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Original article

Pentraxin 3 as a biomarker for acute coronary syndrome: Comparison with biomarkers for cardiac damage

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Summary
Background: Pentraxin 3 (PTX3) is increased in circulating blood during the acute stage of acute coronary syndrome (ACS). Therefore, we compared diagnostic values of PTX3 for ACS with those of biomarkers for myocardial damage, such as troponin T (TnT) and heart-type fatty acid binding protein (H-FABP).
Methods and results: Patients ($n = 87$) undergoing coronary angiography (CAG), consisting of 16 ACS and 71 non-ACS patients were enrolled. Non-ACS consists of 12 patients with normal CAG, 30 stable angina pectoris (SAP) patients controlled by medical treatment, and 29 SAP patients who required elective coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft). Age, gender, or prevalence of diabetes, hypertension, or smoking was not significantly different between ACS and non-ACS groups. Serum total, high-density lipoprotein, or low-density lipoprotein cholesterol, or triglyceride levels were not significantly different between ACS and non-ACS. PTX3 levels were not significantly correlated with lipid profiles or different between those with and without conventional risk factors. Circulating PTX3, TnT, and H-FABP levels were significantly higher in ACS than non-ACS. In receiver-operating characteristic (ROC) curves, area under the curve (AUC) values for PTX3, TnT and H-FABP were 0.920, 0.674, and 0.690, respectively. ROC curves of PTX3 (AUC: 0.901), TnT (AUC: 0.731), and H-FABP (AUC: 0.633) for ST-elevation ACS were similar to those for whole ACS. In a TnT-negative subgroup, the AUC values of PTX3 and H-FABP for ACS were 0.981 and 0.489, respectively.
Conclusions: PTX3 is a sensitive and specific biomarker for the diagnosis of ACS, and shows additional diagnostic values when measured in combination with TnT.

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Introduction

Onset of acute coronary syndrome (ACS) involves rupture or erosion of atherosclerotic plaques in coronary arteries. Although biomarkers for ischemic myocardial damage, such as troponin-T (TnT) and heart-type fatty acid binding protein (H-FABP), have been clinically utilized to diagnose ACS, diagnostic sensitivity and specificity for ACS, especially at the earliest stage, remain insufficient. Pro-inflammatory responses and oxidative stresses, including oxidized low-density lipoprotein (Ox-LDL), appear to play key roles in atherosclerotic progression and atherosclerotic plaque rupture or erosion, by inducing cell apoptosis, and production and activation of matrix metalloproteinases (MMPs) [1,2]. High-sensitivity C-reactive protein (hs-CRP) is a well-known inflammatory biomarker which reflects these proinflammatory responses [3,4]. Furthermore, other proinflammatory biomarkers, such as interleukin (IL)-6 and IL-18, have also been suggested as ACS biomarkers [5,6]. In addition, N-terminal pro-B-type natriuretic peptide (NT-proBNP) is also a biomarker for cardiovascular disease risks including ACS [7,8]. Our previous studies have shown that soluble lectin-like oxidized LDL receptor-1 (sLOX-1), a soluble protein corresponding to an Ox-LDL receptor, is also suggested as an ACS biomarker [9—13].

Pentraxin 3 (PTX3), a member of CRP-like inflammatory protein group, is abundantly expressed in atherosclerotic plaques, as well as in cardiac myocytes [14,15]. Previous studies have shown that circulating PTX3 levels were significantly elevated in the acute stages of acute myocardial infarction (AMI) and unstable angina pectoris (UAP) [15,16], which are collectively termed as ACS. In addition, prognostic values of PTX3 for future AMI and mortality, in patients with ACS without ST elevation and ST elevation AMI, respectively, have also been demonstrated [17,18]. As a diagnostic test, however, its diagnostic sensitivity and specificity have not yet been compared with other biomarkers.

In the present study, therefore, we have examined the diagnostic values of PTX3, comparing with those of TnT [19—22] and H-FABP [21—24] which are currently utilized to detect AMI in clinical practice.

