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Long-Term Prognostic Value of Procalcitonin Level in Patients with Acute ST Segment Elevation Myocardial Infarction

Akut ST Segment Yükselmeli Miyokard Infarktüsü Olan Hastalarda Prokalsitonin Düzeyinin Uzun Dönem Prognostik Değeri

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ABSTRACT

Objective: Previous studies have suggested that there is a relationship between coronary artery disease (CAD) and procalcitonin (PCT) levels. We aimed to evaluate the relationship between PCT levels and long-term major adverse cardiovascular events (MACE) and all-cause mortality in patients with ST segment elevation myocardial infarction (STEMI).

Method: Patients were divided into two groups based on their serum PCT values. Patients with PCT levels <0.05 ng/ml were accepted as low PCT group (n=235) and those with PCT levels >0.05 ng/ml as high-PCTgroup (n=87). MACE were defined as cardiovascular mortality, reinfarction, or target vessel revascularization (TVR). MACE and all-cause mortality were retrospectively screened from their files during the mean follow-up of 55 months of the patients included in the study. Demographic and laboratory values were recorded in SPSS.

Results: MACE and all-cause mortality were found to be significantly higher in the high-PCT group than in the low-PCT group (p=0.003 and p=0.002, respectively). In multivariate analysis, high PCT levels and age were identified as significant independent predictors of long-term all-cause mortality after adjusting for other risk factors. Moreover, white blood cell, C-reactive protein, glucose, and Hemoglobin A1c were higher in the high-PCT group.

Conclusion: High PCT levels during hospitalization in patients with STEMI are associated with long-term MACE and all-cause mortality. Although PCT is widely used in infectious diseases, it is an ideal inflammation marker for long-term adverse outcomes in patients with STEMI.

Keywords: major adverse cardiac events, all-cause mortality, procalcitonin, STEMI

ÖZ

Giriş: Önceki çalışmalar, koroner arter hastalığı (KAH) ile prokalsitonin (PCT) seviyeleri arasında bir ilişki olduğunu göstermişti. ST segment yükselmeli miyokard infarktüsü (STEMI) olan hastalarda PCT düzeyleri ile uzun dönem majör kardiyovasküler olaylar (MACE) ve tüm nedenlere bağlı mortalite arasındaki ilişkiyi değerlendirmeyi amaçladık.

Yöntem: Hastalar serum PCT değerlerine göre iki gruba ayrıldı. PCT düzeyi <0.05 ng / ml olan hastalar düşük PCT grubu (n=235) ve PCT düzeyi> 0.05 ng / ml olanlar yüksek PCT grubu (n=87) olarak kabul edildi. MACE, kardiyovasküler mortalite, reinfarktüs veya hedef damar revaskülarizasyonu (TVR) olarak tanımlandı. Çalışmaya dahil edilen hastaların ortalama 55 aylık takip süreleri boyunca MACE ve tüm nedenlere bağlı mortalite geriye dönük olarak dosyalarından tarandı. Demografik ve laboratuvar değerleri SPSS'ye kaydedildi.

Bulgular: MACE ve tüm nedenlere bağlı mortalite, yüksek PCT grubunda düşük PCT grubuna göre anlamlı olarak daha yüksek bulundu (sırasıyla p=0.003 ve p=0.002). Çok değişkenli analizde, yüksek PCT seviyeleri ve yaş, diğer risk faktörleri için ayarlama yapıldıktan sonra uzun vadeli tüm nedenlere bağlı ölümlerin anlamlı bağımsız prediktörleri olarak tanımlandı. Ayrıca, yüksek PCT grubunda beyaz kan hücresi, C-reaktif protein, glukoz ve Hemoglobin A1c daha yüksekti.

Sonuç: STEMI'li hastalarda hastaneye yatış sırasında yüksek PCT seviyeleri, uzun süreli MACE ve tüm nedenlere bağlı mortalite ile ilişkilidir. PCT, enfeksiyon hastalıklarda yaygın olarak kullanılmasına rağmen, STEMI'li hastalarda uzun vadeli olumsuz sonuçlar için ideal bir inflamasyon belirtecidir.

