Diagnostic and Prognostic Significance of Neutrophil Gelatinase-Associated Lipocalin and Pentraxin-3 in Acute Coronary Syndrome

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Abstract

Aim: The aim was to evaluate the levels of serum pentraxin-3 (PTX-3) and neutrophil gelatinase-associated lipocalin (NGAL) and the efficiency of making a diagnosis and to estimate the prognosis in patients with chest pain.

Materials and Methods: The study was conducted in the Necmettin Erbakan University Meram Medicine School Emergency Department. Patients who had chest pain and met the inclusion criteria were accepted. They were divided into the following groups: acute coronary syndrome (ACS), a diagnosis other than ACS (non-ACS), and control. The patients in theACS and non-ACS groups were divided into five sub-group -groups: ST Elevated Myocardial Infarction (STEMI) Non- ST Elevated Myocardial Infarction (NSTEMI), Unstable Angina Pectoris (USAP), stable angina, and pulmonary embolus. For all patients, serum PTX-3, serum NGAL, troponin I, and creatine kinase-MB fraction (CK-MB) levels were measured.

Results: There were 199 patients in the ACS and non-ACS groups and 30 patientsin the control group. There was no significant difference among the study groups in terms of age and PTX-3 and NGAL levels. When comparing survival and non-survival in terms of in-hospital death, CK-MB and troponin I levels were significantly higher in the ACS and non-ACS groups than in the control groups, whereas there was no significant difference in terms of PTX-3 and NGAL levels.

Conclusion: The results of our study demonstrated that PTX-3 and NGAL are not effective biomarkers in the differential diagnosis and the determination of in-hospital mortality in ACS. However, the limitations of the study should be considered. The results confirmed that CK-MB and Troponin I can be safely used in the differential diagnosis and the prediction of mortality.

Keywords: Acute coronary syndrome, biomarker, neutrophil gelatinase-associated lipocalin, pentraxin-3

Introduction

Chest pain is one of the main reasons for admission to emergency departments (EDs). Among patients with such admissions, 30% to 50% have acute coronary syndrome (ACS). Coronary artery disease (CAD) is the most common cardiovascular diseases and is related to high mortality rates (1, 2).

Chest pain-related admissions to EDs are important ongoing problem for physicians. Despite the clinical experience of physicians and presence of electrocardiogram (ECG) and biochemical parameters, 2%-5% of patients with ACS remain undiagnosed (3). Cardiac troponin is a highly sensitive and specific biomarker that demonstrates myocardial damage. However, it is not specific as high levels of it can also be detected in many clinical conditions (renal failure, gastrointestinal bleeding, respiratory disease, subarachnoid hemorrhage and ischemic stroke) other than ACS (4-8). In spite of this, cardiac troponins have recently been accepted as the gold standard biomarker in ischemic myocardial damage (9).

Pentraxin-3 (PTX-3) and neutrophil gelatinase-associated lipocalin (NGAL) are believed to be involved in the pathophysiology of ACS (10). It has been reported that PTX-3 is secreted from cardiomyocytes in cardiac ischemia and that it is anindicator of myocyte injury. PTX-3 has also been reported to appear with acute myocardial infarction (AMI), which reaches its peak level at the seventh hour, regresses within several days, and finally returns to its normal plasma level (11). NGAL has been shown to be primarily produced in neutrophils and

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subsequently in cardiomyocytes, and its levels are elevated in pathological conditions such as atherosclerosis (12-16).

The aim of this study was to investigate whether the new-generation biomarkers NGAL and PTX-3 have a diagnostic value superior to the routinely used biomarkers CK-MB and troponin I in patients suspected of having ACS and to determine the relationship of these biomarkers with hospital mortality rates.

Materials and Methods

The Ethics Committee of Necmettin Erbakan University Meram Medicine School approved this controlled prospective clinical study on January 3, 2014 (number, 2014-570). This study included 229 patients who met with the inclusion criteria, who had presented to the Necmettin Erbakan University Meram Medicine School Emergency Department (ED) with chest pain and equivalent complaints, and who were followed up with a pre-diagnosis of ACS in the ED.

Study groups

Group 1 included patients with ACS (including MI with ST segment elevation (STEMI), MI with non-STEMI (NSTEMI), and unstable angina pectoris (USAP)]; Group 2 included patients with a diagnosis other than ACS (non-ACS) (including pulmonary embolism and stable angina), and Group 3 was the control group, which included patients with a diagnosis other than ACS or non-ACS. The patients were consecutively enrolled. Cardiac biomarkers were evaluated between survival and non-survival groups.

