Long-term prognostic significance of pentraxin-3 in patients with acute myocardial infarction: 5-year prospective cohort study

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ABSTRACT

Objective: A predictive role of serum Pentraxin 3 (PTX3) for short-term adverse cardiovascular events including mortality in acute myocardial infarction (AMI) was reported in recent studies. The aim of the study was to investigate long-term prognostic significance of serum PTX3 in an AMI with 5-year follow-up period in this study.

Methods: In this prospective study, 140 patients, who were admitted to the emergency department between January 2011 and December 2011 with acute chest pain and/or dyspnea and diagnosed with AMI and 60 healthy controls were included. PTX3 levels were measured at admission by using an ELISA method. The study group was divided into tertiles on the basis of admission PTX3 values: the high-PTX3 group ($\geq$4.27 ng/mL), the middle-PTX3 groups (4.27–1.63 ng/mL), and the low-PTX3 group ($\leq$1.63 ng/mL).

Results: PTX3 level was significantly more greatly increased in the AMI group than in the controls (2.27±0.81 vs. 0.86±0.50 ng/mL, p<0.001). PTX3 level was found to be significantly positively correlated with TIMI score (r=0.368, p=0.037), high sensitive C-reactive protein (hsCRP) (r=0.452, p=0.024), pro-BNP (r=0.386, p=0.029), troponin I (r=0.417, p=<0.001), and GRACE score (r=0.355, p=0.045), and negatively correlated with HDL cholesterol (r=−0.203, p=0.016) and LVEF (r=−0.345, p=0.028). In multivariate analysis, PTX3 (OR=1.12, 95% CI 1.04–1.20; p=0.001) was a significant independent predictor of long-term cardiovascular mortality, after adjusting for other risk factors.

Conclusion: PTX3 is a novel biomarker that may help to identify high risk individuals with AMI, who are potentially at risk of early major adverse cardiovascular events including mortality in the long-term period.

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Keywords: pentraxin-3, acute myocardial infarction, long-term prognosis, mortality, cardiovascular event

Introduction

Acute coronary syndrome (ACS) is the leading cause of mortality worldwide (1). The major pathophysiologic events for the development of ACS are partial or complete coronary artery occlusion caused by vulnerable atherosclerotic plaque rupture and thrombus formation or acute occlusion of a coronary artery by emboli or vasospasm (1). Several biomarkers have been used for early diagnosis and prognosis of acute myocardial infarction, such as creatine kinase, troponin, short pentraxin C-reactive protein (CRP), and serum amyloid A protein (1–3).

Highly sensitive C-reactive protein is produced in the liver in response to inflammatory mediators, especially interleukin-6. It is a member of the pentraxin family of proteins and is a sensitive indicator of inflammation, which is closely related to the progress of coronary plaque vulnerability. The correlation of hsCRP with other inflammatory and cardiac damage markers has been reported in various cardiovascular diseases, including acute myocardial infarction and heart failure (4–6). PTX3 and CRP relate to surrogate biomarkers of atherosclerosis and are independently associated with the risk of developing major adverse cardiovascular events. While CRP's sequence and regulation have altered for different species, PTX3 is highly conserved in evolution. Moreover, CRP is only produced from the liver, whereas PTX3 is synthesized by various cell types. They have also been reported to be positively correlated with each other in various

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cardiovascular diseases including coronary artery disease, acute myocardial infarction, and heart failure (4–7).

Pentraxin 3 (PTX3) is structurally associated but distinct from classic pentraxins. It is either synthesized locally by vascular endothelial cells, smooth muscle cells, fibroblasts, and macrophages at the inflammatory sites or by monocytes/macrophages upon exposure to primary inflammatory signals such as tumor necrosis factor-, IL-1, oxidized low-density lipoprotein, and bacterial products (8, 9). A raised expression of PTX3 has been reported in vascular cells and vascular inflammatory cells of human atherosclerotic plaques (10, 11) and in human myocardial cells from dilated cardiomyopathy and control hearts (12). Moreover, an increased plasma level of PTX3 have been demonstrated in ACS (13) and chronic heart failure (14), suggesting that PTX3 may have clinical utility for early diagnosis and appropriate treatment.