Methods

Patient samples

We examined 87 patients, who consecutively underwent coronary angiography (CAG) at the Cardiovascular Center, Osaka Red Cross Hospital, and whose circulating PTX3 levels were measured. ACS was defined as acute onset of prolonged chest pain or chest discomfort accompanied by ST-segment elevation or depression evolving into pathological Q waves or inverted T wave, as well as emergency CAG-documented total occlusion or marked delayed filling of a coronary artery as previously described [9—12]. Sixteen patients were diagnosed with ACS, and 71 patients were without ACS (non-ACS). Non-ACS consists of 12 patients without significant luminal narrowing in CAG, 30 patients with medically controlled stable angina, and 29 patients with stable angina who required elective percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG). Patients with

vasospastic angina, symptomatic peripheral artery disease or stroke were excluded from this study. Informed consent was obtained from all the participants. This study was carried out in accordance with the principles of the declaration of Helsinki and had been approved by a local ethical committee.

Laboratory tests

Serum samples were collected from the peripheral venous blood during the CAG. In ACS cases, the mean time interval from the symptom onset to the blood sampling was 4.8 h. These samples had been stored at $-80\,°C$ until assays were performed. Circulating PTX3 levels were measured by a sandwich enzyme-linked immunosorbent assay (ELISA) which was commercially available (Alexis, Lausen, Switzerland). Levels of hs-CRP, TnT, and H-FABP were determined on the same serum samples as those for PTX3 by commercially available particle-enhanced immunonephelometry (Dade Behringer, Tokyo, Japan), electro-chemiluminescent immunoassay kit (Roche, Basel, Switzerland), and ELISA (Marco Pharmaceutical, Tokyo, Japan), respectively [9—12]. All the assays were carried out by personnel who had no knowledge of the clinical diagnosis of the patients.

Statistical analyses

Distribution of PTX3, hs-CRP, TnT, and H-FABP was skewed; therefore, Wilcoxon/Kruskal—Wallis test was applied to examine statistically significant differences. Statistically significant differences in total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, and LDL cholesterol were assessed by ANOVA. Statistically significant correlations between two parameters were evaluated by Spearman's test. All the statistical analyses were carried out by use of JMP IN (SAS Institute, Cary, NC, USA).

Results

Characteristics of study subjects

Characteristics of the 87 patients (71 non-ACS and 16 ACS), who underwent CAG and were involved in this study, are indicated in Table 1. Age ($p = 0.541$), gender ($p = 0.817$), and prevalence of conventional cardiovascular risk factors, such as diabetes ($p = 0.984$), smoking ($p = 0.947$), and hypertension ($p = 0.248$), were not significantly different between ACS and non-ACS patients. In addition, neither total cholesterol ($p = 0.086$), triglyceride ($p = 0.094$), HDL cholesterol ($p = 0.220$), nor LDL cholesterol ($p = 0.566$) levels were significantly different between the ACS and non-ACS groups (Table 1).

PTX3 levels and conventional cardiovascular risk factors

Circulating PTX3 levels were not significantly different between males and females (median: 0.03 vs. 0.02 ng/mL, $p = 0.618$), or with and without conventional risk factors, such as diabetes (median: 0.03 vs. 0.02 ng/mL, $p = 0.438$),

Table 1 Characteristics of study subjects.

|	Total	ACS	non-ACS	p-value
Patient number	87	16	71	
Age	66.1 ± 10.5	64.1 ± 13.3	66.0 ± 10.4	0.541
Male gender (%)	57 (66.3)	11 (68.8)	46 (65.7)	0.817
Diabetes (%)	27 (31.0)	5 (31.3)	22 (31.0)	0.984
Smoking (%)	32 (36.8)	6 (37.5)	26 (36.6)	0.947
Hypertension (%)	38 (44.2)	5 (31.5)	33 (47.2)	0.248
Total cholesterol (mg/dL)[a]	195.0 ± 37.3	179.0 ± 32.6	198.0 ± 37.5	0.086
Triglycerides (mg/dL)[a]	136.2 ± 71.5	108.3 ± 28.5	137.6 ± 65.1	0.094
HDL cholesterol (mg/dL)[a]	48.0 ± 14.2	44.1 ± 13.0	49.2 ± 14.5	0.220
LDL cholesterol (mg/dL)[a]	120.0 ± 34.7	115.4 ± 31.4	121.1 ± 35.7	0.566
PTX3 (pg/mL)[b]	0.03 (0, 0.16)	0.36 (0.225, 1.39)	0.015 (0, 0.06)	<0.0001
TnT (ng/mL)[b]	0.01 (0.01, 0.01)	0.025 (0.01, 0.208)	0.01 (0.01, 0.01)	0.0026
H-FABP (ng/mL)[b]	3.3 (2.6, 5.7)	12.4 (2.9, 105.3)	3.2 (2.6, 4.6)	0.018

