

Lipoprotein (a) level is associated with plaque vulnerability in patients with coronary artery disease: An optical coherence tomography study

Yusuke Muramatsu, Yoshiyasu Minami *, Ayami Kato, Aritomo Katsura, Toshimitsu Sato, Ryota Kakizaki, Teruyoshi Nemoto, Takuya Hashimoto, Kazuhiro Fujiyoshi, Kentaro Meguro, Takao Shimohama, Junya Ako

Department of Cardiovascular Medicine, Kitasato University School of Medicine, Sagami-hara, Japan

ARTICLE INFO

Article history:

Received 15 March 2019

Accepted 5 June 2019

Available online 13 June 2019

ABSTRACT

Background: High lipoprotein (a) [Lp(a)] levels are an independent factor for worse prognosis in patients with coronary artery disease (CAD). However, the association between serum Lp(a) level and coronary plaque vulnerability remains to be determined.

Methods: A total of 255 consecutive patients with CAD who underwent optical coherence tomography imaging of culprit lesions were included. Patients were divided into 2 groups according to their Lp(a) levels (the higher Lp(a) group [≥ 25 mg/dL], $n = 87$; or the lower Lp(a) group [< 25 mg/dL], $n = 168$).

Results: The prevalence of thin-cap fibroatheroma (TCFA) was significantly higher in the higher Lp(a) group than in the lower Lp(a) group (23% [$n = 20$] vs. 11% [$n = 19$], $p = 0.014$). Although the prevalence of TCFA was comparable between the 2 groups among patients with a lower LDL cholesterol (LDL-C) level (< 100 mg/dL), TCFA was significantly more prevalent in the higher Lp(a) group than in the lower Lp(a) group (39% [14/36] vs. 10% [5/50], $p = 0.001$) among patients with a higher LDL-C level (≥ 100 mg/dL).

Conclusions: A higher Lp(a) level was associated with a higher frequency of TCFA, particularly in patients with a higher LDL-C level.

© 2019 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

High lipoprotein (a) [Lp(a)] levels are associated with the incidence of cardiovascular disease. Previous studies, including meta-analyses [1], Mendelian randomization [2], and genome-wide association studies [3], demonstrated its impact on the increased risk of cardiovascular disease, particularly acute coronary syndrome [4]. The worse clinical outcome in patients with elevated Lp(a) is often explained by the atherogenic nature of Lp(a) particles, which comprise an apolipoprotein (apo) B-containing low-density lipoprotein (LDL)-like segment and the plasminogen-like glycoprotein apo(a) segment. Both segments are considered to contribute to promoting proatherogenic and antifibrinolytic reactions in the arterial wall, leading to the progression or rupture of coronary plaques, in combination with other atherogenic particles that include LDL-cholesterol (LDL-C). In fact, a recent meta-analysis demonstrated that patients with the combination of elevated Lp(a) and LDL-C had worse clinical outcomes than other patients [5]. However, to date, the association between Lp(a) and detailed coronary plaque vulnerability remains unclear, although an association with the severity of coronary plaques has been demonstrated in several studies using

angiography and computed tomography [6,7]. Thus, in the present study, we aimed to clarify: 1) the association between Lp(a) levels and plaque vulnerability of coronary lesions using intra coronary optical coherence tomography (OCT); and 2) the additive effect of LDL-C levels on plaque vulnerability.

2. Methods

2.1. Study population

This was a retrospective observational study conducted between June 2016 and March 2018 at a single center. From a total of 765 consecutive patients who underwent percutaneous coronary intervention (PCI), we identified 338 patients who were assessed for culprit lesions using OCT. After excluding patients without serum Lp(a) values ($n = 83$), we finally included 255 patients in the present study (Supplementary Fig. 1). The comparisons in clinical characteristics and OCT analysis of culprit lesions between patients with Lp(a) measurement and those without Lp(a) measurement are shown in Supplementary Tables 1 and 2. The distribution of Lp(a) values in the present cohort is shown in Supplementary Fig. 2. Patients were divided into 2 groups according to their Lp(a) levels (the higher Lp(a) group [≥ 25 mg/dL], $n = 87$; or the lower Lp(a) group [< 25 mg/dL], $n = 168$). Serum Lp(a) values were examined within one month before or after PCI. The Lp(a) cutoff

* Corresponding author at: Department of Cardiovascular Medicine, Kitasato University School of Medicine, 1-15-1 Kitasato, Minami-ku, Sagami-hara, Kanagawa 252-0373, Japan.
E-mail address: nrg12391@yahoo.co.jp (Y. Minami).

value of 25 mg/dL was based on the Receiver-operating characteristic (ROC) analysis to identify the presence of thin-cap fibroatheroma on OCT images (OCT-TCFA) (Fig. 1). Other blood samples were obtained within 1 month before PCI. The study protocol was approved by the Human Research Committee of Kitasato University School of Medicine, and all patients provided written informed consent before the procedure.

2.2. OCT image acquisition and assessment

Culprit lesions were assessed using a frequency domain OCT system (C7-XR OCT Intravascular Imaging System; St. Jude Medical, St. Paul, MN, USA) after intracoronary administration of 100–200 µg of nitroglycerin before balloon dilation or stenting. All images were analyzed using offline proprietary software (St. Jude Medical). Qualitative and quantitative analyses were performed at 0.2-mm intervals. The morphologies of all plaques on OCT were analyzed using previously established criteria [8,9]. When lipid was present at $\geq 90^\circ$ in any of the cross sectional OCT images within the plaque, it was considered as a lipid-rich plaque [10]. Fibrous cap thickness was measured at the thinnest part 3 times, and the average value was calculated [11]. OCT-TCFA was defined as a lipid plaque with a lipid arc $>90^\circ$ and a fibrous cap thickness <65 µm. Macrophage accumulation was characterized by signal-rich, distinct, or confluent punctate regions that exceed the intensity of background speckle noise [9]. Microchannels were defined as small black holes or tubular structures of 50–100 µm diameter that were present within a plaque in at least 3 consecutive cross-sectional frames [12]. Calcifications were defined as signal-poor or heterogeneous areas delimited by sharp borders. Calcified lesions subtending an arc $<90^\circ$ and extending in length for 1–4 mm were classified as spotty calcium [13]. Thrombus was defined as a mass >250 µm attached to the luminal surface or float- ing within the lumen [14].