Matsui et al. (15) reported that PTX3 is a strong independent predictor for six-month cardiovascular events in patients hospitalized for unstable angina pectoris (USAP) or non-ST elevation myocardial infarction (NSTEMI). Similar findings were presented with prediction for 3-month mortality in the study of Latini et al. (16). Furthermore, Akgül et al. (17) demonstrated a significant relation between raised admission PTX3 and increased in-hospital cardiovascular mortality and 2-year all-cause mortality in patients with ST elevation myocardial infarction (STEMI) who underwent primary percutaneous coronary intervention (PCI).

Since there is little information about the long-term prognostic significance of serum PTX3 levels in patients with AMI, we aimed to investigate this relation with longer follow-up period in this study. We hypothesized that increased PTX3 levels would be associated with in-hospital and long-term adverse outcomes after AMI.

Methods

Patient selection

In this prospective cohort study, 140 patients (102 men and 38 women, mean age 59.72±12.32 years) admitted to the emergency department of a training and research hospital between January 2011 and December 2011 with acute chest pain and/or dyspnea and diagnosed with AMI (STEMI or NSTE-ACS) and 60 healthy control subjects were included. AMI patients were enrolled according to the 2012 European Society of Cardiology Universal Definition of MI Guideline (18). The control group was composed of individuals who were admitted to emergency service with acute atypical chest pain and/or dyspnea without any acute dynamic ECG changes and/or rise of cardiac enzymes. Furthermore, the control group participant's exertional test or myocardial perfusion imaging tests, which were performed electively after exclusion of AMI, were normal.

Age >80 years, history of previous myocardial infarction, heart failure or arrhythmia, history of PCI or coronary artery bypass graft surgery, history of cardiogenic shock, severe valvular heart disease, congenital heart disease, paced rhythm, pres-

ence of bundle branch blocks, acute death due to unexplained causes within the first 48 hours, renal or hepatic failure, malignancy, acute or chronic inflammatory or infectious disease were exclusion criteria of the present study.

Baseline demographic, clinical, and laboratory characteristics of the study groups were recorded from hospital records. ECG was recorded for each patient just after hospital admission to obtain the MI type. Cardiac risk scores, which are useful for predicting in-hospital, short, and long-term prognosis for AMI patients, such as "The Thrombolysis in Myocardial Infarction" (TIMI) and "Global Registry of Acute Coronary Events" (GRACE) (19, 20) were calculated, and coronary angiography procedure images were evaluated by one expert cardiologist who was unaware of the data from this study. Moreover, the height and weight of each study participant were measured, and body mass index (BMI) was calculated as body weight in kilograms divided by the square of the height in meters (kg/m^2).

Guideline approved medications were given to all study patients before specific AMI therapy including 300 mg acetylsalicylic acid, 300 mg (600 mg in STEMI patients undergoing PCI) clopidogrel, an angiotensin converting enzyme inhibitor, a beta-blocker, a statin, and a low molecular weight heparin (enoxaparin). Patients with STEMI were also treated with either fibrinolytic agent alteplase or PCI. PCI procedure was performed on 94.6% of STEMI patients, and the mean duration from the first medical contact to balloon time was 4.6±1.2 hours. In addition, patients with NSTE-ACS underwent coronary angiography (mean duration was 6.8±3.6 hours) if patients had persistent typical chest pain, findings for acute heart failure, or hemodynamically significant arrhythmia, and the PCI procedure was performed in 92.8% of NSTEMI cases. Glycoprotein IIb/IIIa inhibitors (tirofiban), unfractionated heparin, and nitrates were used according to the discretion of the attending physician. Primary PCI was initiated using a standard Judkin's technique. The access approach was either transfemoral or transradial. During the procedure, non-ionic, low-osmolality contrast media were used, and the coronary artery was confirmed to be clinically significant if its stenosis was more than 50% for the left main coronary artery and 70% for other coronary arteries. Angiographic procedures with detailed evaluations were made by means of a visual assessment by one expert interventional cardiologist who was unaware of the study.

All study participants underwent 2-D transthoracic echocardiographic examination to determine left ventricle ejection fraction (LVEF) by using a Vivid S5 3S-RS probe (GE Healthcare, WI, USA) with a 1.7/3.4-MHz phased array transducer. It was performed by an experienced operator in a left lateral supine position. LVEF was determined using Simpson's method of discs (21).

The study complies with the Declaration of Helsinki, and the trial protocol was approved by the local Ethics Committee.