ACS, acute coronary syndrome; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PTX3, pentraxin 3; TnT, troponin T; H-FABP, heart-type fatty acid binding protein.
[a] Mean ± S.D.
[b] Median (25th percentile, 75th percentile).
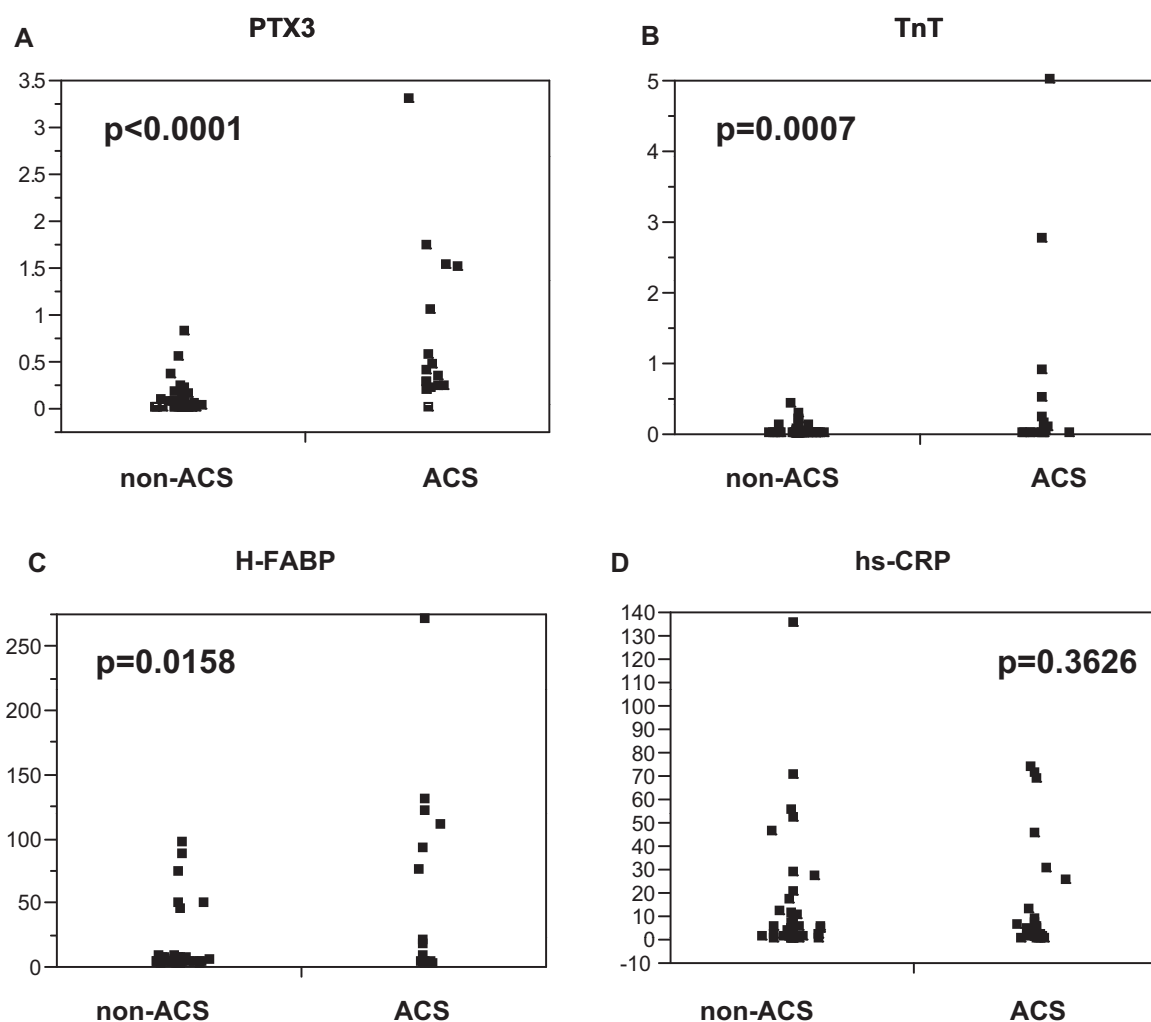
Figure 1 Comparison of circulating PTX3, hs-CRP, TnT, and H-FABP levels between ACS and non-ACS. Circulating PTX3 (panel A), TnT (panel B), H-FABP (panel C), and hs-CRP (panel D) levels are compared between ACS and non-ACS. PTX3, TnT, and H-FABP, but not hs-CRP, levels were significantly higher in ACS than in