IJC Heart & Vasculature 43 (2022) 101120

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature

Lipoprotein (a) levels and vulnerable characteristics in nonculprit plaque in patients with acute coronary syndrome☆

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ARTICLE INFO

Keywords:
Optical coherence tomography
Plaque rupture
Thin-cap fibroatheroma

ABSTRACT

Background: High plasma levels of Lp(a) are associated with a worse prognosis in patients with coronary artery disease. The aim of the present study is to clarify the association between high lipoprotein a [Lp(a)] levels and vulnerable characteristics of nonculprit plaques in patients with acute coronary syndrome (ACS).

Methods: A total of 185 consecutive patients with ACS who underwent optical coherence tomography imaging of nonculprit plaques in the culprit vessels were enrolled. Patients were divided into the high Lp(a) group (≥30 mg/dL; 50 nonculprit plaques in 49 patients) or the low Lp(a) group (<30 mg/dL; 139 nonculprit plaques in 136 patients).

Results: The prevalence of thin-cap fibroatheroma (TCFA) was significantly higher in the high Lp(a) group than in the low Lp(a) group (38.0 vs. 21.6%, $p = 0.034$). Multivariate logistic analysis demonstrated that a high Lp(a) level was independently associated with the prevalence of TCFA (odds ratio, 1.18; 95% confidence interval, 1.01–1.36; $p = 0.033$). The prevalence of TCFA was significantly higher in the high Lp(a) group than in the low Lp(a) group among patients with plaque erosion (50.0 vs. 9.4%, respectively; $p = 0.027$), although the difference was not statistically significant between the two groups in patients with plaque rupture.

Conclusions: High Lp(a) levels were associated with a high prevalence of TCFA in nonculprit plaques among patients with ACS, particularly in patients with plaque erosion. The present results may partly explain the pathogenesis of worse clinical outcomes in patients with ACS and a high Lp(a) level as shown in clinical studies.

1. Introduction

Lipoprotein (a) [Lp(a)] is a low-density lipoprotein (LDL)–like particle consisting of apolipoprotein(a) bound to apo-B100. Several Mendelian randomization studies have demonstrated that elevated Lp(a) is a causal risk factor for atherosclerotic cardiovascular diseases, including acute coronary syndrome (ACS) [1], stroke [2], and peripheral arterial disease [3]. Elevated Lp(a) levels are also associated with an increased incidence of myocardial infarction [4,5] and nonculprit lesion–related repeat revascularization in patients who underwent percutaneous coronary intervention (PCI) [6]. An elevated Lp(a) level is a risk factor for recurrent cardiovascular events in patients with recent myocardial infarction regardless of low-density lipoprotein cholesterol (LDL-C) levels [7]. Thus, elevated Lp(a) levels are considered a "residual risk" among patients with coronary artery disease. Lp(a) infiltrates the arterial wall, binds to components of the extracellular matrix, and activates foam cell formation, smooth muscle cell proliferation, and inflammatory reactions, leading to subsequent plaque instability [8–11]. Because plasma Lp(a) levels are genetically determined via variation in the apolipoprotein(a) gene and remain almost stable throughout life without environmental influences [12], individuals with high plasma Lp(a) levels are continuously exposed to an increased risk of plaque development and instability. Therefore, the higher incidence of cardiovascular disease in patients with a high Lp(a) level is considered the result of a higher prevalence of vulnerable plaques in the coronary artery. Muramatsu et al. demonstrated a significant association between elevated Lp(a) levels and a higher prevalence of thin-cap fibroatheroma in culprit coronary lesions [13]. Because a recent study demonstrated that the incidence of nonculprit lesion–related adverse events is approximately two-fold higher than that of culprit lesion–related events

☆ This author takes responsibility for all aspects of reliability and freedom from bias of data presented and their discussed interpretation.

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https://doi.org/10.1016/j.ijcha.2022.101120
Received 4 June 2022; Received in revised form 31 July 2022; Accepted 2 September 2022

among patients with ACS in the current clinical setting, the risk of recurrent events is more attributable to the vulnerability of atherosclerosis in nonculprit lesions than culprit lesions. However, the association between high Lp(a) levels and the prevalence of vulnerable plaques in nonculprit lesions among patients with ACS remains unclear. Thus, the present study focused on the vulnerability of nonculprit plaques among patients with ACS to further clarify the potential risk of future events caused by elevated Lp(a) levels.

