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ARAŞTIRMA / RESEARCH

Biyobelirteçler, koroner arter hastalığının şiddetini gösterebilir mi?

Can biomarkers indicate the severity of coronary artery disease?

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Abstract

Purpose: Biomarkers are useful measures assisting the diagnosis, treatment, and prognosis of cardiovascular diseases. They can predict the severity of cardiovascular diseases, especially in acute myocardial infarction at the emergency department. We aimed to investigate the severity of cardiovascular disease using three biomarkers, namely cardiac troponins, C-reactive protein (CRP), and procalcitonin in patients with ST-elevation myocardial infarction who presented to the emergency department.

Material and Methods: The study included a total of 166 patients that presented with ST-elevation myocardial infarction (STEMI) in the first three hours of symptom onset and underwent coronary angiography. SYNTAX (SS) scores were calculated, and based on these scores, two groups were formed. High-sensitivity troponin T (Hs-TnT), high-sensitivite CRP (Hs-CRP), and procalcitonin levels were measured at the presentation.

Results: Although the high sensitive troponin, Hs-CRP values were higher in the SYNTAX score>20 groups, there was no statistically significant difference between the two groups. There was no significant difference in the PCT measurements between the two groups

Conclusion: When Hs-TnT and Hs-CRP are evaluated together in patients with STEMI with a high SS, it may be predictive in early determining the severity of coronary artery disease.

Keywords: Biomarker, myocardial infarction, SYNTAX

Öz

Amaç: Biyobelirteçler kardiyovasküler hastalıkların teşhisi, tedavisi ve prognozunu tayin etmede önemlidir. Acil serviste özellikle akut miyokard enfarktüsünde kardiyovasküler hastalıkların ciddiyetini tahmin edebilirler. Bu çalışmada acil servise başvuran ST elevasyonlu miyokard enfarktüsü tanısı olan hastalarda kardiyovasküler hastalıkların şiddetini kardiyak troponinler, C-reaktif protein (CRP) ve prokalsitonin olmak üzere üç biyobelirteç kullanarak araştırmayı amaçladık.

Gereç ve Yöntem: Çalışmaya ST elevasyonlu miyokard enfarktüsü tanısı alan semptomlarının ilk 3 saati içerisinde başvuran ve koroner anjiografi yapılan 166 hasta alındı. SYNTAX (SS) skoruna göre hastalar iki gruba ayrıldı. Başvuru sırasında ölçülen Hs-troponin T, Hs-CRP ve prokalsitonin düzeyleri ölçüldü.

Bulgular: SYNTAX skoru 20 nin üstünde olan grupta Hs-troponin ve Hs-CRP düzeyleri yüksek olmasına rağmen iki grup arasında istatistiksel olarak anlamlı fark saptanmadı. İki grup arasında prokalsitonin düzeyleri açısından istatistiksel olarak anlamlı fark saptanmadı.

Sonuç: SYNTAX skoru yüksek olan ST elevasyonlu miyokard enfarktüs geçiren hastalarda Hs-troponin T ve Hs-CRP birlikte değerlendirildiğinde, erken dönemde koroner arter hastalığının şiddetini belirlemede öngörücü olabilir.

Anahtar kelimeler: Biyobelirteç, miyokard enfarktüs, SYNTAX

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INTRODUCTION

Cardiovascular disease is widespread in both men and women and is one of the leading causes of death. It accounts for 30% of total deaths worldwide, including 40% of those seen in high-income countries and about 28% in developing countries[1]. In addition to ischemic symptoms, changes in the electrocardiogram, and combinations of elevated serum biomarkers are used to diagnose acute coronary syndrome (ACS)[2]. Elevated troponin levels also guide the diagnosis and prognosis of ACS. Many studies have shown the association of short- and long-term mortality, adverse cardiovascular events, and all-cause mortality with the maximum peak level of troponin in ACS[3-5]. In patients with ST-segment elevation myocardial infarction (STEMI), the peak troponin value increases as the area of infarction in the heart increases[6].

Scoring systems are needed to decide for revascularization strategy for coronary artery disease (CAD)[7,8] or to predict mortality and adverse cardiac events[9,10]. In this context, the SYNTAX score (SS) is a commonly used system developed to cumulatively measure the extent, severity, and complexity of CAD[8]. SS was calculated using angiographic data, such as how many coronary arteries are affected, lesion location, calcification and thrombus, length of the lesion, and coronary segments involved[7,8].

