Association between inflammatory biomarkers and thin-cap fibroatheroma detected by optical coherence tomography in patients with coronary heart disease

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Abstract

Introduction: The relationship between plaque morphology detected by optical coherence tomography (OCT) and inflammatory biomarkers is not well known.

Material and methods: This study included 47 patients with ischemic heart disease (22 patients with acute coronary syndrome and 25 patients with effort angina pectoris) who underwent percutaneous coronary intervention (PCI). Before PCI, peripheral blood levels of the inflammatory biomarkers high-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6) were measured. The OCT can detect thin-cap fibroatheroma (TCFA), a lesion with high potential for adverse cardiac events. We investigated the relationships between TCFAs in culprit lesions detected by OCT and the peripheral blood levels of these biomarkers.

Results: We observed 12 lesions detected as TCFAs. The natural logs of hs-CRP and IL-6 levels in the TCFA group were higher than those in the non-TCFA group (hs-CRP 0.87 (–0.96 to 0.87) vs. –0.47 (–0.92 to 0.30) mg/l, $p = 0.027$; and IL-6 1.63 (0.63–3.23) vs. 0.53 (–0.21 to 1.05) pg/dl, $p = 0.005$, respectively). In multivariate logistic regression analysis, log IL-6 was an independent predictor for TCFA detected by OCT (log IL-6, 0.970 pg/dl, $p = 0.023$). Receiver operating characteristic curve analysis confirmed that IL-6, compared to hs-CRP, has a higher area under the curve for predicting TCFA (0.783 vs. 0.715, respectively).

Conclusions: Peripheral blood levels of both hs-CRP and IL-6 were associated with TCFAs, as detected by OCT. Moreover, IL-6 has a higher potential than hs-CRP for predicting TCFA.

Key words: vulnerable plaque, biomarkers, optical coherence tomography.

Introduction

Since the 1990s, it has been gradually accepted that the inflammation mechanism is closely associated with the progress and instability of atherosclerosis [1, 2]. Recent advances have led to a better understanding of the association between inflammatory biomarkers and progress of atherosclerosis [3–5]. Several investigators have examined a variety of circulating inflammation markers to predict the risk of future vascular events

[6–8]. Among them, C-reactive protein (CRP), which has been the best studied, is the most consistently related to future risk [6, 7]. And according to recent studies, interleukin-6 (IL-6) is also known as a predictor of future cardiac events [6, 8].

Recently developed imaging modalities provide precise and accurate evaluations of culprit lesions in coronary arteries. Optical coherence tomography (OCT) has approximately 10 times higher (15–20 µm) resolution for cross-sectional images of vessels than that of intravascular ultrasound [9] and can measure fibrous cap thickness and detect lipid plaques and thrombi with higher sensitivity and specificity [9–11]. Therefore, OCT can detect thin-cap fibroatheroma (TCFA), a lesion with high potential for plaque rupture, the most common cause of acute coronary thrombosis, which can lead to severe critical outcomes, including sudden death [12, 13]. However, the relationship between plaque morphology and inflammatory biomarkers has not been fully elucidated *in vivo*.

This study aimed to evaluate the correlation between peripheral levels of inflammatory biomarkers, including high-sensitivity C-reactive protein reaction (hs-CRP) and IL-6, and TCFAs, as detected on OCT.

Material and methods

Study population

From August 2011 to July 2012, 50 cardiovascular disease patients who underwent percutaneous coronary intervention (PCI) at our hospital were enrolled in this study. There were 24 acute coronary syndrome (ACS) patients, including 13 patients with acute myocardial infarction (AMI), 11 patients with unstable angina pectoris (UAP), and 26 patients with stable angina pectoris (SAP). The AMI was diagnosed in patients with continuous chest pain, changes in serial electrocardiographic findings, and abnormal levels of cardiac enzymes (creatine kinase-MB or troponin-I). The UAP was diagnosed if there was angina at rest or a crescendo electrocardiogram pattern without increase in cardiac enzyme levels. The SAP was diagnosed if there was no change in frequency, duration, and intensity of angina symptoms within 6 weeks preceding the intervention. We excluded patients who had left main coronary artery disease, multivessel disease, congestive heart failure, renal dysfunction with baseline serum creatinine more than 1.5 mg/dl, a residual infection or other inflammatory diseases within the previous 6 months, collagen disease, or malignant disease. Patients who were treated with steroids were also excluded. A culprit lesion of the coronary artery was identified by a combination of echocardiographic left ventricular abnormalities, angiographic findings, and cardiac scintigraphic defects. We divided our patients into 2 groups, those who had a TCFA (TCFA group) and those who did not (non-TCFA group), and investigated the relationship between TCFAs in culprit lesions and inflammatory biomarkers. This study was approved by our hospital's ethics committee, and all patients provided written informed consent before participation.