2.3. Definitions

Acute coronary syndrome (ACS) consisted of ST-segment elevation myocardial infarction (STEMI), non-STEMI, and unstable angina pectoris. Hypertension was defined as arterial blood pressure $>140/90$ mm Hg or the use of antihypertensive medication. Dyslipidemia was defined as high-density lipoprotein cholesterol <40 mg/dL, LDL-C >140 mg/dL, or triglycerides >150 mg/dL, or the use of dyslipidemia medication. The diagnosis of familial hypercholesterolemia (FH) was based on a modified form of the Dutch Lipid Clinic Network criteria

(Supplementary methods), in which the diagnosis of Achilles tendon xanthoma is based on radiographic criteria rather than physical exam [15]. In the present analysis, both 'definite FH' and 'probable FH' were included as the FH. Diabetes mellitus was defined as symptoms of diabetes plus casual plasma glucose concentration >200 mg/dL, fasting plasma glucose concentration >126 mg/dL, 2-h plasma glucose concentration >200 mg/dL during a 75-g oral glucose tolerance test, or the use of diabetes medication. Chronic kidney disease was defined as an estimated glomerular filtration rate of <60 mL/min per 1.73 m².

2.4. Statistical analysis

Continuous variables with a normal distribution are expressed as mean $\pm$ standard deviation, whereas the median (25–75th percentile) was reported when data were not normally distributed. Continuous variables were analyzed using a *t*-test or Mann–Whitney *U* test. Categorical outcome data were summarized as counts (percentages), and between-group comparisons were performed using Fisher's exact test or the chi-squared test, as appropriate, depending on the expected frequency distribution under the null hypothesis. ROC curves were constructed using the Lp(a) values. The area under the curve (AUC), sensitivity, and specificity were calculated to identify OCT-TCFA. The best cut-off value of Lp(a) was identified by maximizing the sum of sensitivity and specificity. Multivariate logistic regression analysis was performed to determine the independent factors for the presence of OCT-TCFA, including factors that suggested an association with the presence of TCFA [16,17]. Statistical significance was defined as $p < 0.05$. All statistical analyses were performed using JMP 13.0 version (SAS Institute, Cary, NC, USA).

3. Results

3.1. ROC analysis for the presence of OCT-TCFA

A ROC curve was constructed to assess the ability of Lp(a) to identify OCT-TCFA among all patients (Fig. 1-A) and patients with LDL-C ≥ 100 mg/dL (Fig. 1-B). The AUC for the identification of OCT-TCFA was 0.613 (95% CI: 0.516–0.710; $p = 0.005$) in all patients and 0.740 (95% CI: 0.620–0.859; $p = 0.013$) in patients with a higher LDL-C value. The best cut-off for the Lp(a) value to detect OCT-TCFA was 25.0 mg/dL in all patients (sensitivity 70%, specificity 51%) and 25.0 mg/dL in patients with a higher LDL-C value (sensitivity 74%, specificity 67%), respectively.

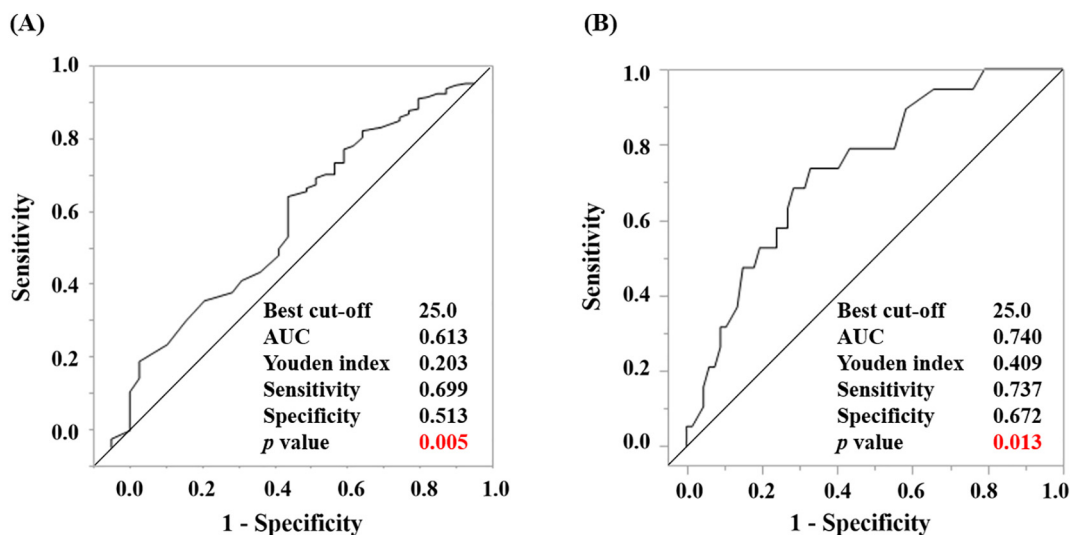


Fig. 1. ROC analysis for the presence of OCT-TCFA. A, All patients; B, patients with LDL-C ≥ 100 mg/dL. AUC, area under the curve; LDL-C, low-density lipoprotein cholesterol; ROC, receiver operator characteristics; OCT-TCFA, thin-cap fibroatheroma on OCT images.

