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Could serum ACE2 levels predict infarct size in acute phase of ST-segment elevation myocardial infarction: a comparative study with classical biomarkers

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Abstract. – OBJECTIVE: Serum ACE2 level in the acute phase of ST-segment elevation myocardial infarction may be an indicator of heart failure, however, limited studies have reported conflicting results. Therefore, in our study, we aimed to evaluate the relationship between serum ACE2 level and infarct size in the acute phase of ST-segment elevation myocardial infarction and compare the predictive value of ACE2 level with classical biomarkers.

PATIENTS AND METHODS: Sixty-six patients after the primary percutaneous coronary intervention were included in the study. For the measurement of serum ACE2 levels, blood samples were taken twice from the patients: in the first 24 hours and on the 5th day of the infarction, and once from 30 healthy volunteers. hs-cTnT, BNP, and CRP levels were measured daily, and their peak values were taken. On the 7th day of ST-segment elevation myocardial infarction, gSPECT was used with the 99mTc-MIBI method for assessment of infarct size.

RESULTS: Baseline ACE2 values were found to be higher in patients compared to controls, and ACE2 values obtained on the 5th day were found to be higher than the baseline values in the patients. There was no significant correlation between serum ACE2 levels and the RSS (%), while peak levels of hs-cTnT, BNP, and CRP were assessed as predictive factors for the RSS (%).

CONCLUSIONS: Although serum ACE2 levels increased in the acute phase of ST-segment elevation myocardial infarction, this increase was not associated with infarct size. Serum ACE2 level did not provide additional benefit to classical biomarkers for infarct size-related prognosis prediction.

Key Words:
ACE-2, Infarct size, ST-segment elevation myocardial infarction, gSPECT.

Introduction

Ischemic heart disease, including ST-segment elevation myocardial infarction (STEMI), continues to be an important reason for morbidity and mortality worldwide[1]. Although there is a decrease in acute mortality after STEMI in parallel with advances in percutaneous coronary intervention (PCI) and pharmacological treatments, a high rate of heart failure (HF) could be seen in patients after STEMI[1,2]. In most patients, the cause of STEMI is a complete thrombotic occlusion from atherosclerotic plaque in the epicardial coronary vessel. The infarct size (IS) after total occlusion depends on various factors including the size of the ischemic area, the duration of coronary occlusion, the presence of collateral coronary circulation, microvascular obstruction, and ischemia/reperfusion injury[3]. Reperfusion with primary percutaneous coronary intervention (PPCI) in the early phase of STEMI is the most effective intervention to limit myocardial ischemia and IS, thus it could reduce the risk of HF and other complications after STEMI[4]. Despite the mechanical reperfusion provided by PPCI, damage at the myocardial tissue level may continue in some patients due to pathophysiological mechanisms such as microvascular obstruction and ischemia/reperfusion injury[3]. Therefore, to improve long-term outcomes in STEMI, one of the main aims of treatment should be to limit the IS. In this context, the current STEMI guideline of the European Society of Cardiology (ESC) states that a specific infarct-limiting therapy should be defined in clinical practice[5].

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Various biomarkers and imaging methods have been used to measure IS, which is accepted as one of the best predictors of long-term mortality and HF in survivors after STEMI[6,7]. In the ESC current STEMI guideline, single-photon emission computed tomography (SPECT), cardiac magnetic resonance imaging (MR), and positron emission tomography (PET) have been recommended as imaging modalities for measuring IS[5]. Technetium (Tc)-99m SPECT is currently considered to be the best technique for measuring IS[8]. It is also important to evaluate the imaging method according to local suitability and expertise. On the other hand, because of their widespread use and cost-effective benefits, cardiac biomarkers are frequently used in clinical practice for IS prediction in STEMI. However, given the complex pathophysiology of STEMI, it is difficult to identify an ideal biomarker. Today, it is recommended to use multiple biomarker models to reflect most of the underlying pathophysiological mechanisms[9]. Many clinical studies[9-16] have evaluated the association of myocardial injury, myocardial pressure/strain, and inflammation biomarkers with IS in patients with STEMI. In these studies, it has been reported that the peak values of high-sensitive cardiac troponin T (Hs-cTnT), B-type natriuretic peptide (BNP), and C-reactive protein (CRP) could be important indicators of IS.

