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SERUM PENTRAXIN-3 (PTX3) LEVEL AS IN-HOSPITAL MAJOR CARDIOVASCULAR EVENTS PREDICTOR IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

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Abstract
Background: Acute myocardial infarction is a condition caused by ruptured of atherosclerotic plaque. Atherosclerosis is an inflammation process since formation until acute coronary syndrome events. Pentraxin-3 (PTX3) is an acute phase glycoprotein which secreted by haemopoietic and endothelial cells. PTX3 in early phase of acute myocardial infarction was found to be a prognostic marker in patients with myocardial infarction.
Method: This is a prospective cohort study, in 87 consecutively acute myocardial infarction patients in Adam Malik General Hospital Medan. Serum PTX3 levels were checked on admission at Emergency Room. All patients were observed during hospitalization to determine major cardiovascular events (MACE) including acute heart failure, cardiogenic shock, arrythmia, and death. Data were analysed using SPSS version 24.
Results: Serum PTX3 levels were significantly higher in acute myocardial infarction with MACE than in events free patients ($p < 0.001$) with median of 4.45 (0.29-10.76) ng/mL. Using ROC curve, the optimal cut-off value was 3,61ng/mL for predicting MACE with a sensitivity of 63 % sensitivity and specificity of 72%. In multivariate logistic regression analysis, serum PTX3 levels with OR value of 1,388 (95% CI 1,142-1,686 ; p value 0,001) independently predicted MACE along with sex, heart rate, symptom onset and GRACE score.
Conclusion: Serum PTX3 predicted in-hospital MACE and might be used as a marker to determine high-risk patients with acute myocardial infarction.

Introduction
Coronary heart disease is the leading of morbidity and mortality worldwide, despite the advances in management of patients with acute myocardial infarction and all actions to impede this disease in general population.[1] Coronary heart disease occurs due to inflammatory processes and the accumulation of cholesterols in the walls of coronary arteries, this process called atherosclerosis.[2] Inflammation is an essential process in atherosclerosis, and many inflammatory markers have been analyzed in relation to long-term and short-term prognosis in patients with coronary heart disease.[3] The relationship between increased levels of acute phase protein and the progression of atherosclerosis and its complications has been investigated in several studies.[4]

Pentraxin-3 (PTX3) is an acute phase inflammatory glycoprotein that resembles C-Reactive Protein (CRP) both in structure and function, which has been found to be produced both by hematopoietic cells such as macrophages, dendritic cells, neutrophils and by nonhematopoietic cells such as fibroblast and endothelial cells, which may reflect localized inflammation at atherosclerotic lesions.[5,6] Studies have shown that serum PTX-3 levels increased during acute coronary syndromes and if measured at early stages were found to be prognostic markers.[7,8] This study aims at assessing the role of serum PTX3 levels in predicting in-hospital major cardiovascular events in patients with acute myocardial infarction.

Methods
This study is an observational cohort study which performed at Haji Adam Malik General Hospital Medan with permission from Research Ethics Committee of the Faculty of Medicine, University as Sumatera Utara-RSHAM. Subjects were recruited consecutively from April to July 2019. The inclusion criteria were patients who were clinically confirmed as acute myocardial infarction with symptom onset less than 3 days. While exclusion criteria were Killip class IV on admission, history of revascularization either with Percutaneous

Coronary Intervention (PCI) or Coronary Artery Bypass Graft (CABG), history of malignancy, worsening liver function, severe infection and refuse to take part in the study.

Study Procedure

Subject's clinical and demographic characteristics who admitted in the ER with acute myocardial infarction as working diagnose were recorded. Blood samples were taken from all subjects upon admission. The samples were than placed in EDTA containing tubes and were stored at optimal temperature and kept freeze until examination. Serum PTX3 levels were studied using Human Pentraxin-3 ELISA Kit by Bioassay Technology Laboratory. Major cardiovascular events such as acute heart failure, cardiogenic shock, arrythmias, and death were observed from index events until discharged.

Statistical analysis

Categorical variables are presented by number or frequency (n) and percentage (%). Numerical variables are represented by mean and standard deviation for normally distributed data, if data not normally distributed, the data shown by median. For bivariat analysis, Mann Whitney test was conducted between serum PTX3 levels and in-hospital MACE. Receiver Operating Characteristic (ROC) analysis were used to determine the optimal cut-off value for PTX3, then Area Under Curve (AUC) were analyzed to assessed the prognostic significance. Multivariate analysis of independent variables was tested with logistic regression. All the data were analyzed using SPSS version 24.0, the value of $p < 0.05$ was said to be statistically significant.