3.2. Clinical characteristics

There was no significant difference in clinical characteristics other than the mean value of LDL-C, renal function and the prevalence of angiotensin converting enzyme inhibitor or angiotensin II receptor blocker and statin intake between the higher Lp(a) group and the lower Lp(a) group (Table 1).

3.3. OCT analysis of culprit lesion

Comparisons of the results of qualitative and quantitative OCT analyses of culprit lesions are shown in Table 2. The prevalence of OCT-TCFA was significantly higher in the higher Lp(a) group than in the lower Lp(a) group (23% [$n = 20$] vs. 11% [$n = 19$], $p = 0.014$). The fibrous cap was significantly thinner in the higher Lp(a) group than in the lower Lp(a) group (0.08 ± 0.04 vs. 0.10 ± 0.04 mm, $p = 0.026$) (Fig. 2). Although the difference was not statistically significant, trends toward higher prevalence of lipid-rich plaque and smaller minimum lumen

Table 1
Clinical characteristics.

Variables	Lp(a) ≥ 25 N = 87	Lp(a) < 25 N = 168	p value
Age, year	68 $\pm$ 10	68 $\pm$ 10	0.941
Male, n (%)	72 (83)	132 (79)	0.428
Body mass index, kg/m ²	23.5 $\pm$ 3.8	24.4 $\pm$ 3.6	0.026
Acute coronary syndrome, n (%)	14 (16)	21 (13)	0.429
Risk factors, n (%)			
Hypertension	67 (77)	127 (76)	0.802
Dyslipidemia	70 (81)	125 (74)	0.280
Diabetes mellitus	41 (47)	79 (47)	0.988
Current smoker	18 (21)	32 (19)	0.771
Family history of IHD	22 (26)	44 (27)	0.853
Chronic kidney disease	48 (55)	72 (43)	0.062
Hemodialysis	12 (14)	11 (7)	0.056
Familial hypercholesterolemia	20 (23)	23 (14)	0.060
Definite	5 (5.8)	1 (0.6)	0.046
Probable	15 (17.2)	22 (13.1)	
Past history, n (%)			
Myocardial infarction	22 (25)	60 (36)	0.091
PCI	37 (43)	82 (49)	0.341
CABG	0 (0)	6 (4)	0.075
Medication at PCI, n (%)			
ARB/ACEI	54 (62)	129 (77)	0.013
Beta-blocker	48 (55)	101 (60)	0.447
CCB	36 (41)	79 (47)	0.390
DPP4I	25 (29)	42 (25)	0.521
Insulin	5 (6)	14 (8)	0.449
SGLT2I	3 (4)	8 (5)	0.625
Statin	68 (78)	149 (89)	0.025
Ezetimibe	7 (8)	15 (9)	0.812
Warfarin	7 (8)	6 (4)	0.124
iPCSK9	0 (0)	0 (0)	–
NOAC	4 (5)	15 (9)	0.212
Aspirin	66 (76)	144 (86)	0.050
Thienopyridine	63 (72)	135 (80)	0.149
Laboratory findings			
Lp(a), mg/dL	43 [32, 58]	11 [6, 16]	<0.001
HbA1c, %	6.4 $\pm$ 0.9	6.5 $\pm$ 1.0	0.468
LDL-C, mg/dL	98 $\pm$ 34	90 $\pm$ 32	0.019
HDL-C, mg/dL	51 $\pm$ 16	50 $\pm$ 13	0.951
Triglyceride, mg/dL	144 $\pm$ 97	162 $\pm$ 104	0.230
Creatinine, mg/dL	1.00 [0.81, 1.22]	0.93 [0.77, 1.09]	0.022
eGFR, mL/min/1.73 m ²	52 $\pm$ 25	59 $\pm$ 21	0.019
BNP, pg/mL	88 [31, 261]	72 [36, 153]	0.371
EPA/AA	0.37 $\pm$ 0.29	0.40 $\pm$ 0.30	0.373

AA, arachidonic acid; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNP, brain natriuretic peptide; CABG, coronary artery bypass graft; CCB, calcium channel blocker; DPP4I, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; EPA, eicosapentaenoic acid; HbA1c, hemoglobin A1c; HDL-C, high density lipoprotein cholesterol; IHD, ischemic heart disease; LDL-C, low-density lipoprotein cholesterol; NOAC, non-vitamin K antagonist oral anticoagulant; PCI, percutaneous coronary intervention; iPCSK9, proprotein convertase subtilisin/kexin type 9 inhibitor; SGLT2I, sodium glucose cotransporter 2 inhibitor.

Table 2
OCT analysis of culprit lesion.