2. Methods

2.1. Study population

The present study was a retrospective observational study conducted at a single center. From a total of 392 patients with ACS who underwent optical coherence tomography (OCT) imaging of the culprit vessels during PCI between January 2016 and December 2020, we identified 365 eligible patients after excluding those with poor OCT images (n = 16) and those without available Lp(a) measurements (n = 11). After the further exclusion of 180 patients without nonculprit plaques, we included 185 patients with 189 nonculprit plaques (Supplemental Fig. 1). Patients were classified into the high Lp(a) group (50 nonculprit plaques of 49 patients) or the low Lp(a) group (139 nonculprit plaques of 136 patients) according to plasma Lp(a) levels = 30 mg/dL [6,14]. Serum lipoprotein(a) [Lp(a)] levels were measured by a latex agglutination turbidimetric immunoassay at a central clinical laboratory (SRL Inc., Tokyo). All patients provided written informed consent for the procedure. This study was conducted in compliance with the Declaration of Helsinki and approved by the institutional ethics committee.

2.2. Definition

ACS consisted of ST-segment elevation myocardial infarction and non-ST-segment elevation ACS. A culprit lesion was defined as a lesion causing ACS and subsequently requiring PCI, which was determined using clinical findings on electrocardiography, echocardiography, and angiography [15]. Nonculprit plaques were defined as plaques with intimal thickening of > 0.5 mm, $>90^\circ$ arc, length ≥ 2 mm, and location > 5 mm from the edges of culprit lesions [16], which were not treated by PCI and imaged by OCT pullbacks during PCI for culprit vessels. All strategies and devices, including OCT use during PCI procedures, were determined by physicians. Other definitions are described in the Supplemental methods.

2.3. OCT image acquisition and analysis

OCT images of the culprit vessels were acquired after the administration of 100–200 μg intracoronary nitroglycerin using frequency domain OCT (ILUMIEN OCT Intravascular Imaging Systems; Abbott, Santa Clara, CA, USA). All images were analyzed using offline proprietary software at the cardiovascular laboratory of the Kitasato University School of Medicine. The images were qualitatively and quantitatively analyzed at 0.2-mm intervals. The plaque characteristics were evaluated using previously validated criteria [17,18]. Fibrous cap thickness (FCT) was measured at the thinnest point of the overlying fibrous cap within the plaque. Thin-cap fibroatheroma (TCFA) was defined as a lipid-rich plaque with an FCT of < 65 μm. Macrophage was defined as the presence of high-intensity signal-rich linear regions with sharp attenuation. A layered plaque was defined as one or more layers with different optical densities and a clear demarcation from underlying components on OCT [19]. The pathogenesis of ACS was estimated by OCT findings of the culprit lesions and categorized into plaque rupture, plaque erosion, calcified plaque, or others according to an established criterion [20]. Other definitions of plaque characteristics are described in the Supplemental methods. The analysis was conducted by two independent investigators blinded to the patients' clinical characteristics. In cases of discordance between the investigators, consensus was obtained by consultation with a third independent investigator.

2.4. Statistical analysis

Continuous variables were compared using Student's *t*-test or Mann–Whitney *U* test for comparisons between independent groups according to the data distribution. Categorical variables are reported as n (%) and were compared using Fisher's exact test or the chi-squared test according to the data distribution. Normally distributed data are reported as mean ± SD. Lesion-based comparisons were performed using generalized estimating equations to consider the potential cluster effects of multiple segments in a single patient [19]. Logistic regression models with generalized estimating equations, including age, sex, conventional risk factors, laboratory findings, and medications, were used to identify independent associations between Lp(a) levels and each plaque characteristic (variables are listed in Supplemental tables). These variables were chosen because of their potential associations with the presence of vulnerable plaques (Supplemental methods) [21]. Statistical significance was defined as $p < 0.05$. Statistical analyses were performed using R version 4.0.2. (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Clinical characteristics

The median Lp(a) level in the present cohort was 15 mg/dL (interquartile range, 8–33 mg/dL). The clinical characteristics are shown in Table 1. The LDL-C levels were significantly higher in the high Lp(a) group than in the low Lp(a) group.