non-ACS. ACS, acute coronary syndrome; H-FABP, heart-type fatty acid binding protein; hs-CRP, high-sensitivity C-reactive protein; PTX3, pentraxin 3; TnT, troponin T.
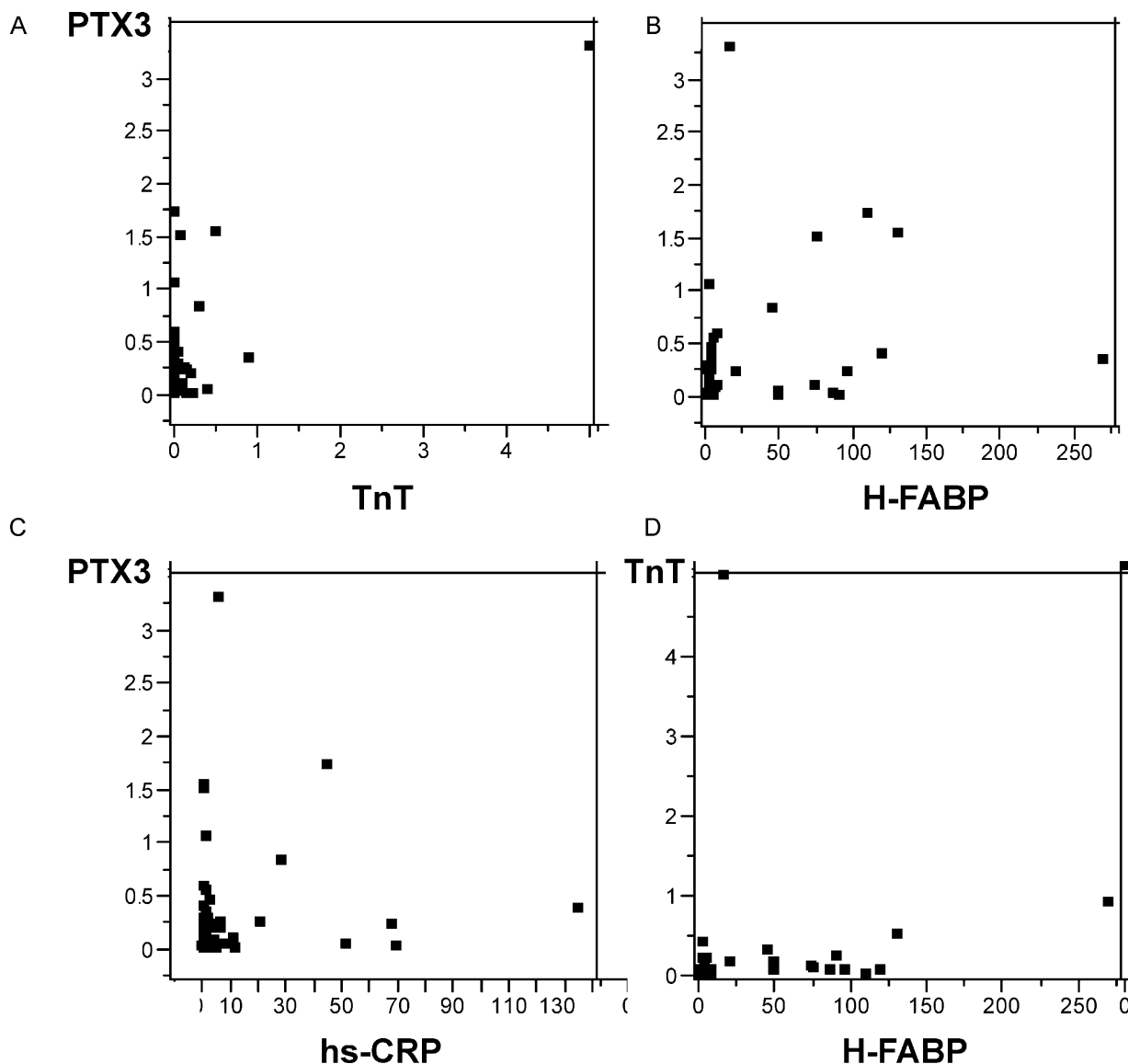
Figure 2   Correlation of circulating PTX3 with TnT, H-FABP, and hs-CRP levels. Correlation of circulating PTX3 with TnT (panel A), H-FABP (panel B), or hs-CRP (panel C) is shown. Circulating PTX3 did not show significant correlation with TnT, H-FABP or hs-CRP. H-FABP, heart-type fatty acid binding protein; hs-CRP, high-sensitivity C-reactive protein; PTX3, pentraxin 3; TnT, troponin T.