The role of the Renin-angiotensin system (RAS) in the pathophysiological process progressing from ischemia/infarction to heart failure in STEMI is well known. Hemodynamic changes after STEMI cause strong RAS activation both systemically and locally[17]. While activation of the RAS is beneficial for preventing hemodynamic collapse and maintaining tissue perfusion in the acute phase, its overactivation in the chronic phase causes HF and cardiac remodeling[18].

Angiotensin-converting enzyme (ACE) and angiotensin-converting enzyme-2 (ACE2) are key enzymes involved in the synthesis of RAS components. They are counterproductive in the regulation of RAS under both physiological and pathological conditions. ACE converts angiotensin I (Ang I) to angiotensin II (Ang II). Ang II has pro-inflammatory and proatherosclerotic effects and induces cardiac remodeling and HF by promoting hypertrophy and fibrosis[19]. ACE2 is an enzyme that has beneficial effects on the cardiovascular system by converting Ang II to Ang (1-7) and it reduces infarct area, inflammation, cardiac hypertrophy, and remodeling in STEMI[20,21]. On the other hand, in pathological RAS activation, an increase is observed in both tissue ACE2 expression and plasma ACE2 level. While ACE2 in cardiac tissue creates a cardioprotective effect, ACE2 levels detected in plasma can be used to predict the development and progression of cardiovascular diseases (CVD)[22].

Although it has been suggested that serum ACE2 level in the acute phase of STEMI may be a predictor of the development of HF, there are limited studies in the literature with conflicting results. Therefore, in our study, we aimed to evaluate the serum ACE2 level in the acute phase of STEMI in patients who underwent PPCI. In addition to the serum ACE2 level, we aimed to investigate the relationship of the classical biomarkers (Hs-cTnT, CRP, BNP levels) with IS and compare the predictive value of ACE 2 level with these classical biomarkers of HF.

Patients and Methods

Study Population and Protocol

Sixty-six patients, without a history of known coronary artery disease (CAD), diagnosed with STEMI for the first time, applied within the first 2 hours after the onset of chest pain, successfully revascularized by standard medical treatment and PPCI in line with the recommendations of current guidelines (2017 ESC STEMI guideline) were included to our study. PPCI was performed with drug-eluting stent implantation into the infarct-related artery as standard. Patients with TIMI 3 flow after stent implantation were included in the study. Patients with TIMI 0-2 flow and who received additional antithrombotic therapy (glycoprotein IIb/IIIa inhibitor) due to a thrombotic complication were excluded from the study. In addition, multi-vessel patients with critical lesions other than the infarct-related artery and patients with collateral circulation in the infarct-related artery region were excluded from the study. During the process, the treatment of the patients was started by physicians other than the study group. The participants were given acetylsalicylic acid (300 mg oral loading dose followed by 100 mg maintenance) and ticagrelor (180 mg oral loading dose followed by 90 mg maintenance) as standard antiplatelet therapy, and unfractionated heparin (70-100 IU/kg iv bolus) as an anticoagulant therapy. Beta-blockers (50-100 mg metoprolol) and high-intensity statin therapy

(atorvastatin, 40-80 mg) were routinely started in the first 24 hours after PPCI and spironolactone 25 mg was added if LV EF was ≤ 40% and not contraindicated. RAS blocker (ramipril 2.5-5 mg) was also started in patients. Patients who could not receive or interrupt this standard treatment for any reason were excluded from the study. It has been proven in previous studies that ACE inhibitors do not affect serum ACE2 levels[23]; using ACE inhibitors was not determined as an exclusion criterion. In addition, those with prior CAD, HF, heart valve disease, chronic renal failure, and cerebrovascular disease were excluded from the study. The control group was randomly selected from healthy individuals who were in the same age range as the patient group, who applied to the cardiology outpatient clinic with non-specific chest pain, and who did not have a current cardiac disease.