Result

A total of 87 patients with acute myocardial infarction were included in this study. Most of the subjects were men (77%) with average age of 58,11 years old. Subjects with majority of traditional cardiovascular risk factors were seen in this study, such as obesity with average BMI of 25,4, 43,7% with history of hypertension, 51,7% with history of diabetes mellitus and 59,8% were smoker. Subject with ST-segment elevation myocardial infarction (STEMI) were 48,3 %, and the rest were diagnosed with Non ST-segment elevation myocardial infarction (NSTEMI). Clinical presentation with median value of systolic blood pressure were 120mmHg and average value for heartrate was 81bpm. Risk stratification were measured using Killip class, TIMI Risk and GRACE score. Laboratory data and other findings of the subject of this study are presented in table 1.

Table 1. Baseline Characteristics

Variable	(n:87)
Age (years)	58,1 ± 10,1
Male sex (n,%)	67 (77%)
BMI, kg/m2	25,4 ± 3,5
Diabetes Mellitus	45 (51,7%)
Hypertension	38 (43,7%)
Smoking	52 (59,8%)
Family History	23 (26,4%)
Clinical Characteristics	
Symptom Onset (hours)	14 (0,5-72)
Heartrate (bpm)	81 ± 19
Systolic BP (mmHg)	120 (70-180)
Diastolic BP (mmHg)	80 (60-120)
GRACE Score	120 (61 – 167)
Killip (n,%)	
I	59 (67,8%)
II	21 (24,1%)
III	7 (8%)
Diagnosis	
STEMI	42 (48,3%)
NSTEMI	45 (51,7%)

Laboratory Characteristics	
Hb (g/dL)	13,1 ± 2,3
Leukocyte (x10^3µL)	11.240 (4.830 – 27.070)
Thrombocyte (x10^3µL)	250 (97 – 797)
MPV	10 (8,3 – 13)
Blood Glucose Levels (mg/dL)	152 (85 – 511)
Creatinine (mg/dL)	1 (0,54 – 11,2)
PTX3 (ng/mL)	3,1 (0,27 – 10,76)
Troponin-I (ng/mL)	1,37 (0,06 – 32)
CKMB (U/L)	64 (14 – 673)
Therapies	
DAPT	87 (100%)
Statin	87 (100%)
Anticoagulant	
Enoxaparin	43 (49,4%)
Fondaparinux	29 (33,3%)
Unfractioned Heparin	15 (17,2%)

There were 38 subjects (43,7%) having in-hospital MACEs, including arrythmias (8%), cardiogenic shock 12,6%), acute heart failure (16,1%) and death (6,9%) (Figure 1). All the subjects were divided into two groups, with and without MACEs. There was no differences in cardiovascular risk factors between two groups. Table 2 shows the paramaters that were significantly different between patients with and without MACEs.