smoking (median: 0.0125 vs. 0.03 ng/mL, $p = 0.141$), or hypertension (median: 0.03 vs. 0.025 ng/mL, $p = 0.916$). In addition, circulating PTX3 levels were not significantly correlated with age (Spearman's $\rho = 0.0153$, $p = 0.888$), total cholesterol (Spearman's $\rho = -0.167$, $p = 0.165$), triglyceride (Spearman's $\rho = 0.0046$, $p = 0.969$), LDL cholesterol (Spearman's $\rho = 0.001$, $p = 0.993$), or HDL cholesterol (Spearman's $\rho = -0.213$, $p = 0.0666$) levels.

PTX3 levels and ACS

Peripheral blood biomarker levels were compared between ACS and non-ACS groups. As shown in Fig. 1A, circulating PTX3 levels were significantly higher in ACS than in non-ACS (median: 0.36 ng/mL vs. 0.015 ng/mL, $p < 0.0001$). Serum TnT (median: 0.438 vs. 0.0329 ng/mL, $p = 0.00425$, Fig. 1B) and H-FABP (median: 12.4 vs. 3.3 ng/mL, $p = 0.0225$,

Fig. 1C) levels also were significantly higher in ACS than in non-ACS, as previously reported. In contrast, serum hs-CRP levels were not significantly different between the ACS and non-ACS groups (median 1.71 mg/L vs. 1.64 mg/L, $p = 0.678$, Fig. 1D) in our study cohort.

Correlation of PTX3 with other biomarkers

We, furthermore, explored the correlation among these biomarkers. Circulating PTX3 levels showed significant correlation with TnT levels (Spearman's $\rho = 0.337$, $p = 0.0015$, Fig. 2A) and H-FABP (Spearman $\rho = 0.264$, $p = 0.0139$, Fig. 2B) levels; however, their correlation with hs-CRP levels was not statistically significant (Spearman's $\rho = 0.252$, $p = 0.0588$, Fig. 2C). In addition, TnT and H-FABP levels showed
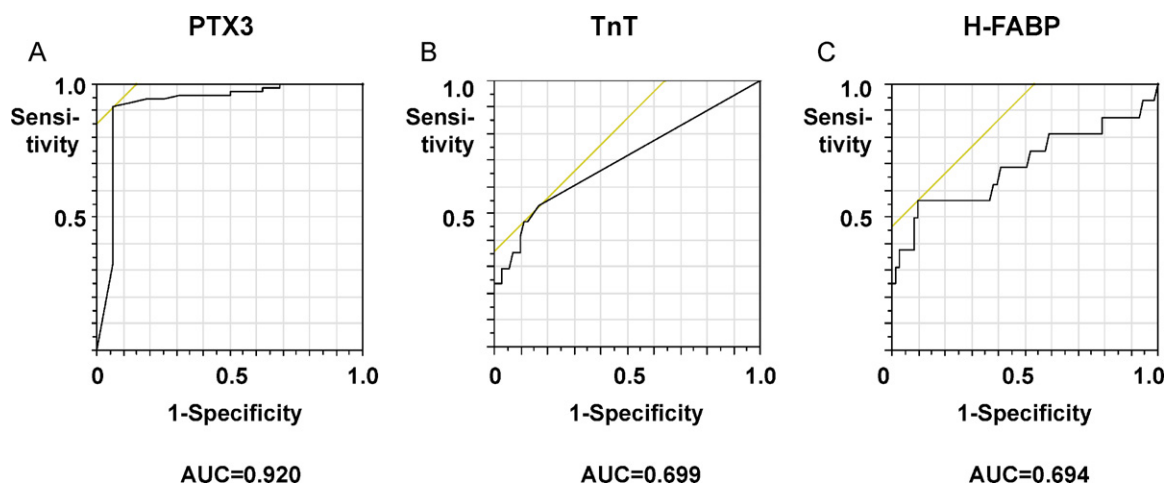
Figure 3 Comparison of ROC curves for diagnosis of ACS among PTX3, TnT and H-FABP. ROC curves demonstrate that PTX3 (panel A) showed higher sensitivity and specificity for detection of ACS than TnT (panel B) and H-HABP (panel C). AUC values for PTX3, TnT, and H-FABP were 0.920, 0.699, and 0.694, respectively. ACS, acute coronary syndrome; AUC, area under the curve; H-FABP, heart-type fatty acid binding protein; PTX3, pentraxin 3; ROC, receiver-operating characteristic; TnT, troponin T.