Anahtar Kelimeler: başlıca olumsuz kardiyak olaylar, tüm nedenlere bağlı mortalite, prokalsitonin, STEMI

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INTRODUCTION

Inflammation plays a crucial role in the pathophysiology of every step of atherosclerosis. During the atherogenesis process, many inflammatory mediators are released, which may be an indicator of atherosclerosis burden. Research has shown that one of these inflammatory mediators, procalcitonin (PCT), has a role in atherogenesis (1, 2). Procalcitonin (PCT) is an established biomarker for the diagnosis of sepsis. There is increasing evidence that PCT concentration is associated with atherosclerosis and coronary artery disease (CAD).

Procalcitonin, a 13-kDa protein, is an inflammatory marker that is involved in 116 amino acids and is physiologically synthesized by the C-cells of the thyroid gland and pulmonary neuroendocrine cells (3). Procalcitonin (PCT) is used for many clinical conditions, such as controlling the success of treatment, measuring the activity of the systemic inflammatory response, and predicting prognosis (4). An increase of PCT concentrations occurs in patients with sepsis, cardiogenic shock, and trauma. Further bacterial endotoxins and proinflammatory cytokines induce (5).

Recent studies have found that PCT levels were correlated with the extent of atherosclerosis in patients with coronary artery disease (CAD) and were even associated with adverse outcomes (6-10). In this study, the relationship between PCT levels in long-term cardiovascular adverse events and all-cause mortality are investigated in patients admitted to our center with STEMI.

METHODS

This retrospective study enrolled a total of 322 patients consisting of 44 women and 278 men with an average age of 54.06 ± 12.1 who had been admitted to the Mehmet AkifErsoy Thoracic and Cardiovascular Surgery Training and Research Hospital Coronary Intensive Care Unit between February 2012 and April 2012. All the patients included in this study had been diagnosed with ST segment elevation myocardial infarction (STEMI) and taken to the catheter room for primer or rescue percutaneous coronary intervention (PCI). The inclusion criteria were as follows: (1) presentation within 12 h (18 h for cardiogenic shock) of the onset of symptoms (typical chest pain lasting for > 30 min), (2) increased serial serum markers of myocardial damage > 2-fold over the upper normal range for creatine kinase (CK) and troponin I, (3) ST-segment elevation of at least 2 mm in at least two contiguous electrocardiographic (ECG) leads or new onset of complete left bundle branch block, and (4) treatment by primary PCI (angioplasty and/or stent deployment). The exclusion criteria were active or chronic inflammatory disease or clinical evidence of active infection.

On admission, venous blood was obtained from all patients. Biochemistry measurements were carried out by our biochemistry department using standard methods. Twelve-hour fasting serum levels of total cholesterol, triglyceride, low-density lipoprotein (LDL) and high-density lipoprotein cholesterol (HDL) were measured with standard enzymatic methods.Serum procalcitonin (PCT) level was measured using the enzyme-linked fluorescent assay (ELFA) method from a specific PCT kit on mini-VIDAS equipment (VIDAS® B.R.A.H.M.S PCT™, BioMérieux's Diagnostics, Marcy l'Etoile, France). Serum procalcitonin (PCT) levels of the patients were evaluated 48 hours after admission.

At admission, medical history and a special questionnaire on lifestyle and risk factors were taken from each patient. Patients with diabetes mellitus were identified on admission as those with documented diabetes mellitus using either oral hypoglycemic agents or insulin treatment. Hypercholesterolemia was defined as total cholesterol at least 200mg/dl. A positive family history for coronary artery disease (CAD) was defined as documented evidence of CAD in a parent or sibling before the age of 60 years. Hypertension was defined as the previous use of antihypertensive medications, a systolic pressure more than 140mmHg or a diastolic pressure more than 90mmHg for at least two separate measurements. Smoking was defined as the current regular use of cigarettes. Body Mass Index was calculated as the weight in kilograms divided by the square of the height in meters. ECGs, laboratory parameters, demographic data and treatment

modalities of the patients included in the study have been obtained from patient files registered with the hospital's archives.

All patients underwent PPCI within at most 12 h after the onset of chest pain and received 300 mg of chewable aspirin, 600 mg of clopidogrel, and intravenous heparin at a dose of 12 μ/kg before beginning the procedure. After the procedure, all patients received twice-daily doses of 1 mg/kg enoxaparin SC, 100 mg acetylsalicylic acid, and 75 mg clopidogrel. After stenting, patients were evaluated based on thrombolysis in myocardial infarction (TIMI) flow grades. TIMI flow grades below 3 were defined as "no reflow."

