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Araştırma

The Prediction of the Prognosis After Acute Myocardial Infarction by Multi-Biomarker Approach

Çoklu Biyobelirteç Yaklaşımı ile Miyokard Enfarktüsü Sonrası Prognozun Öngörülmesi

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ABSTRACT

Aim: Early risk classification after acute myocardial infarction is very important for the prediction of complications. In this study, it was aimed to find the most sensitive panel in the prediction of prognosis after acute myocardial infarction by multi-biomarker approach.

Materials and Methods: 120 patients who were diagnosed with the acute coronary syndrome were included. Patients' heart failure and death outcomes that accrued after acute myocardial infarction were followed up. Heart failure and all causes of death were noted and the predictive values of the markers and new panels for these poor outcomes were examined.

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Results: In the prediction of heart failure after acute myocardial infarction, glucose's area under the curve (AUC), was 0.714, hs-cTnT's 0.779, and NT-proBNP's 0.842 (p=0.035, p=0.002, p<0.001 respectively). In the panel created using hs-cTNT, NT-proBNP, copeptin, myoglobin, and glucose, the AUC reached 0.917. In mortality prediction, copeptin's AUC was 0.696, myoglobin's 0.713, and glucose's 0.800 (p=0.045, p=0.003, p=<0.001 respectively). In the panel created using hs-cTNT, copeptin, myoglobin, and glucose, the AUC reached 0.865 in prediction of mortality.

Conclusion: Biomarker combinations may increase the predictive values of biomarkers. It is demonstrated that the powerful prognostic panels were created using serum hs-cTNT, NT-proBNP, copeptin, myoglobin, and glucose levels in this study.

Key words: Troponin T, Natriuretic Peptide, Myoglobin, Myocardial Infarction, Prognosis

ÖZET

Amaç: Akut miyokard enfarktüsü sonrası erken risk sınıflandırması komplikasyonların öngörülmesinde çok önemlidir. Bu çalışmada, multi-biomarker yaklaşımı ile akut miyokard enfarktüsü sonrası prognozun öngörülmesinde en duyarlı paneli bulmak amaçlandı.

Gereç ve Yöntem: Akut koroner sendrom tanısı almış 120 hasta dahil edildi. Akut myokard infaktüsü sonrası hastalarda gelişen kalp yetmezliği ve ölüm sonlanımları takip edildi. Bu kötü prognozların öngörülmesinde belirteçlerin ve yeni panellerin prediktif değerleri incelendi.

Bulgular: Akut myokard infarktüsü sonrası gelişen kalp yetmezliği öngörüsünde glukozun ROC eğrisi altında kalan alanı 0.714, hs-cTnT'nin 0.779 ve NT-proBNP'nin 0.842 (sırasıyla p=0.035, p=0.002, p<0.001) idi. hs-cTNT, NT-proBNP, kopeptin, miyoglobin ve glukoz kullanılarak oluşturulan panelde eğri altında kalan alan 0.917'ye ulaştı. Mortalite tahmininde kopeptinin ROC eğrisi altında kalan alanı 0.696, miyoglobinin 0.713 ve glukozun 0.800 (sırasıyla p=0.045, p=0.003, p=<0.001) idi. hs-cTNT, kopeptin, miyoglobin ve glukoz kullanılarak oluşturulan panelde, mortalite tahmininde ROC eğrisi altında kalan alan 0.865'e ulaştı.

Sonuç: Biyobelirteç kombinasyonları, biyobelirteçlerin prediktif değerlerini artırabilir. Bu çalışmada serum hs-cTNT, NT-proBNP, kopeptin, miyoglobin ve glukoz düzeyleri kullanılarak güçlü prognostik panellerin oluşturulduğu gösterilmiştir.

Anahtar Kelimeler: Troponin T, Natriüretik Peptid, Miyoglobin, Miyokardiyal Infarktüs, Prognoz

INTRODUCTION

Cardiovascular diseases (CVD) are the most common cause of death (1). An estimated 17.9 million people died because of CVDs in 2019, this was 32% of all deaths (2). The most common clinical manifestation of coronary artery disease is an acute coronary syndrome (ACS) that includes unstable angina pectoris (UAP), non-ST-segment elevation myocardial infarction (NSTEMI), or ST-segment elevation myocardial infarction (STEMI), describes the range of myocardial ischemic states, and is an important cause of morbidity and mortality (3). After ACS within 30 days, the rate of rehospitalization is 17-25% (4) and mortality is 2-3% (5). In-hospital mortality of STEMI is 6-14% and approximately 12% of the patients die within 6 months (6). Fibrinolysis, percutaneous coronary intervention, and early treatment of myocardial ischemia, such as coronary artery bypass graft, have a positive influence on the prognosis after AMI (7). Therefore, rapid management of the diagnosis and therapeutic processes and early risk stratification is very important (8).

