



Angiographic features of patients with coronary plaque erosion

Hyung Oh Kim^a, Chong-Jin Kim^b, Osamu Kurihara^a, Vikas Thondapu^a, Michele Russo^a, Erika Yamamoto^a, Tomoyo Sugiyama^a, Francesco Fracassi^a, Hang Lee^c, Taishi Yonetsu^{d,*}, Ik-Kyung Jang^{a,b,**}

^a Cardiology Division, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

^b Division of Cardiology, Kyung Hee University, Seoul, South Korea

^c Division of Biostatistics, Massachusetts General Hospital, Harvard Medical School, USA

^d Department of Interventional Cardiology, Tokyo Medical and Dental University, Japan

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ABSTRACT

Background: Although an in vivo diagnosis of coronary plaque erosion has become possible by optical coherence tomography (OCT), angiographic characteristics of erosion have not been studied. The aim of this study was to investigate the angiographic features of plaque erosion in patients with non-ST elevation acute coronary syndromes (NSTEMI-ACS).

Methods: Patients with NSTEMI-ACS who underwent OCT of the culprit lesion were collected at 11 institutions from 6 countries. Patients were classified as erosion or non-erosion based on OCT images. Angiographic features of both groups were compared.

Results: Among 494 cases with NSTEMI-ACS, 242 had plaque erosion and 252 had non-erosion. Compared to non-erosion group, erosion patients had less multivessel disease (28.5% vs. 49.6%, $p < 0.001$), lower Jeopardy score (4.2 vs. 5.0, $p < 0.001$), lower Gensini score (21.3 vs. 25.6, $p = 0.014$), and lower Syntax score (8.9 vs. 11.5, $p < 0.001$). With regard to the culprit lesion morphology, plaque erosion group had smaller reference diameter (2.8 mm vs. 3.0 mm, $p = 0.032$), less frequent type B2/C lesions (51.2% vs. 71.8%, $p < 0.001$), and lower prevalence of calcification (4.1% vs. 13.9%, $p < 0.001$) and thrombus (16.5% vs. 28.2%, $p = 0.002$). In the mid left anterior descending artery (LAD), erosion was significantly more frequent than non-erosion (30.2% vs. 21.8%, $p = 0.034$).

Conclusions: Patients with NSTEMI-ACS caused by plaque erosion have less complex angiographic features both at the 3-vessel level and at the culprit lesion level. Plaque erosion was frequently found in the mid LAD.

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1. Introduction

Underlying mechanisms for sudden cardiac death and acute coronary syndromes (ACS) are plaque rupture, plaque erosion, and calcified nodules [1]. Pathology studies showed that these different entities have distinctly different morphologic characteristics. Plaque rupture has massive disruption of vascular structure, plaque erosion is characterized by preserved vascular integrity, and calcified plaque is found in the area with substantive superficial calcification. Recent data suggest that

patients with plaque erosion may be treated conservatively without stenting [2]. If the patients with high probability of plaque erosion can be identified by angiogram, intravascular optical coherence tomography (OCT) may be selectively performed only in this group of patients to guide a tailored therapy with anti-thrombotic agents and avoid stent implantation. Detailed analysis of coronary angiogram in patients with plaque erosion has not been reported. The aim of the current study was to investigate coronary angiographic features of plaque erosion and to compare these features with those of non-erosion patients.

2. Methods

2.1. Study population

Patients who met the following criteria were selected from the "Identification of Predictors for Coronary Plaque Erosion in Patients with Acute Coronary Syndrome study" [NCT03479723] database. The database consists of ACS cases selected from the Massachusetts General Hospital OCT registry (N = 181) and from the new database which was created to study the predictors of plaque erosion (N = 1518). Inclusion criteria for the current study were: 1) non-ST elevation acute coronary syndrome (NSTEMI-ACS); 2) OCT imaging of the culprit lesion. Patients were defined as NSTEMI-ACS when they were compatible with acute myocardial ischemia or infarction with the absence of persistent ST segment elevation

Abbreviations: ACS, acute coronary syndrome; LAD, left anterior descending artery; LCX, left circumflex artery; NSTEMI-ACS, non-ST elevation acute coronary syndrome; NSTEMI, non-ST elevation myocardial infarction; OCT, optical coherence tomography; RCA, right coronary artery; ROC, receiver operating characteristics; TIMI, Thrombolysis In Myocardial Infarction.