3.2. OCT analysis of nonculprit plaques

The results of the OCT analysis of the nonculprit plaques are shown in Fig. 1 and Table 2. The prevalence of TCFA and plaques with a maximum lipid arc $\geq 180^\circ$ was significantly higher in the high Lp(a) group than in the low Lp(a) group (38.0 vs. 21.6%, $p = 0.034$; 54.0 vs. 35.3%, $p = 0.024$). Mean plaque length was significantly longer in the high Lp(a) group than in the low Lp(a) group (12.0 vs. 10.7 mm, $p = 0.032$). The prevalence of plaques with macrophage tended to be higher in patients with a high Lp(a) (52.0 vs. 35.3%, $p = 0.050$). A Receiver-operating characteristic curve was constructed to assess the ability of Lp(a) to identify TCFA in nonculprit plaques (Supplemental Fig. 2). The area under the curve was 0.618 ($p = 0.007$), and the best cut-off for the Lp(a) value was 23.5 mg/dL (sensitivity 47%, specificity 71%). The characteristics of the culprit plaques are described in Supplemental table 1.

3.3. Logistic analysis for plaque components

Univariate and multivariate logistic analyses were conducted to demonstrate the independent association between high Lp(a) levels and the presence of each plaque component in the nonculprit lesions (Fig. 2). After the adjustment for confounding factors, a high Lp(a) level was significantly associated with the presence of TCFA (odds ratio [OR], 1.175; 95% confidence interval [CI], 1.013–1.362; $p = 0.033$) (Supplemental table 2), plaques with a maximum lipid arc $> 180^\circ$ (OR, 1.204; 95% CI, 1.032–1.403; $p = 0.018$) (Supplemental table 3), and plaques with macrophage (OR, 1.180; 95% CI, 1.013–1.373; $p = 0.033$) (Supplemental table 4) among the nonculprit plaques. The results of univariate and multivariate logistic analyses to demonstrate the independent association between high Lp(a) levels and the presence of each plaque component in the culprit lesions are described in Supplemental figure 4 and Supplemental table 5.

Table 1
Clinical characteristics.

	All n = 185	High Lp(a) n = 49	Low Lp(a) n = 136	*p* value
Age	70 (59–76)	69 (58–76)	70 (60–75)	0.803
Male, n (%)	153 (82.7)	36 (73.5)	117 (86.0)	0.076
Body mass index, kg/m^2	24.7 (22.2–27.1)	24.4 (21.5–26.3)	24.7 (22.7–27.3)	0.355
Clinical presentation, n (%)				0.867
STEMI	78 (42.2)	20 (40.8)	58 (42.6)	
NSTE-ACS	107 (57.8)	29 (59.2)	78 (57.4)	
Risk factors, n (%)				
Hypertension	121 (65.4)	29 (59.2)	92 (67.6)	0.298
Hyperlipidemia	108 (58.4)	29 (59.2)	79 (58.1)	1.000
Diabetes mellitus	72 (38.9)	15 (30.6)	57 (41.9)	0.176
Family history of IHD	35 (18.9)	9 (18.4)	26 (19.1)	1.000
Current smoker	20 (10.8)	4 (8.2)	16 (11.8)	0.598
History of MI, n (%)	33 (17.8)	7 (14.3)	26 (19.1)	0.520
Laboratory data				
Lp(a), mg/dL	15 (8–33)	50 (41–77)	12.5 (7–17)	<0.001
LDL-C, mg/dL	112 (85–140)	125 (101–147)	106 (82–136)	0.025
HDL-C, mg/dL	48 (42–56)	46 (42–56)	49 (42–56)	0.915
Triglyceride, mg/dL	123 (80–181)	119 (96–153)	128 (75–207)	0.541
HbA1c, %	6.2 (5.7–6.9)	6.1 (5.7–6.5)	6.2 (5.8–7.1)	0.117
eGFR, mL/min/1.73 m^2	60 (47–73)	57 (45–68)	63 (49–75)	0.104
Medication, n (%)				
P2Y12 inhibitor	32 (17.3)	7 (14.3)	25 (18.4)	0.661
Aspirin	61 (33.0)	18 (36.7)	43 (31.6)	0.596
ARB/ACEi	76 (41.1)	16 (32.7)	60 (44.1)	0.176
β-blocker	47 (25.4)	9 (18.4)	38 (27.9)	0.187
Calcium channel blocker	54 (29.2)	13 (26.5)	41 (30.1)	0.715
Statin	84 (45.4)	23 (46.9)	61 (44.9)	0.868
Insulin	12 (6.5)	3 (6.1)	9 (6.6)	1.000

Data given as n (%), median (IQR). ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; IHD, ischemic heart disease; LDL-C, low-density lipoprotein cholesterol; Lp(a); lipoprotein a; MI, myocardial infarction; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction.

