Elevated Levels of Systemic Pentraxin 3 are Associated With Thin-cap Fibroatheroma in Coronary Culprit Lesions

Assessment by Optical Coherence Tomography and Intravascular Ultrasound

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Abstract

Objectives: The present study aimed to determine whether or not systemic levels of pentraxin 3 (PTX3), a novel inflammatory marker, are associated with thin-cap fibroatheroma (TCFA).

Background: Biomarkers predicting the presence of TCFA in vivo have not been established.

Methods: We evaluated 75 patients (stable angina pectoris (SAP), n = 47; acute coronary syndrome (ACS), n = 28) with de novo culprit lesions that were examined by optical coherence tomography (OCT) and intravascular ultrasound (IVUS). We defined TCFA as lipid-rich plaque with a fibrous cap < 65 μm thick. Systemic levels of PTX3 were compared between patients with and without TCFA.

Results: Thirty-eight and 37 patients with and without TCFA, respectively, were identified. Levels of PTX3 were significantly higher in patients with, than without TCFA ($p < 0.001$) and correlated inversely with fibrous cap thickness ($r = -0.71$, $p =$

0.001) and positively with the remodeling index (r = 0.25, p = 0.037). Multivariate logistic regression analysis showed that a higher PTX3 level was the most powerful predictor of TCFA (odds ratio: 3.26, 95% confidence interval: 1.75 to 6.05, p < 0.001). Receiver operator characteristic curve analysis showed that > 3.24 ng/ml of PTX3 could predict TCFA with 84% sensitivity and 86% specificity.

Conclusions: Higher levels of systemic PTX3 are associated with TCFA. Systemic PTX3 levels comprise a useful inflammatory marker that reflects coronary plaque vulnerability.

Key words: vulnerable plaque, pentraxin 3, optical coherence tomography, thin-cap fibroatheroma

Condensed abstract

The present study examines associations between systemic levels of pentraxin 3 (PTX3) and thin-cap fibroatheroma (TCFA) assessed by optical coherence tomography and intravascular ultrasound in 75 patients with coronary artery diseases. Levels of PTX3 were significantly higher in patients with than without TCFA. Multivariate logistic regression analysis showed that a higher PTX3 level was the most powerful predictor of TCFA. Receiver operator characteristic curve analysis showed that > 3.24 ng/ml of PTX3 predicted TCFA with 84% sensitivity and 86% specificity. In conclusion, PTX3 levels might reflect coronary plaque vulnerability leading to the development of acute coronary syndrome.

Abbreviations and acronyms

ACS = acute coronary syndrome

AMI = acute myocardial infarction

CSA = cross-sectional area

EEM = external elastic membrane

hsCRP = high-sensitivity C-reactive protein

IVUS = intravascular ultrasound

OCT = optical coherence tomography

PTX3 = pentraxin 3

SAP = stable angina pectoris

TCFA = thin-cap fibroatheroma

Introduction

Pathological studies of patients with sudden cardiac death suggest that acute coronary syndromes (ACS) mostly arise as a result of thrombotic coronary occlusion after rupture of a thin-cap fibroatheroma (TCFA) that is also referred to as vulnerable plaque (1). Vascular inflammation is considered to play a key a role in plaque vulnerability (2).

Although acute-phase C-reactive protein (CRP) is widely considered an indicator of systemic inflammation, the response is not specific to vascular inflammation and it is triggered by many disorders that are unrelated to cardiovascular disease. Pentraxin 3 (PTX3) is a member of the pentraxin superfamily that includes CRP and serum amyloid P. High levels of PTX3 are locally expressed in vascular endothelial, smooth muscle and vascular inflammatory cells in human atherosclerotic lesions (3,4). Plasma PTX3 is also implicated as an acute indicator and as a predictor of adverse clinical outcomes of ACS (5,6). However, the association between circulating PTX3 levels and vulnerable plaque

has not been directly explored.

Optical coherence tomography (OCT) is new intravascular imaging modality that allows clear visualization of the various features of vulnerable plaques including TCFA (7). When combined with intravascular ultrasound (IVUS), OCT is presently the optimal approach to evaluating plaque characteristics. Therefore, we investigated whether systemic PTX3 levels could reflect plaque characteristics including TCFA in coronary culprit lesions assessed by OCT and IVUS.

Methods

Study population.

Between April 2009 and February 2012, 101 consecutive patients with coronary artery disease who underwent both OCT and IVUS to de novo culprit lesions in the native coronary artery at Nagasaki University Hospital were considered for inclusion in this prospective study. The exclusion criteria comprised a left main lesion, ostial,

chronic total occlusion or severely calcified lesions, cardiogenic shock or renal insufficiency (baseline serum creatinine > 2.0 mg/dl without maintenance hemodialysis). Patients with a history of treatment for, or diagnosis of carotid artery stenosis, thoracic/abdominal aortic aneurysm, peripheral artery, collagen, malignant, infectious and other systemic inflammatory diseases were also excluded, because these conditions might affect PTX3 or CRP levels (5,8). We excluded 22 patients according to these criteria and four others with low-quality OCT or IVUS images. Thus, data from 75 patients with ACS (n = 28) and stable angina pectoris (SAP, n = 47) were included in the final analysis. ACS included acute myocardial infarction (AMI, n = 17) and unstable angina pectoris (n = 11). We defined AMI as chest pain that persisted for > 30 minutes, arrival at hospital within 12 hours of the onset of chest pain, new ST-T changes or a new left bundle-branch block on 12-lead electrocardiograms and elevated cardiac markers (creatine kinase-MB or troponin T) (9). We defined unstable angina pectoris as angina at rest, accelerated angina, or new-onset angina without elevation of cardiac markers. We

defined SAP as no change in the frequency, duration, or intensity of angina symptoms within six weeks before admission. This study complied with the Declaration of Helsinki with regard to investigations in humans, and the Ethics Committee of Nagasaki University Hospital approved the protocol. All participants provided written, informed consent before enrollment in the study.

Angiographic analysis

Patients were examined by quantitative coronary angiography using a CASS II system (Pie Medical Imaging, Maastricht, The Netherlands). The minimum lumen diameter, reference vessel diameter, and length of the culprit lesion were measured. Culprit lesions were identified from a combination of left ventricular wall motion abnormalities, electrocardiographic findings, scintigraphic defects and angiographic lesion morphology.