Laboratory measurements

A 5 mL sample of venous blood was collected in EDTA-coated vacutainer tubes and separated by centrifugation at the

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time of hospital admission. The serum was stored at −80°C until analysis. The admission HbA1c level was assayed using an automated, high-performance, liquid chromatography analyser (Trinity Biotech, Jamestown, NY, USA). Biochemical parameters such as fasting blood glucose, creatinine, troponin I, total cholesterol, high-density lipoprotein (HDL) cholesterol, LDL cholesterol, and TG, were measured using an Abbott Diagnostics C8000i (Abbott, Germany) auto-analyzer with commercial kits. The LDL cholesterol was assayed by applying Friedewald's formula for samples with TG ≤400 mg/dl. Hematological parameters were obtained using the Coulter LH 780 Hematology Analyzer (Beckman Coulter Ireland, Inc., Mervue, Galway, Ireland).

Plasma PTX3 concentrations were measured by an enzyme-linked immunosorbent (ELISA) method (Perseus Proteomics Inc., Tokyo, Japan). This assay can measure plasma PTX3 concentration linearly between 0.1 and 20 ng/mL. The coefficient of variation for the PTX3 assay was 3.7% at 0.2 ng/mL and 1.4% at 2.2 ng/mL. All samples were assessed in duplicate, and the mean values were used in subsequent calculations.

Highly sensitive C-reactive protein levels were measured by using an immunoturbidimetry assay methods with commercial kit (Cat. number: k050836 Sentinel CH. SRL, Via Robert Koch, 2, Milan, Italy). The detection range of this kit is 0.1–160 mg/L. Intra-assay precision (precision within an assay) is 0.5 and inter-assay precision (precision between assays) is 2.51%.

Quantitative assessment of pro-BNP was performed using an ELISA assay method with commercial kit (Cat. Number: k060964 Fujirebio Diagnostics, Inc., 201 Great Valley Parkway Malvern, PA, US). The detection range of this kit is 0 - ≥4000 ng/mL. Intra-assay precision (precision within an assay) is 1.7% and inter-assay precision (precision between assays) is 6.7%.

Study endpoints and follow-up

The patient and the control group participants with their medications were followed-up for 5 years. Follow-up data of the study patients were obtained from hospital records or by interviewing patients, their families, or their family physicians directly or by telephone. The primary endpoint of the study was cardiovascular mortality; secondary end-points were reinfarct, stroke, life-threatening arrhythmia, hospitalization for heart failure, and need for target vessel revascularization (TVR). Cardiovascular mortality was defined as unexplained sudden death or death due to acute STEMI or NSTEMI, decompensated heart failure, or hemodynamically significant arrhythmia. TVR was defined as the need for PCI or coronary artery bypass surgery due to restenosis or reocclusion of the infarct related artery. Study patients were divided into two sub-groups, STEMI and NSTE-ACS, and they were followed-up for 5 years for cardiovascular outcomes.

Statistical analysis

Continuous, normally distributed variables will be expressed as mean±standard deviation and non-normally distributed variables as median (interquartile range). Categorical variables will be expressed as frequencies and/or percentages. The variables will be investigated using visual (histograms, probability plots) and analytical (Kolmogorov-Smirnov) methods to determine if they are normally distributed. Kruskal-Wallis and Mann-Whitney U tests were used for continuous non-normally distributed variables, and the student t-test for continuous normally distributed variables. The differences in the patient characteristics between PTX3 tertiles were compared using one-way analysis of variance (ANOVA) for continuous variables. Categorical variables were compared by the chi-square test. Correlations between variables were assessed using the Pearson or Spearman rank correlations test. A receiver operating (ROC) curve analysis was done to investigate the predictive role of PTX3, Troponin, hsCRP, and pro-BNP for long-term prognosis in terms of cardiovascular mortality. A univariate and backward stepwise multivariate Cox regression analysis, which included variables with a p-value of less than 0.1, were performed to identify independent predictors of cardiovascular mortality. Cox proportional hazard regression was used for cardiovascular mortality and risk estimates (RR) and 95% confidence intervals (CI) were obtained for continuous variables. An overall 5% type-I error level was used to infer statistical significance, and a p value of less than 0.05 was considered significant. Two-sided p values <0.05 were considered to be statistically significant. All statistical analyses were carried out using SPSS statistical software, version 21.0 (SPSS Inc., Chicago, Illinois, USA).