Measurement of plasma biomarkers

In ACS (UAP and AMI) patients, blood samples were collected from an upper limb vein before emergent coronary angiography, and the blood was collected from the same vein on the second morning after admission in the SAP group. For plasma preparation, 2Na-EDTA was added to whole blood. After that, the blood sample was immediately centrifuged at 3000 rpm for 10 min, and the plasma was obtained and stored at –80°C until biomarker detection testing. The hs-CRP level in plasma was assayed according to the manufacturer's protocols (N-Latex CRP II; Siemens Healthcare Diagnostics, Malvern, PA, USA). The IL-6 was measured by commercially available ELISA kits, according to the protocols of the manufacturer (R&D Systems, Minneapolis, MN, USA).

Optical coherence tomography imaging

The OCT examinations were performed before PCI. All patients were administered 100 U/kg heparin before the procedure. A 6 Fr or 7 Fr guiding catheter was introduced into the coronary artery, and nitroglycerin (0.1–0.2 mg) was administered through the guiding catheter. The OCT images were obtained with a time-domain (M3 OCT system; LightLab Imaging/St Jude Medical, Westford, MA, USA) or a frequency-domain OCT C7XR system and Dragon Fly catheter (LightLab Imaging/St Jude Medical). In the M3 OCT system, a 0.016-inch OCT imaging catheter (LightLab Imaging) was inserted into the distal end of the culprit lesion through the central lumen in an occlusion balloon catheter (Helios; Avantec Vascular Corp, Sunnyvale, CA, USA). While the images were acquired during a pullback of the catheter, the occlusion balloon, which was positioned at the proximal site of the culprit lesion, was inflated to 0.5–0.7 atm, and Ringer's lactate solution was infused at 0.6–0.8 ml/s. When the target lesion was located close to the ostium of the coronary artery, a continuous-flushing nonocclusive technique was used for a detailed evaluation. Low-molecular-weight dextran L (Otsuka Pharmaceutical Factory, Tokushima, Japan) was directly infused through the guiding catheter at 3.0–4.0 ml/s to remove blood from the coronary artery. The OCT

pullback speed was 1.0 mm/s. Furthermore, in the C7XR system, a 2.7 Fr OCT imaging catheter was carefully inserted into the distal end of the culprit lesion. The automated pullback system was performed at 20 mm/s while blood was displaced by flushing with contrast medium or dextran using the guiding catheter. The culprit lesions in patients with ACS with a Thrombolysis in Myocardial Infarction (TIMI) flow grade of 0–2 were evaluated after thrombectomy using the thrombus aspiration catheter (Thrombuster III; Kaneka Medical Products, Osaka, Japan). In this study, we evaluated the presence of plaque rupture, coronary thrombus, and TCFA in the culprit lesion. A plaque rupture was defined as a plaque containing a cavity that communicated with the lumen with an overlying residual fibrous cap fragment [6]. Intracoronary thrombus was identified by the mass images protruding into the vessel lumen from the vessel wall [11]. The TCFA was defined as a lipid-rich plaque (signal-poor and attenuated area with 2 or more quadrants) of the vessel lumen with the thinnest part of the fibrous cap measuring ≤ 65 µm [12]. In nonruptured plaques, the thinnest fibrous cap thickness was defined as the distance from the arterial lumen to the inner border of the lipid pool. In ruptured plaques, the thinnest fibrous cap thickness was defined as the minimum residual fibrous cap identified as a flap between the arterial lumen and the cavity caused by the plaque [13, 14]. An average of 3 measurements of the minimum fibrous cap thickness in the culprit plaque were taken (Figures 1 and 2). These plaque morphologies were observed by 2 independent observers who were blinded to the clinical presentation. The OCT images were digitalized and analyzed using proprietary software from LightLab Imaging.