A thorough investigation of the high-sensitivity troponin T (Hs-TnT), high-sensitivity C -reactive protein (Hs-CRP), procalcitonin (PCT) and Syntax Score (SS) relation in various clinical conditions may provide the scientific community with a more in-depth understanding of the inflammation according to immune response in atherosclerosis and lead to better risk stratification and clinical decision-making.

In this study, we aimed to predict the severity of cardiovascular disease using SS and biomarkers measured at the emergency department, namely Hs-TnT, Hs-CRP, and PCT.

MATERIALS AND METHODS

Participants

This study was conducted in Bakirkoy Dr. Sadi Konuk Training and Research Hospital between January 2020-2021. The study was started with 170 patients. Four patient were excluded because of the cardiogenic shock. A total of 166 patients, who presented to the emergency department with chest pain, received a diagnosis of STEMI and underwent coronary angiography were included prospectively in the study. STEMI was diagnosed based on the presence of ST-segment elevation > 1 mm in two contiguous electrocardiographic leads, or with presumably new left bundle-branch block and chest pain exceeding 30 minutes by two experienced cardiologist. The study patients were divided into two groups according to SS as SS ≤ 20 (n=38) and SS > 20 (n=128)[11]. The Bakirkoy Dr. Sadi Konuk Training and Research Hospital Clinical Trials and Ethics Committee approval was obtained for the study (2019/450). The privacy of all participants was protected, and written informed consent was obtained before the procedures by the principles of the Declaration of Helsinki (2013). Patients under the age of 18, those with an active infection at the time of presentation, those with chest pain lasting for more than 3 hours, and those with a glomerular filtration rate (GFR) below 30, with a history of cardiogenic shock, cardiac arrest were excluded from the study. Age, gender, and risk factors (presence of smoking, family history, diabetes, hypertension) for CAD were recorded for all patients. SYNTAX score was calculated for all the patients included in the study.

Biochemical analyses

At the time of presentation, venous blood samples were taken, and the Hs-TnT (ng/mL), Hs-CRP (mg/dL), and PCT (ng/mL) levels were measured using the e411 Autoanalyzer (Roche diagnostics, USA).

Syntax Score calculation

The SYNTAX score is calculated using a computer program using a series of consecutive, interactive questions. It contains 12 basic questions. The first three questions cover the dominancy, the total number of lesions, and the vessel segment where the lesions are located. SYNTAX scoring system, which is prepared by using features such as the number of lesions, functional importance and location of the lesion angiographically, provides important data in determining the severity of coronary artery disease.

The SYNTAX score is the sum of the points assigned to all lesions causing 50% stenosis in the coronary artery with a ≥1.5 mm diameter. The coronary tree is divided into 16 segments. Each segment is given a

score of 1 or 2 based on the presence of disease and this score is then weighted based on a chart, with values ranging from 3.5 for the proximal left anterior descending artery (LAD) to 5.0 for left main, and 0.5 for smaller branches. An aorto-ostial lesion is worth one point, severe tortuosity of vessel is worth two points, lesion length greater than 20 mm is worth one point, heavy calcification is worth 2 points, thrombus is worth 1 point, and diffuse disease or small vessel is at 1 point per segment involvement. For multiple lesions less than three reference vessel diameters apart, these are scored as a single lesion. However, at greater distance than three vessel diameters, these are considered separate lesions.

The SS for each patient was calculated with software (http://www.syntaxscore.com) by an experienced interventional cardiologist. And also clinical follow up of all patients were performed by this cardiologist. We followed up with the patients diagnosed with ACS for 72 months and identified those who did not attend follow-up and those who died during this period by accessing the state's official database that is only open to physicians. When evaluating cardiovascular mortality, we did not include deaths from other causes.

Statistical analysis

MedCalc Statistical Software version 12.7.7 (MedCalc Software, Belgium) was used for all analyses. Continuous variables were presented as mean±standart deviation and categorical variables were presented as percentage (%). The independent-samples t-test was used to compare two groups in terms of continuous independent variables with normal distribution. The comparison of two groups was assessed with the Mann-Whitney U. The Mann-Whitney U test was used for the comparison of parameters not showing normal distribution. A value of $p<0.05$ was considered statistically significant (95 % confidence interval). Pearson's correlation analysis was used to determine the correlational relationships between the variables meeting the standard distribution assumption.