Results

At the beginning of the study, we enrolled 150 patients with AMI as a patient group in our study. However, ten patients (n=4 for history of previous myocardial infarction or coronary artery bypass graft surgery, n=2 for severe renal failure, n=4 for acute or chronic inflammatory or infectious disease), for whom demographic, clinical, and laboratory characteristics were similar, were excluded from the study. In total, 140 patients with AMI as a patient group were included in our statistical analysis. The subgroups of the ACS group were as follows: NSTEMI (n=57) (40.7%) and STEMI (n=83) (59.3%).

During the 5-year follow, the rate of use of medications for patient and control groups was as follows: acetylsalicylic acid (97.3% vs. 32.6%), clopidogrel (88.2% vs. 2.4%), beta blockers (91.5% vs. 36.8%), statins (78.9% vs. 8.2%), and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (84.2% vs. 18.6%).

Baseline demographic, clinical, and laboratory characteristics of the patient and control groups were summarized in Table 1, 2. Age, rate of smoking, female gender, history of obesity, pulse rate, pulse pressure, LDL, triglyceride, NT-pro-BNP, hsCRP, white blood cell count, and HbA1c were significantly higher in patients with AMI than in the control group. However, HDL cholesterol and LVEF were found to be significantly lower in the patient group than in the control group. Furthermore, PTX3 level was significantly higher in the AMI group than in the controls (2.27±0.81

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Table 1. Baseline demographic and clinical characteristics of the patient and control groups

	AMI (n=140)	Control (n=60)	*P*
Age, y	59.72±12.32	52.77±9.8	<0.001*
Gender, M/F, n (%)	102/38 (72.9/27.1)	25/35 (41.7/58.3)	<0.001*
Height, cm	167.81±8.07	165.35±7.77	0.047*
Weight, kg	77.31±13.63	77.22±13.53	0.963
BMI, kg/m²	27.26±4.09	27.93±4.46	0.307
Smoking, n (%)	74 (52.9)	13 (21.7)	<0.001*
DM, n (%)	46 (32.9)	14 (23.3)	0.178
Hypertension, n (%)	83 (59.3)	32 (53.3)	0.435
Hyperlipidemia, n (%)	35 (25)	19 (31.7)	0.330
Family history, n (%)	46 (32.9)	21 (35)	0.769
Heart failure, n (%)	4 (2.9)	0 (0)	0.319
Stroke, n (%)	6 (4.3)	1 (1.7)	0.677
Obesity, n (%)	48 (34.3)	11 (18.3)	0.023*
SBP, mm Hg	130.09±24.6	124.38±14.01	0.094
DBP, mm Hg	74±15.04	75.37±10.04	0.520
Pulse rate, min	84.79±18.93	73.4±11.77	<0.001*
Pulse pressure, mm Hg	56.09±19.4	49.1±12.78	0.011*

AMI - acute myocardial infarction; BMI - body mass index; DBP - diastolic blood pressure; DM - diabetes mellitus; SBP - systolic blood pressure. Data were compared between two groups; if they are normally distributed; Kruskal-Wallis and Mann-Whitney U tests were used for continuous non-normally distributed variables, and student t-test for continuous normally distributed variables. Categorical variables were compared by the likelihood ratio chi-square test

Table 2. Baseline laboratory characteristics of the patient and control groups

	AMI (n=140)	Control (n=60)	*P*
Urea, mg/dL	21.29±11.47	18.33±9.78	0.083
Creatinine, mg/dL	1.91±7.78	2.01±9.32	0.942
TC, mg/dL	187.09±45.01	189.38±54.73	0.758
LDL, mg/dL	143.91±33.69	115.27±27.88	<0.001*
HDL, mg/dL	37.79±10.39	49.53±10.15	<0.001*
TG, mg/dL	187.26±102.88	129.58±40.92	<0.001*
Hemoglobin, g/dL	13.48±4.54	13.77±1.88	0.625
Hct, %	37.72±6.76	39.31±5.83	0.115
WBC, (x10³)	11.1±4.24	7.9±2.19	<0.001*
RBC, (x10³)	4.24±0.77	4.47±0.47	0.035*
Platelet, (x10³)	238.19±65.23	247.83±65.75	0.340
MPV, fL	10.97±25.64	8.27±0.98	0.417
Pro-BNP, pg/mL	444.11±577.29	101.12±82.01	<0.001*
hsCRP, mg/L	7.64±5.14	1.83±2.43	<0.001*
HbA1C, %	6.83±1.8	5.83±0.46	<0.001*
LVEF, %	41.09±8.61	58.42±6.06	<0.001*