OCT image acquisition and analysis

Patients with TIMI flow grade ≤ 2 underwent aspiration thrombectomy using a

Thrombuster III aspiration catheter (Kaneka Medics, Tokyo, Japan) before OCT imaging. We performed OCT using the balloon occlusion method (10) and a 0.016-inch guidewire-based OCT ImagingWire catheter (LightLab Imaging Inc., Westford, MA, USA) and a Helios occlusion balloon catheter (Goodman Co. Ltd., Nagoya, Japan). An imaging run proceeded using automated pullback at 1.0 mm/s. Acquired OCT images were analyzed using proprietary offline software from LightLab Imaging.

Two independent experienced observers who were blinded to the angiographic and clinical data analyzed the OCT images using validated criteria for plaque characterization (10). Discordance between observers was resolved by taking a consensus reading. Signal-poor lesions with unclearly delineated borders on OCT images indicated a lipid core and signal-rich homogeneous lesions overlying a lipid core indicated a fibrous cap. The thinnest part of a fibrous cap was measured three times, and the average was defined as fibrous cap thickness. The arc of a lipid core on cross-sectional OCT images was measured and semiquantified according to the number

of involved quadrants. When a lipid core comprised over two quadrants, it was deemed to be lipid-rich plaque (Fig. 1A). We defined TCFA as a lipid-rich plaque with the thinnest part of the fibrous cap measuring < 65 μm (Fig. 1B). Ruptured plaque was defined as fibrous cap discontinuity and cavity formation in the plaque (Fig. 1C). Intracoronary thrombus was identified as a mass protruding into the vessel lumen from the surface of the vessel wall (Fig. 1D). Intra-and inter-observer variability yielded acceptable concordance for the presence of TCFA (κ = 0.81 and 0.84, respectively). The mean inter- and intra-observer differences in the fibrous-cap thickness were 5.9 ± 6.6 and 5.2 ± 5.7 μm, respectively. Intra- and inter-observer correlation coefficients for measurements of the fibrous cap thickness were 0.85 and 0.82, respectively.

IVUS image acquisition and analysis

After OCT analysis, IVUS images were obtained using the iLab system (Boston Scientific, Natick, MA, USA) and an Atlantis Pro Imaging catheter (40 MHz, Boston Scientific) during automated motorized pullback at 0.5 mm/s. Images were digitally

stored for subsequent offline analysis.

The IVUS analysis proceeded using validated software (echoPlaque 3.0 INDEC Medical Systems, Santa Clara, CA, USA) according to the American College of Cardiology Clinical Expert Consensus Document (11). Cross-sectional images were quantified for lumen cross-sectional area (CSA), external elastic membrane (EEM) CSA, and plaque plus media CSA calculated as EEM minus lumen CSA. Plaque burden was calculated as plaque plus media divided by EEM CSA. The IVUS parameters were measured at the minimum lumen CSA sites and a reference site. The remodeling index was defined as EEM CSA at the target lesion divided by EEM CSA at the average reference (12).

Blood samples

Venous blood samples were withdrawn before coronary angiography from the forearms of patients with ACS and with SAP who had fasted overnight. The mean interval from symptom onset to blood sampling from patients with AMI was 6.4 hours.

Venous blood samples were collected into EDTA vacuum containers for PTX3, centrifuged for 10 minutes and the plasma was stored at -80°C until assay. Levels of PTX3 were measured using a high-sensitivity enzyme-linked immunosorbent assay system for human plasma (Perseus Proteomics, Tokyo, Japan). The normal physiological concentration of plasma PTX3 is about 2 ng/ml (13). High-sensitivity CRP (hsCRP) was measured at SRL Co. Ltd, Tokyo, Japan. The estimated glomerular filtration rate was calculated as: $194 \times age^{-0.287} \times$ serum $creatinine^{-1.094}$ (if female, × 0.739) (14).

Statistical analysis

Continuous values are expressed as means ± SD for normally distributed variables or medians (interquartile ranges) for skewed variables, and analyzed by the paired t-test, the Mann-Whitney U test, or the Kruskal-Wallis test. Categorical data are presented as numbers (%) and analyzed using the chi-square test or Fisher's exact test. Relationships between biomarkers and plaque characteristics were evaluated using Spearman's rank

correlation coefficient. Significant factors indicating the presence of TCFA were determined using multivariate logistic regression analysis. Factors with $p < 0.05$ in the univariate analysis were entered into multivariable models. Receiver-operating characteristic curves were constructed to identify optimal biomarker cutoff points, defined as the point closest to 100 in the top left corner. Inter- and intra-observer agreement for TCFA identification was evaluated by Cohen's κ test of concordance. Intra- and inter-observer variability in measuring fibrous cap thickness values was evaluated by linear regression. A probability of $p < 0.05$ was considered statistically significant. All other data were statistically analyzed using IBM SPSS version 20 (IBM Corp., Somers, NY, USA).

Results

Characteristics of patients

Among 75 culprit plaques in 75 patients, 38 (51%) of them were diagnosed as

TCFA based on OCT findings. Table 1 summarizes the baseline clinical characteristics. The prevalence of ACS was higher, whereas both the frequency of statin usage and hemoglobinA1c levels, were lower in patients with, than without TCFA. No other characteristics significantly differed between patients with and without TCFA.

Angiographic, OCT and IVUS findings

Table 2 shows the angiographic, OCT and IVUS findings between patients with and without TCFA. Reference vessel diameter, EEM CSA, plaque plus media CSA, plaque burden, and remodeling index were significantly greater in patients with, than without TCFA. As expected from the definition of TCFA, the arc of the lipid core was greater and the fibrous cap was thinner in patients with TCFA.

Relationships between PTX3, hsCRP and lesion characteristics

Table 3 compares PTX3 or hsCRP levels among the lesion characteristics determined by OCT. Levels of PTX3 were significantly higher in patients with than without TCFA, but elevations in those of hsCRP did not reach significance. Levels of

PTX3 significantly and inversely correlated with fibrous cap thickness and tended to increase with increasing lipid quadrants. Levels of both PTX3 and hsCRP were significantly elevated in patients with ruptured plaque or thrombus.

