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

Servet Altay, Hüseyin Altuğ Çakmak, Tuğba Kemaloglu Öz, Fatma Özpanuk Karadeniz, Ayça Türer, Hatice Betül Erer, Gülen Feyzan Kilic, İbrahim Keleş, Günay Can, Mehmet Eren

Department of Cardiology, Faculty of Medicine, Trakya University; Edirne-Turkey

Departments of Cardiology and Biochemistry, Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital; İstanbul-Turkey

Departments of Cardiology, Department of Public Health, Cerrahpaşa Faculty of Medicine, İstanbul University; İstanbul-Turkey

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 a 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 (≥4.27 ng/mL), the middle-PTX3 group (4.27–1.63 ng/mL), and the low-PTX3 group (≤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=0.388, 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.

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...
Prognostic Significance of pentraxin-3 in acute myocardial infarction

Anatol J Cardiol 2017; 17: 202-9

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 NSTEMI) 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 exclusively after exclusion of AMI, were normal.

Laboratory measurements

A 5 mL sample of venous blood was collected in EDTA-coated vacutainer tubes and separated by centrifugation at the...
time of hospital admission. The serum was stored at −80°C until 
analyzed. The admission HbA1c level was assayed using an auto-
mated, high-performance, liquid chromatography analyser (Trin-
ity 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 chole-
sterol 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 concentra-
tion linearly between 0.1 and 20 ng/mL. The coefficient of vari-
ation 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: k050636 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: 
k069064 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 inter-
viewing patients, their families, or their family physicians directly 
or by telephone. The primary endpoint of the study was cardio-
vascular 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 reste-
nosis 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 vari-
ables 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 vari-
ables, 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 in-
vestigate 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 cardiovas-
cular mortality. Cox proportional hazard regression was used for 
心血管 mortality and risk estimates (RR) and 95% confi-
dence intervals (CI) were obtained for continuous variables. An 
overall 5% type-I error level was used to infer statistical signifi-
cance, and a p value of less than 0.05 was considered significant. 
Two-sided p <0.05 were considered to be statistically sig-
nificant. All statistical analyses were carried out using SPSS sta-
tistical 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 
by-pass graft surgery, n=2 for severe renal failure, n=4 for acute 
or chronic inflammatory or infectious disease), from whom de-
ographic, 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 characteris-
tics 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 sig-
nificantly higher in the AMI group than in the controls (2.27±0.81
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 period, 2 patients (1.4%) had dopamine infusion, and 2 patients (1.4%) had dobutamine infusion. Moreover, during the 5-year follow-up period, 2 patients (1.4%) had dopamine infusion, and 2 patients (1.4%) had dobutamine infusion. However, 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 STEMI group than in the NSTEMI (p <0.05). Both pro-BNP and hsCRP levels were demonstrated to be increased in the STEMI and NSTEMI groups. PTX3 levels were found to be significantly higher in the STEMI group than in the NSTEMI (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,

| 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 | 0.983 |
| 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* |
| LVEF, % | 41.09±8.61 | 58.42±6.06 | <0.001* |
| **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. 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 ng/mL). 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 period, 2 patients (1.4%) had dopamine infusion, and 2 patients (1.4%) had dobutamine infusion. Moreover, during the 5-year follow-up period, 2 patients (1.4%) had dopamine infusion, and 2 patients (1.4%) had dobutamine infusion. However, 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±577.29 vs. 364.55±54.10 pg/mL, p<0.001). 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,
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.