* Correspondence to: T. Yonetsu, Department of Interventional Cardiology, Tokyo Medical and Dental University, 1-5-45, Yushima, Bunkyo Ward, Tokyo 113-8519, Japan.

** Correspondence to: I. K. Jang, Cardiology Division, Massachusetts General Hospital, Harvard Medical School, GRB 800, 55 Fruit Street, Boston 02114, MA, USA.

E-mail addresses: t-yonetsu.cvm@tmd.ac.jp (T. Yonetsu), ijang@mgh.harvard.edu (I.-K. Jang).

on the electrocardiogram at the time of the event [3]. Exclusion criteria were: 1) suboptimal coronary angiogram (vessel overlap, foreshortening); 2) poor quality OCT images; 3) coronary artery bypass graft; 4) coronary anomaly. Baseline characteristics and laboratory profiles were collected. The study was approved by the Institutional Review Board at each participating site and all patients were provided written informed consent.

2.2. Assessment of underlying pathology

A frequency-domain OCT system (C7/C8 ILLUMIEN OCT Intravascular Imaging Systems, St. Jude Medical, St. Paul, Minnesota) or a time-domain OCT system (M2/M3 Cardiology Imaging System, St. Jude Medical, Westford, Massachusetts) were used. Plaque erosion was defined when there was no fibrous cap disruption with the presence of thrombus on OCT. Plaque rupture was defined when there was a presence of fibrous cap discontinuity with a clear cavity formed inside the plaque. Calcified plaque was defined when a superficial calcified plaque was visualized often with overlying thrombus within the culprit lesion [4]. Plaque rupture and calcified plaque were categorized as non-erosion. The representative OCT images of 3 pathologies of NSTEMI-ACS are illustrated in Supplementary Fig. 1.

2.3. Angiographic analysis

Coronary angiographic profiles were collected and analyzed with the Cardiovascular Angiography Analysis System (Pie Medical Imaging B.V., Maastricht, the Netherlands). Information of culprit vessel, number of diseased vessels, the presence of non-target chronic total occlusion, left main coronary artery length, target vessel Thrombolysis In Myocardial Infarction (TIMI) flow, quantitative coronary analysis profiles, American Heart Association lesion type categorization by A/B1 and B2/C, were collected. A lesion was described as a bifurcation if there was no lesion-free area between the main branch minimal luminal diameter and the side branch ostium [5]. If dense shadow moving synchronously with cardiac contraction was visualized on fluoroscopy, it was considered calcification [6]. Thrombus was defined as an intraluminal filling defect or a haze seen in multiple angiographic projections during contrast injection [7]. The most commonly used 3 angiographic scoring systems were selected [8]: Jeopardy Score [9], Gensini score [10], and Syntax score [11]. Culprit lesion location was categorized as left main coronary artery, proximal left anterior descending artery (LAD), mid LAD, distal LAD, proximal left circumflex artery (LCX), distal LCX, proximal right coronary artery (RCA), mid RCA, distal RCA, diagonal branch, obtuse marginal branch, posterior descending artery and right posterolateral artery. The coronary segment was defined by Syntax score criteria [11].

2.4. Statistical analysis

Categorical variables were presented as case numbers and proportions (%) and were compared using Chi-square test or Fisher's exact test as appropriate. Continuous variables were presented as means and standard deviations and were compared using standardized *t*-test. Univariate binary logistic regression analysis was done for angiographic profiles. Statistically significant factors by univariate analysis were included in the multivariate analysis to determine the factors increasing the risk of plaque erosion in NSTEMI-ACS patients. Receiver operating characteristics (ROC) analysis was performed to determine the discriminatory capability of the independent predictors from the multivariate regression model. A 2-tailed $p < 0.05$ was considered significant. All statistical analyses were performed using SPSS 22.0 (SPSS, Inc., Chicago, IL).

3. Results

Among 1699 ACS patients from the database, 458 patients were excluded due to suboptimal image quality, 646 due to ST-elevation myocardial infarction, 96 due to incomplete angiography, 4 due to coronary artery bypass graft status, and 1 due to congenital anomaly (Supplementary Fig. 2). Therefore, 494 cases (242 plaque erosion and 252 non-erosion) were included in the analysis. The non-erosion group consisted of 190 cases of rupture and 62 cases of calcified plaque.