Table 4 shows correlations between PTX3 or hsCRP levels and QCA and IVUS data. Levels of PTX3 correlated significantly and positively with reference vessel diameter and levels of both hsCRP and PTX3 correlated significantly and positively with EEM CSA, lumen CSA, plaque plus media CSA and the remodeling index.

On the other hand, PTX3 levels significantly differed between patients with ACS and those with SAP (4.90 (3.31 - 9.53) vs. 2.33 (1.68 - 3.58) ng/ml, respectively; $p < 0.001$). Similarly, hsCRP levels also differed between ACS and SAP (5.30 (1.16 - 14.15) vs. 0.89 (0.40 - 3.04) mg/l, respectively; $p < 0.001$). Thus, we evaluated PTX3 or hsCRP levels separately in patients with ACS and in those with SAP because these values might be influenced by the presence of ACS (Fig. 2). Among patients with ACS, PTX3 levels were significantly higher in those with than without TCFA [6.22 (3.80 - 14.52) vs.

2.50 (2.00 - 3.31) ng/ml; p = 0.003, Fig. 2A]. Among patients with SAP, PTX3 levels were higher in patients with than without TCFA [3.58 (3.03 - 5.15) vs. 1.94 (1.44 - 2.68) ng/ml; p < 0.001, Fig. 2B]. However, both patients with and without TCFA had similar levels of hsCRP in ACS [5.33 (1.12 - 20.00) vs. 1.31 (0.89 - 9.81) mg/l; p = 0.41] (Fig. 2C) and in SAP [0.89 (0.39 - 2.13) vs. 0.83 (0.41 - 3.26) mg/l; p = 0.85] (Fig. 2D).

The patients with ACS and SAP were categorized based on whether PTX3 or hsCRP levels were in the lowest, middle, and highest tertiles, and the frequency of TCFA was compared in each group (Fig. 3). The frequency of TCFA increased significantly from the lowest to the highest tertiles of PTX3 levels both in patients with SAP and in those with ACS (Figs. 3A and B), but this trend was not evident among hsCRP tertiles (Figs. 3C and D).

Predictors of TCFA

We used both univariate and multivariate logistic regression analysis to identify significant factors predicting the presence of TCFA. The univariate analysis identified

ACS, higher PTX3 levels and remodeling index, larger reference vessel diameter, EEM CSA, plaque plus media CSA, and plaque burden were significant predictors for TCFA, and complication of diabetes mellitus and statin use had lower probability of its presence. Among these factors, higher PTX3 levels and larger plaque plus media CSA values significantly correlated with TCFA with the multivariate analysis (Table 5). We analyzed only patients with SAP to predict the presence of TCFA in patients who have not yet developed ACS. We found that a higher PTX3 level and a greater reference vessel diameter were significant factors associated with TCFA in SAP patients (Table 6). Figure 4 shows the receiver-operating characteristic curves of PTX3 levels for predicting TCFA in all patients and in those with SAP. The area under the curve of PTX3 in all patients (Fig. 4A) was 0.89 (95% confidence interval [CI], 0.81 to 0.97; $p < 0.001$). A PTX3 cut-off value of 3.24 ng/ml distinguished TCFA from non-TCFA with 84% sensitivity and 86% specificity. In contrast, the area under the curve of PTX3 was 0.84 (95% CI, 0.71 to 0.98; $p < 0.001$) in patients with SAP (Fig. 4B). A PTX3 value of

2.88 ng/ml identified TCFA with 80% sensitivity and 78% specificity in these patients.

Discussion

The main findings of the present study are as follows: systemic PTX3 levels were significantly higher in patients with than without TCFA; the frequency of TCFA significantly increased according to elevations in PTX3 levels; and higher levels of PTX3 were the most powerful predictor of TCFA in patients with SAP and the entire study population.

The liver produces the short pentraxin, CRP, in response to interleukin-6. Elevated CRP values correlate with increased risk of cardiovascular disease in both healthy and high-risk individuals (15). However, the CRP response is not specific to vascular inflammation and it can be triggered by various disorders that are unrelated to cardiovascular disease. On the other hand, endothelial cells, monocytes/macrophages and neutrophils locally produce long PTX3 at sites of inflammation, predominantly in

response to proinflammatory signals including tumor necrosis factor-α, interleukin-1β, oxidized low-density lipoprotein and lipopolysaccharide (3,4,16). Blood levels of PTX3 can increase in response to subtle inflammation caused by coronary plaque. Circulating plasma PTX3 is a predictor of adverse cardiac events in patient with ACS as well as in those with SAP (5,6,17). Furthermore, plasma PTX3 is more closely associated with the angiographic complexity and severity of coronary artery disease than hsCRP (18). However, whether or not systemic PTX3 levels can reflect plaque characteristics remains unclear. The present study therefore evaluated the relationship between systemic PTX3 levels and coronary plaque vulnerability assessed by OCT and IVUS.

The typical morphology of TCFA is that of a large plaque burden, a large necrotic core, a thin fibrous cap with infiltrating macrophages and positive remodeling (19). We evaluated these features of TCFA using OCT and IVUS and found that patients with TCFA had significantly higher levels of systemic PTX3. We also discovered that systemic PTX3 levels correlated inversely with fibrous cap thickness and positively

with EEM CSA, plaque plus media CSA and the remodeling index. Furthermore, the multivariate analysis identified higher PTX3 levels were the most powerful predictor of TCFA. We separately evaluated PTX3 levels in patients with ACS and in those with SAP to control for any influence the presence of ACS may have had on PTX3 levels. Importantly, PTX3 levels comprised a significant predictor of TCFA even in patients with SAP. These findings suggest that systemic PTX3 levels reflect the vulnerability of coronary culprit plaque. In addition, systemic PTX3 levels might predict TCFA in patients with SAP who have not yet developed ACS. This superior predictive value of PTX3 might be associated with the higher specificity of PTX3 for localized inflammation. Thus, routinely measuring systemic PTX3 levels in patients with SAP in daily clinical practice can help to identify those who are likely to be at higher risk for ACS. Iwata et al. (20) recently reported that statin therapy (atorvastatin 10 mg/day) for six to eight months significantly decreases the plasma PTX3 levels in patients with SAP. Further study is needed to determine whether reducing PTX3 levels with statin can lead

to the prevention of ACS.