Study protocol

Patients who had presented to the ED with chest pain and who had agreed to participate were physically examined by an emergency physician (EP) and underwent electrocardiography; then, they were taken to the chest pain unit (CPU) for follow-up. The investigators analyzed the patients who were taken to the CPU for compatibility with the inclusion criteria, informed the proper patients, and obtained their consents (Table 1). The demographic characteristics, contact information, and laboratory and radiological examinations requested by the EP were recorded. NGAL and PTX-3 levels of the patients were also determined. The patients were followed up, and their in-hospital clinical courses were recorded.

Table 1. Inclusion and exclusion criteria of patients in the study

A. Inclusion criteria
1. Patients who were ≥18 years of age
2. Patients who agreed to join the study
3. Admission to the ED with chest pain or equivalent complaints
B. Exclusion criteria
1. Female patients who were pregnant or breast feeding
2. Patients who were <18 years age
3. Patients who refused to join the study
4. Patients with a history of chronic renal failure
5. Patients who had a history of active or previous cancer
ED: emergency department

Biochemical evaluation

Having performed tests for the differential diagnosis of chest pain, the sera and plasma of the venous blood drawn at admission from the included patients were used as samples. Blood samples were centrifuged at 4000 g for 5 min. The blood samples to be analyzed for N-GAL and PTX-3 level were transferred into plastic and sealed Eppendorf tubes and storedat -80°C until biochemical analysis. On the day of analysis, they were obtained from the Eppendorf tubes and incubated at room temperature and analyzed. NGAL (Lot no: 5031059529) (Boster®, USA) and PTX-3 (Lot no: 5111059529) (Boster®, USA) levels were determined by ELISA using ELISA kits. An ELISA washer and a semi-automatic ELISA reader were used. CK-MB and troponinI levels were analyzed using a Beckman Coulter DXI 800 instrument by the chemiluminescence method.

Statistical analysis

The data obtained were analyzed using Statistical Package For Social Sciences version 16.0 (SPSS Inc.; Chicago, Illinois, ABD). Descriptive data are expressed as mean±standard deviation and percentage. Normally distributed data (parametric or non-parametric) were analyzed using the Kolmogorov-Smirnov Test. Non-normally distributed variables were expressed as median±the interval between quarters (25%-75%). The Mann-Whitney U and Kruskal-Wallis tests were used for the comparison of non-parametric variables. The chi-square test was used to determine the significance of the differences among the patient and control groups with regard to the demographic characteristics and comorbid situations. The Pearson test was used for correlation analysis. A p value of <0.05 was accepted as statistically significant.

Results

A total of 229 patients were included (Table 2). Their mean age was 60.48±14.84 years. A statistically significant difference was observed among the groups with regard to the mean age (p=0.001). The mean age in patients in Group 2 was lower than those patients in the other groups. Totally, 69% (n=158)of the patients were males and 31% (n=71) were females. No difference was observed amongthe groups with regard to gender distribution (p=0.353). The number of patients with an additional disease in Group 1 was significantly higher than that in the other groups (p=0.001). The number of patients with an atherosclerotic cardiac disease was significantly higher in Group 1 than in the other groups (p=0.013). No difference was observed among the groups with regard to the history of diabetes mellitus, hypertension, hyperlipidemia, and smoking (p=0.174, p=0.063, p=0.075, and p=0.431, respectively) (Table 2).

The patient group that was classified according to the diagnosis included 28% (n=55) NSTEMI, 28% (n=55) STEMI, 24% (n=48) stable angina, 16% (n=32) USAP, and 4% (n=9) pulmonary embolism. Sixteen (7%) patients included in the study died during the course of hospitalization, which was statistically significantly different among the study groups (p=0.024). The mortality rate in Group 1 was 10.6%, and no mortality was observed in Group 3 (Table 2).

A significant difference was observed among the groups with regard to NGAL, CK-MB, and troponin I levels (p<0.001, p<0.001, and p<0.001, respectively). However, no difference was observed among the groups with regard to PTX-3 levels (p=0.978) (Figure 1).