For the measurement of serum ACE2 levels in the patients included in the study, 5 ml venous blood samples were taken between 7 and 9 a.m. in the first 24 hours and on the 5th day of STEMI. In addition, the blood samples were obtained from 60 healthy volunteers with similar demographic characteristics. All blood samples from patients and controls were centrifuged and stored at -80 °C until analysis. Routine biomarkers such as Hs-TnT, BNP, and CRP were measured daily during the hospitalization of the patients, and their peak values were taken. Gated single-photon emission computed tomography (gSPECT) with the 99mTc-MIBI method was used for the measurement of IS on the 7th day of STEMI, as it caused an overestimation of IS in the first 5 days. The rest summed score (RSS) and RSS (%) were used for the assessment of IS. Ejection fraction (EF) (%), end-diastolic volume (EDV), and end-systolic volume (ESV) were also assessed.

Analyzing ACE 2 Levels

After 12-hour fasting, blood samples were obtained from the patients as they were seated and rested for 20 minutes. The blood sample was obtained from the antecubital vein. After the samples were centrifuged for 10 minutes at 5000 rpm, the serum was separated (NF 400 centrifuges). Until an expert clinical biochemist performed ACE2 level analyses, samples were stored at 80°C. The enzyme-linked immunosorbent assay (ELISA) method was used to measure the serum ACE2 level (Bioassay Technology Laboratory, Shanghai, China).

Gated Single-Photon Emission Computed Tomography (gSPECT) Imaging Protocol

gSPECT with 99mTc-MIBI was performed with a rest protocol on all patients. First, sublingual nitroglycerin was administered to the patients. Then, 740 MBq of 99mTc-MIBI were intravenously given while the patient was at rest, and 45 minutes later, the gSPECT was taken. With the double-head Gamma camera (Siemens, Monaco, Germany) fitted with a high-resolution low-energy collimator, the gSPECT data were collected while the patients were supine. Eight frames per cardiac cycle of the electrocardiogram were used for the gating. The energy window of about 140 keV, or about 20%, was used to capture the emission photos. In a non-circular orbit, a total of 32 projections (35 s/projection, 64 x 64 matrix, and eight frames per cardiac cycle) were obtained. Utilizing the software program Quantitative Gated SPECT [(QGS) - Cedars-Sinai Health System™, Los Angeles, CA, USA] the gSPECT data were processed and examined. The short axis, vertical long axis, and horizontal long axis views of the obtained data were represented as myocardial tomographic slices. The American Society of Nuclear Cardiology, the American College of Cardiology, and the American Heart Association Guidelines were used to divide the myocardium into 17 segments[24]. A previously described 5-point scoring system was employed to assess the size of the left ventricular (LV) perfusion defect severity and its extent[25]. Each segment was given a score from 0 to 4, with 0 indicating normal activity, 1 indicating equivocal activity, 2 indicating moderate activity, 3 indicating severely reduced activity, and 4 indicating the absence of detectable activity. A scale from 0 to 4 was also used to grade the degree of wall motion (0: Normal, 1: Mildly hypokinetic, 2: Hypokinetic, 3: Akinetic, and 4: Dyskinetic), and also a scale of 0-3 for grading thickening (0: Normal, 1: Mildly decreased, 2: Moderately to severely decreased, and 3: No thickening) by automatic scores for each of the segments. Summed motion and summed thickening scores were also calculated as well as RSS and RSS (%).