3.4. Prevalence of TCFA according to pathogenesis of ACS

The prevalence of TCFA in nonculprit plaques was further compared between the two groups according to the pathogenesis of ACS based on the morphologies of the culprit plaques (Supplemental figure 3). Among the patients with plaque erosion, the prevalence of TCFA was significantly higher in the high Lp(a) group than in the low Lp(a) group (50.0 vs. 9.4%, $p = 0.027$), while the difference in the prevalence was not statistically significant between the two groups in other cohorts.

4. Discussion

The main findings of this study were as follows. 1) The prevalence of vulnerable characteristics, including TCFA, in nonculprit plaques was significantly higher in patients with a high Lp(a) level than in those with a low Lp(a) level among patients with ACS. 2) A high Lp(a) level was independently associated with the presence of vulnerable characteristics, including TCFA, large lipid and macrophages. 3) The prevalence of TCFA was significantly higher in patients with a high Lp(a) level than in those with a low Lp(a) level among patients with plaque erosion.

4.1. Lp(a) and plaque vulnerability

The association between a high Lp(a) level and the presence and progression of coronary plaques has been demonstrated in several clinical studies. Muramatsu et al. investigated the association between Lp(a) level and the characteristics of culprit coronary plaques observed using OCT in a cohort mainly including patients with stable coronary disease [13]. The authors demonstrated an increased prevalence of TCFA with increasing Lp(a) levels. Kaiser et al. investigated the impact of a high Lp(a) level (≥70 mg/dL) on the progression of coronary plaques assessed by serial observation on computed tomography in patients

Table 2
Characteristics of nonculprit plaques according to Lp(a) levels.

	High Lp(a) N = 50	Low Lp(a) N = 139	*p* value
Vessel			0.430
LAD	21 (42.0)	65 (46.8)	
LCX	6 (12.0)	16 (11.5)	
Left main	3 (6.0)	2 (1.4)	
RCA	20 (40.0)	56 (40.3)	
Quantitative analysis			
Max lipid arc	195 (99–253)	148 (69–253)	0.291
MLA, mm^2	4.3 (2.6–5.8)	4.1 (2.9–5.5)	0.966
MLD, mm	2.3 (1.8–2.7)	2.3 (1.9–2.6)	0.631
Proximal RA, mm^2	7.4 (5.1–9.8)	7.8 (5.1–9.9)	0.711
Proximal RD, mm	3 (2.5–3.5)	3.1 (2.5–3.5)	0.893
Distal RA, mm^2	6.8 (4.4–9.3)	6.1 (4.2–8.5)	0.619
Distal RD, mm	3.0 (2.5–3.5)	3.1 (2.5–3.5)	0.538
Qualitative analysis			
Microchannels	13 (26.0)	37 (26.6)	0.912
Cholesterol crystals	3 (6.0)	10 (7.2)	0.766
Calcification	34 (68.0)	93 (66.9)	0.937
Layered plaque	16 (32.0)	57 (41.0)	0.292
Thrombus	4 (8.0)	6 (4.3)	0.382

Data given as median (IQR). AS indicates area stenosis; LAD, left anterior descending artery; LCX, left circumflex artery; MLA, minimum lumen area; MLD, minimum lumen diameter; RA, reference lumen area; RCA, right coronary artery; RD, reference lumen diameter.