close correlation with each other (Spearman's $\rho = 0.507$, $p < 0.0001$, Fig. 2D).

Diagnostic values of PTX3 for ACS

To compare the diagnostic specificity and sensitivity of PTX3 for ACS with those of TnT and hs-CRP, receiver-operating characteristic (ROC) curves for the detection of ACS were compared (Fig. 4). Sensitivity and specificity of PTX3 (Fig. 3A) for the diagnosis of ACS appear to be higher than those of TnT (Fig. 3B) and H-FABP (Fig. 3C). Area under the curve (AUC) values for PTX3, TnT, and H-FABP were 0.920, 0.674, and 0.690, respectively. Diagnostic values of PTX3 were also evaluated in ST-elevation ACS (STE-ACS) alone, comparing them with those of TnT and H-FABP, by exclusion of non-ST-elevation ACS (NSTE-ACS) patients. The STE-ACS subgroup consisted of 12 patients. As shown in Fig. 4, ROC curves of PTX3, TnT, and H-FABP in the STE-ACS appeared to be similar to those in the whole ACS population (Fig. 3). AUC values of PTX3, TnT, and H-FABP for detection of STE-ACS were 0.901, 0.731, and 0.633, respectively.

## Diagnostic values of PTX3 for TnT-negative ACS

Because TnT currently is considered as a golden standard biomarker for the diagnosis of AMI in clinical practice, ROC curves were also evaluated in the TnT-negative (less than 0.03 ng/mL) subpopulation. Numbers of TnT-negative subjects in the non-ACS group and the ACS group were 58 and 8, respectively. The ROC curves in the TnT-negative subgroup are shown in Fig. 5. The AUC values of PTX3 (Fig. 5A) and H-FABP (Fig. 5B) for ACS were 0.981 and 0.489, respectively, in the TnT-negative subgroup. ROC curves of PTX3 for ACS appeared similar between the whole population (Fig. 3A) and the TnT-negative subgroup (Fig. 5A), indicating the additional diagnostic values of PTX3 when measured in combination with TnT. In contrast, the ROC curves of H-FABP for ACS in the TnT-negative subgroup showed much lower diag-

nostic sensitivity and specificity (AUC: 0.489, Fig. 5B) when compared with the whole population (AUC: 0.633, Fig. 3B).

Discussion

Onset of ACS appears to involve rupture or erosion of vulnerable atheromatous plaques with thin fibrous caps, large lipid cores, and infiltration of abundant macrophages and T-lymphocytes. Pro-inflammatory and oxidative stresses appear to play key roles in the formation of erosion- and rupture-prone vulnerable plaques, by apoptosis of vascular endothelial and smooth muscle cells and macrophages, production and activation of matrix metalloproteinases, as well as induced expression of chemokines and endothelial-leukocyte adhesion molecules. PTX3 is one of the molecules that are expressed in atherosclerotic plaques and suggested to be involved in plaque vulnerability. Previous reports showed that circulating PTX3 levels were elevated in AMI [15] and in UAP [16]; however, diagnostic values of this biomarker for AMI or UAP have not been fully clarified. We, therefore, have explored diagnostic sensitivity and specificity of PTX3 for ACS, comparing with other biomarkers. The present results show that PTX3 appears to be superior to TnT and H-FABP in early diagnosis of ACS. In addition, circulating PTX3 levels do not show any significant differences between presence and absence of conventional risk factors, such as diabetes, smoking, and hypertension. Furthermore, PTX3 shows no significant correlation with lipid profiles, TnT, H-FABP, or another inflammatory biomarker hs-CRP, thus indicating that PTX3 is an independent biomarker.