Statistical Analysis

The study's analysis was carried out using SPSS statistical software 21.0 (IBM Corp., Armonk, NY, USA). Multiple units (n), percent (%), means, standard deviations, medians, and

minimum-maximum values were given for summary statistics of the data. Using the Q-Q Plot Normality and Shapiro-Wilk tests, the data distribution was analyzed. Categorical variables were compared using the Chi-square test, while continuous variables were compared using univariate analysis (Student's *t*-test, Mann-Whitney U test, paired Monte Carlo test). A partial correlation test was used to assess the correlation of biomarkers with clinical parameters related to left ventricular function for controlling the effect of age and gender. The predictive effects of parameters on RSS (%) were evaluated using the regression models. A *p*-value of ≤ 0.05 was defined as significant.

Results

As shown in Table I, there was no difference between the patient group and the control group in terms of age and gender. Similarly, there was no difference between the groups in terms of cardiac risk factors including smoking, hypertension, and diabetes mellitus. The most common MI type was anterior MI in the patient group, and the responsible lesion was determined as left anterior descending (LAD). As given in Table II, after gSPECT was applied on the 7th day of STEMI, the RSS was 16.22 ± 12.27, the RSS (%); was 23.80 ± 18.07, and the EF (%) was 53.21 ± 11.09.

Baseline ACE2 values were found to be higher in STEMI patients compared to controls (Table III). Also, ACE2 values obtained on the 5th day were found to be statistically significantly higher than the baseline values in the STEMI group ($p<0.001$) (Table III). When we classified the patients according to the type of lesion as a left anterior descending artery lesion ($p<0.001$) and others ($p=0.003$), the significant difference in baseline and fifth day ACE2 levels continued. Peak levels of hs-cTnT, BNP, and CRP levels were positively correlated with RSS, RSS (%), and EDV; they were also negatively correlated with EF (%) (Table IV). On the other hand, there was no significant correlation between serum ACE 2 levels and RSS, RSS (%), EF (%), and EDV (Table IV).

The regression model was statistically significant ($p<0.001$), and peak levels of Hs-cTnT, BNP, and CRP, as well as increasing sodium (Na) levels and decreasing HDL levels, were assessed as predictive factors for RSS (%) (Table V). Peak hs-cTnT and BNP levels were identified as the first two most important predictors (Table V) (Figures 1 and 2). Serum ACE2 level was not found as a predictor (Table V).

Table I. Clinical characteristics of the participants.

	Patients (N = 66)	Controls (N = 60)	*p*-value
Age (Mean ± sd)	61.00 ± 10.85	56.05 ± 9.24	0.19
Sex (N, %)			
Female	12, 18.2%	12, 20%	0.76
Male	54, 81.8%	48, 80%	
Type of MI (N, %)			
Anterior MI	42, 63.6%	–	–
Inferior MI	20, 30.3%		
Lateral MI	2, 3.0%		
Posterior MI	2, 3.0%		
Responsible lesion (N, %)			
LAD	44, 66.7%	–	–
Cx	6, 9.1%		
RCA	16, 24.2%		
Type 2 diabetes (N, %)			
Positive	12, 18.2%	–	–
Negative	54, 81.8%		
Hypertension (N, %)			
Positive	12, 18.2%	–	–
Negative	54, 81.8%		
Smoking (N, %)			
Positive	56, 84.8%	50, 83.4%	0.69
Negative	10, 15.2%	10, 16.6%	

Myocardial infarction; MI, left anterior descending artery; LAD.

Table II. Clinical parameters of the patients.