Paired comparisons were made among the groups. NGAL levels were determined to be significantly higher in Group 3 than in groups

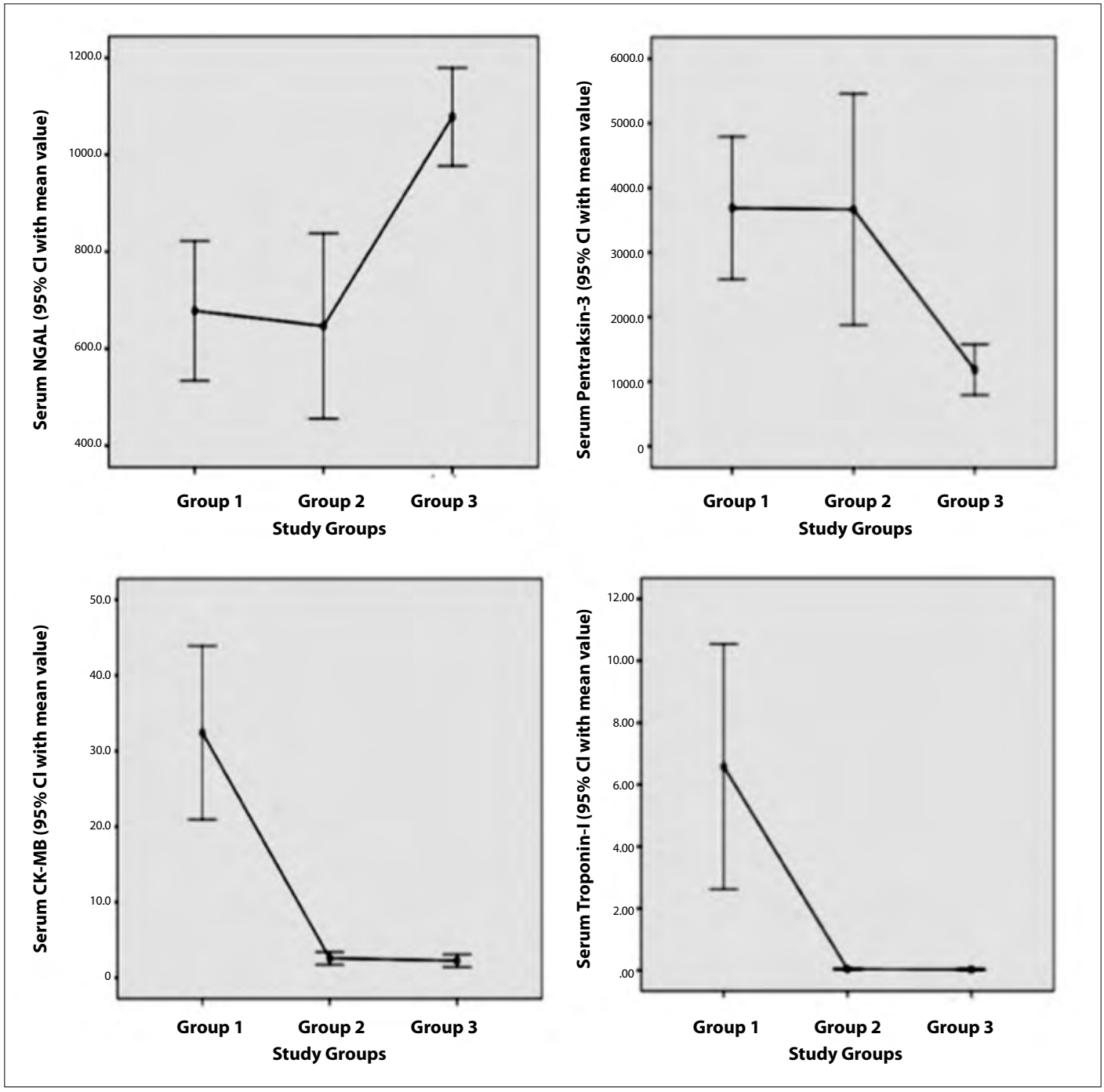

Figure 1. Comparison of the values of groups NGAL, pentraxin-3, CK-MB and troponin I

1 and 2 (p<0.001 and p=0.003, respectively). No difference was observed between groups 1 and 2 with regard to NGAL level (p=0.270). CK-MB levels were significantly higher in Group 1 than group 2 and 3 (p<0.001). No difference was observed between groups 2 and 3 with regard to CK-MB levels (p=0.810). Troponin I levels were significantly higher in Group 1 than in groups 2 and 3 (p<0.001 and p<0.001, respectively). No difference was observed between groups 2 and 3 with regard to Troponin I levels (p=0.675) (Table 2).