3.1. Patients characteristics and laboratory findings

Baseline characteristics and laboratory findings are summarized in Table 1. Baseline characteristics did not show a difference between the 2 groups. Two-thirds of the patients had non-ST elevation myocardial infarction (NSTEMI) and one-third unstable angina. The plaque erosion group showed higher hemoglobin (14.1 g/dL vs. 13.7 g/dL, $p = 0.049$) and lower creatinine (0.91 mg/dL vs. 1.20 mg/dL, $p = 0.010$) levels than the non-erosion group.

Table 1
Baseline characteristics and laboratory findings.

	Plaque erosion (N = 242)	Non-erosion (N = 252)	p value
Baseline characteristics			
Age, years	62.8 (± 13.1)	63.2 (± 11.3)	0.309
BMI, kg/m ²	25.4 (± 3.3)	26.0 (± 4.1)	0.282
Male	185 (76.4)	196 (77.8)	0.725
Asian	187 (77.3)	188 (74.6)	0.488
Current smoking	93 (38.4)	93 (36.9)	0.727
HTN	150 (62.0)	172 (68.3)	0.144
Dyslipidemia	139 (57.4)	152 (60.3)	0.516
DM	57 (23.6)	78 (31.0)	0.065
Previous MI	19 (7.9)	27 (10.7)	0.274
Previous PCI	30 (12.4)	40 (15.9)	0.268
Family history of CAD	41 (16.9)	37 (14.7)	0.491
CKD	10 (4.1)	21 (8.3)	0.054
Presentation			
NSTEMI	153 (63.2)	169 (67.1)	0.370
UAP	89 (36.8)	83 (32.9)	
Laboratory findings			
WBC, cells/uL	8182 (± 2933)	8328 (± 3025)	0.599
Hb, g/dL	14.1 (± 1.6)	13.7 (± 1.9)	0.049
Total cholesterol, mg/dL	189.8 (± 45.2)	192.4 (± 42.7)	0.576
LDL cholesterol, mg/dL	116.9 (± 40.6)	118.7 (± 36.8)	0.688
HDL cholesterol, mg/dL	45.6 (± 12.4)	45.2 (± 12.5)	0.792
Triglyceride, mg/dL	128.2 (± 106.8)	115.8 (± 86.7)	0.224
Creatinine, mg/dL	0.91 (± 0.82)	1.20 (± 1.58)	0.010
HbA1C, %	6.7 (± 2.3)	6.7 (± 2.4)	0.857
hs-CRP, mg/dL	0.4 (± 1.0)	0.5 (± 1.2)	0.342

Values are expressed as mean (\pm SD) or number (%), BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; DM, diabetes mellitus; Hb, hemoglobin; HbA1C, hemoglobin A1C; HDL, high-density lipoprotein; hs-CRP, high specific C-reactive protein; HTN, hypertension; LDL, low-density lipoprotein; MI, myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation; UAP, unstable angina pectoris; WBC, white blood cell count.

3.2. Angiographic findings

Angiographic findings are summarized in Table 2. Angiographic findings of erosion patients showed less multivessel disease (28.5% vs. 49.6%, $p < 0.001$), lower Jeopardy score (4.2 vs. 5.0, $p = 0.001$), lower Gensini score (21.3 vs. 25.6, $p = 0.014$) and lower Syntax score (8.9 vs. 11.5, $p < 0.001$), compared to those of non-erosion patients. Culprit lesion angiographic characteristics of erosion patients showed smaller reference diameter (2.8 mm vs. 3.0 mm, $p = 0.032$), less frequent type B2 or C lesions (51.2% vs. 71.8%, $p < 0.001$), and lower prevalence of calcification (4.1% vs. 13.9%, $p < 0.001$) and thrombus (16.5% vs. 28.2%, $p = 0.002$), compared to non-erosion patients. In the mid LAD segment, the prevalence of plaque erosion was significantly higher than that of non-erosion (30.2% vs. 21.8%, $p = 0.034$) (Fig. 1) compared to other coronary segments.