Clinical parameters	
RSS (Mean ± SD)	16.18 ± 11.40
RSS (%) (Mean ± SD)	23.77 ± 16.79
EF (%) (Mean ± SD)	53.21 ± 11.09
EDV (Mean ± SD)	83.46 ± 29.80
ESV (Mean ± SD)	42.87 ± 14.32
Peak HsTcT (ng/L) [Median (Min-Max)]	1517.79 (617.21-7866.00)
Peak CK-MB (UL) [Median (Min-Max)]	164.53 (106.00-444.00)
Peak BNP (ng/L) [Median (Min-Max)]	2325.71 (1192.02-6158.00)
Peak CRP (mg/L) [Median (Min-Max)]	31.47 (22.69-88.00)
Fasting blood glucose (mg/dL) (Mean ± SD)	117.53 ± 30.87
Sodium (mmol/L) (Mean ± SD)	134.27 ± 17.89
Potassium (mmol/L) (Mean ± SD)	4.33 ± 0.41
Creatine (mg/dL) (Mean ± SD)	4.25 ± 1.34
GFR (ml/min/1.73 m^2) (Mean ± SD)	83.28 ± 25.02
Total Cholesterol (mmol/L) (Mean ± SD)	177.00 ± 39.47
LDL (mg/dL) (Mean ± SD)	121.53 ± 40.22
Triglyceride (mg/dL) (Mean ± SD)	146.26 ± 50.89
HDL (mg/dL) (Mean ± SD)	40.30 ± 8.13

Rest summed score; RSS, Ejection fraction; EF, End-diastolic volume; EDV, End-systolic volume; ESV, NT-pro-B-type natriuretic peptide; BNP, Peak C-reactive protein; CRP, Glomerular filtration rate; GFR, Low-Density Lipoprotein; LDL, High-Density Lipoprotein; HDL.

Discussion

Our study is the first comprehensive study that evaluated the serum ACE2 level for HF prediction and its relationship with IS in the acute phase of STEMI, as well as compared the predictive value of the ACE2 level with that of classical biomarkers in STEMI. The main findings of our study are as follows: 1- Serum ACE2 level measured in the first 24 hours of STEMI was higher than healthy controls, and a significant increase was observed in serum ACE2 levels measured on the 5th day compared to the first measurements. 2- The increase in serum ACE2 levels in the acute phase of STEMI was not a predictor of RSS% indicating IS. 3- All of the classical biomarkers

Table III. Comparison of ACE2 levels.

Group	Baseline ACE2 ng/mL median (min-max)	5. days ACE2 ng/mL median (min-max)
Controls (N = 60)	1.45 (1.08-7.36)*	–
Patients (N = 66)	1.50 (1.14-8.53)	1.67 (1.19-14.74)**

Serum Angiotensin Converting Enzyme 2; ACE2. *$p < 0.05$ for comparison between baseline values in controls and patients by Mann-Whitney U test. **$p < 0.001$ for comparison between baseline and 5 days values in patients by paired Monte Carlo test.

Table IV. Comparison of ACE2 levels.

Control variables	Peak hs-cTnT (ng/L)	Peak CK-MB (UL)	Peak (BNP) (ng/L)	Peak CRP (mg/L)	5. day ACE2 (ng/mL)
RSS	.871**	-.142	.735**	.777**	.011
RSS%	.876**	-.150	.730**	.781**	.019
EF%	-.811**	.200	-.650*	-.797**	.040
EDV	.845**	-.200	.652*	.866**	-.075
ESV	.845**	-.178	.740**	.896**	-.113

Partial correlation (Controlling for age and sex). *$p < 0.05$, **$p < 0.001$.

Table V. Predictors of RSS% in the linear regression model.

	B	Beta	*p*-value
Peak hs-cTnT (ng/L)	.005	.673	.002
Peak BNP (ng/L)	.008	.378	.007
Sodium (mmol/L)	.185	.057	.029
HDL (mg/dL)	-.446	-.201	.044
Peak CRP (mg/L)	.179	.264	0.48
GFR (ml/min/1.73 m^2)	7.198	3.493	.059
Age (years)	.000	.000	.063
Creatinine (mg/dL)	-1.771	.941	.060

Method = BSTEP(WALD). NT-pro-B-type natriuretic peptide; BNP, Peak C-reactive protein; CRP, Glomerular filtration rate; GFR, Low-Density Lipoprotein; LDL, High-Density Lipoprotein; HDL.

were predictors of RSS% showing IS, and the most relevant predictors were found to be peak hs-cTnT and peak BNP.