Levels of systemic PTX3 were significantly higher in our ACS patients with than without TCFA. Systemic levels of PTX3 in such patients should be carefully interpreted. Firstly, the major sources of systemic PTX3 in these patients might be heart tissues with severe ischemia or infarction rather than coronary vulnerable plaques. Nebuloni et al. (21) found that PTX3 is produced by macrophages, the endothelium, and to a lesser extent, myocardiocytes, and that it localizes in the interstitium of heart tissues from patients with AMI at autopsy. Secondly, systemic PTX3 levels are influenced by time-dependent changes from the onset of AMI. Peri et al. (6) showed that plasma PTX3 levels peak at a median of 7.5 hours after AMI and return to normal after three days. Our results might be biased by variation in intervals between symptom onset in patients with AMI and blood sampling.

The present study identified a significant relationship between hsCRP and ruptured plaque or thrombus. Our findings are consistent with those of previous IVUS and OCT

studies (22). In contrast, we did not discover a significant association between hsCRP and the presence of TCFA. Tanaka et al. (23) reported that hsCRP levels inversely correlate with fibrous cap thickness measured by OCT in patients with ACS. Matsuo et al. (24) showed using OCT that hsCRP levels are significantly higher in patients with ACS with, than without TCFA. Sawada et al. (25) found similar hsCRP levels in patients who had SAP regardless of the presence or absence of TCFA. The most likely explanation for these inconsistencies might be as follows. Since the inflammatory responses of coronary plaque might be subtle, TCFA alone might not influence systemic inflammatory markers such as hsCRP, especially in patients with SAP. Plaque rupture leading to ACS might induce higher levels of systemic inflammation compared with unruptured plaque and then increase hsCRP levels in the peripheral circulation. However, the early detection of unruptured TCFA as opposed to ruptured plaque is more important for the prediction and prevention of ACS. From this viewpoint, systemic hsCRP might be less useful than PTX3.

In the present study, diabetes mellitus had a lower probability for predicting TCFA by only a univariate analysis. In contrast, a previous OCT study demonstrated that plaques in patients with diabetes frequently had vulnerable features including TCFA (26). This disagreement might be caused by the finding that our patients with diabetes had a significantly higher proportion of statin use than those without diabetes (63% vs. 35%, $p = 0.027$).

We could not ascertain a causal relationship between elevated PTX3 and coronary plaque characteristics. Savchenko et al. (4) reported that PTX3 might play a causal role in the progression of atherosclerotic lesions through soluble pattern recognition in innate immunity. In contrast, PTX3 in apolipoprotein E-knockout mice was recently implicated in an atheroprotective effect (27) and it plays a cardioprotective role in mouse models of AMI (28). Elevated PTX3 might reflect a compensatory cardioprotective response to an activated inflammatory response. However, the present study found only that systemic PTX3 is a useful inflammatory marker of TCFA. The

pathogenic role of elevated PTX3 in coronary plaque vulnerability requires further study.

Study limitations

Our study has several limitations. First, the small patient cohort from a single center imposed inherent limitations. In addition, since we evaluated only limited patients who did not meet many exclusion criteria and who underwent both OCT and IVUS, our results could have been affected by selection bias and cannot be generalized to all patients. Second, we assessed only culprit plaque morphology in culprit vessels. Assessment of multiple plaques by OCT in three-vessel coronary trees is ethically unacceptable, especially in patients with ACS because repeated balloon occlusion is required along with a larger volume of flushing solution. Third, although we did not enroll patients with carotid artery stenosis, thoracic/abdominal aortic aneurysms or peripheral artery disease, we could not exclude the possibility that vulnerable plaques in

other vascular beds might affect PTX3 levels. To demonstrate local PTX3 production in the coronary circulation, PTX3 levels should also be measured at the coronary sinus or coronary artery. Fourth, several thrombi might reduce the ability of OCT to assess the details of plaque morphology, because thrombus might shadow or obscure underlying structures. Finally, we did not assess whether PTX3 levels can predict clinical outcomes and whether TCFA would lead to ACS in the future. Future longitudinal and prospective studies are needed to address these issues.

Conclusions

Levels of systemic PTX3 are higher in patients with than without TCFA assessed by OCT. Higher PTX3 levels comprise a powerful indicator of TCFA, even in patients with SAP. These findings suggest that systemic PTX3 can serve as a biomarker that reflects plaque vulnerability.

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Figure legends

Figure 1. Representative Optical Coherence Tomography Images

(**A**) Lipid-rich plaque. (**B**) Thin-cap fibroatheroma. Fibrous cap (arrows) is 60 μm thick. (**C**) Ruptured plaque (arrow). (**D**) Intracoronary thrombus (arrow heads).

Figure 2. Comparisons of PTX3 and HsCRP Levels Based on Presence of TCFA in Patients with ACS and SAP

Box and whisker plots show distribution of PTX3 (**A** and **B**) and hsCRP levels (**C** and **D**). ACS = acute coronary syndrome; hsCRP = high-sensitivity C-reactive protein; PTX3 = pentraxin 3; SAP = stable angina pectoris; TCFA = thin-cap fibroatheroma.

Figure 3. Frequency of TCFA According to PTX3 and HsCRP Levels

Comparison of TCFA frequency among PTX3 tertiles (**A** and **B**) or hsCRP levels (**C** and **D**) in patients with ACS and SAP. P values indicate trends across tertiles. Abbreviations

are the same as those in Figure 2.

Figure 4. Receiver-operating Characteristic Curves of PTX3 Levels for Predicting TCFA

Areas under curves (AUC) of PTX3 levels were obtained from all patients (**A**) and from patients with SAP (**B**). Other abbreviations are the same as those in Figure 2.

