Original Article

Correlation of B-type Natriuretic Peptide with Severity of Coronary Artery Disease Assessed by SYNTAX Score II in ST Elevation Acute Coronary Syndrome Patients

Onur Tasar, Gonenc Kocabay[1], Metin Cagdas[2], Yavuz Karabag[2]

Department of Cardiology, Elazig Research and Training Hospital, Elazig, [1]Department of Cardiology, Kartal Kosuyolu Heart and Research Hospital, Istanbul, [2]Department of Cardiology, Kars Kafkas University, Kars, Turkey

ORCID:

Onur Tasar: https://orcid.org/0000-0003-2030-3810
Gonenc Kocabay: https://orcid.org/0000-0002-1439-0252
Metin Cagdas: https://orcid.org/0000-0001-6704-9886
Yavuz Karabag: https://orcid.org/0000-0002-8156-315X

Abstract

Background: We aimed to evaluate the role of B-type natriuretic peptide (BNP) in assessing severity of coronary artery disease by SYNTAX score (SS) II in a prospective study among ST elevation acute coronary syndrome (ACS) patients. **Methods:** One thousand and six patients with ST elevation myocardial infarction (STEMI) who admitted for primary percutaneous intervention were included. The patients were divided into two groups according to SS II values (≤32 and >32). The independent predictors of high SS II were investigated, and the best cutoff value of BNP, high-sensitivity C-reactive protein (hs-CRP), peak troponin I, and hemoglobin level in predicting high SS II was determined. **Results:** There was a positive correlation between BNP, white blood cell, hs-CRP, fasting blood glucose, peak troponin I, and SS I. SS II and hemoglobin were negative, but other parameters were positively correlated. High SS II group independent predictors of hypertension, diabetes mellitus, smoking, multivessel disease, high Killip class, BNP, peak troponin I, hemoglobin, and hs-CRP levels were found in STEMI patients. The value of BNP >87.15 pg/ml with 59% sensitivity and 77% specificity (area under the curve [AUC]: 0.722 [95% confidence interval [CI]: 0.689–0.756], $P < 0.001$), hs-CRP >10.85 mg/dl with 64% sensitivity and 64% specificity (AUC: 0.685 [95% CI: 0.65–0.72], $P < 0.001$), peak troponin I >77.83 ng/mL with 68% sensitivity and 63% specificity (AUC: 0.704 [95% CI 0.67–0.738], $P < 0.001$), and hemoglobin >16.75 g/dL with 4% sensitivity and 97% specificity (AUC: 0.345 [95% CI: 0.309–0.382] $P < 0.001$) independently predicted high SS II group. **Conclusion:** Serum BNP level was independently associated with the severity of coronary atherosclerosis in patients with ACS together with multivessel disease, left ventricular ejection fraction, hs-CRP, and troponin. Therefore, BNP assessment gives additional prognostic information for early risk stratification of patients with ACS.

Keywords: Acute coronary syndrome, B-type natriuretic peptide, coronary artery disease

Introduction

The SYNTAX score (SS) is an angiographic scoring system based on the severity and complexity of coronary lesions.[1,2] To overcome the pitfalls of a system score based on coronary angiograms, seven clinical parameters, namely age, creatinine clearance (CrCl), left ventricular ejection fraction (LVEF), presence of unprotected left main, peripheral vascular disease (PVD), female sex, and chronic obstructive pulmonary disease (COPD), have been added to SS to obtain SS II.[3]

Received: 25-Jun-19 **Revision:** 18-Aug-19 **Accepted:** 01-Sep-19
Published Online: 25-Nov-19

Access this article online

Quick Response Code:

Website: http://www.ijcva.com

DOI: 10.4103/IJCA.IJCA_36_19

Address for correspondence: Dr. Onur Tasar, Department of Cardiology, Elazig Research and Training Hospital, Elazig, Turkey.
E-mail: tasaronur@hotmail.com

How to cite this article: Tasar O, Kocabay G, Cagdas M, Karabag Y. Correlation of B-type natriuretic peptide with the severity of coronary artery disease assessed by SYNTAX score II in ST elevation acute coronary syndrome patients. Int J Cardiovasc Acad 2019;5:129-33.