The most important biomarker used in the management of ACS is cardiac troponin (3). Cardiac troponin, especially high-sensitivity cardiac troponin (hs-cTn), provides prognostic information for both short-term and long-term mortality (9-11) and high hs-cTn levels are associated with a high risk of death (12-14). B-type natriuretic peptide (BNP) and its more stable form of N terminal pro-BNP (NT-proBNP) also provide information, especially for the prediction of heart failure (HF) after ACS (9). Both cardiac

troponin and BNP/NT-proBNP are definitive biomarkers of ACS, but it is necessary to discover more biomarkers for the management of the patient (15).

Copeptin (c-terminal provasopressine) is a new marker that can be used in the diagnosis of AMI or to rule out this diagnosis (16, 17). Copeptin, a 5 kDa glycopeptide, originates from preprovasopressine along with arginine-vasopressin and neurophysines II (6). Although copeptin is not relevant to the pathophysiology of cell necrosis, its levels are elevated at the onset of MI due to endogenous stress, therefore copeptin can be used to rule out the diagnosis of acute myocardial infarction (AMI) (18-20). It has been also shown that copeptin has a prognostic value after AMI (21-23) and copeptin has entered the guidelines as a diagnostic and prognostic marker (9).

Due to its low molecular weight and cytoplasmic localization, myoglobin is the earliest marker that increases in circulation after AMI. It is used to rule out the diagnosis of AMI because of its negative predictive value (100%). Although it has lost its diagnostic importance with the widespread use of hs-cTn, myoglobin is already a suitable biomarker for the detection of cardiac damage and the prediction of prognosis (24, 25).

Plasma glucose levels increase due to endogenous stress response and high levels of glucose result in the increase of free oxygen radicals, inflammation, and endothelial dysfunction (26) and acute hyperglycemia, which is independent of the diagnosis of diabetes, has been associated with poor prognosis after AMI (27, 28).

In this study, we aimed to compare the prognostic values of serum hs-cTnT, NT-proBNP, copeptin, myoglobin, and glucose after AMI and to find out the most sensitive marker combination for the prediction of prognosis of AMI by multi-biomarker approach.

MATERIALS and METHODS

Subjects

In this prospective study that was conducted with the approval of the local ethics committee according to the principles of the Declaration of Helsinki, 120 adult patients who applied to our hospital's emergency service were diagnosed with acute coronary syndrome by experienced independent cardiologists. The exclusion criteria were malignancy, major surgery or trauma within the last 1 month, pregnancy, end-stage renal failure, anemia (hemoglobin < 10 g/dl), and being under 18 years of age. Serum hs-cTnT levels were measured at the time of admission and, measurement of hs-cTnT was repeated if it was necessary. Twelve derived electrocardiography were conducted.

The patients were evaluated and diagnosed by independent cardiologists with clinical findings, ECG, cardiac marker, and angiography results. According to the final diagnoses, patients were divided into 3 groups STEMI, NSTEMI, and UAP.

Blood samples were taken on admission and the 3rd day after AMI. All of the blood samples were centrifuged within 30 minutes at 3.000 g for 5 minutes. Serums were separated and stored at -80 °C. Serum copeptin, myoglobin, and glucose measurements were examined with the samples taken on admission and the NT-proBNP levels were measured from the 3rd day's samples.

The patients were followed for one year and their clinical control (electrocardiography, echocardiography, if needed exercise stress testing, and coronary angiography) was performed. HF (ejection fraction < 45%) and all causes of death were noted. The prediction values of the markers for poor outcomes were evaluated.

Methods of measurements

Serum hsTnT, NT-proBNP, and myoglobin levels were measured with electro-chemiluminescence immunoassay method in

Cobas e 411 analyzer (Roche, Mannheim, Germany), copeptin levels were measured with sandwich immunoluminometric assay in Kryptor (BRAHMS AG, Germany). Serum glucose levels were measured by the enzymatic colorimetric method in a Roche/Hitachi Modular (Roche, Mannheim, Germany) analyzer.