Table 1. Patients' Characteristics

	Patients without TCFA (n = 37)	Patients with TCFA (n = 38)	p Value
Age, y	69 ± 10	66 ± 12	0.31
Male	30 (81)	30 (79)	0.82
ACS	5 (14)	23 (61)	<0.001
AMI	0	17 (45)	
UAP	5 (14)	6 (16)	
Body mass index, kg/m^2	23.8 ± 3.4	23.5 ± 3.6	0.66
Coronary risk factors			
Hypertension	25 (68)	26 (68)	0.94
Hypercholesterolemia	18 (49)	16 (42)	0.57
Diabetes mellitus	16 (43)	8 (21)	0.050

Current smoker	7 (19)	15 (40)	0.075
Statin use	22 (60)	11 (29)	0.008
Lipid profiles, mg/dl			
Total cholesterol	168 ± 28	177 ± 33	0.19
LDL cholesterol	98 ± 24	110 ± 34	0.10
HDL cholesterol	43 ± 12	47 ± 15	0.32
Triglyceride	110 (83-154)	92 (70-122)	0.058
Blood glucose profiles			
Fasting blood glucose, mg/dl	95 (90-128)	100 (87-116)	0.92
HemoglobinA1c, %	5.5 (5.3-6.7)	5.3 (5.1-5.9)	0.021
eGFR, ml/min/1.73 m^2	61.5 ± 20.8	65.9 ± 23.5	0.39

Data are means ± SD, n (%), or medians (interquartile range). ACS = acute coronary syndrome; AMI = acute myocardial infarction; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TCFA = thin-cap

fibroatheroma; UAP = unstable angina pectoris.

Table 2. Lesion Characteristics Determined by Angiography, IVUS, and OCT

	Patients without TCFA (n = 37)	Patients with TCFA (n = 38)	p Value
Angiographic analysis			
Multivessel disease	12 (32)	11 (29)	0.74
Culprit vessel			0.33
LAD	19 (54)	17 (45)	
LCX	7 (19)	4 (11)	
RCA	11 (30)	17 (45)	
Lesion location			0.33
Proximal	12 (32)	17 (45)	
Mid	13 (35)	14 (37)	
Distal	12 (32)	7 (18)	

QCA data			
Reference vessel diameter, mm	2.66 ± 0.46	3.03 ± 0.55	0.003
Minimum lumen diameter, mm	0.84 ± 0.33	0.88 ± 0.42	0.70
Diameter stenosis, %	68 ± 13	71 ± 12	0.26
Lesion length, mm	13.9 ± 7.2	16.7 ± 8.7	0.14
OCT analysis			
Fibrous cap thickness, μm	167 (100-296)	57 (50-59)	<0.001
Arc of lipid core,°	134 ± 47	198 ± 58	<0.001
IVUS analysis			
EEM CSA, mm^2	11.3 ± 4.8	16.8 ± 5.7	<0.001
Lumen CSA, mm^2	2.4 ± 0.7	2.7 ± 0.9	0.072
Plaque plus media CSA, mm^2	8.9 ± 4.5	14.1 ± 5.4	<0.001
Plaque burden, %	77 ± 8	83 ± 6	0.01
Remodeling index	1.04 ± 0.22	1.15 ± 0.14	0.018

Data are mean ± SD, n (%), or median (interquartile range). CSA = cross-sectional area; EEM = external elastic membrane; IVUS = intravascular ultrasound; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; OCT = optical coherence tomography; QCA = quantitative coronary angiography; RCA = right coronary artery; other abbreviations as in Table 1.

Table 3. PTX3 and HsCRP Levels According to Lesion Characteristics Assessed by OCT

	PTX3, ng/ml	p Value	hsCRP, mg/l	p Value
Fibrous cap thickness (μm)	r = -0.71	< 0.001	r = -0.24	0.050
Lipid core quadrants		0.002		0.21
One (n = 7)	1.87 (1.65-2.16)		0.62 (0.32-0.96)	
Two (n = 39)	3.19 (1.68-4.00)		1.12 (0.45-5.26)	
Three (n = 25)	4.07 (2.53-5.70)		1.45 (1.08-6.67)	
Four (n = 4)	8.18 (3.60-22.50)		1.29 (0.78-15.38)	
TCFA		< 0.001		0.058
Yes (n = 38)	4.54 (3.38-6.99)		1.49 (0.79-8.48)	
No (n = 37)	2.13 (1.55-2.64)		0.96 (0.47-3.93)	
Ruptured plaque		< 0.001		0.002
Yes (n = 20)	6.15 (3.82-13.53)		5.30 (1.17-18.70)	

No (n = 55)	2.51 (1.75-3.60)	0.96 (0.45-3.29)	
Thrombus		< 0.001	0.031
Yes (n = 27)	5.15 (3.19-10.27)	1.63 (0.94-14.80)	
No (n = 48)	2.34 (1.70-3.83)	1.03 (0.46-4.25)	

Data are shown as medians (interquartile range) and r indicates Spearman's rank correlation coefficient. hsCRP = high-sensitivity C-reactive protein; PTX3 = pentraxin 3; other abbreviations as in Table 1 and 2.

Table 4. Levels of PTX3 and HsCRP According to QCA and IVUS Data

	PTX3, ng/ml	p Value	hsCRP, mg/l	p Value
QCA analysis				
Reference vessel diameter	r = 0.27	0.021	r = 0.15	0.20
Minimum lumen diameter	r = 0.02	0.88	r = 0.08	0.51
Lesion length	r = 0.05	0.67	r = 0.03	0.79
IVUS analysis				
EEM CSA	r = 0.43	< 0.001	r = 0.27	0.018
Lumen CSA	r = 0.25	0.033	r = 0.23	0.048
Plaque plus media CSA	r = 0.40	< 0.001	r = 0.26	0.027
Plaque burden	r = 0.22	0.057	r = 0.11	0.35
Remodeling index	r = 0.25	0.037	r = 0.28	0.017

r, Spearman’s rank correlation coefficient. All other abbreviations are the same as those in Tables

1, 2 and 3.

Table 5. Logistic Regression Analysis of TCFA in All Patients

	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p Value
ACS, yes	9.81 (3.12-30.84)	<0.001		
Diabetes mellitus, yes	0.35 (0.13-0.97)	0.043		
Statin use, yes	0.28 (0.11-0.73)	0.009		
PTX3, per 1 ng/ml	3.00 (1.75-5.16)	<0.001	3.26 (1.75-6.05)	<0.001
Reference vessel diameter, per 0.1 mm	1.16 (1.04-1.30)	0.006		
EEM CSA, per 1 mm^2	1.23 (1.10-1.37)	<0.001		

Plaque plus media CSA, per 1 mm^2	1.25 (1.11-1.40)	<0.001	1.25 (1.07-1.46)	0.006
Plaque burden, per 1%	3.22 (1.52-6.84)	0.002		
Remodeling index, per 0.1	1.39 (1.04-1.84)	0.024		

CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1 and 2.