3.3. Binary logistic regression and ROC analysis

Angiographic profiles with statistical differences between plaque erosion and non-erosion were included in univariate binary logistic regression analysis to determine factors that increase the risk of plaque erosion among NSTEMI-ACS patients. Mid LAD location of the culprit lesion (OR 1.547, 95% CI 1.031–2.322, $p = 0.035$) increased the probability of plaque erosion in NSTEMI-ACS patients. Presence of multivessel disease (OR 0.426, 95% CI 0.295–0.622, $p < 0.001$), type B2/C lesion (OR 0.404, 95% CI 0.278–0.587, $p < 0.001$), thrombus (OR 0.505, 95% CI 0.326–0.781, $p = 0.002$), calcified lesion (OR 0.267, 95% CI 0.129–0.553, $p < 0.001$), high Jeopardy score (OR 0.895, 95% CI 0.839–0.955, $p < 0.001$), high Gensini score (OR 0.988, 95% CI 0.979–0.998, $p = 0.015$), and high Syntax score (OR 0.935, 95% CI 0.907–0.963, $p < 0.001$) decreased the probability of plaque erosion among NSTEMI-ACS patients. These

Table 2
Angiographic findings.

	Plaque erosion (N = 242)	Non-erosion (N = 252)	p value
Overall angiographic findings			
Coronary dominance			0.877
Right dominance	199 (82.2)	203 (80.6)	
Balanced dominance	28 (11.6)	31 (12.3)	
Left dominance	15 (6.2)	18 (7.1)	
Involved vessel			0.205
LAD	138 (57.0)	124 (49.2)	
LCX	44 (18.2)	51 (20.2)	
RCA	60 (24.8)	77 (30.6)	
Number of diseased vessel			<0.001
1 vessel	173 (71.5)	127 (50.4)	
2 vessels	54 (22.3)	90 (35.7)	
3 vessels	15 (6.2)	35 (13.9)	
Multivessel disease	69 (28.5)	125 (49.6)	<0.001
Jeopardy score	4.2 (±2.7)	5.0 (±2.9)	<0.001
Gensini score	21.3 (±19.3)	25.6 (±19.6)	0.014
Syntax score	8.9 (±5.5)	11.5 (±7.0)	<0.001
Culprit lesion angiographic findings			
Diseased vessel pre-PCI TIMI flow			0.906
0	15 (6.2)	14 (5.6)	
1	8 (3.3)	10 (4.0)	
2	45 (18.6)	42 (16.7)	
3	174 (71.9)	186 (73.8)	
QCA profiles			
MLD, mm	0.9 (±0.6)	0.8 (±0.6)	0.374
RD, mm	2.8 (±0.7)	3.0 (±0.7)	0.032
Lesion length, mm	14.8 (±6.1)	15.6 (±8.0)	0.206
Diameter stenosis, %	70.5 (±18.8)	72.8 (±18.2)	0.175
Symmetric index	0.52 (±0.26)	0.49 (±0.24)	0.330
AHA lesion type			<0.001
A and B1	118 (48.8)	71 (28.2)	
B2 and C	124 (51.2)	181 (71.8)	
Bifurcation	88 (36.4)	88 (35.1)	0.763
Calcified lesion	10 (4.1)	35 (13.9)	<0.001
Thrombus	40 (16.5)	71 (28.2)	0.002

Values are expressed as mean (±SD) or number (%), AHA, American Heart Association; LAD, left anterior descending artery; LCX, left circumflex artery; MLD, minimal lumen diameter; PCI, percutaneous coronary intervention; QCA, quantitative coronary analysis; RCA, right coronary artery; RD, reference diameter; SD, standard deviation; TIMI, Thrombolysis in Myocardial Infarction.

statistically significant predictors were included in multivariate analysis. Upon multivariate analysis, the risk of plaque erosion in NSTEMI-ACS patients was increased with mid LAD location (OR 1.785, 95% CI 1.144–2.786, $p = 0.011$), and decreased with the presence of multivessel disease (OR 0.476, 95% CI 0.314–0.722, $p < 0.001$), type B2/C lesions (OR 0.519, 95% CI 0.345–0.782, $p = 0.002$), thrombus (OR 0.442, 95% CI 0.276–0.709, $p < 0.001$), and calcified lesion (OR 0.317, 95% CI 0.144–0.696, $p = 0.004$). Regression analysis is summarized in Fig. 2. ROC analysis curve showed area under curve of 0.706, which is a fair discriminatory performance grade [12]. Cutoff sensitivity and specificity were 0.628 and 0.659, respectively (Supplementary Fig. 3).