Cardiovascular biomarkers, such as B-type natriuretic peptide (BNP), high-sensitivity C-reactive protein (hs-CRP), and troponin I, have been suggested to relate to coronary artery disease (CAD) severity.[4] Furthermore, BNP has been used as a marker for prognosis in patients with acute coronary syndrome (ACS).[5-7] Although several studies in ACS patients demonstrated an association between increased BNP levels and poor clinical outcome,[5,6] it is not known if there is a relation between the quantity of BNP levels and the severity of CAD assessed by SS II.

We aimed to evaluate the role of BNP in assessing severity of CAD by SS II in a prospective study among ST elevation ACS patients.

Methods

This was a single-center study that was screened 1214 patients with ST elevation myocardial infarction (STEMI) who admitted for primary percutaneous intervention between January 2015 and March 2018. Exclusion criteria were previous myocardial infarction history, systemic inflammatory disease, hepatic disease, malignant disease, renal failure, and previous coronary artery bypass grafting. Finally, 1006 patients were included in the study. The research protocol was approved by our institution's ethics committee. All patients gave written inform consent. Clinical data, including sex, age, cardiovascular risk factors, medications, coronary angiogram, medical history, transthoracic echocardiography, and biochemical parameters, were collected. STEMI was defined as a presentation with acute chest pain, or suffocating shortness of breath, together with persistent ST-segment elevation >1 mm in 2 or more adjacent leads, or with a new or presumed new left bundle branch block or right bundle branch block on electrocardiography.[8] Hypertension (HT) was defined as repeated systemic blood pressure measurements exceeding 140/90 mmHg or treatment with antihypertensive drugs for a known diagnosis of HT. Diabetes mellitus (DM) was diagnosed by fasting blood glucose ≥126 mg/dL, blood glucose >200 mg/dL at any time, or a history of DM, including those treated with diet, oral medications, or insulin. Hypercholesterolemia was defined as a baseline cholesterol level >200 mg/dL and/or a low-density lipoprotein cholesterol level >130 mg/dL or previously diagnosed and treated hypercholesterolemia. Active smokers were those with regular smoking in the previous 6 months.

Baseline BNP, hs-CRP, and other routine blood tests were measured at admission. The BNP levels were measured by the enzyme immunoassay kit, based on standards and which ELISA technology (Biomedica Medizinprodukte GmbH, Wien, Divischgasse) (normal <100 pg/ml). hs-CRP, lipid profile, and peak cardiac enzyme levels were also obtained from all patients. Emergent coronary angiography was performed by the Judkins technique (Siemens Axiom Artis zee 2010; Siemens Healthcare, Erlangen, Germany). Percutaneous coronary intervention (PCI) procedures were performed using standard techniques. The type of stents (bare metal or drug eluting) using the thrombectomy and balloon was also left to the operator's discretion. All patients were treated with aspirin, clopidogrel or ticagrelor, and unfractionated heparin with the recommended doses after hospital admission. During and after the procedures, the use of glycoprotein 2b/3a inhibitors was at the operator's choice. At the hospital, medical treatments of patients were performed according to international guidelines.[8] At the admission, standard two-dimensional transthoracic echocardiography was performed for all patients (S5; GE Medical System, Horten, Norway). LVEF was measured by the Simpson method. The SS I and SS II were calculated according to baseline coronary angiography in all patients by two trained interventional cardiologists who were blinded to the patients' laboratory and clinical data. The SS I was determined for all coronary lesions with >50% diameter stenosis in a vessel >1.5 mm, based on the SYNTAX and SS II calculator (www.syntaxscore.com). PVD was defined as aorta or arteries other than coronaries, with exercise-related claudication, or revascularization surgery, or reduced or absent pulsation measured by duplex ultrasonography, or angiographic stenosis of more than 50% in case of severe symptoms. COPD was defined as the long-term use of a chronic bronchodilator or steroids for lung disease. CrCl was defined by the Cockcroft–Gault formula, expressed in ml/min. The patients were divided into two groups according to SS II values (≤32 and >32). All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All patients provided written informed consent.