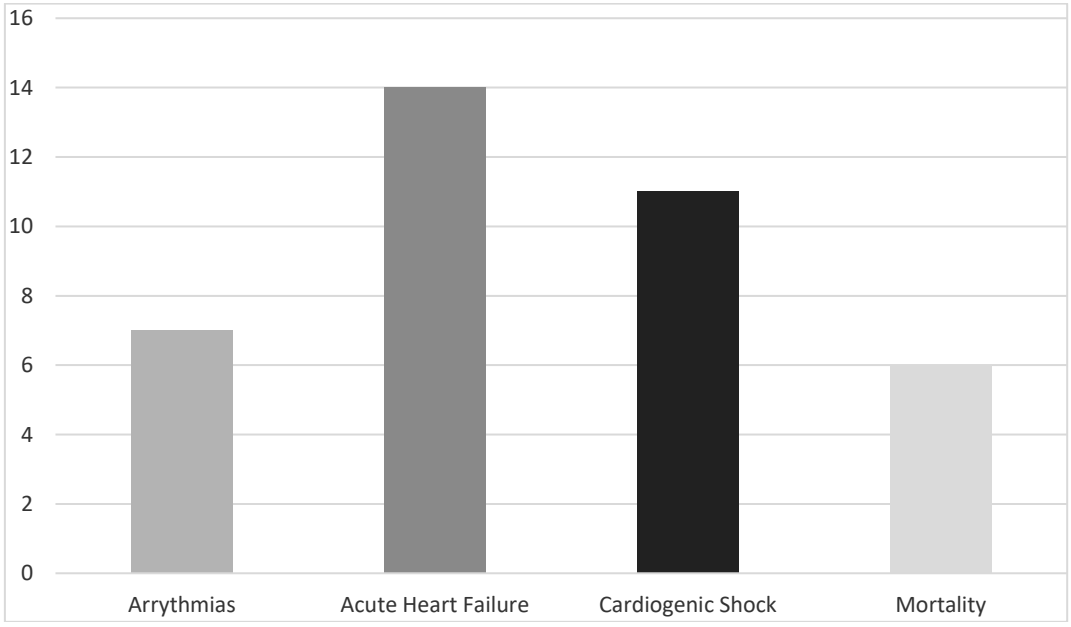

Figure 1. In-Hospital MACEs in Patients with Acute Myocardial Infarction

Table 2. Bivariate Analysis in patients with and without MACEs

	With MACEs (n=38)	**Without MACEs (n=49)**	**p**
Male sex	24 (35,8 %)	43 (64,2%)	0,014
Age (years)	61 ± 11	56 ± 8	0,010
BMI, kg/m^2	24,8 ± 3.4	25,9 ± 3,6	0,190
Diabetes Mellitus	21 (46,7%)	24 (53,3%)	0,715
Hypertension	14 (36,8%)	24 (63,2%)	0,361
Smoking	22 (42,3%)	30 (57,7%)	0,925
Family History	10 (43,5%)	13 (56,5%)	> 0,999
Symptom Onset (hours)	10 (0,5-72)	16 (2-72)	0,073
Heartrate (bpm)	87 ± 19	76 ± 18	0,019
Systolic BP (mmHg)	110 (70-180)	130 (90-180)	0,030
Diastolic BP (mmHg)	70 (60-120)	80 (60-100)	0,049
GRACE Score	135 ± 20	109 ± 27	<0,001
Diagnosis			
STEMI	19 (45,2%)	23 (54,8%)	0,946
NSTEMI	19 (42,2%)	26 (57,8%)	
Killip Class			
I	22 (37,3%)	37 (62,7%)	
II	12 (57,1%)	9 (42,9%)	0,218
III	4 (57,1%)	3 (42,9%)	
Laboratory Characteristics			
Hb (g/dL)	12.4 ± 2.5	13.7 ± 1.9	0,010
Leukocyte (x10^{3}µL)	12 (4,83 – 22,12)	10,96 (5,46 – 27,07)	0,091
Neutrophil	73,70 ± 11,16	67,36 ± 14,27	0,027
Lymphocyte	17,52 ± 9,81	20,14 ± 8,58	0,190
Monocyte	7,5 (2,1 – 16,8)	7,3 (0,9 – 16,8)	0,590
Thrombocyte (x10^{3}µL)	244 (97 – 563)	260 (133 – 797)	0,590
MPV (fL)	10.25 (8.8-13)	9.8 (8.3-12.3)	0,081
Creatinine (mg/dL)	1.31 (0.54-11.2)	0.87 (0.54-3.11)	0,002
PTX3 (ng/mL)	4.45 (0.29-10.76)	1.18 (0.27-9.6)	<0,001
Troponin-I (ng/mL)	1,94 (0,06 – 32)	1,3 (0,1 – 32)	0,901
CKMB (U/L)	67 (14-673)	64 (14-673)	0.732
Revascularization Strategy			
PCI	16 (57,1%)	12 (42,9%)	
CABG	0 (0%)	5 (100%)	0,213
Conservative	22 (40,7%)	32 (59,3%)	

At multivariate analysis, several paramaters such as male sex, heart rate, systolic blood pressure, symptom onset and serum PTX3 levels were having prognostic significance. Serum PTX3 levels with OR 1,388 95% CI 1,142-1,686 ; p value 0,001 was an independent predictor of in-hospital MACE. Predictors of in-hospital MACE by multivariate analysis are reported in Table 3.