The study groups were classified as "survival" and "non-survival" groups according to in-hospital mortality (Table 3). The mean age of the patients in the non-survival group was significantly higher (p<0.001). No difference was observed between the groups with regard to gender or comorbidity (p=0.560 and p=0.540, respectively). No difference was observed between the groups with regard to NGAL and PTX-3 levels, whereas a significant difference was determined for CK-MB and troponin I levels, which were higher in the non-survival group (p=0.547 and p=0.973 vs. p=0.001 and p<0.001, respectively) (Table 3).

When the cardiac biomarkers were evaluated with regard to correlation, a significant correlation was observed only between CK-MB and troponin I (r=0.723, p<0.001). No correlation was determined between the other biomarkers (NGAL and PTX-3).

Table 2. Distribution of gender, age, comorbidities results among the study groups

Groups Parameters	All Groups (n=229)	Group 1 (n=142)	Group 2 (n=57)	Group 3 (n=30)	p
Age (Mean value±standart deviation)	60.48±14.84	63.11±13.67	53.82±15.78	60.67±14.82	0.001
Gender[α]					
Male	158 (69)	102 (71.8)	35 (61.4)	21 (70)	0.353
Female	71 (31)	40 (28.2)	22 (38.6)	9 (30)	
Comorbidity[α]					
Yes	156 (68.1)	109 (76.8)	33 (57.9)	14 (46.7)	0.001
No	73 (31.9)	33 (23.2)	24 (42.1)	16 (52.3)	
ASCD[α]					
Yes	101 (44.1)	70 (49.3)	25 (43.9)	6 (20)	0.013
No	128 (55.9)	72 (50.7)	32 (56.1)	24 (80)	
DM α					
Yes	37 (16.2)	28 (19.7)	6 (10.5)	3 (10)	0.174
No	192 (83.8)	114 (80.3)	51 (89.5)	27 (90)	
Hypertension[α]					
Yes	97 (42.4)	68 (47.9%)	21 (36.8%)	8 (26.7%)	0.063
No	132 (57.6)	74 (52.1%)	36 (63.2%)	22 (73.3%)	
Hyperlipidemia[α]					
Yes	27 (11.8)	22 (15.5)	4 (7)	1 (3.3)	0.075
No	202 (88.2)	120 (84.5)	53 (93)	29 (96.7)	
Cigarette smoking[α]					
Yes	69 (30.1)	45 (31.7)	18 (31.6)	6 (20)	0.431
No	160 (69.9)	97 (68.3)	39 (68.4)	24 (80)	
In-hospital mortality[α]					
Survival	213 (93)	127 (89.4)	56 (98.2)	30 (100)	0.024
Non-survival	16 (7)	15 (10.6)	1 (1.8)	0 (0)	
Biomarkers[β]					
NGAL	223 (33.5-4974.4)	171.55 (33.5-4974.4)	211.1 (39.6-3012.8)	1099.64 (513.7-1568.6)	<0.001
PTX-3	707.75 (13.7-21.000)	709.51 (13.7- 21.000)	705.98 (18.9-21.000)	916.46 (308-4789.3)	0.978
CK-MB	2.6 (0.2-299)	4.2 (0.6-299)	1.8 (0.2-20.5)	1.6 (0.8-13.1)	<0.001
Tn-I	0.03 (0.01-198)	0.14 (0.01-198)	0.01 (0.01-0.51)	0.01 (0.01-0.4)	<0.001

ASCD: atherosclerotic cardiac disease; CK-MB: creatine kinase-MB fraction; DM: diabetes mellitus; NGAL: neutrophil gelatinase associated lipocalin; PTX-3: pentraxin3; Tn-I: troponinI
[α]Described by number (n) and percentage (%)
[β]Described by median value (minimum-maximum values)

The ROC curve of NGAL revealed an area under the curve (AUC) value of 0.729 (p<0.001) (Figure 2). The sensitivity, specificity, and accuracy of NGAL were 62%, 35%, and 54%, respectively, when the optimal threshold value was accepted as 502.1 ng/mL.