ACE2 is an endogenous counterregulatory of RAS. The serum ACE2 level is thought to be an indicator of the pathological activation of the RAS[22]. Therefore, it has been stated that serum ACE2 levels can be used to predict the development and progression of CVD. Furthermore, since its discovery in 2000, the prognostic value of serum ACE2 level has been widely tested in the general population and many subgroups with cardiovascular disease[22,26-30]. Available evidence from all studies indicates a strong association between elevated serum ACE2 levels and major adverse cardiovascular events (MACE). However, studies in the STEMI cohort are limited. In studies[31-34], it has been reported that in the acute phase of STEMI, cardiac ACE2 expression also increases to balance the activated cardiac RAS, and the serum ACE2 level increases in this relation. On the contrary, few studies were showing that serum ACE2 is not elevated in the acute phase of STEMI. In a study[35] of patients with the acute coronary syndrome (ACS), serum ACE2 activity was found higher than in healthy controls, although this increase was not significant. In our study, serum ACE2 levels in STEMI patients were found to be higher compared to healthy controls. Additionally, it was observed that ACE2 levels were statistically significantly higher in the second measurement, which was obtained on the fifth day, than in the first measurement. Our results support the literature reporting pathological activation of the RAS in the pathogenesis of both atherosclerosis and STEMI.

The number of studies evaluating serum ACE2 level as a prognostic marker in the acute phase of STEMI was also limited. In a prospective study[36], the relationship between plasma ACE2 level and MACE in the HF and ACS cohort was investigated during a 5-year follow-up. It was found that