3.4. Additional analysis

Angiographic analysis of NSTEMI patients showed less frequent TIMI 3 flow at culprit vessel before the intervention, smaller minimal lumen diameter, and a higher degree of diameter stenosis, compared to those of unstable angina patients. OCT findings of NSTEMI patients demonstrated more frequent lipid-rich plaque and macrophage compared to those of unstable angina patients (Supplementary Table 1). Since intravascular ultrasound was not performed, we could not provide accurate plaque burden. However, angiographic findings suggest greater atherosclerotic burden and OCT demonstrated more vulnerable features in NSTEMI patients.

4. Discussion

Our study demonstrated that in NSTEMI-ACS patients, compared to non-erosion patients, those with plaque erosion had less complex angiographic features both at the 3-vessel coronary level and at the culprit lesion level. Also, plaque erosion culprit lesion was more frequently located in the mid LAD segment.

4.1. Overall plaque burden difference between plaque erosion and non-erosion

Although there were no differences in the traditional atherosclerosis risk factors between the 2 groups, our study demonstrated that plaque erosion was associated with less complex angiographic features than non-erosion. Jeopardy score and Gensini score are determined by the number of diseased vessels [9] or the sum of lesion scores [10]. Syntax score is more lesion specific, but the score is calculated by the sum of each lesion scoring [11]. Thus, all 3 scoring systems reflect overall atherosclerosis burden rather than lesion specific characteristics. The erosion group has significantly lower scores using all 3 systems, indicating that the overall plaque burden is lower in the erosion group compared to the non-erosion group.

The majority of patients in the non-erosion group had plaque rupture. Plaque rupture is typically associated with more severe disruption of vascular structure and formation of cavity. Compared to plaque erosion, plaque rupture would cause more local flow disturbances and activation of platelets, leading to greater thrombus burden. Thrombus, in the case of plaque erosion, may embolize easily to the distal segment due to preserved and larger lumen with smooth inner wall. In addition, the response to anti-thrombotic therapy is more favorable in the case of plaque erosion [13]. Residual thrombus will be organized resulting in step-wise rapid progression of a plaque. This may explain lower atherosclerotic burden in the erosion group.

Higher hemoglobin and lower creatinine levels were noted for plaque erosion patients compared to non-erosion patients. Previously, it was reported that decreased hemoglobin level is associated with more severe atherosclerosis [14]. This may be due to exaggerated left ventricular hypertrophy [15], to low shear stress by low blood viscosity [16], or to decreased renal function in anemia [17], which all can advance atherosclerosis. The renal dysfunction hypothesis is consistent with higher creatinine levels in non-erosion patients in this study.

4.2. Traditional atherosclerosis risk factor distribution in NSTEMI-ACS erosion patients

Previous in-vivo studies with NSTEMI-ACS patients demonstrated similar prevalence of traditional risk factors between patients with plaque erosion and those with plaque rupture [4,18,19]. One potential explanation for this is a local factor. Recently, Yamamoto et al. [20] reported that local endothelial shear stress and plaque geometry might be important factors for development of plaque erosion. High endothelial shear stress may play an important role, not only in local endothelial damage, but also in activation of platelets leading to thrombus formation. Depending on plaque geometry, thrombus pattern would be determined. With better control of vascular inflammation, these local factors may become more important and thus, the relative incidence of plaque erosion might have been steadily increased.

4.3. Culprit lesion specific angiographic features

At the culprit lesion, lower prevalence of calcification and thrombus were noted in the erosion group. Calcification is more frequent in an advanced stage of atherosclerosis [21]. Less calcification in erosion patients may indicate less severe atherosclerosis and this can be another supporting evidence for different underlying pathobiology. Less thrombus is consistent with a previous report, which described that plaque