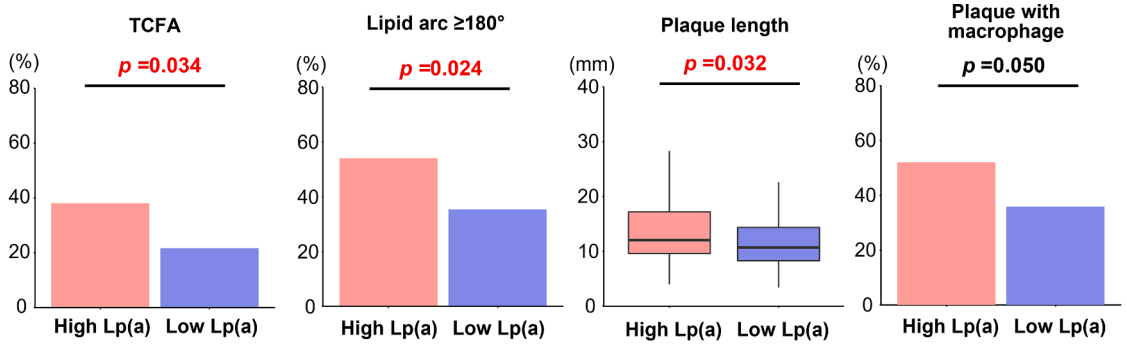

Fig. 1. Comparisons of vulnerable characteristics in nonculprit plaques according to Lp(a) levels Y-axis represents the prevalence. Lp(a), lipoprotein a; TCFA, thin-cap fibroatheroma.

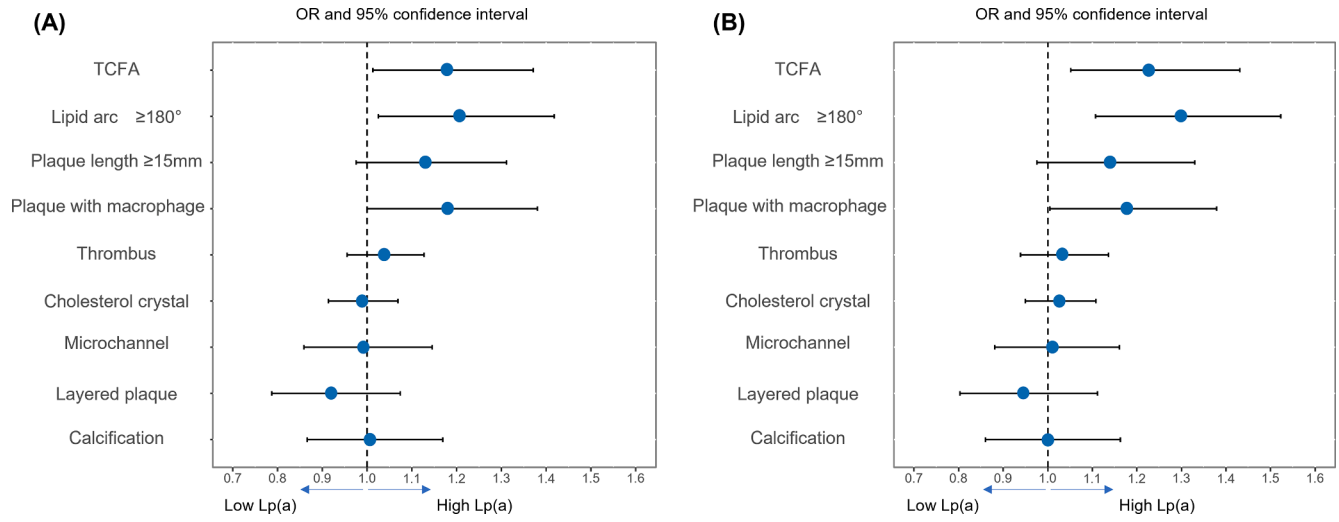

Fig. 2. Association between Lp(a) and plaque components in nonculprit plaques A, Unadjusted; B, After adjustment for confounders including age, sex, conventional risk factors, laboratory findings, and medications (confounders are listed in Supplemental tables). Lp(a), lipoprotein a; TCFA, thin-cap fibroatheroma.