RESULTS

The study was performed with a total of 166 patients, of whom 157 were male, and the mean age was 46.33±9.37 in patients with SS≤ 20 and 58.34±12.24 in patients with SS>20. The risk factor of patients were family history (19%, n=31), smoking (42%, n=69), diabetes (15%, n=24), hypertension (%49, n=82). The demographic and laboratory characteristics of the patients are presented in Table 1. The Hs-TnT values were measured as 0.42 ± 1.21 ng/mL in patients with SS <20 and 0.51 ± 1.26 ng/mL in those with SS > 20. Although the Hs-TnT values were higher in the SS >20 group, this was not statistically significant (p = 0.360). The mean Hs-

Table 1. Demographic and laboratory characteristics of the patients according to SYNTAX score

(n) Mean ± SD Median (Min-Max)	SS ≤ 20	SS > 20	p
Age	(n=38) 46.33±9.37 46.5-(26-63)	(n=128) 58.34±12.24 58-(36-94)	0.001
Left ventricular ejection fraction (%)	(n=38) 51.75±5.61 50-(40-65)	(n=128) 45.74±9.42 45-(20-65)	0.001*
Low-density lipoprotein (mg/dl)	(n=38) 140.35±34.98 149-(61-206)	(n=128) 131.03±40.96 129-(39-260)	0.191
High-density lipoprotein (mg/dl)	(n=38) 39.94±7.75 39-(27-66)	(n=128) 40.53±9.09 40-(21-70)	0.686
Triglyceride (mg/dl)	(n=38) 171.42±147.33 132-(44-810)	(n=128) 116.1±62.35 97-(4-391)	0.043*
Glucose (mg/dl)	(n=38) 124.89±47.79 105.5-(84-294)	(n=128) 151±63.84 125-(74-374)	0.001
Creatinine (mg/dl)	(n=38) 0.87±0.13 0.9- (0.6-1.1)	(n=128) 0.97±0.23 1- (0.5-2.2)	0.004
Hypertension [n, (%)]	8 (21.05%)	74 (57.81%)	0.001

Mann-Whitney U test *Independent-samples t-test; SS: SYNTAX Score, SD: Standard Deviation, Min: Minimum, Max: Maximum

Table 2. Comparison of the variables according to the SYNTAX score

(n) Mean ± SD Median (Min-Max)	SS ≤ 20	SS > 20	p
Hs-TnT (ng/ml)	(n=38) 0.42±1.21 0.04-(0-5.53)	(n=128) 0.51±1.26 0.06-(0-10)	0.360
Hs-CRP (mg/dl)	(n=38) 6.59±6.3 3.91-(0.23-26.9)	(n=127) 9.34±14.79 4.25-(0.34-92.57)	0.585
Procalcitonin (ng/ml)	(n=40) 0.07±0.07 0.05-(0.05-0.44)	(n=129) 0.06±0.04 0.05-(0.05-0.44)	0.303
Four-year mortality	(n=40) 2.16±0.58 2.1- (1.1-3)	(n=129) 8.11±7.56 5.7- (3-55.2)	<0.001

Mann-Whitney U test,*Independent-samples t-test; SS: SYNTAX Score, SD: Standard Deviation, Min: Minimum, Max: Maximum, Hs-TnT: High-sensitivity troponin T, Hs-CRP: High-sensitivity C-reactive protein

CRP values were 6.59 ± 6.3 mg/dL for the 38 patients with SS ≤ 20 and 9.34 ± 14.79 mg/dL for the 127 patients with SS > 20. Although the Hs-CRP levels were higher in the SS > 20 group, there was no statistically significant difference (p = 0.558). The PCT values were 0.07 ± 0.07 ng/mL and 0.06 ± 0.04 ng/mL for the SS ≤ 20 and SS > 20 groups, respectively. There was no significant difference in the PCT measurements between the groups. The four-year mortality of the patients with ACS was evaluated, and as expected, the mortality rate was higher in patients with SS > 20 than those with SS ≤ 20 (Table 2).