Variables	Lp(a) ≥ 25 N = 87	Lp(a) < 25 N = 168	p value
Culprit vessel			
LAD/LCX/RCA/LMT, n (%)	47 (54)/15 (17)/25 (29)/0 (0)	96 (57)/23 (14)/44 (26)/5 (3)	0.346
Qualitative assessment, n (%)			
Lipid-rich plaque	36 (41)	50 (30)	0.063
OCT-TCFA	20 (23)	19 (11)	0.014
Macrophages	31 (38)	63 (38)	0.769
Microchannels	22 (25)	45 (27)	0.797
Calcification	55 (63)	122 (73)	0.122
Spotty calcification	69 (79)	133 (79)	0.978
Thrombus	3 (4)	5 (3)	0.838
Quantitative assessment			
FCT, mm	0.08 $\pm$ 0.04	0.10 $\pm$ 0.04	0.026
Max lipid arc, °	267.2 $\pm$ 79.4	270.5 $\pm$ 77.4	0.799
MLA, mm ²	1.44 $\pm$ 0.71	1.52 $\pm$ 0.84	0.131
Proximal RVA, mm ²	7.07 $\pm$ 2.85	6.92 $\pm$ 2.79	0.650
Distal RVA, mm ²	4.99 $\pm$ 3.95	4.56 $\pm$ 2.26	0.549
Percent area stenosis, %	74.2 $\pm$ 9.4	72.3 $\pm$ 11.8	0.374
Lesion length, mm	31.1 $\pm$ 14.4	33.4 $\pm$ 13.3	0.101

FCT, fibrous cap thickness; eGFR, estimated glomerular filtration rate; LAD, left ascending coronary artery; LCX, left circumflex coronary artery; LMT, left main trunk; MLA, minimum lumen area; OCT, optical coherence tomography; OCT-TCFA, thin-cap fibroatheroma on OCT images; RCA, right coronary artery; RVA, reference vessel area. P values with statistical significance ($P < 0.05$) are shown as bold.

area in the higher Lp(a) group were observed. The incremental prevalence of OCT-TCFA according to Lp(a) levels was observed (Fig. 3, Supplementary Table 3).

3.4. Independent factors for the presence of OCT-TCFA

A multivariate model demonstrated that higher Lp(a) was independently associated with the presence of OCT-TCFA (Table 3, Supplementary Table 4).

3.5. Prevalence of OCT-TCFA according to LDL-C levels

The significance of higher Lp(a) on the presence of OCT-TCFA according to the LDL-C level was further evaluated. Although the prevalence of OCT-TCFA was comparable between the 2 groups among patients with a lower LDL-C level (< 100 mg/dL), it was significantly higher in the higher Lp(a) group than in the lower Lp(a) group (39% vs. 10%, $p = 0.001$) among patients with a higher LDL-C level (≥ 100 mg/dL) (Fig. 4). The combination of higher Lp(a) and higher LDL-C levels had a greater odds for the prevalence of OCT-TCFA (4.938 [95% confidence interval (CI): 2.219–10.87], $p < 0.001$) than the higher Lp(a) level (2.341 [95% CI: 1.1713–4.701], $p = 0.016$) or higher LDL-C level (2.113 [95% CI: 1.054–4.230], $p = 0.035$).

4. Discussion

The main findings of this study were as follows: 1) The prevalence of OCT-TCFA was significantly higher in the higher Lp(a) group than in the lower Lp(a) group, particularly in patients with high LDL-C levels. 2) Higher Lp(a) was independently associated with a higher prevalence of OCT-TCFA.

4.1. Lp(a) and coronary plaque morphologies

Several previous studies have demonstrated the association between a higher Lp(a) value and the severity of coronary atherosclerosis. Dahren et al. investigated the correlation between the Lp(a) level and the presence and severity of coronary disease in Caucasian patients

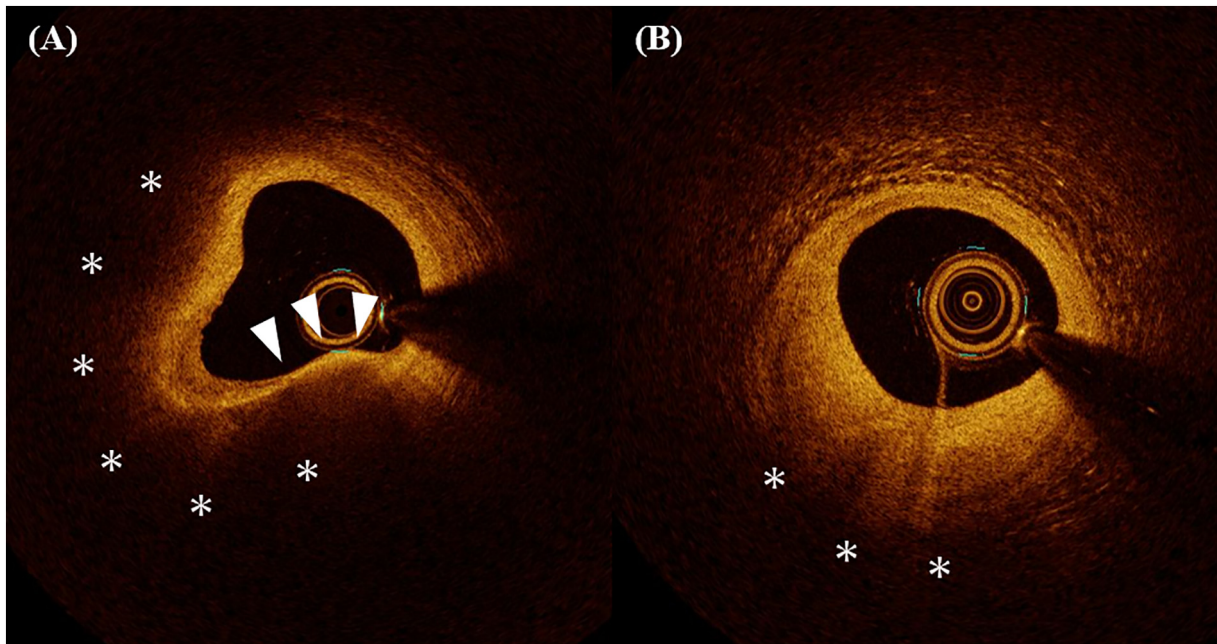


Fig. 2. Representative images of lipid-rich plaque. A, OCT-TCFA in patients with Lp(a) ≥ 25 mg/dL; B, lipid-rich plaque without OCT-TCFA in patients with Lp(a) < 25 mg/dL. Asterisks represent the presence of lipid. Arrowheads represent the thin fibrous cap overlying lipid.