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

<table>
<thead>
<tr>
<th>PTX3</th>
<th>&lt;1.63 (&lt;25%)</th>
<th>≥1.63–2.28 (≥25%–50%)</th>
<th>≥2.28–4.27 (≥50%–75%)</th>
<th>≥4.27 (≥75%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC, mg/dL</td>
<td>189.46±45.67</td>
<td>191.14±48.24</td>
<td>170.83±45.26</td>
<td>182.09±46.47</td>
<td>0.249</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>121.71±43.71</td>
<td>120.26±38.61</td>
<td>113.89±43.64</td>
<td>125.49±40.98</td>
<td>0.666</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>40.54±11.28</td>
<td>37.8±5.93</td>
<td>37.97±10.24</td>
<td>34.83±5.99</td>
<td>0.049</td>
</tr>
<tr>
<td>TG, mg/dL</td>
<td>179.43±92.47</td>
<td>198.31±145.22</td>
<td>171±72.51</td>
<td>177.46±107.55</td>
<td>0.836</td>
</tr>
<tr>
<td>Pro-BNP, pg/mL</td>
<td>361.58±537.97</td>
<td>311.51±310.91</td>
<td>423±473.4</td>
<td>518.57±894.54</td>
<td>0.703</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>29.14±43.77</td>
<td>18.1±20.92</td>
<td>26.65±42.44</td>
<td>37.3±60.21</td>
<td>0.712</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.24±2.01</td>
<td>13.21±2.04</td>
<td>14.67±8.30</td>
<td>12.79±2.24</td>
<td>0.619</td>
</tr>
<tr>
<td>Hct, %</td>
<td>38.63±5.35</td>
<td>37.01±8.38</td>
<td>37.98±6.83</td>
<td>37.27±6.29</td>
<td>0.798</td>
</tr>
<tr>
<td>WBC, (x10^3)</td>
<td>10.21±2.99</td>
<td>11.31±3.91</td>
<td>11.95±6.12</td>
<td>10.95±3.18</td>
<td>0.619</td>
</tr>
<tr>
<td>Platelet, (x10^3)</td>
<td>236.37±56.12</td>
<td>249.54±65.15</td>
<td>235.95±65.61</td>
<td>230.89±74.16</td>
<td>0.704</td>
</tr>
<tr>
<td>MPV, fl</td>
<td>10.22±11.67</td>
<td>8.18±0.89</td>
<td>16.86±50</td>
<td>8.62±1.12</td>
<td>0.217</td>
</tr>
<tr>
<td>Urea, mg/dL</td>
<td>19.69±6.29</td>
<td>22.6±12.62</td>
<td>18.29±8.70</td>
<td>24.6±15.45</td>
<td>0.256</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.99±0.35</td>
<td>1.22±1.23</td>
<td>4.08±15.38</td>
<td>1.37±1.71</td>
<td>0.886</td>
</tr>
<tr>
<td>HbA1C, %</td>
<td>6.7±1.65</td>
<td>6.67±1.38</td>
<td>6.67±2.06</td>
<td>7.28±2.01</td>
<td>0.474</td>
</tr>
<tr>
<td>Killip score</td>
<td>1.26±0.61</td>
<td>1.23±0.73</td>
<td>1.34±0.8</td>
<td>1.40±0.88</td>
<td>0.666</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>43.83±8.31</td>
<td>43.23±11.15</td>
<td>41.86±10.92</td>
<td>42.06±9.51</td>
<td>0.893</td>
</tr>
<tr>
<td>TIMI score</td>
<td>3.77±1.61</td>
<td>3.89±1.49</td>
<td>4.11±1.76</td>
<td>4.60±1.68</td>
<td>0.097</td>
</tr>
<tr>
<td>GRACE score</td>
<td>130.97±42.82</td>
<td>139.34±37.65</td>
<td>150.43±35.74</td>
<td>150±47.28</td>
<td>0.255</td>
</tr>
<tr>
<td>CK, U/L</td>
<td>629.77±522.72</td>
<td>731.3±742.93</td>
<td>950.93±913.17</td>
<td>698.03±523.91</td>
<td>0.291</td>
</tr>
<tr>
<td>CKMB, U/L</td>
<td>98.86±104.16</td>
<td>100.66±102.8</td>
<td>133.88±125.99</td>
<td>100.49±101.19</td>
<td>0.546</td>
</tr>
<tr>
<td>Troponin, ng/mL</td>
<td>17.41±19.34</td>
<td>20.29±20.12</td>
<td>21.61±21</td>
<td>20.39±20.17</td>
<td>0.597</td>
</tr>
</tbody>
</table>

AMI - acute myocardial infarction; CK - creatine kinase; CKMB - creatine kinase-MB; HbA1C - glycated hemoglobin A1c; Hct - hematocrit; hsCRP - highly 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 - triglyceride; 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

<table>
<thead>
<tr>
<th>Variable</th>
<th>r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.072</td>
<td>0.394</td>
</tr>
<tr>
<td>Troponin</td>
<td>0.417</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>pro-BNP</td>
<td>0.484</td>
<td>0.028</td>
</tr>
<tr>
<td>LVEF</td>
<td>-0.345</td>
<td>0.028</td>
</tr>
<tr>
<td>TIMI score</td>
<td>0.368</td>
<td>0.037</td>
</tr>
<tr>
<td>GRACE score</td>
<td>0.355</td>
<td>0.045</td>
</tr>
<tr>
<td>CK</td>
<td>-0.229</td>
<td>0.335</td>
</tr>
<tr>
<td>CKMB</td>
<td>0.067</td>
<td>0.322</td>
</tr>
<tr>
<td>hsCRP</td>
<td>0.337</td>
<td>0.001</td>
</tr>
<tr>
<td>HDL</td>
<td>-0.203</td>
<td>0.016</td>
</tr>
</tbody>
</table>

AMI - acute myocardial infarction; 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.
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

---

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

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

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.

---

![ROC Curve](image1.png)

Figure 1. The discriminatory value of PTX3 levels for long-term cardiovascular mortality in STEMI group by receiver operating (ROC) curve analysis

![ROC Curve](image2.png)

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

---

**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.
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).

**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.

**Conflict of interest:** None declared.

**Peer-review:** Externally peer-reviewed.


**References**

2. de Beer FC, Hind CR, Fox KM, Allan RM, Maseri A, Pepys MB. Measurement of serum C-reactive protein concentration in myocardial ischaemia and infarction. Br Heart J 1982; 47: 239-43. [Crossref]
5. Lepojärvi ES, Piira OP, Kiviniemi AM, Miettinen JA, Kenttä T, Ukkola O, et al. Usefulness of Highly Sensitive Troponin as a Predictor of Short-Term Outcome in Patients With Diabetes Mellitus and Stable Coronary Artery Disease (from the ARTEMIS Study). Am J Cardiol 2016; 117: 515-21. [Crossref]