Statistical analysis

SPSS version 20 (IBM, Chicago, IL, USA) was used for all analyses. All categorical variables are expressed as frequencies and percentages and were compared using the χ^2 or Fisher's exact test, as appropriate. Continuous data are expressed as mean ± standard deviation for normally distributed variables or median (25^{th} to 75^{th} percentiles) for non-normally distributed variables. Differences between continuous variables were compared using unpaired Student's *t*-test or the Mann-Whitney tests, as appropriate. The distribu-

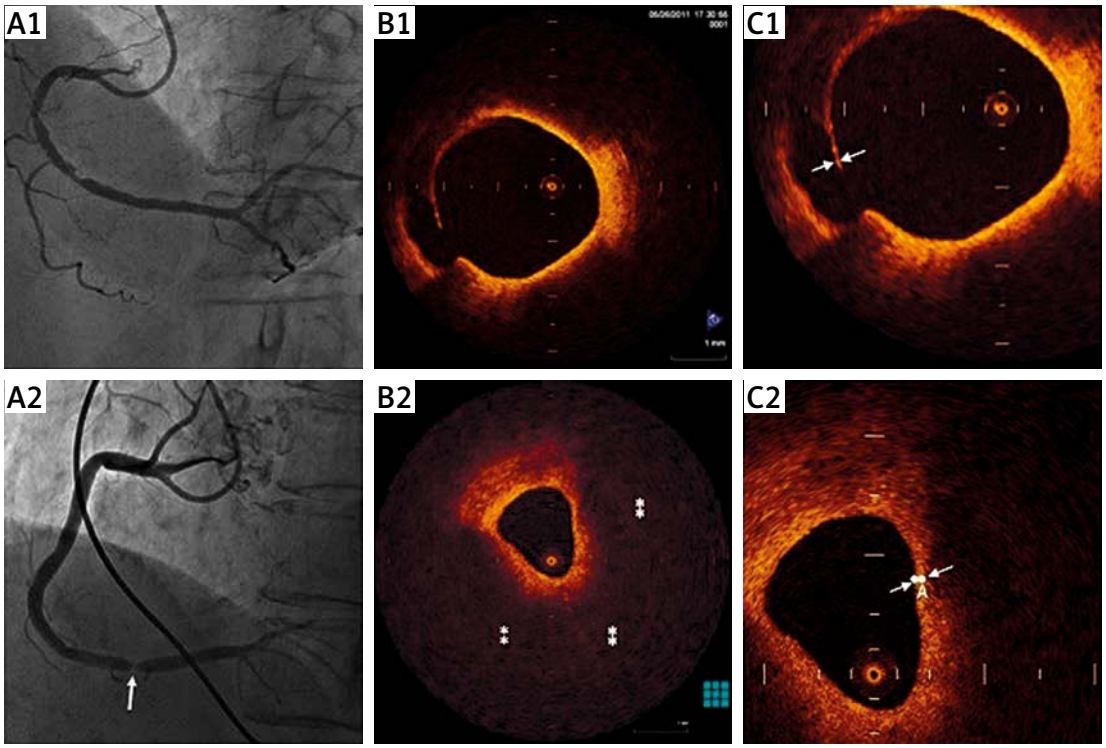


Figure 1. Thin capped fibroatheroma (TCFA) with rupture and without rupture in a patient with acute myocardial infarction. **A1, B1, C1** – Culprit lesion in right coronary artery (RCA). (A1) Coronary angiogram shows a severe stenosis with haziness in the middle of the RCA. Optical coherence tomography (B1, C1) reveals ruptured plaque; the thinnest part measures 50 µm. Serum CRP and IL-6 in this patient were 1.23 mg/l and 12.3 pg/dl respectively. **A2, B2, C2** – Culprit lesion in RCA in a patient with unstable angina pectoris. (A2) Angiographic finding in culprit lesion in a patient with unstable angina pectoris. Severe stenosis in distal RCA was observed. Optical coherence tomography (B2, C2) in culprit lesion shows a large lipid-rich (⁂) plaque covered by a thin fibrous cap (thinnest part 60 µm). Minimum lumen area is 1.6 mm^2. Peripheral blood level of CRP and IL-6 is 0.47 mg/l and 3.42 pg/dl respectively