Electrocardiography (ECG) was performed on admission and immediately after and 90 min after the procedure. On ECG, no reflow was defined as < 75% resolution of the ST segment at the end of the procedure compared with baseline. Left ventricular ejection fraction (LVEF) was measured by transthoracic echocardiographic examination within the first 24 h after admission using the biplane Simpson method. Patients were divided into two groups: high (n = 87) and low (n = 235) 48-h PCT. PCT was defined as high when it was above 0.05 ng/ml.
Major adverse cardiovascular events (MACE) and all-cause mortality were retrospectively screened from their files during the mean follow-up of 55 months of the patients included in the study. Cardiovascular mortality was defined as unexplained death, death from myocardial infarction (MI), heart failure, or arrhythmia. MACE were defined as cardiovascular mortality, reinfarction, or target vessel revascularization (TVR). Reinfarction was defined as an increase in the CK-MB enzyme levels of twice the upper limit of normal and ST-segment re-elevations.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows (version 17.0; SPSS Inc, Chicago, Illinois, USA). A P value less than 0.05 was considered statistically significant. Qualitative variables were expressed as percentages (%), and quantitative variables were expressed as mean value standard deviation (SD). The parametric values were compared between the two groups with the two-tailed Student's t-test. Categorical variables were compared with the likelihood-ratio chi-square or Fisher's exact test. A backward stepwise multivariate Cox regression analysis, which included variables with p value less than 0.1, was performed to identify independent predictors of long-term all-cause mortality. The cumulative survival curve for all-cause mortality was constructed using the Kaplan–Meier method, with differences assessed using log-rank tests.

RESULTS

The clinical and demographic characteristics of both groups are listed in Table 1. Diabetes mellitus was more common in the high-PCT group (p=0.008). The admission Killip class was more than 1 (p<0.001) and the duration of hospital stay (p=0.005) was significantly higher in the high-PCT group. Postprocedure TIMI 3 flow was significantly lower in the high-PCT group (p=0.049). These data indicate that major adverse cardiac events are seen more often in patients with myocardial infarction and high PCT levels. Other outcomes were similar between groups.

Table 2 shows the laboratory findings for both groups. White blood cell (WBC), C-reactive protein (CRP), admission glucose, Hemoglobin A1c, and peak CK-MB values were significantly higher in the high-PCT group. Other laboratory results were similar between groups.

Table 3 shows the long-term MACE and all-cause deaths. Median follow-up time was 55 months. All-cause deaths were detected in 12 patients (13.8%) in the high-PCT group and in 14 patients (6%) in the low-PCT group. It was determined that the relationship between high PCT level and all-cause mortality was statistically significant (p=0.002). There was a statistically significant difference in MACE rates between the two groups. The number of patients with MACE in the low-PCT group was 51 (21.7%), and the number was 33 (37%) in the high-PCT group (p=0.003).

Table 1: Baseline Characteristics of Study Patients						
		Low PCT group		Low PCT group		P
		n	%	n	%	
Age (years)		53.5±12.2		55.6±12.1		0.17
Gender	Male	201	85.5	77	88.5	0.49
	Female	34	14.5	10	11.5	0.61
Diabetes Mellitus		78	33.2	43	49.4	0.008
Hypertension		90	38.3	40	46.0	0.223
Current Smoker		132	56.2	51	58.6	0.69
Previous History CAD		9	3.8	2	2.3	0.24
Family History CAD		46	19.6	18	20.7	0.82
Hyperlipidemia		11	50	38	43.7	0.297
Body Mass Index		27.9± 4.3		28.37 ± 5.5		0.592
Pain-To-Balloon Time		203.85 ± 218.4		293.0 ± 400.2		0.154
Door-To-Balloon Time		56.62± 67.28		46.28 ± 41.1		0.50
Discharge Time		77.57 ±57.18		125.5 ±112.86		0.005
Killip Class >1		44	18.7	29	33.3	<0.001
Left ventricular ejection fraction		48.6± 8.8		47.2 ± 8.7		0.93
Post TIMI 3 flow		226	96.1	77	88.5	0.049
Infarct Related Artery	Left Anterior Descending	116	49.4	40	46	0.425
	Circumflex	36	15.3	12	13.8	
	Right	77	33	30	34.5	
	Other (Im.Om)	6	2.6	4	4.6	
	None	0	0	1	1.1	

Mean values (standart deviation) and % (n) are reported for continuous and categorical variables respectively. CAD : coronary artery disease.