Discussion

Despite advances in the diagnosis and treatment of ACS, the mortality, hospitalization, and recurrent infarction rates among patients with ACS remain high (2). Many biomarkers are being used and tested to perform risk analysis for diagnosing ACS that would result in early treatment. Cardiac troponins have high sensitivity and specificity in the diagnosis of myocardial injury. It should not be forgotten that cardiac troponins are currently used as the gold standard. However, an elevation in their levels may be observed in many situations other than cardiac events (17). In light of this information, new biomarkers are required.

One of the important risk factors for ACS is age. The mean ages of patients were 62.6±13, 62.1±12, and 62.83±12.9 years in the studies by Leurent et al. (19), Ariza-Sole et al. (18), and Salama

Table 3. Comparison of serum biomarkers between survival and non-survival groups according to the in-hospital mortality

Groups Parameters	Survival group (n=213)	Non-survival group (n=16)	p
Age (Mean value± standard elevation)	59.25±14.40	76.81±10.48	<0.001
Gender[α]			
Male	148 (69.5)	10 (62.5)	0.560
Female	65 (30.5)	6 (37.5)	
Comorbidity[α]			
Yes	144 (67.6)	12 (75)	0.540
No	69 (32.4)	4 (25)	
Biomarkers[β]			
NGAL	226.3 (33.5-4974.4)	221.3 (51.6-2317.5)	0.547
PTX-3	714.79 (13.7-21000)	616.2 (113.5-21000)	0.973
CK-MB	2.5 (0.2-299)	24.55 (1.9-238.6)	0.001
Tn-I	0.02 (0.01-198)	4.44 (0.01-100)	<0.001

CK-MB: creatine kinase-MB fraction; NGAL: neutrophil gelatinase-associated lipocalin; PTX-3: pentraxin3; Tn-I: troponin I
[α]Described by number (n) and percentage (%)
[β]Described by median value (minimum–maximum values)

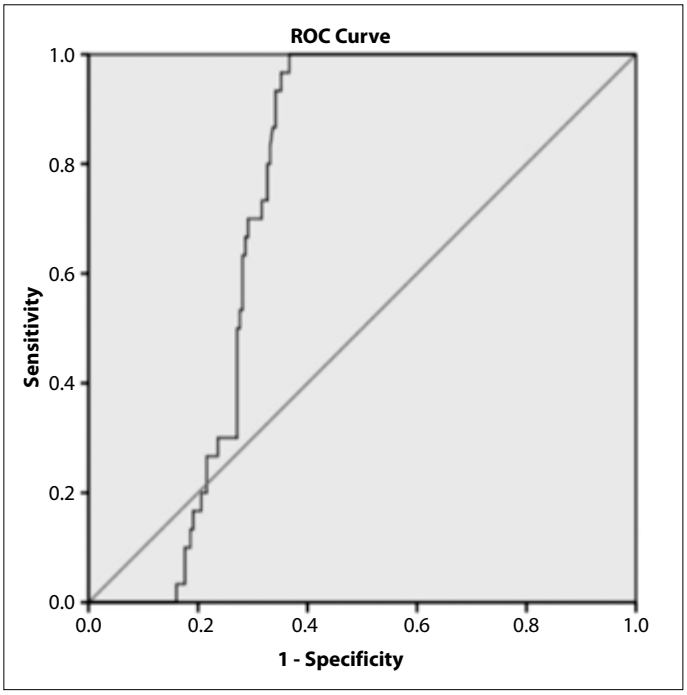

Figure 2. The ROC Curve of NGAL

et al. (20), respectively. In our study, the mean age of the patients was 63.11±13.67 years, which was similar to those reported in the literature.

Various rates of STEMI, NSTEMI, and USAP have been reported in case series published in the literature. In a study including patients presenting to the emergency unit with a complaint of chest pain, 41% of patients had NSTEMI and STEMI, 27% had USAP, and 32% had non-cardiac chest pain; in another study, one-third of the patients with ACS had STEMI and the remaining had NSTEMI and USAP (21, 22). In other studies, various rates have been reported for patients with ACS, such as 54%-61% in NSTEMI and 33%-45.6% in STEMI (20, 23, 24). In our study, 39% of the patients with ACS had NSTEMI, 39% had STEMI, and 22% had USAP.