who underwent coronary angiography [6]. The authors reported that Lp(a) values were independently associated with the presence of coronary artery disease and tended to correlate with lesion scores, which consisted of the number and degree of coronary stenosis. Kral et al. examined the correlation between the serum Lp(a) value and findings on coronary computed tomography angiography in healthy African-Americans. The authors demonstrated that subjects with Lp(a) > 40 mg/dL were 4-fold more likely to have stenosis $> 50\%$ [7]. Hartmann et al. reported a positive correlation between Lp(a) values and changes in the plaque-plus-media area in a study using serial intravascular ultrasound observation [18]. In accordance with these previous reports, in the present study, we demonstrated an association between higher Lp(a) values and smaller lumen area with higher prevalence of lipid-rich plaques. This correlation between higher Lp(a) values and vulnerable

plaque features is explained by the LDL-like proatherogenic nature of Lp(a) particles. Serum Lp(a) is taken up by macrophages, leading to foam cell formation, which promotes the formation and progression of atherosclerotic plaques [19]. Lp(a) may further stimulate macrophage transition to foam cells mediated by Lp(a) internalization via a very low-density lipoprotein receptor and an apo(a) receptor [20]. The greater affinity of Lp(a) to proteoglycans and the extracellular matrix compared with that of LDL also contributes to the formation and progression of coronary plaques [21]. In contrast, the significance of the prothrombotic nature of Lp(a) particles on the process of plaque formation and progression remains unknown. In the present study, the prevalence of thrombus in the culprit lesions was comparable between both Lp(a) groups. However, the significance of a higher Lp(a) value on the prevalence of coronary thrombus was not sufficiently evaluated because the number of patients with ACS was limited in the present study. Further studies with a larger number of patients with ACS may clarify the significance of a higher Lp(a) value on the formation of coronary plaques mixed with thrombus.

4.2. Association of the combination of Lp(a) and LDL-C with plaque morphologies

With regard to the prevalence of TCFA, Niccoli et al. demonstrated a higher prevalence in patients with Lp(a) ≥ 30 mg/dL compared with those with Lp(a) < 30 mg/dL (38 vs. 10%, $p = 0.04$) in a small OCT cohort ($n = 51$) [22]. In the present study, we further demonstrated the

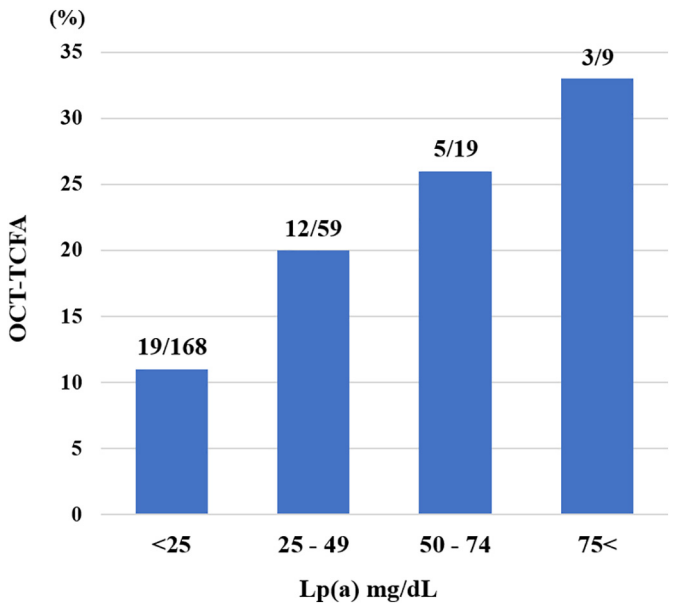


Fig. 3. Prevalence of OCT-TCFA according to Lp(a) values. OCT-TCFA, thin-cap fibroatheroma on OCT images.

Table 3
Multivariate logistic regression analysis for independent factors affecting the presence of OCT-TCFA.

Variables	Multivariate analysis		
	Odds ratio	95% CI	p value
Statin	0.765	0.291–2.171	0.601
eGFR, mL/min/1.73 m ²	0.998	0.982–1.014	0.799
LDL-C, mg/dL	1.008	0.996–1.019	0.195
Lp(a), mg/dL	1.016	1.003–1.029	0.014

OCT-TCFA, thin-cap fibroatheroma on OCT images; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol. P values with statistical significance ($P < 0.05$) are shown as bold.

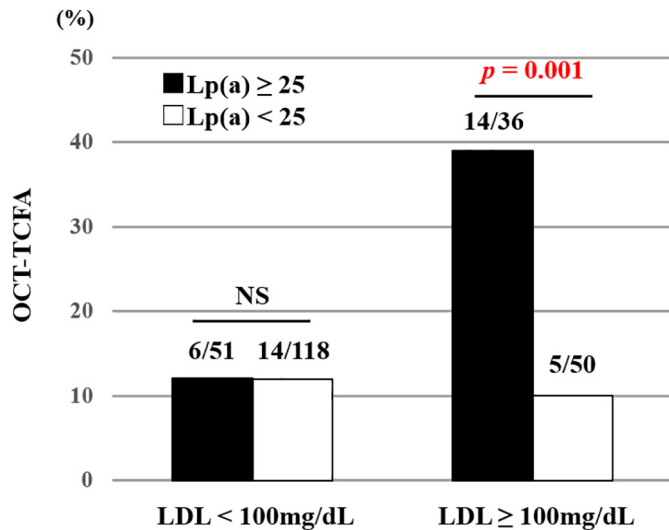


Fig. 4. Prevalence of OCT-TCFA according to Lp(a) and LDL-C levels. LDL-C, low-density lipoprotein cholesterol; OCT-TCFA, thin-cap fibroatheroma on OCT images; NS, not significant.