Table 2: Laboratory Findings of Patients			
	Low PCT group (n:235)	High PCT group (n:87)	p
Uric Acid (mg/dl)	5.31±1.48	5.97±1.63	0.67
Platelet (×10^9/L)	270.1±67.9	268.8±104.5	0.135
WBC (×10^9/L)	11.13±2.79	13.5±4.9	<0.001
Creatinine (mg/dL)	0.85±0.2	1.08±1.27	0.093
C-Reactive Protein (mg/L)	21.8±26.7	76.5±84.4	<0.001
RDW	12.8±1.1	13.2±1.09	0.323
Peak Troponin I (ng/ml)	22.2±18.74	31.15±19.0	0.622
Total Cholesterol (mg/dl)	196.7±45.6	186.6±43.9	0.91
LDL (mg/dl)	130.9±36.4	120.8±30.0	0.366
HDL (mg/dl)	41.3±15.4	37.6±10.6	0.678
Triglyceride (mg/dl)	148.2±94.2	146.7±95.0	0.840
Glucose (mg/dL)	146.1±60.7	178.0±111.4	0.013
Hemoglobin, (g/dL)	14.3±1.6	14.1±1.9	0.08
Hemoglobin A1c	6.4±1.58	6.88±1.94	0.04
MPV (fl)	8.74±0.91	8.71±0.97	0.85
Peak CK-MB	52.62±74.84	85.16±102.72	0.042
Glomerular filtration rate	101.4±28.5	92.6±28.2	0.88

Mean values (standart deviation) are reported for continuous, RDW : Red cell distributation rate, LDL : Düşük dansiteli lipoprotein, HDL : Yüksek dansiteli lipoprotein, MPV : Mean Platelet Volume.

Table 3: All-Cause Mortality and Major Adverse Cardiac Events					
	Low PCT group (n:235)		High PCT group (n:87)		P Value
	n	%	n	%	
All- Cause Mortality	14	6	12	13.8	0.002
MACE	51	21.7	33	37	0.003
PCT : Procalcitonin, MACE : Major adverse cardiac events.					

The Kaplan–Meier survival plot for all-cause mortality at 55 months follow-up in both groups is presented in Figure 1. Long-term all-cause mortality was 13.8% in the high-PCT group and 6% in the low-PCT group, and there was a statistically significant difference (log rank, p = 0.024).

We conducted a univariate and multivariate analysis to identify factors associated with long-term all-cause mortality. The independent predictors for all-cause mortality, including age, gender, hemoglobin, and PCT group, were included in a Cox regression model and analyzed in a stepwise fashion. In the multivariate analysis, the high-PCT group (odds ratio=2.619 [1.058–6.481], *p*=0.037) and age (odds ratio=1.109 [1.059–1.162], *p*=0.001) were found to be significant independent predictors of long-term all-cause mortality (Table 4).

DISCUSSION

In this study, MACE and all-cause mortality were found to be significantly higher in the high-PCT group than in the low-PCT group. In the multivariate analysis, high PCT levels and age were found to be significant independent predictors of long-term all-cause deaths after adjustment for other risk factors. To the best of our knowledge, our study is the longest follow-up study evaluating the effect of high PCT on all-cause mortality and MACE in STEMI patients.

The prevalence of atherosclerosis in patients with CAD and peripheral artery disease is associated with increased PCT levels (11). In a study, it was shown that serum PCT and CRP levels increased in patients with acute coronary syndrome (12). In recent studies, high PCT levels were found to correlate with the extent of atherosclerosis in patients with CAD and were even associated with adverse outcomes (6-10).Post-myocardial infarction risk assessment plays an important role in choosing treatment regimen and predicting prognosis.

