 HU, $P=.038$). The histograms of LAD-PCAT attenuation are shown in Figure 2G. The prevalence of high-risk plaques in LAD was significantly greater in patients with NAFLD than that in those without NAFLD ($P=.042$). No difference in the prevalence of significant stenosis in the LAD was found between the 2 groups ($P=.390$).

3.2. Patient characteristics and coronary computed tomography angiography findings according to pericoronary adipose tissue attenuation

The patients were classified into 2 groups based on the median value of the LAD-PCAT attenuation (-72.5 HU): high PCAT attenuation group (≥ -72.5 HU, $n=78$) and low PCAT attenuation group (< -72.5 HU, $n=78$). As shown in Table 2, high PCAT attenuation was observed in male patients ($P=.028$) and in patients with NAFLD ($P=.001$). With regard to coronary CTA findings, no differences in the prevalence of high-risk plaques ($P=.114$) and significant stenosis ($P=.667$) were found between the high and low PCAT attenuation groups.

3.3. Association between nonalcoholic fatty liver disease and pericoronary adipose tissue attenuation

As shown in Table 3, univariate logistic regression analysis revealed that male sex and NAFLD were significantly associated

with high PCAT attenuation. In multivariate logistic regression analysis, NAFLD was independently associated with high PCAT attenuation with an odds ratio of 2.912 (95% confidence interval: 1.386–6.118, $P=.005$) after adjustment for the variables (age, sex, hypertension, diabetes mellitus, dyslipidemia, smoking, obesity). In addition, NAFLD was independently associated with high PCAT attenuation with an odds ratio of 2.851 (95% confidence interval [CI]: 1.340–6.068, $P=.007$) after adjustment for the variables mentioned above plus coronary CTA findings (high-risk plaques and significant stenosis). We further analyzed the association between NAFLD and elevated PCAT attenuation (≥ -70.1 HU, the cut-off value derived from the previous study by Oikonomou et al.^[10]). NAFLD was independently associated with elevated PCAT attenuation with an odds ratio of 4.392 (95% confidence interval: 1.851–10.417, $P=.001$) (Data not shown).

4. Discussion

To our knowledge, this is the first study to demonstrate that NAFLD was significantly associated with high PCAT attenuation on coronary CTA. This result suggests that patients with NAFLD have greater pericoronary inflammation as compared to patients without NAFLD. Our findings may help identify underlying mechanisms between NAFLD and cardiovascular events.

Chronic inflammation plays a critical role in the development of atherosclerosis and plaque rupture leading to acute coronary syndrome.^[7] It is recognized that chronic low-grade systemic inflammation is a key feature of NAFLD.^[16] In the Framingham Heart Study, the presence of liver fat measured by CT was linked to the increased level of plasma inflammatory biomarkers.^[5] In addition, the levels of interleukin-6, high-sensitivity C-reactive protein, and tumor necrosis factor- α have been reported to increase in line with hepatic histological severity.^[6,17] Thus, NAFLD has a systemic foundation for the development of atherosclerosis. On the other hand, high PCAT attenuation

Table 2
Patient characteristics according to high or low PCAT attenuation.

N	High PCAT attenuation	Low PCAT attenuation	P value
	(≥ -72.5 HU) 78	(< -72.5 HU) 78	
Age, yrs	62 ± 13	62 ± 11	.951
Males	64 (82)	52 (67)	.028
Body mass index, kg/m ²	26 ± 3	26 ± 4	.951
Hypertension	29 (37)	25 (32)	.501
Diabetes mellitus	42 (54)	46 (59)	.518
Dyslipidemia	42 (54)	46 (59)	.518
Current smoker	23 (30)	21 (27)	.722
*Obesity	44 (56)	38 (49)	.374
β blocker	13 (17)	21 (27)	.121
Calcium channel blocker	27 (35)	30 (39)	.618
ACE-I or ARB	37 (47)	30 (39)	.258
Statin	24 (31)	24 (31)	1.000
eGFR, ml/min/1.73 m ²	71 ± 18	69 ± 15	.536
AST, IU/L	27 ± 14	25 ± 9	.282
ALT, IU/L	32 ± 18	28 ± 16	.123
Total cholesterol, mg/dL	190 ± 35	194 ± 37	.548
LDL cholesterol, mg/dL	116 ± 36	122 ± 32	.287
HDL cholesterol, mg/dL	52 ± 11	53 ± 15	.637
Triglyceride, mg/dL	129 (97–190)	121 (98–189)	.792
Hemoglobin A1c, %	6.5 ± 1.2	6.2 ± 0.9	.153
hsCRP, mg/dL	0.12 (0.06–0.22)	0.11 (0.06–0.30)	.958
High-risk plaques in LAD	15 (19)	8 (10)	.114
Significant stenosis in LAD	12 (15)	14 (18)	.667

Data are presented as mean ± standard deviation, number (%), or median (25th–75th percentile).

* Obesity was defined as body mass index ≥ 25 kg/m².

ACE-I = angiotensin-converting enzyme inhibitor, ALT = alanine aminotransferase, ARB = angiotensin receptor blockers, AST = aspartate aminotransferase, eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein, hsCRP = high-sensitivity C-reactive protein, HU = Hounsfield units, LAD = left anterior descending artery, LDL = low-density lipoprotein, NAFLD = non-alcoholic fatty liver disease, PCAT = pericoronary adipose tissue.

represents changes in the PCAT composition driven by inflammatory signals coming from the inflamed coronary artery. The present study clearly demonstrated that NAFLD played an important role not only in systemic inflammation but also in localized coronary artery inflammation. Further studies are needed to focus on the identification of the mechanisms linking NAFLD to local vascular inflammation.