independent association between a higher Lp(a) value and the higher prevalence of OCT-TCFA in a larger cohort. In addition, we found that patients with the combination of higher Lp(a) and higher LDL-C values had the highest prevalence of OCT-TCFA in patients requiring PCI. The association of this combined elevation of Lp(a) and cholesterol levels with the incidence of cardiovascular disease was demonstrated in several previous studies. A large-sized ($n = 25,558$) retrospective analysis that included patients from 3 studies reported that Lp(a) was associated with the incidence of cardiovascular disease only among those with high total cholesterol levels [23]. Alonso et al. showed that patients with life-long elevated LDL-C with cardiovascular disease had significantly higher Lp(a) levels compared with patients who did not have cardiovascular disease in a cohort of FH, as well as non-FH affected relatives [24]. Although the exact mechanisms of the higher incidence of cardiovascular disease in patients with elevated Lp(a) and cholesterol levels remain unclear, a previous study suggested a higher prevalence of patients with severe coronary artery disease among those patients. Chieng et al. demonstrated that patients with both elevated Lp(a) and elevated LDL-C constituted most of the patients in the highest SYNTAX (the SYNERGY between percutaneous coronary intervention with TAXUS and Cardiac Surgery) tertile, while patients with non-elevated Lp(a) and non-elevated LDL-C were predominant in the lowest SYNTAX tertile [25]. Our results may further explain the underlying morphological mechanisms of the higher incidence of cardiovascular disease in those patients. In contrast, the significant association between the Lp(a) levels and the presence of OCT-TCFA was not observed in patients with LDL-C <100 mg/dL in the present study. This may suggest that Lp(a) is not a major driver to promote the formation of TCFA but a modifier or enhancer to deteriorate the integrity of fibrous cap in combination with elevated LDL-C. Further studies are still needed to clarify the role of Lp(a) for the development of vulnerable plaque, particularly in the condition of low LDL-C levels.

4.3. Potential of Lp(a) measurement for risk stratification of secondary event

In the present study, higher LDL-C values were not independently associated with higher prevalence of OCT-TCFA. This might be due to the high percentage of statin prescription in the present cohort, which could influence both LDL-C values and plaque morphologies and blur the correlation between them [17]. In contrast, Lp(a) is known not to be largely influenced by pharmacological intervention other than the

prescription of proprotein convertase subtilisin/kexin type 9 inhibitor (iPCSK9) [4]. Thus, the serum Lp(a) level could be a reliable indicator for the presence of vulnerable plaques and subsequent cardiovascular events in patients with established CAD treated by statin. In fact, a recent meta-analysis demonstrated a linear correlation between elevated Lp(a) and the risk of cardiovascular disease in patients with established CAD treated by statin [5]. Although more studies are still needed to confirm the efficacy of Lp(a) reduction by iPCSK9 on the reduction of secondary cardiovascular events [26], on-statin CAD patients with elevated Lp(a) may be primary candidates for iPCSK9 prescription.

4.4. Limitations

The present study has some limitations. First, this study was a small-sized retrospective study performed in a single center. In particular, the present study exclusively included patients with plaque assessment by OCT. Thus, the findings of the present study cannot be generalized. Second, we enrolled patients with known coronary artery disease undergoing PCI using OCT, which might be a potential selection bias. Third, we applied Lp(a) ≥ 25 mg/dL as a cutoff based on the ROC analysis to identify OCT-TCFA. However, its potential as a discriminator for OCT-TCFA in overall cohort might be limited because the AUC was only 0.613. In addition, the use of a different cutoff might yield different results. Fourth, we could not discriminate the effect of pharmacological therapy before OCT assessment on the prevalence of vulnerable plaque features including OCT-TCFA. In particular, the high percentage of statin and anti-platelet drugs prescription may blur the difference in the presence of TCFA and other vulnerable plaque features among the groups. Future studies including larger cohort with statin (and/or anti-platelet drugs) naïve may further clarify the impact of higher Lp(a) on the presence of vulnerable plaque features. Finally, the clinical impact of the present findings was not investigated. Further studies may clarify the significance of Lp(a) measurement, in addition to the conventional assessment of cholesterol, on the risk stratification of cardiovascular disease in daily clinical practice.

Disclosures

None.

Declaration of Competing Interest

None.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcha.2019.100382>.

References

- [1] Emerging Risk Factors Collaboration S. Erqou, S. Kaptoge, P.L. Perry, E. Di Angelantonio, A. Thompson, I.R. White, S.M. Marcovina, R. Collins, S.G. Thompson, J. Danesh, Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality, *JAMA* 302 (2009) 412–423.
- [2] R. Clarke, J.F. Peden, J.C. Hopewell, T. Kyriakou, A. Goel, S.C. Heath, S. Parish, S. Barlera, M.G. Franzosi, S. Rust, D. Bennett, A. Silveira, A. Malarstig, F.R. Green, M. Lathrop, B. Gigante, K. Leander, U. de Faire, U. Seedorf, A. Hamsten, R. Collins, H. Watkins, M. Farrall, PROCARDIS Consortium, Genetic variants associated with Lp(a) lipoprotein level and coronary disease, *N. Engl. J. Med.* 361 (2009) 2518–2528.
- [3] P.R. Kamstrup, A. Tybjaerg-Hansen, R. Steffensen, B.G. Nordestgaard, Genetically elevated lipoprotein(a) and increased risk of myocardial infarction, *JAMA* 301 (2009) 2331–2339.
- [4] S. Tsimikas, A test in context: lipoprotein(a) : diagnosis, prognosis, controversies, and emerging therapies, *J. Am. Coll. Cardiol.* 69 (2017) 692–711.