Statistical analysis

Data were analyzed using the SPSS 17.0 version (SPSS Inc., Chicago, Illinois, USA). Normality of the data was determined using the Kolmogorov–Smirnov test. The continuous variables with a normal distribution are presented as mean ± standard deviation values, while those without a normal distribution are presented as median and interquartile range values. Frequency distribution was calculated for the categorical variables (numbers and percentages [%]). The continuous variables of the two groups were compared using the Student's *t*-test or the Mann–Whitney U-test. Categorical data were compared using the Chi-square test or Fisher's exact test. Correlations between different variables were assessed by Pearson's correlation test for continuous variables and Spearman test for noncontinuous variables. Multivariate logistic regression analyses were performed to identify the independent predictors of high SS II, using variables that showed statistically significant association with them in the univariate analyses. Receiver operating characteristic curve analysis was used to determine the best cutoff value of BNP, hs-CRP, peak troponin I, and hemoglobin level in predicting high SS II.

Results

We included 1006 patients (mean age: 57.0 ± 13.0 years; 80% were male) who were diagnosed with STEMI and performed coronary angiography in our clinic. The ischemia-related artery was left anterior descending in 545 patients, right coronary artery in 336 patients, and circumflex artery in 112 patients. Multivessel disease was present in 432 patients. The SS II values of the patients ranged from 13.40 to 80.45, and the median value was 30.5. Patients were divided into two groups according to SS II values. The mean SS I and SS II values of the high SS II group were 18.0 ± 5.0 and 42.9 ± 10.3, respectively, whereas the mean SS and SS II values of the low SS II group were 15.4 ± 3.7 and 22.7 ± 4.6, respectively. The comparison of baseline clinical and laboratory parameters of patients is shown in Table 1. Patients in the high SS II group were older, more diabetic, more hypertensive, more PVD, more smokers, and a higher Killip class than the patients in the lower SS II group. In patients with high SS II group, the use of angiotensin-converting enzyme inhibitors, beta-blocker, and statin was higher, whereas the use of aspirin was similar in both the groups. Higher white blood cell (WBC), fasting blood glucose, peak troponin I, hs-CRP, BNP, lower hemoglobin, and glomerular filtration rate values were present in the high SS II group. Multivessel disease and left main coronary artery involvement were more frequent in the SS II high group, whereas the mean ejection fraction (EF) value in the SS II high group was lower.

When all patients were evaluated, there was a positive correlation between BNP, WBC count, hs-CRP, fasting blood glucose, peak troponin I, and SS I, whereas there was no correlation between hemoglobin and SS. SS II and hemoglobin were negative; on the other hand, other parameters were positively correlated. Patients were divided into the following three groups according to LVEF to reduce the effect of EF on BNP: EF low group with <40%, EF middle range group between 40% and 49%, and high EF group with ≥50%. In the restructured correlation analysis, it was observed that SS I and BNP were positively correlated outside the middle range group, and BNP and SS II were well correlated in all the EF groups. Relation between SS I and SS II with BNP, WBC count, hemoglobin, hs-CRP, fasting blood glucose, and peak troponin I is shown in Table 2.

In multivariate logistic regression analysis, high SS II group independent predictors of HT, DM, smoking, multivessel disease, high Killip class frequency, BNP, peak troponin I, hemoglobin, and hs-CRP levels were found in STEMI patients. Table 3 shows the independent predictors of the high SS II group.

The value of BNP >87.15 pg/ml independently predicted high SS II group with 59% sensitivity and 77% specificity