AMI - acute myocardial infarction; HbA1C - glycated hemoglobin A1c; Hct - hematocrit; HDL - high density lipoprotein cholesterol; hsCRP - high sensitive C-reactive protein; LDL - low density lipoprotein cholesterol; LVEF - left ventricular ejection fraction; MPV - mean platelet volume; Pro-BNP - pro-brain-natriuretic peptide; RBC - red blood cell; TG - trigliserid; WBC - white blood cell. Data were compared between two groups; if they are normally distributed; Kruskal-Wallis and Mann-Whitney U tests were used for continuous non-normally distributed variables, and student t-test for continuous normally distributed variables

vs. 0.86±0.50 ng/mL, p<0.001). PTX3 level was found to be non-significantly higher in the STEMI group than in the NSTEMI (p >0.05). The study group was divided into tertiles according to their admission PTX3 values as follows: the high-PTX3 group (n=35) (≥4.27 ng/mL), the middle-PTX3 groups (n=35) (4.27–1.63 ng/mL), and the low-PTX3 group (n=35) (≤1.63). There was no difference between patient subgroups according to PTX3 tertiles in terms of demographic, clinical, and laboratory characteristics except HDL cholesterol, which was significantly increased in the highest PTX3 tertile (Table 3).

Correlation analysis between PTX3 levels and study variables were summarized in Table 4. PTX3 level was found to be significantly positively correlated with TIMI score (r=0.368, p=0.037), hsCRP (r=0.452, p=0.024), pro-BNP (r=0.386, p=0.029), troponin I (r=0.417, p=<0.001), GRACE score (r=0.355, p=0.045), and negatively correlated with HDL cholesterol (r=–0.203, p=0.016) and LVEF (r=–0.345, p=0.028). There was no correlation between the PTX3 level and the other remaining study variables.

During, in, and post-MI period, treatment strategies were occurred as follows: 103 patients (73.6%) had coronary angiography and PCI procedure, 25 patients (17.9%) had tirofiban infusion, 3 patients (2.1%) had dopamine infusion, and 2 patients (1.4%) had dobutamine infusion. Moreover, during the 5-year follow-up peri-

od, 9 patients (6.4%) died from cardiovascular causes, 17 patients (12.1%) had rehospitalization for heart failure, 12 patients (8.6%) had restenosis, 6 patients (4.3%) had life threatening arrhythmia, 2 patients (1.4%) had ischemic stroke, and 1 patient (0.7%) had TVR. There was no difference between PTX3 tertiles in terms of long-term primary and secondary cardiovascular events. PTX3 level was significantly higher in the restenosis group than in the non-restenosis group (2.95±0.75 vs. 2.23±0.80 ng/mL, p=0.01). In addition, both pro-BNP and hsCRP levels were demonstrated to be increased in the cardiovascular mortality group (973.11±75.17 vs. 364.55±54.10 pg/mL, p=0.016; 8.77±4.10 ng/mL, p=0.003, respectively). When the relations of PTX3 level with primary and secondary study end-points were investigated in STEMI and NSTEMI, PTX3 levels were found to be significantly higher in the events groups than in the non-events group for both subgroups (all p values <0.05). Both pro-BNP and hsCRP levels were also demonstrated to be increased in the events groups than in the non-events group for both subgroups (all p values <0.05).

Receiver operating curve (ROC) analysis was applied to evaluate the discriminatory value of PTX3 levels for long-term cardiovascular mortality in STEMI and NSTEMI groups. PTX3 revealed an area under curve (AUC) level of 0.756 [95% confidence interval (CI): 0.647–0.864; p<0.002] (Fig. 1). Moreover, hsCRP [AUC,

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Table 3. Comparison of demographic, clinical, and laboratory characteristics of the patient groups according to baseline PTX3 tertiles