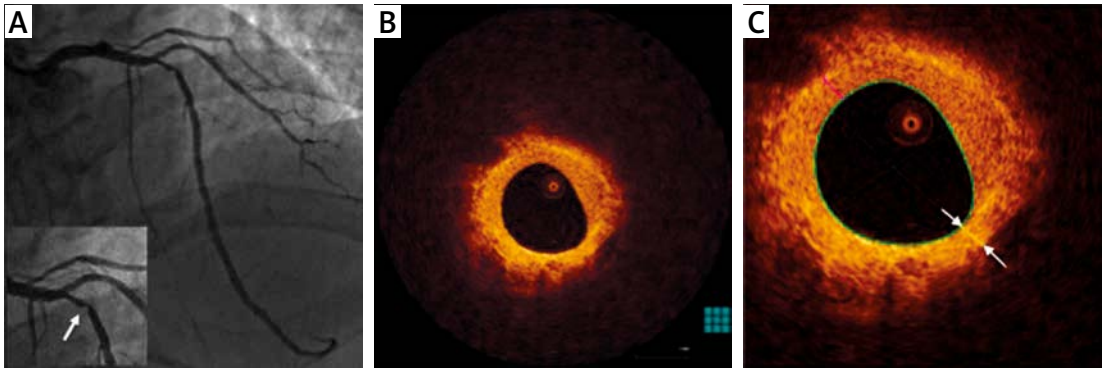


Figure 2. Non-thin cap fibroatheroma (non-TCFA). Culprit lesion in left descending artery (LAD) in a patient with effort angina pectoris. **A** – Coronary angiography in culprit lesion of a patient with effort angina pectoris. Severe stenosis was observed in proximal LAD (arrow). **B, C** – Optical coherence tomography shows fibrous plaque (homogeneous and high reflective area). The thinnest part of the plaque measured 270 µm (arrow). Peripheral blood level of CRP and IL-6 was 0.44 mg/l and 2.38 pg/dl

tion normality was tested with the Shapiro-Wilk test. Stepwise multiple logistic regression analysis was performed to assess independent predictors for TCFA. Receiver operating characteristic (ROC) curves were used to determine the true-positive rate (sensitivity) and false-positive rate (1 – specificity) of serum biomarkers. A p value < 0.05 was considered as statistically significant.

Table I. Patient characteristics

Parameter	TCFA group (n = 12)	Non-TCFA group (n = 35)	Value of p*
Age, mean ± SD [years]	67 ±12	67 ±11	0.861
Female, *n* (%)	0 (0)	8 (23)	0.093
BMI, mean ± SD [kg/m^2]	23.8 ±3.3	22.8 ±2.9	0.289
Hypertension, *n* (%)	8 (67)	27 (77)	0.471
Dyslipidemia, *n* (%)	8 (67)	26 (74)	0.713
DM, *n* (%)	4 (33)	10 (29)	0.731
Smoking, *n* (%)	7 (58)	24 (69)	0.725
MI history, *n* (%)	2 (17)	3 (9)	0.59
Statin use, *n* (%)	2 (17)	13 (5)	0.288
HbA_{1c}, mean ± SD (%)	6.1 ±1.6	5.7 ±0.8	0.696
HDL, mean ± SD [mg/dl]	48 ±15	46 ±11	0.800
LDL, mean ± SD [mg/dl]	107 ±34	103 ±28	0.780
Diagnosis:			
SAP, *n* (%)	2 (17)	23 (66)	0.003
UAP, *n* (%)	3 (25)	7 (20)	0.7
AMI, *n* (%)	5 (14)	7 (58)	0.005
Culprit lesion:			0.969
LAD, *n* (%)	6 (50)	17 (48)	0.933
LCX, *n* (%)	3 (25)	8 (23)	0.880
RCA, *n* (%)	3 (25)	10 (29)	0.811
Laboratory findings, median (interquartile range):			
WBC, 10^9/l	7.85 (5.28–10.40)	6.10 (5.30–7.60)	0.121
hs-CRP [mg/l]	2.62 (0.55–11.40)	0.63 (0.40–1.35)	0.027
IL-6 [pg/dl]	5.13 (1.92–26.18)	1.70 (0.80–1.35)	0.004

ACS – Acute coronary syndrome, AMI – acute myocardial infarction, BMI – body mass index, DM – diabetes mellitus, HbA_{1c} – hemoglobin A_{1c}, hs-CRP – high-sensitivity C-reactive protein, IL-6 – interleukin-6, LAD – left anterior descending artery, LCX – left circumflex artery, MI – myocardial infarction, RCA – right coronary artery, SAP – stable angina pectoris, TCFA – thin-cap fibroatheroma, UAP – unstable angina pectoris, WBC – white blood cell.