Our previous study showed that NAFLD was an independent risk factor for high-risk coronary plaques that increase the likelihood of acute coronary events.^[4] We also demonstrated that the incidence of acute coronary events and the presence of high-risk plaques were significantly greater in patients with NAFLD than in those without NAFLD.^[2] However, the Incident COronary EveNts Identified by Coronary Tomography (ICON-IC) study demonstrated that the relationship between high-risk plaques on coronary CTA and future cardiovascular events was weak,^[18] suggesting that the presence of high-risk plaques could only partly explain the underlying mechanism of cardiovascular events. Meanwhile, PCAT attenuation was reported to be linked with cardiac mortality.^[10] In the present study, the presence of high-risk plaques was not significantly associated with high PCAT attenuation, which is in line with previous data.^[14] Our findings suggest that high-risk plaques and high PCAT attenuation capture different biological information, both of which might be linked to cardiovascular events in NAFLD patients.

Despite the increasing number of NAFLD patients, there are limited therapeutic approaches and no approved pharmacological therapies for NAFLD.^[16] Therefore, the management of metabolic risk factors by lifestyle changes and pharmacological therapies are the essential components for its prevention. Our results suggest that the treatments which reduce PCAT attenuation may potentially prevent CAD in patients with NAFLD.

Table 3
Univariate and multivariate predictors of the high PCAT attenuation.

	Univariate		*Multivariate-1		†Multivariate-2	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Age, per 1 yr	0.999 (0.973–1.026)	.951	0.999 (0.968–1.031)	.948	1.001 (0.969–1.034)	.948
Male	2.286 (1.084–4.818)	.030	2.528 (1.117–5.720)	.026	2.674 (1.150–6.219)	.022
Body mass index, per 1 kg/m ²	0.997 (0.912–1.090)	.951				
Hypertension	1.537 (0.806–2.932)	.192	1.179 (0.545–2.550)	.677	1.154 (0.524–2.542)	.722
Diabetes mellitus	1.255 (0.648–2.430)	.501	1.055 (0.498–2.234)	.889	1.127 (0.523–2.426)	.760
Dyslipidemia	0.812 (0.431–1.530)	.519	0.737 (0.366–1.486)	.394	0.764 (0.373–1.565)	.462
Current smoker	1.135 (0.722–2.281)	.722	0.851 (0.387–1.867)	.687	0.860 (0.381–1.937)	.715
Obesity	1.362 (0.725–2.559)	.337	1.014 (0.494–2.078)	.971	1.094 (0.520–2.301)	.813
Statin	1.000 (0.507–1.974)	1.000				
eGFR, per 1 ml/min/1.73 m ²	1.006 (0.987–1.025)	.534				
Total cholesterol, per 1 mg/dL	0.997 (0.988–1.006)	.545				
LDL cholesterol, per 1 mg/dL	0.995 (0.985–1.005)	.285				
HDL cholesterol, per 1 mg/dL	0.993 (0.967–1.021)	.634				
*Log (Triglyceride), 1 index	1.139 (0.595–2.180)	.694				
Hemoglobin A1c, per 1%	1.263 (0.914–1.747)	.157				
†Log (hsCRP), 1 index	0.898 (0.673–1.200)	.468				
NAFLD	2.855 (1.491–5.465)	.002	2.912 (1.386–6.118)	.005	2.749 (1.275–5.930)	.010
High-risk plaques in LAD	1.828 (0.884–3.781)	.104			1.979 (0.772–5.076)	.155
Significant stenosis in LAD	0.820 (0.401–1.675)	.82			0.444 (0.174–1.131)	.089

* Multivariate-1 model was adjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, smoking, and obesity.

† Multivariate-2 model was adjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, smoking, obesity, high-risk plaques, and significant stenosis.

‡ Triglyceride and hsCRP were logarithm-transformed.

CI = confidence interval, eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein, hsCRP = high-sensitivity C-reactive protein, LAD = left anterior descending artery, LDL = low-density lipoprotein, NAFLD = non-alcoholic fatty liver disease, PCAT = pericoronary adipose tissue.

Statins are well established for the prevention of cardiovascular events, and Dai et al reported that statin therapy over 1 year decreased PCAT attenuation.^[19] However, in our study, NAFLD patients had a higher PCAT attenuation despite almost 40% of patients taking statins, suggesting that further aggressive treatments are needed. Bittner et al recently reported that high levels of eicosapentaenoic acid are associated with lower PCAT attenuation.^[20] Considering the clinical trial data that pure eicosapentaenoic acid supplementation reduced low-attenuation coronary plaque volume on coronary CTA,^[21] omega-3 supplementation would be a promising approach to reduce pericoronary inflammation. Further studies are needed to investigate the effects of these therapies on PCAT attenuation in NAFLD patients and their clinical outcome.

Our study has some limitations that need to be addressed. First, this is a single-center case-control study, and the sample size was small. Our findings need to be confirmed with a larger population. Second, our study population only consisted of patients who were suspected of having stable CAD. Furthermore, only Japanese patients were included. Although several studies on non-Asian populations have recently been reported,^[15,19] the generalizability of our data to other ethnicities remains uncertain. Third, we have not obtained the clinical outcome data yet; therefore, the association between PCAT attenuation and cardiovascular events is not determined.

In conclusion, our study demonstrated that NAFLD was significantly associated with high PCAT attenuation on coronary CTA, which may be considered as a novel marker of coronary inflammation, independent of classical cardiovascular risk factors. Our findings may help to identify underlying mechanisms linking NAFLD to cardiovascular events.

Author contributions

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