Table 1: Baseline characteristics

	All patients	SS II ≤32	SS II >32	*P*
Age of patient	57.0±13.0	50.8±9.9	63.4±11.7	<0.001
Gender of patient (male)	846.0 (80.0)	477.0 (96.4)	325.0 (63.6)	<0.001
Presence of diabetes	254.0 (24.0)	41.0 (8.3)	206.0 (40.3)	<0.001
Presence of hypertension	474.0 (44.8)	159.0 (32.1)	299.0 (58.5)	<0.001
Presence of COPD	47.0 (4.4)	12.0 (2.4)	35.0 (6.8)	<0.001
Presence of peripheral arterial disease	186.0 (17.6)	13.0 (2.6)	167.0 (32.7)	<0.001
Presence of dyslipidemia	425.0 (40.2)	216.0 (43.6)	196.0 (38.4)	0.089
Family history of CAD	230.0 (21.8)	117.0 (23.6)	107.0 (20.9)	0.304
History of smoking	556.0 (52.6)	330.0 (66.7)	203.0 (39.7)	<0.001
Beta-blocker use	86.0 (8.1)	30.0 (6.1)	55.0 (10.8)	0.007
Statin use	197.0 (18.6)	81.0 (16.4)	111.0 (21.7)	0.031
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use	231.0 (21.9)	67.0 (13.5)	156.0 (30.5)	<0.001
Previous medication aspirin use	26.0 (2.5)	12.0 (2.4)	13.0 (2.5)	0.903
Killip class>1 on admission (%)	218.0 (20.6)	53.0 (10.7)	158.0 (30.9)	<0.001
WBC count (/1000)	12.4±4.0	11.8±3.3	13.0±4.6	<0.001
Hemoglobin (g/dL)	13.6±1.9	14.1±1.5	13.1±2.1	<0.001
CRP (mg/dl)	10.8 (5.9-18.3)	7.7 (4.8-13.5)	14.0 (7.7-24.5)	<0.001
Estimated glomerular filtration rate (ml/min/1.73m^2)	85.7±26.5	98.3±20.6	72.8 (26.0)	<0.001
Fasting blood glucose on admission (mg/dL)	128.0 (105.0-172.0)	116.0 (100.0-134.0)	148.0 (118.0-216.0)	<0.001
Peak troponin I (ng/mL)	84.4 (38.8-187.0)	54.4 (21.7-117.7)	121.0 (56.0-237.3)	<0.001
BNP (pg/mL)	72.5 (38.0-135.0)	51.2 (29.4-87.0)	97.1 (56.0-211.0)	<0.001
LVEF (%)	46.4±8.7	50.6±6.4	42.4±8.7	<0.001
Left main CAD presence	15.0 (1.4)	3.0 (0.6)	12.0 (2.3)	0.023
Multivessel disease presence	431.0 (40.8)	153.0 (30.9)	256.0 (50.1)	<0.001
Baseline SS	16.7±4.6	15.4±3.7	18.0±5.0	<0.001
Baseline SS II	33.0±12.9	22.7±4.6	42.9±10.3	<0.001

COPD: Chronic obstructive pulmonary disease, SS: SYNTAX score, CAD: Coronary artery disease, WBC: White blood cell, CRP: C-reactive protein, LVEF: Left ventricular ejection fraction, BNP: B-type natriuretic peptide

Table 2: Relation between SYNTAX score I and SYNTAX score II with B-type natriuretic peptide, white blood cell count, high-sensitivity C-reactive protein, fasting blood glucose, and peak troponin I

	Total				EF <40 (*n*=293)				40 ≤ EF ≤ 50 (*n*=391)				EF >50 (*n*=322)			
	Bazal SS		Bazal SS II		Bazal SS		Bazal SS II		Bazal SS		Bazal SS II		Bazal SS		Bazal SS II	
	Correlation coefficient	*P*	Correlation coefficient	*P*	Correlation coefficient	*P*	Correlation coefficient	*P*	Correlation coefficient	*P*	Correlation coefficient	*P*	Correlation coefficient	*P*	Correlation coefficient	*P*
BNP (pg/mL)	0.311	<0.001	0.486	<0.001	0.262	<0.001	0.358	<0.001	0.101	0.047	0.292	<0.001	0.258	<0.000	0.369	<0.001
WBC count (/1000)	0.189	<0.001	0.221	<0.001	0.111	0.057	0.120	0.040	0.158	0.002	0.074	0.146	−0.021	0.711	−0.159	0.004
Hemoglobin (g/dL)	−0.035	0.253	−0.328	<0.001	0.038	0.514	−0.290	<0.001	0.078	0.123	−0.401	<0.001	−0.177	<0.001	−0.488	<0.001
CRP (mg/dl)	0.257	<0.001	0.403	<0.001	0.162	0.009	0.273	<0.001	0.108	0.048	0.128	0.018	0.086	0.150	0.085	0.155
Fasting blood glucose on admission (mg/dL)	0.125	<0.001	0.443	<0.001	0.158	0.007	0.493	<0.001	−0.015	0.769	0.304	<0.001	0.021	0.713	0.409	<0.001
Peak troponin I (ng/mL)	0.365	<0.001	0.456	<0.001	0.195	<0.001	0.225	<0.001	0.228	<0.001	0.103	0.043	0.108	0.052	0.044	0.436

CRP: C-reactive protein, EF: Ejection fraction, SS: SYNTAX score, BNP: B-type natriuretic peptide, WBC: White blood cell