Table 6. Logistic Regression Analysis of TCFA in Patients with SAP

	Univariate		Multivariate	
	OR (95% CI)	p Value	OR (95% CI)	p Value
PTX3, per 1 ng/ml	2.50 (1.37-4.54)	0.003	2.42 (1.30-4.50)	0.005
Reference vessel diameter, per 0.1 mm	1.19 (1.03-1.37)	0.016	1.23 (1.03-1.48)	0.023
EEM CSA, per 1 mm^2	1.18 (1.04-1.34)	0.01		
Plaque plus media CSA, per 1 mm^2	1.19 (1.04-1.37)	0.011		
Plaque burden, per 1%	1.12 (1.01-1.25)	0.034		

Abbreviations are the same as those in Tables 1, 2, and 5.

Figure 1

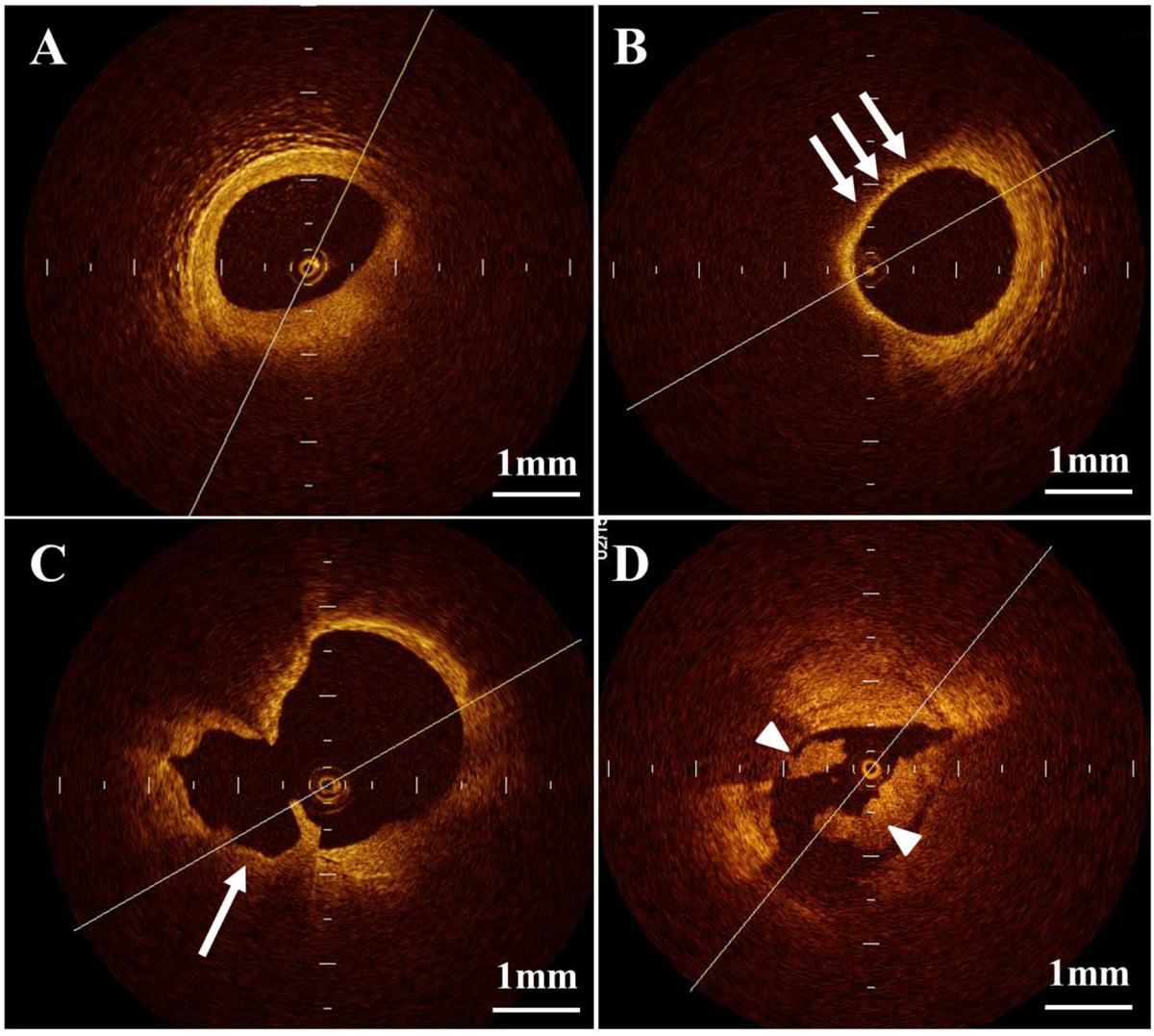


Figure 2

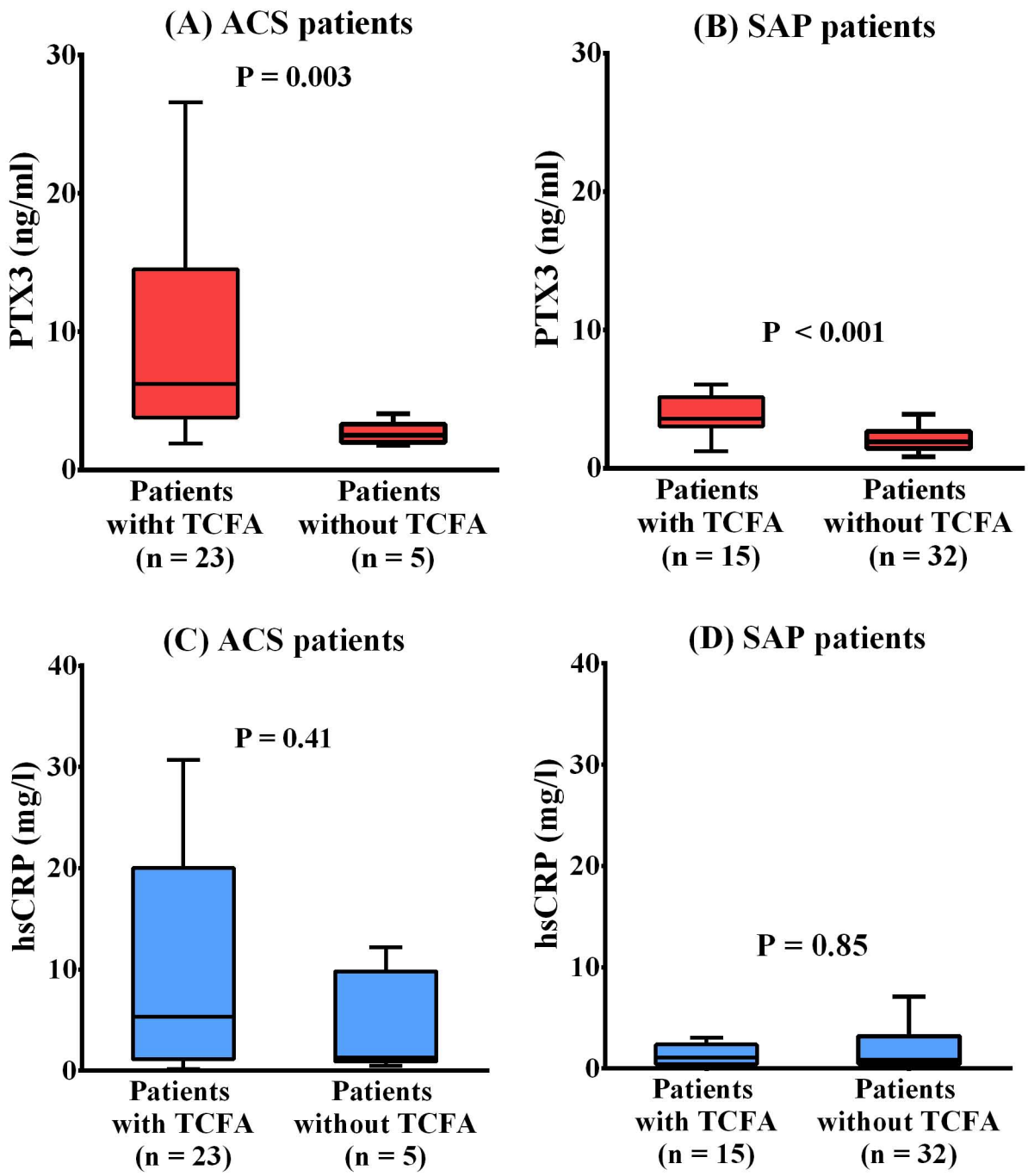

(A) ACS patients
P = 0.003
PTX3 (ng/ml)
30
20
10
0
Patients witht TCFA (n = 23)
Patients without TCFA (n = 5)
(B) SAP patients
P < 0.001
PTX3 (ng/ml)
30
20
10
0
Patients with TCFA (n = 15)
Patients without TCFA (n = 32)
(C) ACS patients
P = 0.41
hsCRP (mg/l)
40
30
20
10
0
Patients with TCFA (n = 23)
Patients without TCFA (n = 5)
(D) SAP patients
P = 0.85
hsCRP (mg/l)
40
30
20
10
0
Patients with TCFA (n = 15)
Patients without TCFA (n = 32)