Table 3. Multivariate Analysis to predict MACEs

	OR (95% CI)	p
Male sex	**4,717 (1,242-17,909)**	**0,023**
Age	1,044 (0,964-1,131)	0,291
BMI	0,957 (0,911-1,004)	0,590
Heart Rate	**1,042 (1,002-1,083)**	**0,040**
Systolic BP	**0,973 (0,946-1,001)**	**0,055**
Diastolic BP	1,056 (0,948-1,177)	0,318
GRACE Score	**1,037 (1,012-1,062)**	**0,004**
Symptom Onset	**0,961 (0,925-0,999)**	**0,043**
Hb	0,971 (0,649-1,454)	0,888
Neutrophil	1,052 (0,978-1,122)	0,174
Lymphocyte	1,053 (0,979-1,132)	0,165
MPV	1,646 (0,839-3,227)	0,147
Creatinine	2,1 (0,971-4.542)	0,059
Revascularization with PCI	2,586 (0,743-9,003)	0,135
PTX3	**1,388 (1,142-1,686)**	**0,001**

A ROC analysis was performed to identify serum PTX3 levels of >3,61 ng/mL at admission as the optimal cut-off to predict in-hospital MACEs with a sensitivity of 63%, specificity of 72% (AUC 0,73, 95% CI 0,624 – 0,835 p<0.001) (Figure 2).

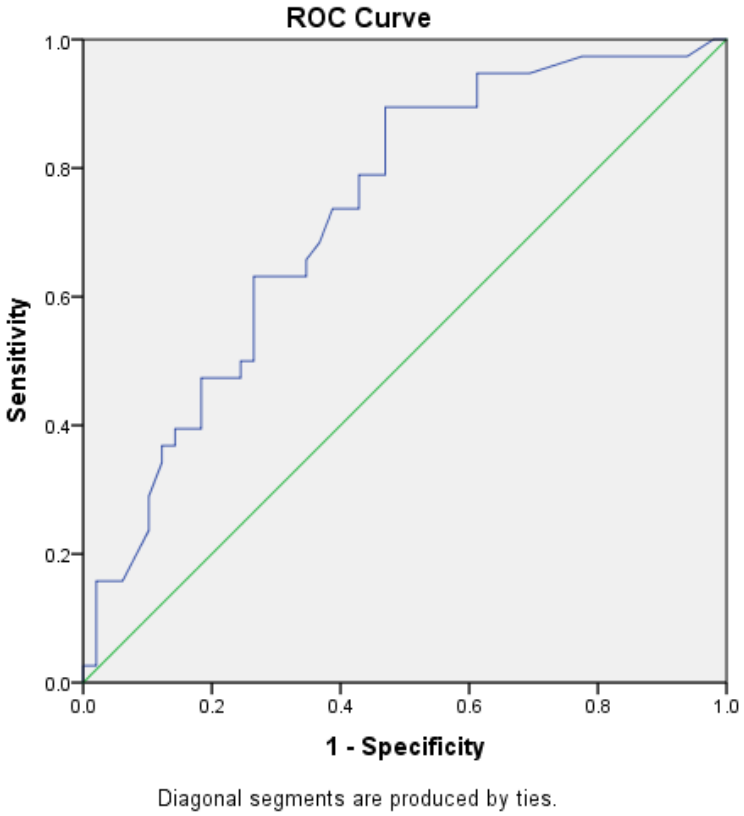

Figure 2. ROC Curve for determining optimal cut-off value of PTX3 to predict MACE

Discussion

Acute myocardial infarction occurs as a result of atherosclerotic erosion or plaque rupture. Atherosclerosis is a complex mechanism that involves the interaction of the inflammatory process.[9] The importance of markers for heart muscle damage in acute myocardial infarction for early diagnosis and as a prognostic stratification has evolved from mere markers of heart muscle necrosis such as CKMB and troponin to inflammatory markers such as short pentraxins such as CRP and SAP.[10] One inflammatory markers that has been suggested by the guidelines is CRP (C-Reactive Protein). Although CRP has been widely used as a diagnostic biomarker of atherosclerosis as a cause of coronary heart disease, elevated levels of CRP in acute conditions such as acute coronary syndromes, particularly acute myocardial infarction are considered nonspecific responses to myocardial damage, so the role of CRP in the pathogenesis of myocardial damage is still debated.[11,12]