PTX3 is abundantly expressed in atherosclerotic plaques [14]; therefore, vulnerable or ruptured atherosclerotic plaques may be major sources of increased circulating PTX3 levels. In addition, circulating PTX3 may also derive from injured myocardium, because PTX3 is also expressed by cardiomyocytes. In fact, PTX3 showed significant correlation with biomarkers for cardiac damage, such as TnT and H-FABP in this study. Although a previous study has indicated time-dependent changes in circulating PTX levels in
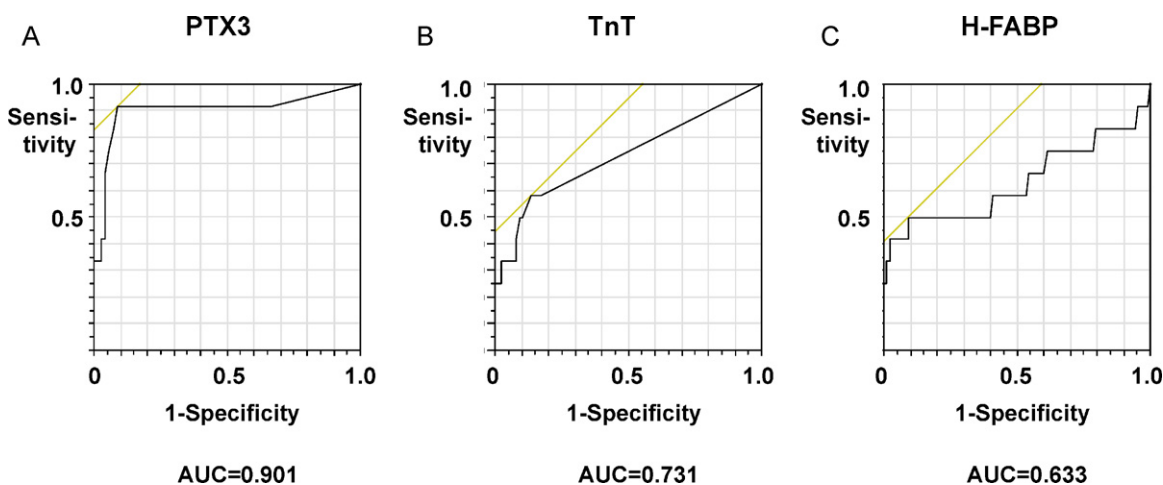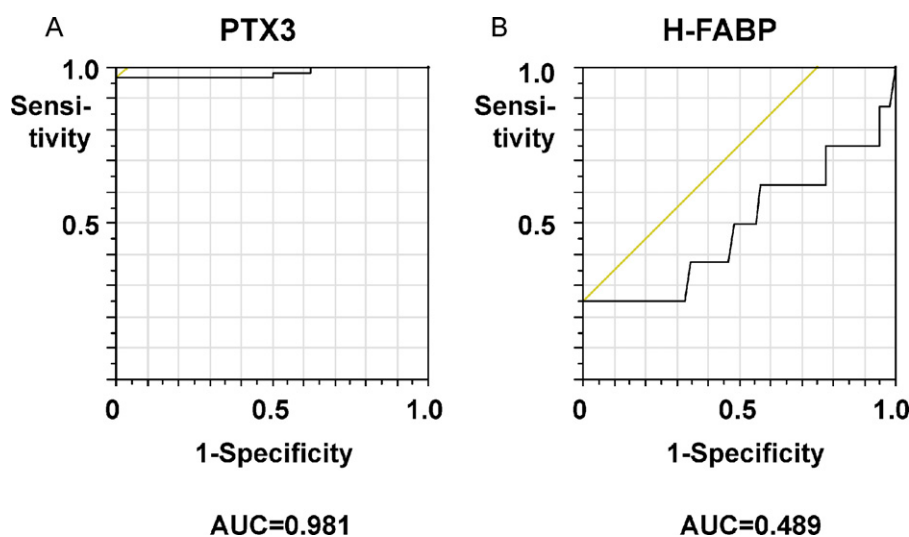
Figure 4 Comparison of ROC curves for diagnosis of ST elevation-ACS among PTX3, TnT, and H-FABP. ROC curves demonstrate that PTX3 (panel A) showed higher sensitivity and specificity for detection of ACS than TnT (panel B) and H-FABP (panel C). AUC values for PTX3, TnT, and H-FABP were 0.901, 0.731, and 0.633, respectively. ACS, acute coronary syndrome; AUC, area under the curve; H-FABP, heart-type fatty acid binding protein; PTX3, pentraxin 3; ROC, receiver-operating characteristic; TnT, troponin T.