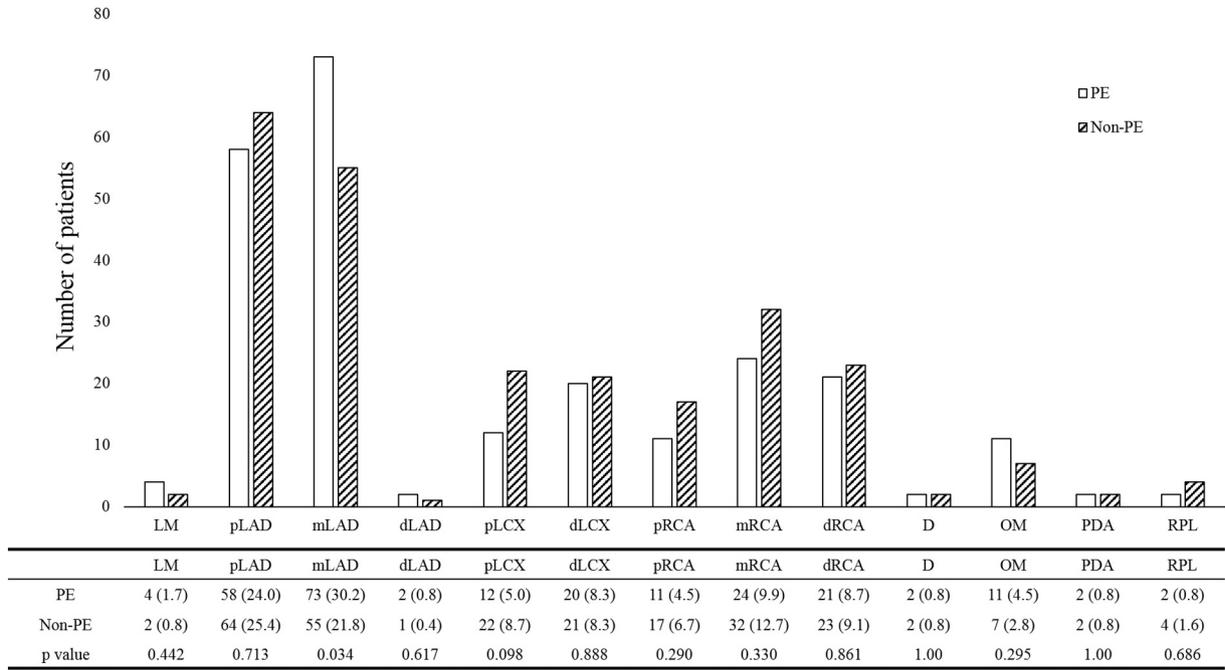


Fig. 1. Prevalence of plaque erosion and rupture in coronary artery segments. Plaque erosion (white) and non-erosion (hatched) are compared for each segment in the coronary tree. In the mLAD, plaque erosion was significantly more prevalent compared to non-erosion (30.2% vs. 21.8%, $p = 0.034$). Values are expressed as number (%). D, diagonal branch; dLAD, distal left anterior descending artery; dLCX, distal left circumflex artery; dRCA, distal right coronary artery; LM, left main coronary artery; mLAD, mid left anterior descending artery; mRCA, mid right coronary artery; OM, obtuse marginal branch; PDA, posterior descending artery; PE, plaque erosion; pLAD, proximal left anterior descending artery; pLCX, proximal left circumflex artery; pRCA, proximal right coronary artery; RPL, right posterolateral branch.

erosion patients had less thrombus burden compared to plaque rupture patients [22] and this may be related to frequent distal embolization or better response to antithrombotic therapy compared to non-erosion. Less frequent calcification and thrombus attribute to the less complex lesion type in the erosion patients. Our result demonstrated smaller reference vessel diameter in plaque erosion, which is in line with the previous reports [18,23]. The cause for this may be negative remodeling

secondary to constrictive adventitial fibrosis and thickening in plaque erosion, which was previously described in a pathology study [24].

4.4. Distribution of plaque erosion and non-erosion

In the mid LAD segment, erosion was significantly more frequent than non-erosion. The mechanism for this finding is unclear. Compared