with stable coronary artery disease [22]. They demonstrated accelerated progression of coronary low-attenuation plaques in patients with high Lp(a) levels. Although both studies clearly showed an association between high Lp(a) levels and coronary plaque vulnerability, this association among patients with ACS has not been thoroughly investigated. In the present study, we demonstrated an independent association between high Lp(a) levels and a higher prevalence of TCFA among nonculprit plaques. An independent association with a higher prevalence of a plaque with a maximum lipid arc $\geq 180^{\circ}$ and a plaque with macrophage was also demonstrated. In addition to the presence of TCFA, the predictive significance of these two characteristics on OCT images in terms of future cardiovascular events was demonstrated in several recent studies [23,24]. Thus, the present results further confirm the association between a high Lp(a) level and an increased risk of future adverse events caused by the vulnerability of nonculprit plaques among patients with ACS. Although a recent study reported that a higher prevalence of TCFA in patients with a high Lp(a) level was mainly observed among patients with high LDL-C levels, we demonstrated an independent association between high Lp(a) levels and a higher prevalence of TCFA irrespective of clinical characteristics including LDL-C. This finding is consistent with the findings of a clinical study showing a correlation between high Lp(a) levels and an increased incidence of recurrent cardiovascular events irrespective of LDL-C levels among patients with myocardial infarction [14].

4.2. Lp(a) and pathogenesis of ACS

The difference in the prevalence of TCFA in nonculprit plaques was not statistically significant between the high Lp(a) and low Lp(a) groups among patients with plaque rupture in the present study, although the prevalence was numerically higher in the high Lp(a) group. This marginal result is partly caused by the fundamental risk of pan-coronary vulnerability in patients with plaque rupture irrespective of Lp(a) levels [15]. On the other hand, differences in the prevalence of TCFA in nonculprit plaques were highlighted among patients with plaque erosion in the present study. Plaque erosion, a major pathogenesis of ACS, is characterized by the focal accumulation of extracellular matrix, eroded endothelial cells, and subsequent thrombus formation via neutrophil activation [25]. The overall process of disease onset and underlying systemic atherosclerosis is largely different from plaque rupture, a representative of systemic atherosclerosis. The prevalence of vulnerable characteristics in carotid plaques and nonculprit coronary plaques in patients with plaque erosion has been reported as lower than that in those with plaque rupture [15,26]. In fact, the prevalence of TCFA was numerically lower in patients with plaque erosion (9.4%) than in those with plaque rupture (38.3%) among patients with low Lp(a) levels in the present study. However, the prevalence of TCFA in patients with a high Lp(a) level was significantly higher than that in those with a low Lp(a) level among plaque erosion and as high as the prevalence in patients with plaque rupture in the present study. These findings suggest that patients with plaque erosion concomitant with high Lp(a) levels may be at a greater risk of future cardiovascular events than those with low Lp(a) levels, although the incidence of adverse events in patients with plaque erosion has been reported as lower than that in patients with plaque rupture [27,28].

5. Limitations

This study had several limitations. First, this was a retrospective cross-sectional observational study. Although we conducted a multivariate analysis to remove potential confounding factors, bias may still affect its results. Second, the present study exclusively involved cases with nonculprit plaques assessed by OCT without analyses using other imaging modalities, including intravascular ultrasound. This may also cause selection bias. Third, we applied 30 mg/dL as the cut-off for a high Lp(a) level based on several previous reports. However, the use of different cutoff values may yield different results. Finally, this study did not investigate the clinical impact.

6. Conclusion

High Lp(a) levels were associated with a higher prevalence of TCFA in nonculprit lesions in patients with ACS, particularly in patients with plaque erosion. This finding might partly explain the pathogenesis of the increased incidence of recurrent cardiovascular events in patients with ACS and high Lp(a) levels as shown in clinical studies.

CRediT authorship contribution statement

Ayami Kato: Formal analysis, Investigation, Writing – original draft, Visualization. **Daisuke Kinoshita:** Formal analysis, Investigation, Writing – original draft, Visualization. **Takako Nagata:** Investigation. **Kiyoshi Asakura:** Investigation. **Masahiro Katamine:** Investigation. **Aritomo Katsura:** Investigation. **Takuya Hashimoto:** Supervision. **Yoshiyasu Minami:** Conceptualization, Data curation, Methodology, Validation, Formal analysis, Visualization, Project administration.

Junya Ako: Supervision, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank Kazuhiro Fujiyoshi, Ryota Kakizaki, Teruyoshi Nemoto, Yusuke Muramatsu, and Toshimitsu Sato for their contributions to the data collection.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2022.101120.

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