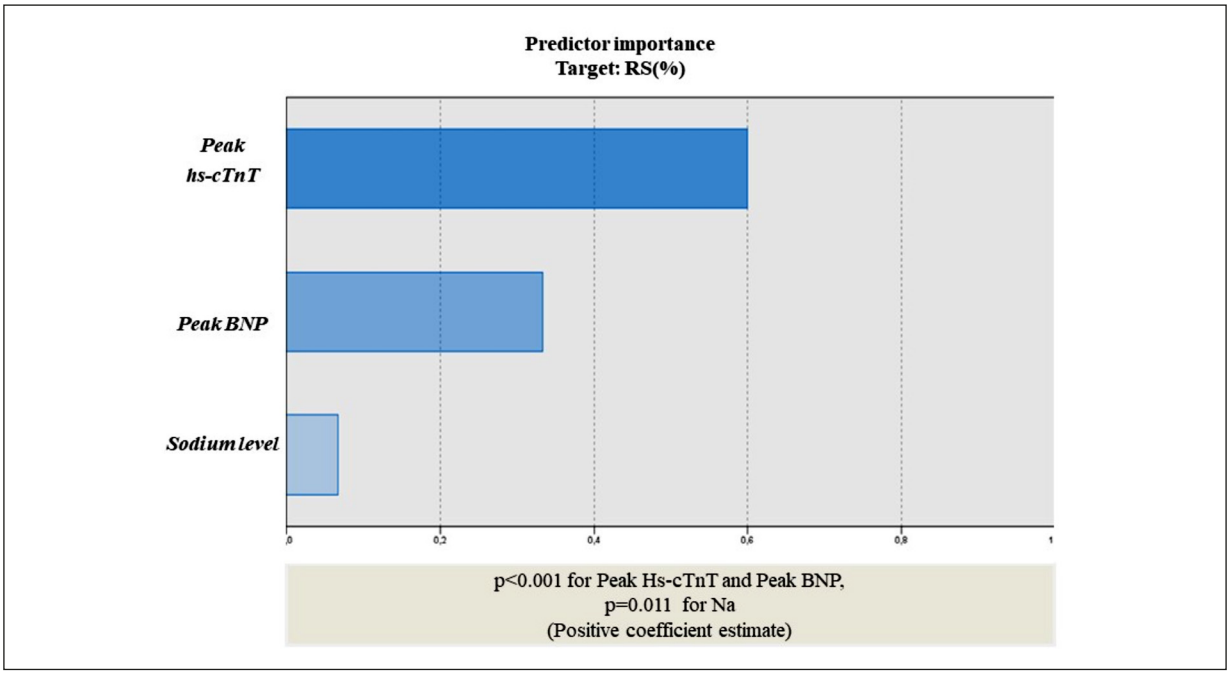
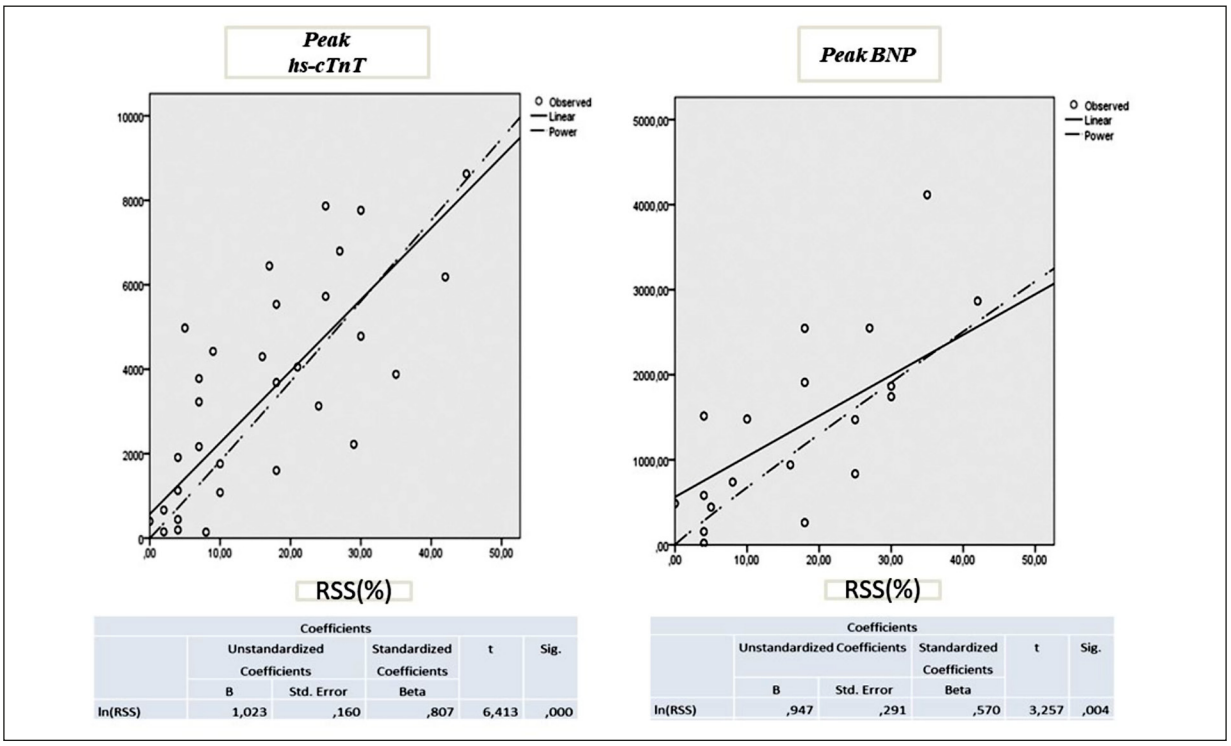


Figure 1. Predictor importance of RSS in the linear regression model. High-sensitive cardiac troponin T (hs-cTnT), B-type natriuretic peptide (BNP), Rest summed score (RSS).