Results

Patient characteristics

Because 3 (2 ACS patients and 1 SAP patient) of the 50 CVD patients were excluded owing to poor OCT imaging quality, we finally investigated 47 patients. Baseline characteristics of the patients are shown in Table I. Mean age was 67 ±11 years, and most of the patients were men. There were no significant differences in medical history, use of medicines, or cholesterol and hemoglobin A_{1c} levels between the TCFA and non-TCFA groups. The incidence of AMI was higher in the TCFA group than in the non-TCFA group. Peripheral blood levels of hs-CRP and IL-6 in the TCFA group were relatively higher than those in the non-TFCA group (hs-CRP 2.62 (0.55–11.40) vs. 0.63 (0.40–1.35) mg/dl, p = 0.027; IL-6 5.13 (1.92–26.18) vs. 1.70 (0.80–1.35) pg/dl, p = 0.004, respectively) (Table I, Figure 3).

Blood samples were collected within hours from onset (mean 9 ±5 h) in all AMI patients.

Plaque morphology by optical coherence tomography

Twelve lesions were identified as TCFAs in our study, among which 10 were plaque ruptures. Thrombus was observed in 15 (43%) of 35 non-TCFA lesions. There was no difference in the minimum lumen area between the TCFA and non-TCFA groups (Table II).

Relationship between plaque morphology and serum biomarkers

Figure 3 shows the levels of inflammatory biomarkers. The log hs-CRP and IL-6 levels were higher in the TCFA group than in the non-TCFA group (log hs-CRP, 0.87 (–0.96 to 0.87) vs. –0.47 (–0.92