acute stages of AMI, comparing those in hs-CRP [15], time-dependent changes in PTX3 levels during acute stages of ACS have not yet been compared with those in biomarkers of cardiac damage, such as TnT and H-FABP. Therefore, molecular mechanisms involved in elevated circulating levels of PTX3 in ACS remain to be fully elucidated in the future, by experiments with suitable animal models in vivo.

In any case, the present report has compared, for the first time, the diagnostic sensitivity and specificity of PTX3 for ACS with other biomarkers, such as TnT and H-FABP. ROC curves clearly indicated that PTX3 showed higher sensitivity and specificity, than TnT and H-FABP, for the diagnosis

of ACS, as well as STE-ACS or AMI. Cardiac TnT currently is considered as a golden standard biomarker for diagnosis of AMI and utilized in clinical practice; therefore, we have further compared the diagnostic sensitivity and specificity of PTX3, as well as H-FABP, in the whole subjects and the TnT-negative subpopulation in this study. Diagnostic specificity and sensitivity of PTX3 were similar between the whole ACS population and the TnT-negative ACS subpopulation, indicating that PTX3 would provide additional diagnostic information for ACS, when measured in combination with TnT. In contrast, H-FABP appeared to exhibit much less diagnostic values for ACS in the TnT-negative sub-

Figure 5 Comparison of ROC curves for diagnosis of ACS between PTX3 and H-FABP in a TnT-negative subpopulation. ROC curves for PTX3 (panel A) and H-FABP (panel B) in the TnT-negative (<0.03 ng/mL) subpopulation are shown. The TnT-negative subpopulation consisted of 8 ACS and 58 non-ACS subjects. ROC curves similarly show that PTX3 (panel A) exhibits higher sensitivity and specificity for detection of ACS than H-FABP (panel B). AUC values for PTX3 and H-FABP in the TnT-negative subpopulation were 0.981 and 0.489, respectively. ROC curves for PTX3 appear to be similar between the total population (Fig. 4A) and the TnT-negative subpopulation (panel A). ACS, acute coronary syndrome; AUC, area under the curve; H-FABP, heart-type fatty acid binding protein; PTX3, pentraxin 3; ROC, receiver-operating characteristic; TnT, troponin T.

population when compared with the whole population, thus indicating its strong dependency upon TnT and less diagnostic values when measured in combination with TnT.

Recently, high-sensitivity troponins T and I have been shown to detect AMI in the early stages [25,26]. In these large-scale international multicenter studies, the ROC curve of the conventional TnT to diagnose AMI appeared similar to ours, thus indicating the appropriateness of our patient samples although the size was small. It should be tested, in the future, whether PTX3 has incremental values to diagnose ACS or AMI in the early stages, in addition to these sensitive assays for troponins.

In conclusion, the present study clearly demonstrates that diagnostic sensitivity and specificity of PTX3 for ACS, in the early stage, appear to be superior to those of TnT and H-FABP, thus, indicating that PTX3 is one of the useful biomarkers for detecting ACS, alone or in combination with other biomarkers including TnT. In addition, a previous study has shown that PTX3 can predict 3-month mortality after AMI [18]; therefore, PTX3 may also be useful for risk stratification and prediction of ACS recurrence after ACS or prediction of ACS in stable coronary artery disease patients, as well as long-term future risk for cardiovascular events in healthy subjects. These points should further be explored in prospective multicenter studies with large sample sizes in the future.

Acknowledgments

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