Coefficients					
	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
ln(RSS)	1,023	,160	,807	6,413	,000

Coefficients					
	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
ln(RSS)	,947	,291	,570	3,257	,004

Figure 2. Curve estimation of predictive factors in the regression model for RSS.

plasma ACE2 level was higher in HF patients and was associated with long-term prognosis. In the ACS cohort, however, no correlation was found between plasma ACE2 levels measured in the first 24 hours of MI and MACE. This may be due to limitations such as measuring plasma ACE2 level once, not evaluating possible increases in the process, lack of comparison with healthy controls, and not providing an idea about causality as stated by the authors. In another study[33], the relationship of ACE2 activity after STEMI with IS and left ventricular systolic function was investigated. In 44 STEMI patients treated with PPCI, serum ACE2 activity was reported to increase at day 7 compared to baseline, and this increase was found to be associated with IS detected by CMR at admission. Also, the relationship of ACE2 activity after STEMI with IS left ventricular systolic function, and cardiac remodeling after MI was investigated[34]. In this study, serum ACE2 activity was measured at 24, 48 hours, and 7 days after admission and to evaluate the LV end-diastolic volume index, LVEF, and IS, CMR was performed on a mean day 6 of admission and repeated at 6 months. Serum ACE activity was found to be higher at the beginning compared to the controls and it was reported an increase on the 7th day. This increase in serum ACE2 activity was found to be associated with IS, left ventricular systolic dysfunction, and cardiac remodeling. However, the authors stated that the correlation between ACE2 activity and IS is weak. On the other hand, in many studies[9-16], it has been proven that the classical biomarkers Hs-cTnT, BNP, and CRP peak values are important indicators of IS. In our study, we found a positive correlation between RSS (%), an important indicator of IS, and classical biomarkers which are frequently used in clinical routines consistent with the current literature. The strongest correlation with IS was seen between peak hs-cTnT and peak BNP levels. However, in our study, we could not find a correlation between the increase of serum ACE2 level on the 5th day of STEMI and IS. The pathophysiological process progressing from ischemia to HF in STEMI is generally divided into two stages, acute and chronic. While RAS activation in the acute stage is moderate and compensatory, RAS hyperactivation in the chronic stage is pathological and contributes to the development of HF[37]. The lack of a relationship between ACE2 level and IS in the acute phase of STEMI in our study may be due to the moderate increase in RAS activity in this period. Another reason may

be the delayed release kinetics of ACE2. Although serum ACE2 levels are assumed to reflect tissue levels, it is unclear whether the increase in ACE2 occurs simultaneously in tissue and plasma. It has been stated that for ACE2 to be detected in plasma, ACE2 expression must first increase in the tissues, and then it must undergo proteolytic degradation[38]. Therefore, in the acute phase of STEMI, it may take time for the plasma ACE2 level to reflect the tissue level. However, the results of our study were lacking in causality that could support these hypotheses.

Conclusions

Our study has some limitations. The small number of patients and the fact that it is a single-center study require confirmation of the results with large-scale studies. Our study population included a stable and relatively narrow cross-section of STEMI patients. It does not include populations with high RAS activation, such as delayed and failed revascularization, multivessel disease, and a history of CVD. Therefore, the results of our study cannot be generalized to all STEMI patients. One of the important limitations of our study is to investigate only the ACE2 level as an indicator of RAS activity. Investigation of both the classical (ACE-Ang II) and regulatory axis (ACE2-Ang1-7) of the RAS provides a better understanding of RAS activation in the acute phase of STEMI as well as polymorphism of ACE2[39].

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

None.

Ethics Approval

Our study was approved by the Local Ethics Committee of City Hospital (2021/375) and was conducted in accordance with the Declaration of Helsinki.

Informed Consent

Signed informed consent was obtained from all participants before participating in the study.

Authors' Contribution

All the authors contributed in planning, researching data, and writing the manuscript.

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