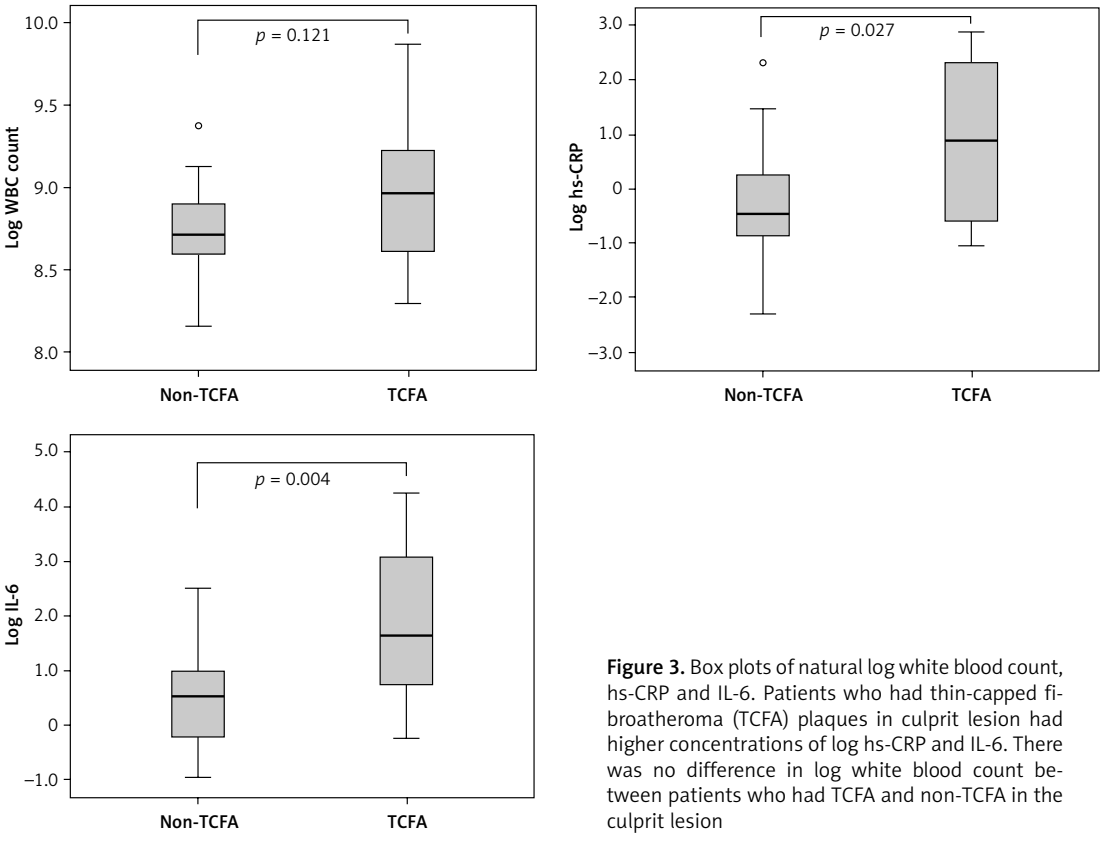


Figure 3. Box plots of natural log white blood count, hs-CRP and IL-6. Patients who had thin-capped fibroatheroma (TCFA) plaques in culprit lesion had higher concentrations of log hs-CRP and IL-6. There was no difference in log white blood count between patients who had TCFA and non-TCFA in the culprit lesion

Table II. Plaque morphology by optical coherence tomography

Variable	TCFA group (n = 12)	Non-TCFA group (n = 35)	Value of p
Minimum fibrous cap thickness, median (interquartile range) [µm]	60 (44–60)	157 (130–210)	< 0.001
Plaque rupture, n (%)	10 (83)	0 (0)	< 0.001
Thrombus, n (%)	11 (92)	15 (43)	0.03
Minimum lumen area, median (interquartile range) [mm^2]	1.53 (1.46–2.20)	1.17 (0.72–1.80)	0.48

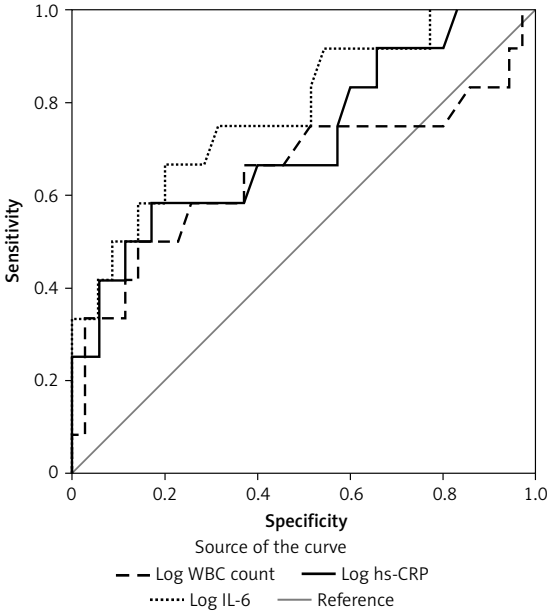
TCFA – Thin-cap fibroatheroma.

Table III. Univariate and multivariate logistic regression analyses for TCFA

Variable	Univariate logistic regression		Multivariable logistic regression		
	β-Coefficient	Value of *p*	β-Coefficient	Value of *p*	OR (95% CI)
Gender ratio (male/female)	20.392	0.999	–	–	–
WBC	0.000	0.060	–	–	–
Statin use	–1.083	0.202	–	–	–
SAP/ACS	–2.260	0.008	–	–	–
Log hs-CRP	0.733	0.011	–	–	–
Log IL-6	1.126	0.005	0.970	0.023	2.638 (1.143–6.085)

ACS – Acute coronary syndrome, AMI – acute myocardial infarction, CI – confidence interval, OR – odds ratio, SAP – stable angina pectoris, TCFA – thin-cap fibroatheroma, UAP – unstable angina pectoris, WBC – white blood cell.

to 0.30), $p = 0.027$; log IL-6, 1.63 (0.63 to 3.23) vs. 0.53 (–0.21 to 1.05), $p = 0.005$, respectively), although there was no difference in the white blood cell count between the 2 groups. In multivariate logistic regression analysis, the natural log of IL-6 was the only independent predictor for TCFA (odds ratio (OR) = 2.638, 95% confidence interval (CI) = 1.143–6.085, $p = 0.023$) (Table III). The ROC curve analysis confirmed that a log hs-CRP cutoff of 0.89 would detect TCFA with a 67% sensitivity and 60% specificity, and a log IL-6 cutoff of 2.56 would detect TCFA with a 75% sensitivity and 69% specificity (Figure 4). The area under the curve of log IL-6 was larger than that for log hs-CRP (0.783 vs. 0.715).