PTX3		<1.63 (<25%) (n=35)	≥1.63–2.28 (≥25%–50%) (n=35)	≥2.28–4.27 (≥50%–75%) (n=35)	≥4.27 (≥75%) (n=35)	P
TC, mg/dL		189.46±45.67	191.14±48.24	170.83±45.26	182.09±46.47	0.249
LDL, mg/dL		121.71±43.71	120.26±38.61	113.89±43.64	125.49±40.98	0.666
HDL, mg/dL		40.54±11.28	37.8±9.93	37.97±10.24	34.83±9.69	0.049
TG, mg/dL		179.43±92.47	198.31±145.22	171±72.51	177.46±107.55	0.836
Pro-BNP, pg/mL		361.58±537.97	311.51±310.91	423±473.4	518.57±894.54	0.703
hsCRP, mg/L		29.14±43.77	18.1±20.92	26.65±42.44	37.32±60.21	0.712
hsCRP	<1	2 (5.7)	3 (8.6)	1 (2.9)	1 (2.9)	
	1–3	2 (5.7)	2 (5.7)	1 (2.9)	3 (8.6)	0.864
	>3	31 (88.6)	30 (85.7)	33 (94.3)	31 (88.6)	
Hemoglobin, g/dL		13.24±2.01	13.21±2.04	14.67±8.30	12.79±2.24	0.619
Hct, %		38.63±5.35	37.01±8.38	37.98±6.83	37.27±6.29	0.798
WBC, (x10^3)		10.21±2.99	11.31±3.91	11.95±6.12	10.95±3.18	0.619
Platelet, (x10^3)		236.37±56.12	249.54±65.15	235.95±65.61	230.89±74.16	0.704
MPV, fL		10.22±11.67	8.18±0.89	16.86±50	8.62±1.12	0.217
Urea, mg/dL		19.69±6.29	22.6±12.62	18.29±8.70	24.6±15.45	0.256
Creatinine, mg/dL		0.99±0.35	1.22±1.23	4.08±15.38	1.37±1.71	0.886
HbA1C, %		6.7±1.65	6.67±1.38	6.67±2.06	7.28±2.01	0.474
Killip score		1.26±0.61	1.23±0.73	1.34±0.8	1.40±0.88	0.666
LVEF, %		43.63±8.31	43.23±11.15	41.86±10.92	42.06±9.51	0.893
TIMI score		3.77±1.61	3.89±1.49	4.11±1.76	4.60±1.68	0.097
GRACE score		130.97±42.82	139.34±37.65	135.43±35.74	150±47.28	0.255
CK, U/L		629.77±522.72	731.3±742.93	950.93±913.17	698.03±523.91	0.291
CKMB, U/L		98.86±104.16	100.66±102.8	133.88±125.99	100.49±101.19	0.546
Troponin, ng/mL		17.41±19.34	20.29±20.12	21.61±21	20.39±20.17	0.597

AMI - acute myocardial infarction; CK - creatine kinase, CKMB - creatine kinase-MB; HbA1C - glycated hemoglobin A1c; Hct - hematocrit; hsCRP - high sensitive C-reactive protein; HDL - high density lipoprotein cholesterol; LDL - low density lipoprotein cholesterol; LVEF - left ventricular ejection fraction; MPV - mean platelet volume; Pro-BNP - pro-brain-natriuretic peptide; RBC - red blood cell; TG - trigliserid; TIMI - thrombolysis in myocardial infarction score; WBC - white blood cell. The differences in the patient characteristics between PTX3 tertiles were compared using one-way analysis of variance (ANOVA) for continuous variables. Categorical variables were compared by the likelihood ratio chi-square test

Table 4. Correlation analysis between PTX3 levels and study variables

	r	P
Age	0.072	0.394
Troponin	0.417	<0.001
Pro-BNP	0.484	0.028
LVEF	-0.345	0.028
TIMI score	0.368	0.037
GRACE score	0.355	0.045
CK	-0.229	0.335
CKMB	0.067	0.322
hsCRP	0.337	0.001
HDL	-0.203	0.016

CK - creatine kinase; CKMB - creatine kinase-MB; GRACE - Global Registry of Acute Coronary Events; hsCRP - highly sensitive C-reactive protein; LVEF - left ventricular ejection fraction; pro-BNP - pro-brain-natriuretic peptide; TIMI - The Thrombolysis in Myocardial Infarction. Correlations between variables were assessed using the Pearson or Spearman rank correlations test

0.775; 95% confidence interval (CI): 0.643–0.906; p=0.001] and pro-BNP [AUC, 0.757; 95% confidence interval (CI): 0.630–0.885; p=0.002] also had significantly discriminative roles for predicting long-term cardiovascular mortality in the STEMI group. In the NSTEMI group (Fig. 2), PTX3 revealed an AUC level of 0.941 [95% confidence interval (CI): 0.878–1.004; p<0.001]. In addition, hsCRP [AUC, 0.982; 95% confidence interval (CI): 0.946–1.018; p<0.001], troponin I [AUC, 0.722; 95% confidence interval (CI): 0.558–0.887; p=0.028] and pro-BNP [AUC, 0.978; 95% confidence interval (CI): 0.941–1.014; p<0.001].