DISCUSSION

Troponins exist in the structure of skeletal and cardiac muscles and play a role in muscle cells[12]. High levels of troponins, which are typically present in trace amounts in the blood and increase in time, suggest damage to myocardial cells. This condition is considered ACS if it is accompanied by cardiac symptoms, such as chest pain, left arm pain, and diaphoresis. In previous-generation cardiac troponin assays, levels < 0.01 μg/L were not detectable, and thus the results were sometimes considered normal, leading to overlooking early myocardial damage[13]. However, newly developed high-sensitivity Hs-TnT tests can detect very low circulating cardiac troponin levels[14].

Yamazaki et al. investigated the relationship between the Hs-TnT levels and SS. In 408 patients with suspected ACS, the Hs-TnT levels were found significantly higher in patients with high or moderate SS than those with low SS (0.044 ± 0.055 vs. 0.018 ± 0.058 μg/L, p = 0.03)[15]. Another study by Hermal et al. showed a correlation between SS and the peak troponin levels[16]. Although we observed an increasing tendency in the Hs-TnT and Hs-CRP values as SS increased in patients with STEMI, the relationships were not statistically significant. CRP is the most common and widely used marker of inflammation. In recent years, cardiac computed tomography has been widely used in the diagnosis of cardiovascular disease. High Hs-CRP levels were detected in patients with large and necrotic atherosclerotic plaques. In ACS, the plaque's necrotic area size is correlated with the Hs-CRP level[17]. The Emerging Risk Factors Collaboration meta-analysis reported that hs-CRP was an independent predictor of future events, and it performed equally well or better than many traditional risk factors or predictive markers[18]. Many studies have shown that high Hs-CRP at presentation is an important predictor of long-term and short-term deaths in unstable angina pectoris and ACS patients with non-ST segment elevation[19-21]. In order to show that CRP is correlated with the severity of ACS, many studies have been conducted to evaluate the relationship between SS and Hs-CRP. For example, in a study by Karadeniz et al., it was shown that high troponin and increased serum Hs-CRP levels were the most powerful predictors of high SS in patients with acute coronary syndrome[22]. Our results are partly consistent with these studies. Although the results were not statistically significant, we determined that the Hs-CRP values tended to increase as SS increased, consistent with the literature on this subject[16, 22-24]. PCT, a newly identified systemic inflammatory

marker, is a calcitonin precursor released from thyroid para-follicular cells in response to immune stimuli and increases not only in patients with the bacterial infection but also in patients with pancreatitis, those undergoing major surgical operations, and those with multiple traumas, heatstroke, or burn injuries[25-27]. Whether serum PCT levels are useful as a diagnostic or prognostic marker in ACS has been previously investigated. Although some literature studies have shown that increased PCT levels are associated with ACS, there are also publications supporting the contrary[27-30]. In our study, no significant increase was seen in the PCT levels of ACS patients.

Interestingly, we found that PCT levels to be lower in patients with higher SS, albeit with no statistically significant difference. In other words, PCT was not determined to be predictive of the severity of CAD in the emergency department. When more sensitive kits are developed to predict the severity of CAD, its relationship with SS and clinical manifestations may be more significant for early diagnosis and improvement of symptoms. Although there are many studies concerning this subject, most do not clearly explain all the research steps. The study's limitations are the small sample size and the different demographic characteristics and laboratory findings of the two SS groups. In the emergency department, rapid and reliable detection of myocardial infarction is crucial because one of the most important parameters is the early diagnosis and treatment of cases with life-threatening diseases, such as CAD.

The limitations of this study are that one is single-center investigation with a small sample size, and the second is, PCT, Hs-TnT and Hs-CRP concentration were measured only at admission and without correction for potential variability.

In conclusion patients with STEMI tended to have increased Hs-TnT and Hs-CRP values with their higher SS. Hs-TnT and Hs-CRP may be early predictors of CAD severity in STEMI in the emergency department. Large-scale and prospective studies will be more guiding for understanding of CAD severity in STEMI. Further, large-scale studies to be conducted by evaluating Hs-TnT and low-cost, easily measurable Hs-CRP together will reveal the relationship of Hs-TnT and Hs-CRP with high SS more clearly, and evaluating these parameters in patients with unstable angina pectoris should determine the high-risk patient group and we think it may play an important role in directing to earlier invasive procedures.

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