	AUC
log WBC count	0.651
log hs-CRP	0.715
log IL-6	0.783

Figure 4. Receiver operator characteristic (ROC) curves for predicting TCFA

Discussion

Our study revealed a relationship between TCFAs in culprit lesions, as detected by OCT, not only with hs-CRP but also with IL-6 levels.

Recent OCT studies showed the relationships between plaque morphology and inflammatory factors. Li *et al.* [15] demonstrated an inverse linear correlation between fibrous cap thickness and plasma levels of inflammatory markers such as IL-18, hs-CRP, tumor necrosis factor-α, and peripheral white blood cell count. In that study, the only independent predictor for TCFA identified by OCT was hs-CRP. Bouki *et al.* [16] also reported that hs-CRP was the only independent predictor for plaque rupture in culprit lesions.

The CRP is mainly produced in the liver. It can be produced within the vascular smooth muscle of diseased coronary arteries, and it may directly lead to the expression of several mediators of the atherosclerotic process [17–19]. Liuzzo *et al.* [20] reported that patients with UAP who had higher CRP levels had more ischemic episodes in the hospital than patients with lower CRP levels. This finding suggested that coronary plaque instability could reflect circulating CRP. The CRP can provide important information, but is a nonspecific marker. It can be affected by systemic inflammatory reactions because it is mainly produced by the liver. Myocardial necrosis caused by infarction induces complement activation and free radical generation, which triggers a cytokine cascade and inflammatory reaction that consequently increases CRP production [21]. According to previous clinical studies [22, 23], CRP levels may begin to increase 6 h after an initial complaint, and a correlation between the extent of the CRP increase and the size of the infarction, as indicated by creatine kinase assay, was observed.

The IL-6 is a 26-kDa cytokine produced by many different cells in the body, including lymphocytes, monocytes, fibroblasts, vascular smooth muscle cells, and endothelial cells. It can stimulate

the expression of tissue factor, monocyte chemotactic protein-1, matrix-degrading enzyme, and low-density lipoprotein receptors in macrophages as well as aggregation of platelets and proliferation of vascular smooth muscle cells [24]. The IL-6 is also a proinflammatory biomarker that several investigators have observed to be expressed in human atherosclerotic lesions. Some reports have shown that IL-6 levels were increased in a patient with AMI [25–27] and that IL-6 levels were higher in patients with UAP than in those with SAP [28], but no correlation was observed between the IL-6 level and size of the infarction as indicated by creatine kinase [26–28]. Therefore, IL-6 has the potential to reflect coronary plaque instability in the presence of myocardial injury. Moreover, the IL-6 levels in patients with UAP who had angina at rest within the past 48 h were higher than in patients who did not have angina at rest [24]. These findings suggest that IL-6 levels could correlate with instability of the atheromatous plaque.

Our present study demonstrated that not only hs-CRP but also IL-6 levels are associated with the presence of TCFA detected by OCT. Furthermore, IL-6 has higher sensitivity and specificity than hs-CRP for the prediction of TCFA. Because of the importance of screening for vulnerable plaques to prevent cardiac adverse events and the need for less invasive detection techniques [29], we suggest that inflammatory biomarkers have potential for detecting vulnerable plaques. In particular, IL-6 can provide surrogate information for risk stratification of patients with ischemic heart disease.

Our study has several limitations. First, the sample size in this study was relatively small. Second, we were able to detect TCFAs by assaying biomarkers, but we investigated only 2 biomarkers. Further studies are needed to find more sensitive and specific biomarkers for detecting vulnerable plaques [30, 31]. Third, it may be necessary to observe not only culprit lesions but also other coronary vessels to more precisely evaluate the relationship between peripheral levels of biomarkers and coronary plaque vulnerability.

In conclusion, increased serum hs-CRP and IL-6 levels are associated with the presence of TCFAs in culprit lesions detected by OCT. The relationship between plaque instability, as detected by OCT, and the levels of inflammatory biomarkers help us better understand plaque vulnerability in patients with coronary atherosclerosis.

Conflict of interest

The authors declare no conflict of interest.

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