Table 3: Independent predictors of high SYNTAX score II group

	P	OR	95% CI for Exp(*B*)	
			Lower	Upper
Presence of diabetes	<0.001	6.789	4.333	10.638
Presence of hypertension	<0.001	2.108	1.476	3.011
History of smoking	<0.001	0.534	0.372	0.766
Killip class >1 on admission (%)	<0.001	2.260	1.393	3.667
Hemoglobin (g/dL)	<0.001	0.766	0.689	0.851
hs-CRP (mg/dl)	<0.001	1.036	1.018	1.054
Peak troponin I (ng/mL)	<0.001	1.005	1.003	1.007
Multivessel disease	<0.001	1.970	1.378	2.816
BNP (pg/mL)	<0.001	1.004	1.002	1.006

OR: Odds ratio, CI: Confidence interval, hs-CRP: High-sensitivity C-reactive protein, BNP: B-type natriuretic peptide

(AUC: 0.722 [95% CI: 0.689–0.756], $P < 0.001$); hs-CRP > 10.85 mg/dl independently predicted high SS II group with 64% sensitivity and 64% specificity (AUC: 0.685 [95% CI: 0.65–0.72]) $P < 0.001$); peak troponin I >77.83 ng/mL independently predicted high SS II group with 68% sensitivity and 63% specificity (AUC: 0.704 [95% CI: 0.67–0.738] $P < 0.001$); and hemoglobin > 16.75 independently predicted high SS II group with 4% sensitivity and 97% specificity (AUC: 0.345 [95% CI: 0.309–0.382] $P < 0.001$).

Discussion

The main finding of this study is that BNP and hs-CRP levels are related to the severity of coronary atherosclerosis assessed by SS II: patients with multivessel disease showed higher BNP levels, and BNP threshold of 88 pg/ml is able to predict the extension and severity of coronary disease with 77% specificity. As far as we know, this article is the first in the literature that evaluates the relation between CAD severity by SS II and biomarker levels (BNP, hs-CRP, and troponin I).

SS I is an important tool that can help clinicians to establish the optimal revascularization approach in patients with CAD. SS II combines the anatomical-based SS with the clinical baseline variables. Seven clinical parameters (age, creatinine clearance, LVEF, presence of unprotected left main, PVD, female sex, and COPD) have been added to SS to obtain SS II.[3] A recent article published by Salvatore *et al*.[3] reported that SS II might present a useful tool to predict the risk of adverse clinical events in patients with ACS and severe CAD undergoing PCI.

Previously, it has been showed that BNP provides predictive information on ACS, and it is related to the severity of CAD in patients with ACS.[9,10] Palazzuoli *et al*.[5] demonstrated that circulating BNP levels are elevated in ACS with diffuse coronary involvement and associated with multivessel disease and the extension of coronary disease. In addition, BNP could be indicators for multivessel disease, poor thrombolysis in myocardial infarction flow, and CAD extension. Although our results are in accordance with their study, we used SS II

system as a different tool to assess the coronary artery severity. Besides the different scoring system, they found that BNP higher than 80 pg/ml, which is lower than our findings, appears able to predict the extension of coronary disease. To calculate SS II, the anatomical SS is combined with age, CrCl, LVEF, and COPD, all of which affect the BNP levels. According to the current study, this new value should be used with SS II scoring system.

Hs-CRP levels on admission are associated with short- and long-term mortality in patients with ACS.[11] Karadeniz *et al*.[12] found that serum hs-CRP levels could predict the severity and complexity of coronary atherosclerosis together with multivessel disease, LVEF, and troponin levels. Nevertheless, they used the SS I to assess the severity of atherosclerosis, and the cutoff point of 5.77 was found as an independent predictor of a high SS I in patients with ACS.

In addition, we investigated the relationship between SS II and clinical and laboratory variables by multiple regression analyses. We found that BNP, hs-CRP, peak troponin I levels as well as diabetes, smoking, and multivessel disease were independent predictors for the high SS II group.

Limitations

Long term follow up could not be possible because this is a cross sectional study. Although it is a single-center study, we recruited a large sample size.

Conclusion

Serum BNP level was independently associated with the severity of coronary atherosclerosis in patients with ACS together with multivessel disease, LVEF, hs-CRP, and troponin. To our knowledge, this is the first study to demonstrate that BNP is an independent predictor of SS II in patients with ACS. Therefore, BNP assessment gives additional prognostic information for early risk stratification of patients with ACS.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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