Figure 3

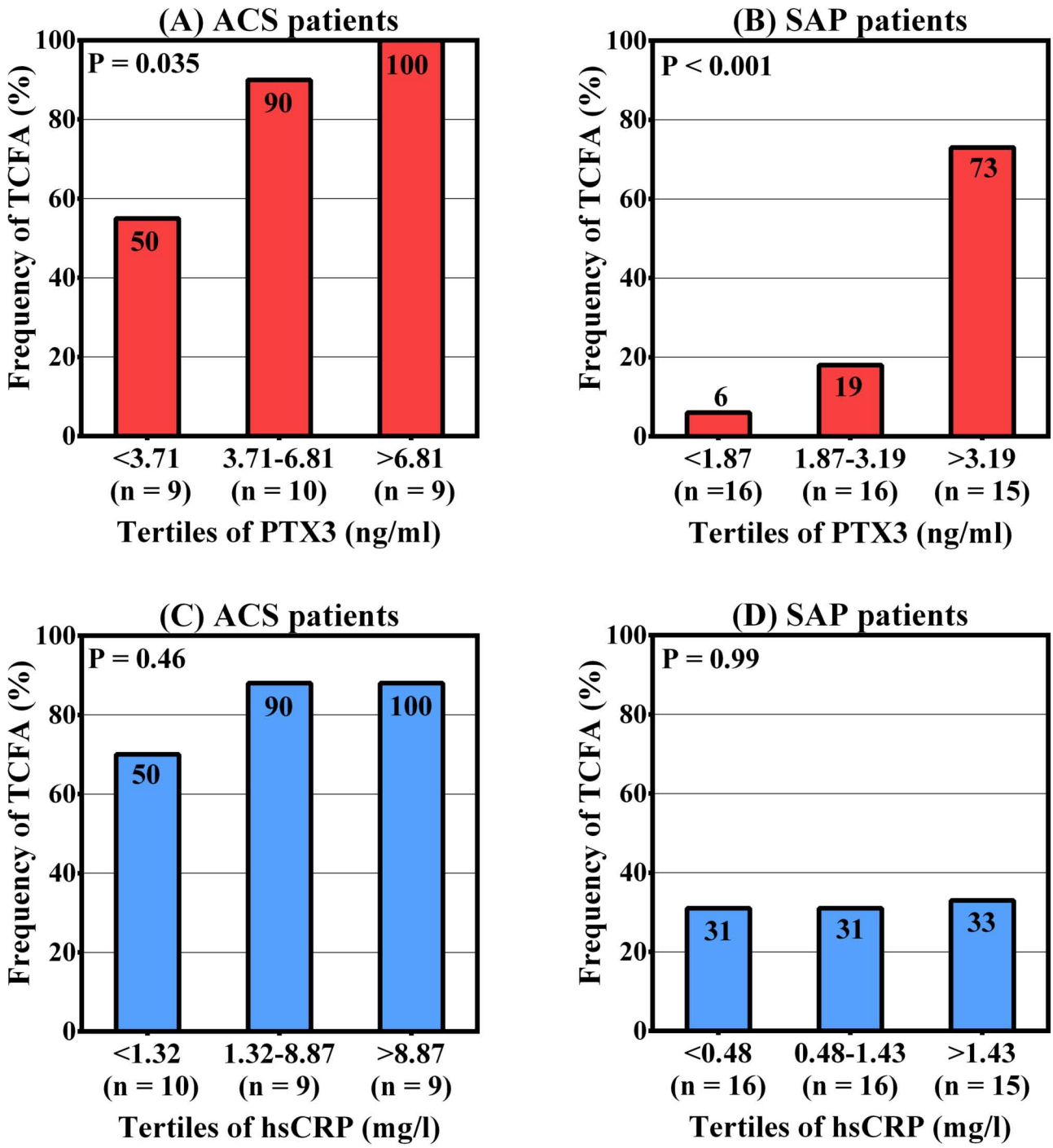
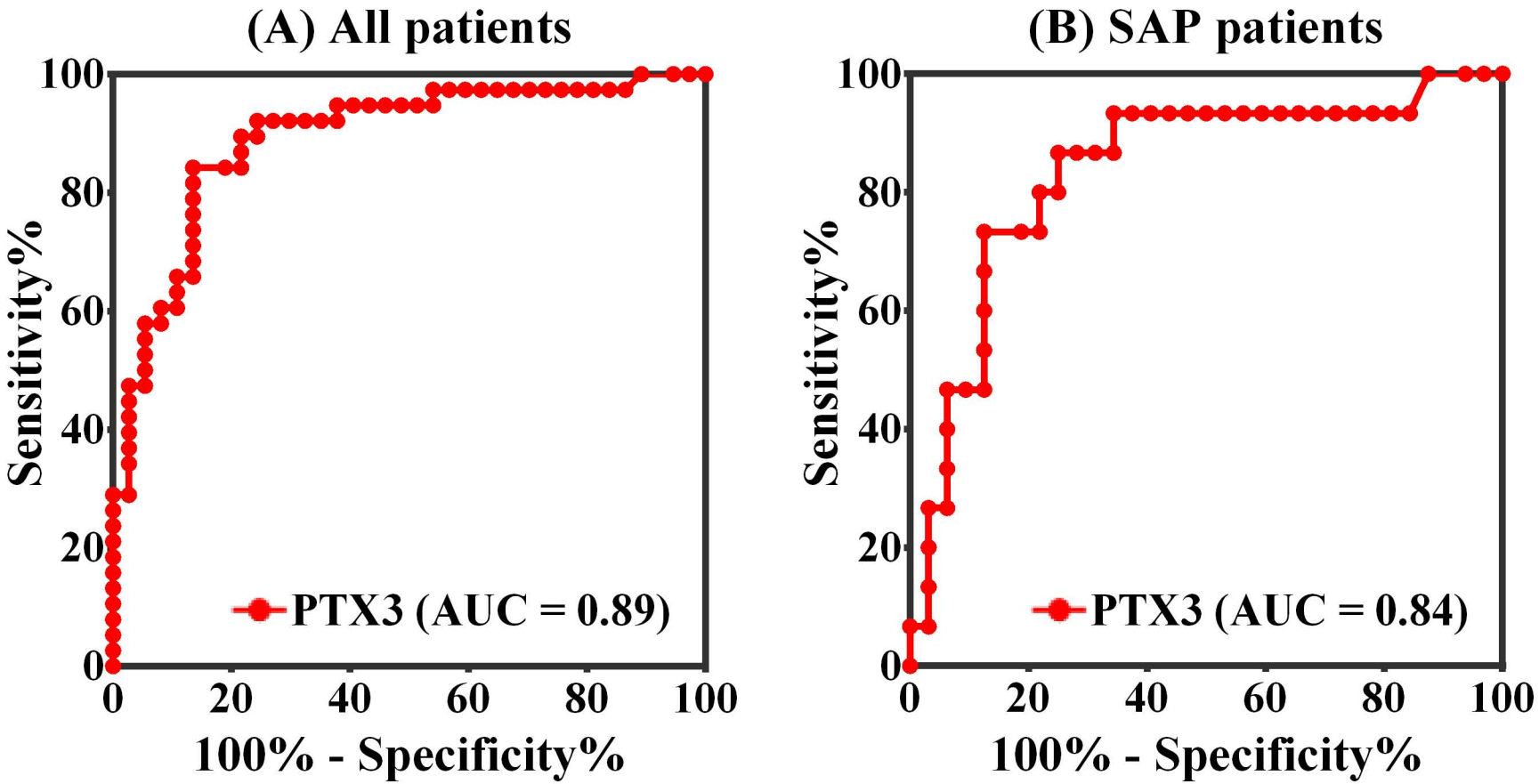

(A) ACS patients
P = 0.035
Frequency of TCFA (%)
100
80
60
40
20
0
50
90
100
<3.71 (n = 9)
3.71-6.81 (n = 10)
>6.81 (n = 9)
Tertiles of PTX3 (ng/ml)
(B) SAP patients
P < 0.001
Frequency of TCFA (%)
6
19
73
<1.87 (n =16)
1.87-3.19 (n = 16)
>3.19 (n = 15)
Tertiles of PTX3 (ng/ml)
(C) ACS patients
P = 0.46
Frequency of TCFA (%)
50
90
100
<1.32 (n = 10)
1.32-8.87 (n = 9)
>8.87 (n = 9)
Tertiles of hsCRP (mg/l)
(D) SAP patients
P = 0.99
Frequency of TCFA (%)
31
31
33
<0.48 (n = 16)
0.48-1.43 (n = 16)
>1.43 (n = 15)
Tertiles of hsCRP (mg/l)

Figure 4


(A) All patients
Sensitivity%
100
80
60
40
20
0
0
20
40
60
80
100
100% - Specificity%
PTX3 (AUC = 0.89)
(B) SAP patients
Sensitivity%
100
80
60
40
20
0
0
20
40
60
80
100
100% - Specificity%
PTX3 (AUC = 0.84)