Pentraxin-3 (PTX3) has been touted as a promising candidate for inflammatory biomarkers. This is because pentraxin-3 is produced at the site of damage so that it may be useful as an indicator of the cardiovascular inflammatory process. Peri, et al reported that pentraxin-3 levels were an early indicator of acute myocardial infarction without any link between pentraxin-3 and CRP.[13,14]

This research is a prospective cohort study to find out the relationship between serum PTX3 levels and in-hospital major cardiovascular events (MACE) in patients with acute myocardial infarction. This research was conducted at RSUP Adam Malik Medan from April to July 2019 and involved 87 samples that met the inclusion and exclusion criteria. Acute myocardial infarction patients in this study consisted of STEMI and NSTEMI, with significant differences in levels of PTX3 between the two groups. Serum PTX3 levels in the STEMI group ranged from 5.04 ± 2.06, whereas in the NSTEMI group with an average of 2.28 ± 1.96. This is consistent with research by Lee et al in 2010 which stated that levels of PTX3 increased higher in patients with STEMI than patients with NSTEMI or unstable angina pectoris. However, Lee et al, found no significant difference in levels of PTX3 between NSTEMI patients and unstable angina pectoris or stable angina pectoris. Higher pentraxin-3 levels in STEMI are related to the amount of damaged myocardium, in accordance with pentraxin-3 levels associated with troponin levels.[4,15]

There were 45 subjects with MACE and 55 subjects did not experience the occurrence of MACE. The MACEs components examined in this study include death, the incidence of acute heart failure or worsening of symptoms of patients who have had chronic heart failure, arrhythmias and cardiogenic shock events. In this study found about 43.6% of the study sample experienced MACEs where the most common events were cardiogenic shock (16.1%), acute heart failure (12.6%), arrhythmias (8%), and death (6%). This is in accordance with research conducted by Haque where the most complications of acute myocardial infarction are heart failure around 53% and arrhythmia around 27%.[16] Acute heart failure is a complication that is quite common in patients with acute myocardial infarction. At the time of admission, the incidence of acute heart failure in patients with acute myocardial infarction can be assessed by assessing the Killip class, with the Killip class above I classified as high risk patients, where the risk of death is above 17%. So patients with this condition must be considered for treatment in the form of an earlier invasive strategy.[17,18]

Among the variables studied, there were several variables that were significantly different in the group that had a major cardiovascular event and who did not experience a major cardiovascular event. Among them are gender, age, BMI, heart rate, systolic blood pressure, diastolic blood pressure, GRACE score, Killip class, symptom onset, Hb, leukocyte, neutrophil, MPV, Creatinine, revascularization stratgeies and PTX3.

PTX3 were increased during the acute phase of myocardial infarction, and had a prognostic significance.[19] So it is thought to be a predictor of the prognosis of patients with acute myocardial infarction.[6] In this study it was found that the serum PTX3 levels can predict in-hospital major cardiovascular events with area under the curve (AUC) of 0,73 with serum PTX3 levels of ≥ 3.61 ng/mL as the optimal cut-off point with sensitivity of 63% and specificity of 72%. This is consistent with study conducted by Matsui et al. states that serum PTX3 levels of more than 3.1 ng/mL are predictors of major cardiovascular events within 6 months, whereas according to Latini et al, PTX3 levels above 10.73 ng/mL are predictors of patient death acute myocardial infarction within 3

months.[20,21] Lee et al used a cut-off point 0.88ng /mL for PTX3 with a sensitivity of 87% and a specificity of 69.1% in predicting deaths during hospitalization based on GRACE scores.[4] This is quite different from this research, perhaps because the previous research did not make observations, but only compared with a scoring system. Our findings shoul be confirmed by large multicenter studies.

Conclusion

Serum PTX3 levels was an independent predictor of in-hospital MACE with optimal cut-off value of >3,61 ng/mL. Serum PTX3 levels might be used as a marker to determine high-risk patients with acute myocardial infarction.

Limitation and Suggestion

There is some limitation of this study such as limited sample, no further follow-up after the patient discharged, no sub-group analysis and variation of timing when collecting blood samples for serum PTX3 levels. Further studies may recruit more sample that represent population with longer follow-up, so the exact prognostic significance of serum PTX3 may be useful.

Conflict of Interest

The authors declare that there is no conflict of interest.

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