Statistical analysis

Normality tests were measured with Kolmogorov-Smirnov and Shapiro-Wilk tests. Continuous quantitative data showing normal distribution were expressed as a mean and standard deviation; and qualitative data not showing normal distribution were expressed as median, 25^{th}, and 75^{th} percentage values. The categorical variables were shown with n or %. Kruskal-Wallis and One-way ANOVA tests were applied to the data consisting of variables. For the data sets showing the categorical structure, Chi-Square tests were applied. Receiver Operating Characteristic (ROC) Curve analysis was conducted to determine the effects of the markers and the effects of the markers were evaluated using the areas under the ROC curve (AUC). Logistic regression analysis was used to determine the common impact of multiple markers. $p<0.05$ probability values were considered significant. All data analyses were performed with SPSS and MedCalc software packages.

RESULTS

Eighty patients (66.7%) were diagnosed with STEMI, 22 (18.3%) NSTEMI, and 18 (15%) UAP. 67 patients (55.8%) were admitted within 0-3 hours after the onset of symptom, 20 patients (16.7%) within 3-6 hours, 14 patients (11.7%) within 6-12 hours, and 11 patients (9.2%) more than 12 hours. The time after chest pain onset could not be recorded for 8 patients. The patients' demographics, clinical characteristics, and laboratory test results on admission are shown in Table 1. A significant difference between the groups in terms of the coronary artery disease (CAD) story was detected ($p=0.017$).

At the end of the one-year follow-up, HF developed in 22 patients (14 in STEMI, 4 in NSTEMI, and 4 in UAP) and the mortality rate was 13.3% (n=16) (15 in STEMI and 1 in NSTEMI). All of the deaths occurred within the first 1 month, and 93.8% of them occurred within the first 48 hours after AMI. There was no significant difference between groups in terms of the development of HF ($p = 0.639$) however a significant difference was found in mortality rates ($p = 0.047$) and the highest mortality rate was in STEMI.

The relationship between those poor outcomes with cardiac marker levels was examined and the sensitivity, specificity, and AUC of the markers were calculated (Table 2). Statistical analyses were performed with 42 patients' data for HF data and 92 for mortality due to patients who dropped out of follow-up.

According to the ROC curve analysis, in the prediction of HF copeptin's AUC was 0.525 ($p=0.807$), glucose's 0.714 ($p=0.035$), hsTnT's 0.779 ($p=0.002$) and NT-proBNP's 0.842 ($p<0.001$). The AUC increased to 0.861 by using NT-proBNP with myoglobin, and to 0.897 with copeptin. In the multi-biomarker panel created using all markers, the AUC reached 0.917 (Figure 1A). In the prediction of mortality, hsTnT's AUC was 0.574, copeptin's 0.696, myoglobin's 0.713 and glucose's 0.800 ($p=0.424$, $p=0.045$, $p=0.003$, $p<0.001$ respectively). It was found that the use of myoglobin and hsTnT together was more significant instead of using hsTnT alone ($p=0.002$). In the multi-biomarker panel created using myoglobin, hsTnT, copeptin, and glucose, the AUC was 0.865 (Figure 1B).

Table 1. The patients' demographics, clinical characteristics and laboratory test results on admission

	STEMI (n=80)	**NSTEMI** (n=22)	**UAP** (n=18)	**p**
Age (years)*	64.4±11.8	62±11.4	64±11.2	0.634
Gender				
Female/Male *n*	21/59	9/13	9/9	0.098
Time of chest pain onset h†	3 (1-6)	3(1-7)	4.5 (2-6)	0.439
Traditional risk factors ‡				
Diabetes Mellitus%	30	45.5	50	0.346
Hypertension%	42.5	54.5	77.8	0.094
Hyperlipidemia%	51.2	54.5	72.2	0.472
Smoking status %	40	27.3	22.2	0.364
Body mass index (kg/m2) > 30 %	15	31.8	38.9	0.118
Family history %	18.8	27.3	27.8	0.780
Known coronary artery disease % ‡	25	45.5	66.7	**0.017**
Drug Utilization ‡				
Angiotensin-converting enzyme inhibitor /angiotensin receptor blocker %	26.2	31.8	38.9	0.361
β Blocker%	21.2	31.8	44.4	0.096
Ca Channel Blocker %	5	0	0	0.262
HMG-CoA reductase inhibitor%	15	13.6	16.7	0.535
N-acetylsalicylic acid%	18.8	36.4	38.9	0.098
Diuretic %	8.8	18.2	11.1	0.427
Glucose (mg/dl) †	147 (121-191)	144 (117-219)	124 (102-154)	0.244