- [5] P. Willeit, P.M. Ridker, P.J. Nestel, J. Simes, A.M. Tonkin, T.R. Pedersen, G.G. Schwartz, A.G. Olsson, H.M. Colhoun, F. Kronenberg, C. Drechsler, C. Wanner, S. Mora, A. Lesogor, S. Tsimikas, Baseline and on-statin treatment lipoprotein(a) levels for prediction of cardiovascular events: individual patient-data meta-analysis of statin outcome trials, *Lancet* 392 (2018) 1311–1320.
- [6] G.H. Dahlen, J.R. Guyton, M. Attar, J.A. Farmer, J.A. Kautz, A.M. Gotto Jr., Association of levels of lipoprotein Lp(a), plasma lipids, and other lipoproteins with coronary artery disease documented by angiography, *Circulation* 74 (1986) 758–765.
- [7] B.G. Kral, R.R. Kalyani, L.R. Yanek, D. Vaidya, E.K. Fishman, D.M. Becker, L.C. Becker, Relation of plasma lipoprotein(a) to subclinical coronary plaque volumes, three-vessel and left main coronary disease, and severe coronary stenoses in apparently healthy African-Americans with a family history of early-onset coronary artery disease, *Am. J. Cardiol.* 118 (2016) 656–661.
- [8] I.K. Jang, G.J. Tearney, B. MacNeill, M. Takano, F. Moselewski, N. Iftima, M. Shishkov, S. Houser, H.T. Aretz, E.F. Halpern, B.E. Bouma, In vivo characterization of coronary atherosclerotic plaque by use of optical coherence tomography, *Circulation* 111 (2005) 1551–1555.
- [9] G.J. Tearney, E. Regar, T. Akasaka, T. Adriaenssens, P. Barlis, H.G. Bezerra, B. Bouma, N. Bruining, J.M. Cho, S. Chowdhary, M.A. Costa, R. de Silva, J. Dijkstra, C. Di Mario, D. Dudek, E. Falk, M.D. Feldman, P. Fitzgerald, H.M. Garcia-Garcia, N. Gonzalo, J.F. Granada, G. Guagliumi, N.R. Holm, Y. Honda, F. Ikano, M. Kawasaki, J. Kochman, L. Koltowski, T. Kubo, T. Kume, H. Kyono, C.C. Lam, G. Lamouche, D.P. Lee, M.B. Leon, A. Maehara, O. Manfrini, G.S. Mintz, K. Mizuno, M.A. Morel, S. Nadkarni, H. Okura, H. Otake, A. Pietrasik, F. Prati, L. Räber, M.D. Radu, J. Rieber, M. Riga, A. Rollins, M. Rosenberg, V. Sirbu, P.W. Serruys, K. Shimada, T. Shinke, J. Shite, E. Siegel, S. Sonoda, M. Suter, S. Takarada, A. Tanaka, M. Terashima, T. Thim, S. Uemura, G.J. Ughi, H.M. van Beusekom, A.F. van der Steen, G.A. van Es, G. van Soest, R. Virmani, S. Waxman, N.J. Weissman, G. Weisz, International Working Group for Intravascular Optical Coherence Tomography (IWG-IVOCT), Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation, *J. Am. Coll. Cardiol.* 59 (2012) 1058–1072.
- [10] K. Kato, T. Yonetsu, S.J. Kim, L. Xing, H. Lee, I. McNulty, R.W. Yeh, R. Sakhuja, S. Zhang, S. Uemura, B. Yu, K. Mizuno, I.K. Jang, Nonculprit plaques in patients with acute coronary syndromes have more vulnerable features compared with those with non-acute coronary syndromes: a 3-vessel optical coherence tomography study, *Circ. Cardiovasc. Imaging* 5 (2012) 433–440.
- [11] T. Yonetsu, T. Kakuta, T. Lee, K. Takahashi, N. Kawaguchi, G. Yamamoto, K. Koura, K. Hishikari, Y. Iesaka, H. Fujiwara, M. Isobe, In vivo critical fibrous cap thickness for rupture-prone coronary plaques assessed by optical coherence tomography, *Eur. Heart J.* 32 (2011) 1251–1259.
- [12] H. Kitabata, A. Tanaka, T. Kubo, S. Takarada, M. Kashiwagi, H. Tsujioka, H. Ikejima, A. Kuroi, H. Kataiwa, K. Ishibashi, K. Komukai, T. Tanimoto, Y. Ino, K. Hirata, N. Nakamura, M. Mizukoshi, T. Imanishi, T. Akasaka, Relation of microchannel structure identified by optical coherence tomography to plaque vulnerability in patients with coronary artery disease, *Am. J. Cardiol.* 105 (2010) 1673–1678.
- [13] L. Di Vito, J.H. Yoon, K. Kato, T. Yonetsu, R. Vergallo, M. Costa, H.G. Bezerra, E. Arbustini, J. Narula, F. Crea, F. Prati, I.K. Jang, COICO group (Consortium of Investigators for Coronary OCT), Comprehensive overview of definitions for optical coherence tomography-based plaque and stent analyses, *Coron. Artery Dis.* 25 (2014) 172–185.
- [14] D. Matsumoto, J. Shite, T. Shinke, H. Otake, Y. Tanino, D. Ogasawara, T. Sawada, O.L. Paredes, K. Hirata, M. Yokoyama, Neointimal coverage of sirolimus-eluting stents at 6-month follow-up: evaluated by optical coherence tomography, *Eur. Heart J.* 28 (2007) 961–967.