In a univariate regression analysis, PTX3, troponin I, hsCRP, TIMI, GRACE, and pro-BNP were significantly associated with long-term cardiovascular mortality. Variables that were statistically significant in a univariate analysis were entered into multivariate stepwise logistic regression analysis. In a multivariate analysis, PTX3, pro-BNP, and GRACE scores were significant independent predictors of long-term cardiovascular mortality,
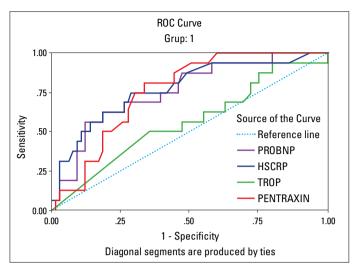
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Figure 1. The discriminatory value of PTX3 levels for long-term cardiovascular mortality in STEMI group by receiver operating (ROC) curve analysis
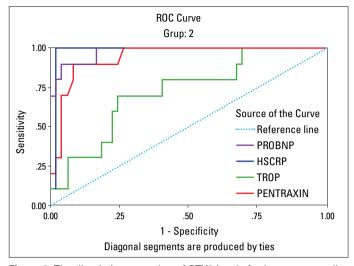

Figure 2. The discriminatory value of PTX3 levels for long-term cardiovascular mortality in NSTEMI group by receiver operating (ROC) curve analysis

Table 5. Univariate and multiple regression analysis of predictors of long-term cardiovascular mortality in patients with AMI

	Univariate			Multiple		
	OR (CI 95%)	β	*P*	OR (CI 95%)	β	*P*
PTX3	2.322 (1.133–4.760)	**0.295**	**0.021**	2.175 (1.425–3.320)	**0.276**	**0.034**
hsCRP	0.865 (0.755–0.991)	**0.127**	**0.047**			
Pro-BNP	1.836 (1.822–1.891)	**0.238**	**0.028**	1.632 (1.452–1.820)	**0.213**	**0.001**
TIMI	1.047 (1.020–1.075)	**0.141**	**0.001**			
GRACE	1.336 (1.122–1.791)	**0.186**	**0.003**	1.132 (1.052–1.520)	**0.127**	**0.001**
LVEF	0.936 (0.923–0.989)	**0.138**	**0.042**			

GRACE - Global Registry of Acute Coronary Events; hsCRP - highly sensitive C-reactive protein; LVEF - left ventricular ejection fraction; pro-BNP - pro-brain-natriuretic peptide; PTX3 - pentraxin-3; TIMI - The Thrombolysis in Myocardial Infarction. A univariate and backward stepwise multiple Cox regression analysis, which included variables with a p value of less than 0.1, were performed to identify independent predictors of cardiovascular mortality

after adjusting for other risk factors (Table 5). Furthermore, in Cox proportional hazard model, PTX3 was found to be a significant risk marker for long-term cardiovascular mortality in AMI [RR=1.18 (95% CI 1.08–1.46), p=0.032].

Discussion

The main finding of the present study was that PTX3 level, as one of the important inflammatory markers, was significantly increased in the setting of AMI. It was reported to be significantly directly related with TIMI score, hsCRP, pro-BNP, troponin I, and GRACE score, and inversely associated with HDL cholesterol and LVEF. Moreover, PTX3 levels were significantly higher in patients who had future adverse cardiac events for both STEMI and NSTEMI. In addition, PTX3, pro-BNP, and GRACE score were significant independent predictors of long-term cardiovascular mortality, after adjusting for other risk factors in patients with AMI. Although the GRACE score has been validated for either 30 days in-hospital or 6-months mortality, we aimed to show independent predictors of long-term cardiovascular mortality in our

study. In light of these findings, PTX3 has clinical utility for the prediction of long-term major adverse cardiovascular events including mortality, which may help appropriate risk stratification and management of ACS.