* One way ANOVA, mean±SD † Kruskal-Wallis, median (25%-75%) ‡ Chi-Square test

Table 2. The predictive values of markers in the prognosis prediction for a year follow-up

	Biomarker	**Sensitivity**	**Specificity**	**Cut-off value**	**AUC**	***p***
Heart Failure	**Myoglobin**	91.7	46.7	66.67	0.656	0.068
	hsTnT	83.3	63.3	0.058	0.779	**0.002**
	Copeptin	100	13.3	10.77	0.525	0.807
	Glucose	58.3	83.3	188.8	0.714	**0.035**
	NT-proBNP	83.3	83.3	2831	0.842	**<0.001**
Mortality	**Myoglobin**	100	41.2	68.07	0.713	**0.003**
	hsTnT	83.3	40	0.034	0.574	0.424
	Copeptin	58.3	86.2	405	0.696	**0.045**
	Glucose	83.3	73.7	178.4	0.800	**<0.001**

Units of biomarkers: Myoglobin ng/ml, hsTnT ng/ml, Copeptin pmol/L, NTproBNP pg/mL and glucose mg/dl

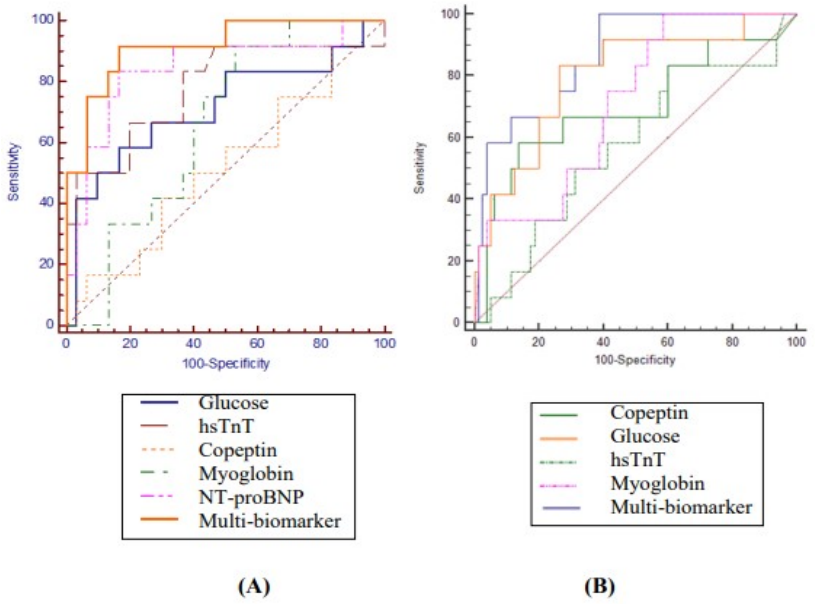

Figure 1. ROC curves of multi-biomarker approach
A: ROC curve in HF prediction. The AUC was reached to 0.917 with multi-biomarker approach.
B: ROC curve in mortality prediction. The AUC was reached to 0.865 with multi-biomarker approach

DISCUSSION

In the early period after ACS, determining the risks of complications is very important for patient management. Various risk factors, clinical properties, ECG findings, and changes in the serum biomarkers have been considered for risk stratification; however, the most widely used marker in the management of patients with AMI is the cardiac troponin, especially hs-cTnT (29). BNP or NT-proBNP, copeptin, c-reactive protein, mid-regional pro-adrenomedullin, growth differentiation factor 15 (GDF-15), heart-type fatty acid-binding protein (h-FABP) may also be used in the prediction of prognosis after AMI and they have a part in the new European Society of Cardiology guideline (9) and research for new biomarkers such as chemokines and circulating noncoding RNAs are still ongoing to explain the activated pathways that are not explained with these conventional markers (30, 31).