- [15] B.G. Nordestgaard, M.J. Chapman, S.E. Humphries, H.N. Ginsberg, L. Masana, O.S. Descamps, O. Wiklund, R.A. Hegele, F.J. Raal, J.C. Defesche, A. Wiegman, R.D. Santos, G.F. Watts, K.G. Parhofer, G.K. Hovingh, P.T. Kovanen, C. Boileau, M. Averna, J. Borén, E. Bruckert, A.L. Catapano, J.A. Kuivenhoven, P. Pajukanta, K. Ray, A.F. Stalenhoef, E. Stroes, M.R. Taskinen, A. Tybjaerg-Hansen, European Atherosclerosis Society Consensus Panel, Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society, *Eur. Heart J.* 34 (2013) 3478–3490.
- [16] S. Takarada, T. Imanishi, K. Ishibashi, T. Tanimoto, K. Komukai, Y. Ino, H. Kitabata, T. Kubo, A. Tanaka, K. Kimura, M. Mizukoshi, T. Akasaka, The effect of lipid and inflammatory profiles on the morphological changes of lipid-rich plaques in patients with non-ST-segment elevated acute coronary syndrome: follow-up study by optical coherence tomography and intravascular ultrasound, *JACC Cardiovasc. Interv.* 3 (7) (2010) 766–772.
- [17] Y. Minami, Z. Wang, A.D. Aguirre, D.S. Ong, C.J. Kim, S. Uemura, T. Soeda, H. Lee, J. Fujimoto, I.K. Jang, Clinical predictors for lack of favorable vascular response to statin therapy in patients with coronary artery disease: a serial optical coherence tomography study, *J. Am. Heart Assoc.* 6 (11) (2017 Nov 1) (pii: e006241).
- [18] M. Hartmann, C. von Birgelen, G.S. Mintz, M.G. Stoele, H. Eggebrecht, H. Wieneke, M. Fahy, T. Neumann, J. van der Palen, H.W. Louwerenburg, P.M. Verhorst, R. Erbel, Relation between lipoprotein(a) and fibrinogen and serial intravascular ultrasound plaque progression in left main coronary arteries, *J. Am. Coll. Cardiol.* 48 (2006) 446–452.
- [19] K.M. Kostner, G.M. Kostner, A.S. Wierzbicki, Is Lp(a) ready for prime time use in the clinic? A pros-and-cons debate, *Atherosclerosis* 274 (2018) 16–22.
- [20] B.G. Nordestgaard, M.J. Chapman, K. Ray, J. Borén, F. Andreotti, G.F. Watts, H. Ginsberg, P. Amarencio, A. Catapano, O.S. Descamps, E. Fisher, P.T. Kovanen, J.A. Kuivenhoven, P. Lesnik, L. Masana, Z. Reiner, M.R. Taskinen, L. Tokgözoğlu, A. Tybjaerg-Hansen, European Atherosclerosis Society Consensus Panel, Lipoprotein(a) as a cardiovascular risk factor: current status, *Eur. Heart J.* 31 (2010) 2844–2853.
- [21] M. Bihari-Varga, E. Gruber, M. Rotheneder, R. Zechner, G.M. Kostner, Interaction of lipoprotein Lp(a) and low density lipoprotein with glycosaminoglycans from human aorta, *Arteriosclerosis* 8 (1988) 851–857.
- [22] G. Niccoli, D. Cin, G. Scalzone, M. Panebianco, S. Abolito, N. Cosentino, F. Jacoangeli, H. Refaat, G. Gallo, G. Salerno, M. Volpe, F. Crea, L. De Biase, Lipoprotein (a) is related to coronary atherosclerotic burden and a vulnerable plaque phenotype in angiographically obstructive coronary artery disease, *Atherosclerosis* 246 (2016) 214–220.
- [23] N.R. Cook, S. Mora, P.M. Ridker, Lipoprotein(a) and cardiovascular risk prediction among women, *J. Am. Coll. Cardiol.* 72 (2018) 287–296.
- [24] R. Alonso, E. Andres, N. Mata, F. Fuentes-Jiménez, L. Badimón, J. López-Miranda, T. Padró, O. Muñoz, J.L. Díaz-Díaz, M. Mauri, J.M. Ordovás, P. Mata, SAFEHEART Investigators, Lipoprotein(a) levels in familial hypercholesterolemia: an important predictor of cardiovascular disease independent of the type of LDL receptor mutation, *J. Am. Coll. Cardiol.* 63 (2014) 1982–1989.
- [25] D. Chieng, J. Pang, K.L. Ellis, G.S. Hillis, G.F. Watts, C.J. Schultz, Elevated lipoprotein (a) and low-density lipoprotein cholesterol as predictors of the severity and complexity of angiographic lesions in patients with premature coronary artery disease, *J. Clin. Lipidol.* 12 (2018) 1019–1026.
- [26] M.L. O'Donoghue, S. Fazio, R.P. Giugliano, E.S.G. Stroes, E. Kanevsky, I. Gouni-Berthold, K. Im, A. Lira Pineda, S.M. Wasserman, R. Češka, M.V. Ezhov, J.W. Jukema, H.K. Jensen, S.L. Tokgözoğlu, F. Mach, K. Huber, P.S. Sever, A.C. Keech, T.R. Pedersen, M.S. Sabatine, Lipoprotein(a), PCSK9 inhibition and cardiovascular risk: insights from the FOURIER trial, *Circulation*. 139 (2019) 1483–1492.