PTX3, which is a preliminary long pentraxin, is produced by macrophages, dendritic cells, and endothelial cells in response to primary inflammatory and immune stimuli (7, 8). An increased level of PTX3 has been demonstrated in rodents after systemic administration of microbial products and inflammatory cytokines or ligation of the left coronary artery to model AMI by the study of Introna et al. (22). PTX3 is also abundantly present in atheroma plaques and small-vessel vasculitis, which is attracted by oxidized LDL in smooth muscle cells of vessels (10). Several recent studies had evaluated a relation between PTX3 and cardiovascular diseases. Dubin et al. (23) presented an association between increased PTX3 and raised risk for all-cause mortality, cardiovascular events, and incident of heart failure in patients with stable coronary artery disease. Short-term prognostic significance of PTX3 in AMI has been investigated in recent studies. George et al. (24) found that the median value of PTX3 was significantly

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higher in STEMI patients than in NSTEMI. Moreover, PTX3 was importantly inversely related with LVEF. After six months follow-up, PTX3 was reported to be an independent predictor for major adverse cardiovascular mortality. Latini et al. (16) reported a predictive role of admission PTX3 for 3-month all-cause mortality after adjustment for major risk factors and other acute-phase prognostic markers such as troponin T, creatine kinase, NT-pro-BNP, and C-reactive protein in patients with STEMI. Moreover, Matsui et al. (15) investigated a prognostic value of PTX3 level in patients hospitalized for unstable angina and NSTEMI within 24 hours after index event, and they reported that PTX3 and NT-pro-BNP may be significant independent markers for 6-month major cardiac events including cardiac death in this setting. In our study, PTX3 level was significantly increased in the setting of AMI, which was found to be higher in the STEMI group than in the NSTEMI. Moreover, concordant with previous studies, PTX3 was significantly positively and negatively correlated with TIMI score and LVEF, respectively. Furthermore, PTX3 levels were significantly higher in patients who had major adverse cardiac events for both STEMI and NSTEMI, which was similar to that reported in some previous studies. Moreover, long-term primary and secondary cardiovascular events were similar between PTX3 tertiles, which may due to few primary and secondary cardiovascular events in each PTX3 tertiles and limited subjects in each of the subgroups.

The information about the long-term prognostic value of admission PTX3 is very limited in the literature. Akgül et al. (17) suggested that an increased admission PTX3 level was related with raised in-hospital cardiovascular mortality and 2-year all-cause mortality in patients with STEMI underwent primary PCI procedure (16). In this study, different from Akgül et al. (17) study with longer follow-up period, we reported an admission PTX3 level as a significant independent predictor for 5-year adverse cardiac outcomes including cardiovascular mortality, after adjusting for other risk factors in patients with AMI including both STEMI and NSTEMI.

The actual pathophysiologic mechanisms between PTX3 and long-term cardiovascular mortality cannot be precisely elucidated. Moreover, selective binding of PTX3 to apoptotic cells in areas of damaged myocardium, PTX3 induced classic pathway of complement activation, amplification of tissue damage, and enhanced procoagulant activity of endothelial cells by PTX3 and inhibitor effects of PTX3 by inactivating of fibroblast growth factor-2 are suggested as potential pathways for this relationship in recent studies (25, 26).

Study limitations

This study has some limitations. First, it arose from a single center and therefore was subject to selection bias. Second, the study population was relatively small; however, we were still able to demonstrate a relationship between PTX3 level and long-term major adverse cardiovascular events including mortality in patients with AMI. Third, since PTX3 were calculated only once during admission, we could not evaluate the changes in PTX3 levels in response to treatment due to lack of serial measurements. Fourth, there is a lack of evidence about the relationship between PTX3 and coronary artery severity and left ventricular diastolic function in terms of SYNTHAX score and relevant echocardiographic parameters for left ventricular diastolic dysfunction, since they have not been measured during the study period.

Conclusion

We demonstrated that patients having a high PTX3 level had more major adverse cardiovascular outcomes including mortality, both while they were still hospitalized for heart failure and need to target vessel revascularization for restenosis or reinfarct during the 5-year follow-up period. In addition, it may be used to detect patients who may require early coronary artery intervention and revascularization in AMI. Larger studies with more study participants will be required to elucidate the pathophysiologic relation between raised PTX3 and cardiovascular mortality in this setting.

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