Hasdai et al. (25) reported the coronary cardiac disease-related mortality rate to be 20% in the 35-55-year age group. In another study, the in-hospital mortality rate among patients with ACS was 4% (26). In another study investigating mortality rates in ACS, the in-hospital mortality rate was 20% for those having STEMI and 10% for those having NSTEMI (27). In our study, the in-hospital mortality rates were 7.2% and 6.3% for patients having STEMI and NSTEMI, respectively.

PTX-3 is an acute-phase reactant that has recently been discovered. Atherosclerosis is known to develop as a reason for an inflammatory process. It was determined that endothelial cells and macrophages are involved in the basic formation of atherosclerosis and that PTX-3 is secreted from atherosclerotic lesions (28). In the study by Matsui et al. (29), elevated serum PTX-3 levels were related to USAP, STEMI, NSTEMI, cardiac failure, and negative cardiovascular events. Ustundag et al. (30) determined the sensitivity and specificity of PTX-3 levels analyzed within the first 6 h to be 98.5% and 92.3%, respectively, in patients with ACS. Buyukkaya et al. (31) investigated PTX-3 levels in patients with cardiac syndrome X and determined a significantly higher PTX-3 level in the study group than in the control group. In many studies conducted on patients with vascular diseases, mortality was seen to have correlated to elevated PTX-3 levels (32, 33). In the study by Latini et al. (32), elevated PTX-3 levels have been suggested to be related to 3-month mortality in patients with MI. However, in our study, serum PTX-3 levels observed in the groups were investigated with regard to the diagnosis and in-hospital mortality, and no significant difference was observed.

Risk factors and correlations for leukocyte activation in atherosclerosis have also been reported in a study, a correlation has been demonstrated between symptomatic cardiovascular diseases and elevated NGAL levels; on the contrary, plasma NGAL levels and non-symptomatic cardiovascular diseases have been demonstrated to be not correlated (34). In another study, the group of patients with CAD confirmed via angiography was compared to the groups of patients with normal coronary arteries, and serum NGAL levels were found to be significantly elevated in the presence of CAD (35). In a similar study, 47 patients with NSTEMI confirmed via angiography were compared to 45 control patients with stable angina (having undergone coronary angiography and determined to have normal coronary arteries), and NGAL levels were positively correlated to lesion complexity and the diffusiveness of CAD in patients with NSTEMI. It was concluded that serum NGAL levels on admission are related to the increased atherosclerotic load in patients with Non-ST elevated Acute Coronary Syndrome(NSTE-ACS)(36).

In the study by Choi et al. (37), serum NGAL levels were determined to be significantly higher in patients with CAD than in the healthy population. Similarly in another study, serum NGAL levels showed an increasing tendency in CAD and AMI, although this was not significant. In the study by Arslan et al. (38) that compared patients with stable CAD and AMI, significantly higher plasma NGAL

levels were detected in the AMI group; however, no difference was found between STEMI and NSTEMI. It was concluded that NGAL NGAL levels are more successful indicator in detecting MI than other inflammatory markers. In our study, NGAL levels were significantly lower in the ACS and non-ACS patient groups (Group 1 and 2) than in the control group, and no difference was detected between the ACS and non-ACS groups.

According to the risk classification of the American College of Cardiology/American Heart Association, a cardiac troponin I level between 0.1 and 1.5 ng/mL indicates a moderate risk, and a level over 1.5 ng/mL indicates a high risk in patients with NSTEMI (39). In another study, troponin levels were observed to increase within 2-3 h after admission to the ED in 80% of patients with MI, and the levels of CK-MB and other cardiac biomarkers were found to start increasing within 6-9 h (40). Similarly, in our study, CK-MB and troponin I had an elevated course in the patient group (group 1 patients), which was statistically significant.

Study limitations

Our study was a single-center prospective study. The control group included patients who had presented to our emergency unit with complaints other than chest pain and whose diagnosis did not comprise chest pain in the differential diagnosis. The amount of time between the onset of chest pain and the time of blood sampling could not be determined. The number of patients was also limited.

Conclusion

In conclusion, the data obtained in our study indicate that NGAL and PTX-3 are not effective biomarkers in the differential diagnosis of chest pain or the prediction of mortality in ACS. This conclusion should be evaluated considering the limitations of our study. The outcomes obtained in this study confirm the use of CK-MB and troponin I, which are used in daily practice, as reliable biomarkers in the differential diagnosis and in the prediction of mortality.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Necmettin Erbakan University Meram School of Medicine (03.01.2014, Decision No: 2014-570).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the authors.

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