In 2007, Khan et al. (32) showed that copeptin was a new prognostic marker for HF and mortality after AMI, and the importance of usage of NT-proBNP along with copeptin was emphasized in the samples taken on the 3^{rd}-5^{th} days after AMI. Potocki et al. (33) found that copeptin was a strong and independent predictive marker for one-year mortality after AMI. In the retrospective study conducted by Afzali et al. (8), it was found that copeptin and TnI levels on admission were significant predictors for 180-day mortality, and in the ROC analysis; AUC was 0.81 for copeptin, 0.76 for TnI and 0.83 in combination.

Although the use of myoglobin for the diagnosis of AMI has decreased due to its low specificity, some studies determine the prognostic importance of myoglobin. Jaffery et al (34) reported that myoglobin was a better predictive biomarker than cTnI for 5-year mortality in ACS. Yao et al. (35) showed that although serum myoglobin, CK-MB, and cTnI are significantly elevated in AMI, only myoglobin is an independent predictor for poor outcomes.

We aimed to evaluate the usage of all these biomarkers, hs-cTnT, copeptin, NT-proBNP, myoglobin, and glucose, together in the prediction of prognosis in AMI and to create a more sensitive management by the panel that is created with these markers. In the prediction

of HF, glucose's AUC was 0.714, hsTnT's 0.779, and NT-proBNP's 0.842 (p=0.035, p=0.002, p<0.001 respectively). According to these results, the best marker was NT-proBNP; however, the AUC was reached at 0.917 with the multi-biomarker panel that was created using all the markers. In the prediction of mortality, copeptin's AUC was 0.696, myoglobin's 0.713, and glucose's 0.800 (p=0.045, p=0.003, p<0.001 respectively). The best marker was found as glucose; however, the AUC of the multi-biomarker panel that was created using myoglobin, hs-cTnT, copeptin, and glucose was 0.865.

Contrary to the high predictive success of NT-proBNP in the prediction of heart failure, the high predictive value of glucose, especially in the prediction of mortality, is one of the most interesting results of our study. Essentially, one of the most common laboratory finding in hospitalized patients with AMI is hyperglycemia, and its prevalence is approximately 40% (36, 37). It was found that acute hyperglycemia which was found in the admissions of patients with AMI was related to poor outcomes such as HF, cardiogenic shock, and death (36). The most emphasized mechanism is an endogenous stress response and the activation of the sympathetic nervous system with increased blood catecholamine and glucocorticoid levels. In this case, the utilization of glucose decreases, and free fatty acids become the main nutritional source for the myocardium. Therefore, the oxygen demand of the myocardium increases, unoxidized products accumulate (38) and collateral development occurs in the myocardium (39). All these changes increase myocardial damage (40). Acute hyperglycemia was found to be associated with a large infarct area (41). Stranders et al. (28) demonstrated that with each increase of 18 mg/dl of the serum glucose levels on admission, mortality increased by 4-5% in diabetic and non-diabetic patients with AMI.

In our study, we wanted to emphasize that new approaches should be tried in the prediction of prognosis after AMI by combining commonly used markers like hs-cTnT and NT-proBNP with less studied parameters such as copeptin, myoglobin, and glucose in this field. Serum hs-cTnT, myoglobin, and glucose levels are already measured on admission if the diagnosis is thought to be AMI. When considering the diagnostic value of copeptin, it is clear that it will be commonly requested on the admission of AMI. It is demonstrated that parameters that are used in diagnostic processes can be used as a powerful prognostic panel by adding NT-proBNP simply by a multi-biomarker approach.

As seen in this study, biomarker combinations have increased the predictive values of biomarkers. Multi-biomarker approaches have been studied using different biomarkers in many studies both in the diagnosis and in the prediction of the prognosis of ACS (42). In these studies, different nonnecrotic biomarkers were added to the conventional markers as troponin and most of these biomarkers have provided independent prognostic information (43, 44).

Multi-biomarker approach may allow the evaluation of various biochemical pathways together, but the performance of the approach is determined by the combination of biomarkers. The panels, formulas, or indices created with these combinations can be used in clinical laboratories with laboratory information systems (LIS) or interface software between autoanalyzer and LIS. However, the increasing number of biomarkers cause an increase in economic burden. Therefore, it should be aimed to determine the most successful combination with the lowest cost.

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COMPETING INTERESTS

Authors have no conflict of interests.

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