Procalcitonin has been used as a characteristic inflammatory marker for early atherosclerosis (6). PCT production can be induced by various stimuli, including polytrauma, burn injuries and surgery with tissue injury. This nonspecific and noninfectious stimulation of PCT is much lower than that of other markers of the inflammatory response. PCT release is associated with a generalized increase in calcitonin-1 gene expression and a consecutive release of PCT from parenchymal tissues and differentiated cell types throughout the body (13,14), but not from circulating leucocytes and peripheral mononuclear cells (15). Human-induced adipose tissue contributes to serum PCT elevation from inflammation and sepsis.In co-culture experiments, stimulated human macrophages were able to induce calcitonin messenger ribonucleic acid (mRNA) in adipocytes (16). Endotoxin and interleukin-(IL-) 1β induce PCT production. Human mesenchymal cells produced from mature adipocytes are the primary location for this production. Several other proinflammatory mediators, such as tumor necrosis

Table 4: The independent predictors of all-cause mortality						
	Univariate			Multivariate		
	OR	CI	P	OR	CI	P
High PCT group	2.526	1.119-5.702	0.026	2.619	1.058-6.481	0.037
Age	1.113	1.070-1.158	0.001<	1.109	1.059-1.162	0.001
Male Sex	3.210	1.301-7.917	0.011			
Hemoglobin (g/dl)	0.709	0.580-0.867	0.001			
OR : odds ratio, CI : confidence interval, PCT : Procalcitonin						

factor-α (TNF-α), interleukin-2(IL-2), and interleukin-6 (IL-6), stimulate PCT production, which might explain why PCT is elevated in noninfected patients after an insult leading to a systemic inflammatory response, such as cardiac arrest, atherosclerosis, and major surgery (17-19).

Under the inflammatory situation, PCT tends to rise rapidly within the first 3–4 hours after the event's onset, peaks in the 6–12 hours, following a decrease after 24 hours and normalization within five days (20-21). In our study, serum PCT levels of the patients were evaluated 48 hours after their hospitalization. In the high PCT group, inflammation markers such as WBC and CRP, as well as admission glucose, Hemoglobin A1c and peak CK-MB values were significantly higher. This supports the conclusion that PCT may be a marker for inflammation in STEMI. Admission killip class was higher than 1 and hospital stay was significantly higher in the high-PCT group. Postprocedure TIMI 3 flow was significantly lower in the high-PCT group. These signs indicate that MACE are more common in patients with myocardial infarction and high PCT levels.

A study in a group of patients with ACS showed that increased PCT within the first 48 hours after hospitalization may be associated with higher early and six-month mortality rates (6). In patients recovering from acute myocardial infarction (AMI), the PCT correlated with the MACE ratio, LV dysfunction, and the remodeling process (7).In a study of a large patient population with CAD, although not as superior to CRP, PCT was correlated with higher cardiovascular mortality (22). In a large prospective study with no previous history of cardiovascular disease, it showed a significant association between PCT levels and the rate of coronary events and cardiovascular mortality (19). In the present study, a significant relationship was found between high PCT levels and MACE and all-cause mortality in STEMI patients during long-term follow-up (55 months–4.6 years). This result was consistent with the results in the literature (6-9).

A recent study found increased PCT levels in ACS (23). PCT values increase less in unstable angina and NSTEMI than in STEMI. PCT levels in ACS diseases are related to the degree of atherosclerosis and the severity of the inflammatory process that occurs. However, another study found that the second 24-hour serum PCT level after hospitalization according to the Gensini score in patients with NSTEMI did not correlate with the severity and extension of CAD (24). Our study was in STEMI patients and predicted long-term prognosis. In the multivariate analysis, high PCT levels and age were identified as significant independent predictors of long-term all-cause mortality after adjusting for other risk factors.The presence of markers that predict early mortality will be effective in directing treatment and preventing possible adverse events.

Limitations of the Study

The limitations of this study are its single-center retrospective approach and the relatively low number of cases. Although this study examined inflammatory markers such as WBC and CRP, it did not examine valuable markers such as TNF-α and IL-6. A multicenter prospective approach and randomized studies are needed to confirm our findings.

Conclusion

Inflammation plays an important role in the development and progression of atherosclerosis. Because, PCT is a well-defined acute inflammatory response marker of atherosclerosis, early detection of serum elevation in STEMI patients provides important information about long-term MACE and all-cause mortality. Although PCT is widely used in infectious diseases, it is an ideal marker for the diagnosis and prognosis of acute and chronic coronary artery diseases.

Conflict of interest
Authors state no conflict of interest regarding the manuscript.

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Ethics Committee Approval
The local ethics committee approved this study (3-02-2017, no:41).

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