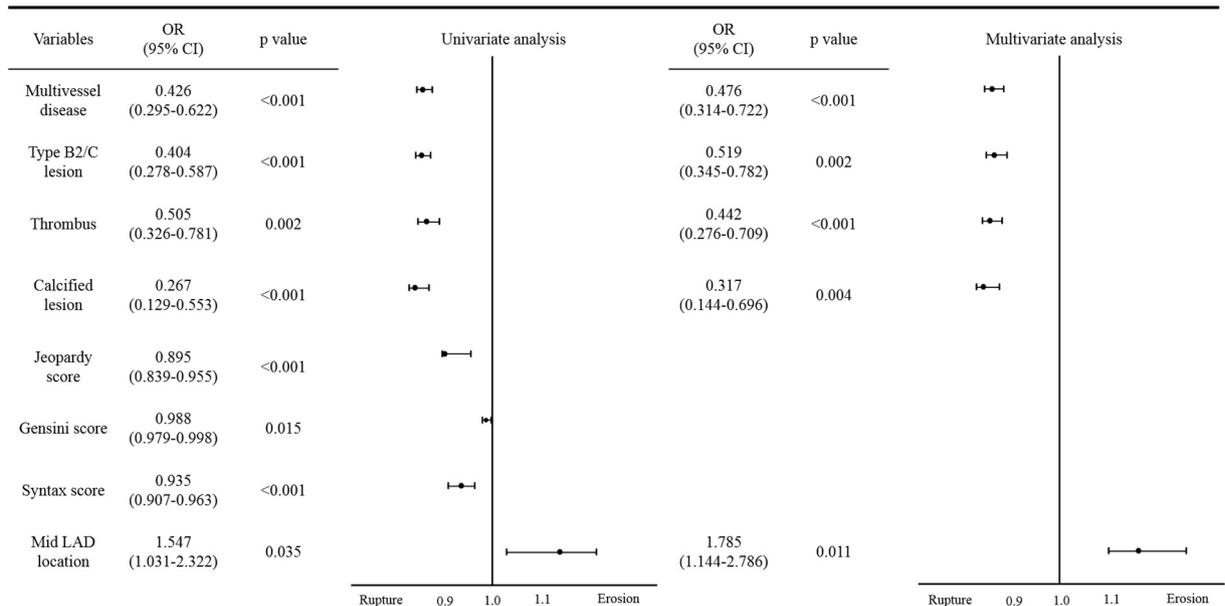


Fig. 2. Binary logistic regression for angiographic predictors of plaque erosion among NSTE-ACS. Univariate binary logistic regression showed that mid LAD location increased, and the multivessel disease, lesion type B2/C, thrombus, calcification, higher Jeopardy score, higher Gensini score, and higher Syntax score decreased the risk of plaque erosion among NSTE-ACS patients. Multivariate analysis showed mid LAD location increased, and the multivessel disease, lesion type B2/C, thrombus, calcification decreased the risk of plaque erosion among NSTE-ACS patients. CI, confidence interval; LAD, left anterior descending artery; NSTE-ACS, non-ST elevation acute coronary syndrome; OR, odds ratio.

to other segments, mid LAD has more side branches (diagonal and septal branches). It is known that the opposite wall of an arterial side branch has low endothelial shear stress, which induces production of inflammatory cell adhesion molecules, cytokines, oxidative species, increased lipid uptake, endothelial permeability, and blood stagnation [16]. These changes may lead to endothelial damage and desquamation.

4.5. Angiographic predictors of plaque erosion and NSTEMI-ACS patients

Although intracoronary OCT is relatively safe, intracoronary imaging has potential risk for serious complications such as coronary dissection, perforation, or acute occlusion. The PROSPECT study showed that 3 vessel imaging was associated with 1.6% of serious complications [25]. Therefore, when a cardiologist looks for plaque erosion for possible conservative management, choosing patients with high probability of erosion for intracoronary imaging may be important. Using the information provided from this study, OCT can be used selectively only for those ACS patients with high likelihood of erosion.

4.6. Limitations

Several limitations should be noted. First, this study was a retrospective analysis of angiograms of the patients who had OCT imaging of the culprit lesion. Therefore, selection bias could not be excluded. Second, due to the limitations of intravascular imaging, the number of segments such as left main and distal segments were small. Third, 458 cases were excluded from the total of 1699 ACS cases of the original database because of poor quality OCT images and this may have affected the result.

5. Conclusion

Patients with plaque erosion showed less complex angiographic features both at 3-vessel and culprit lesion level, compared to those with non-erosion. Plaque erosion was more frequently found in the mid LAD.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2019.03.039>.

Contribution of authors

Study conception and design: Ik-Kyung Jang, Taishi Yonetsu.

Data acquisition: Chong-Jin Kim, Erika Yamamoto, Tomoyo Sugiyama, Francesco Fracassi.

Analysis of data: Hyung Oh Kim, Hang Lee.

Drafting of the manuscript: Hyung Oh Kim.

Primary revision: Osamu Kurihara, Vikas Thondapu, Michele Russo.

Critical revision: Ik-Kyung Jang.

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Conflict of interest

The authors report no relationship that could be construed as a conflict of interest.

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