In-hospital prognostic value of admission plasma B-type natriuretic peptide levels in patients undergoing primary angioplasty for acute ST-elevation myocardial infarction

Akut ST yükselmeli miyokart enfarktüsü nedeniyle primer anjiyoplasti yapılan hastalarda yatıştaki plazma B-tipi natriüretik peptit düzeylerinin hastaneiçi prognostik değeri

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ABSTRACT

Objectives: We assessed in-hospital prognostic value of admission plasma B-type natriuretic peptide (BNP) levels in patients undergoing primary percutaneous coronary intervention (p-PCI) for acute ST-elevation myocardial infarction (STEMI).

Study design: In a retrospective design, we evaluated 992 patients (801 males, 191 females; mean age 56±12 years) treated with p-PCI for STEMI. The patients were divided into two groups according to the admission BNP levels, taking the cut-off value of BNP as 100 pg/ml; i.e, ≥100 pg/ml (n=334, 33.7%) and <100 pg/ml (n=658, 66.3%). Postprocedural angiographic and clinical in-hospital results were recorded.

Results: No-reflow (24% *vs.* 9%), heart failure (32.3% *vs.* 5.5%) and death (15.6% *vs.* 1.7%) were significantly more common in patients with BNP ≥100 pg/ml (p<0.001). In multivariate analysis, elevated baseline BNP level was identified as an independent predictor of no-reflow (OR=1.83; 95% CI 1.22-2.74, p=0.003), acute heart failure (OR=2.67; 95% CI 1.55-4.58, p<0.001), and in-hospital mortality (OR=3.28; 95% CI 1.51-7.14, p=0.003). In receiver operating characteristic curve analysis, the area under the curve and sensitivity/specificity of the cut-off value of BNP (100 pg/ml) for prediction of clinical endpoints were 0.741 and 58.6%/70.3% for no-reflow, 0.822 and 75%/73.3% for heart failure, and 0.833 and 82.5%/69.4% for death, respectively (p<0.001 for all).

Conclusion: Elevated admission BNP level is an independent predictor of angiographic no-reflow, acute heart failure, and mortality in STEMI patients during in-hospital period, suggesting that it might be incorporated into traditional risk scoring systems to improve early risk stratification.

ÖZET

Amaç: Akut ST yükselmeli miyokart enfarktüsü (STEMİ) nedeniyle primer anjiyoplasti uygulanan hastalarda yatıştaki B-tipi natriüretik peptit (BNP) düzeylerinin erken dönem hastaneiçi prognostik değeri araştırıldı.

Çalışma planı: Geriye dönük bir tasarımla çalışmaya, akut STEMİ tanısıyla primer anjiyoplasti uygulanan 992 hasta (801 erkek, 191 kadın; ort. yaş 56±12) alındı. Hastalar, yatıştaki BNP düzeylerine göre, kestirim değeri 100 pg/ml alınarak BNP ≥100 pg/ml (n=334, %33.7) ve <100 pg/ml (n=658, %66.3) olmak üzere iki gruba ayrıldı. İşlem sonrası anjiyografik ve hastaneiçi klinik sonuçlar kaydedildi.

Bulgular: Yüksek BNP düzeyi (≥100 pg/ml) olan hastalarda yeniden akım olmaması (%24 ve %9), kalp yetersizliği (%32.3 ve %5.5) ve ölüm (%15.6 ve %1.7) anlamlı derecede daha sık görüldü (tümü için, p<0.001). Çokdeğişkenli analizde, yatıştaki yüksek BNP düzeyi yeniden akım olmaması (OO=1.83; %95 GA 1.22-2.74, p=0.003), akut kalp yetersizliği gelişimi (OO=2.67; %95 GA 1.55-4.58, p<0.001) ve erken dönem hastaneiçi ölüm (OO=3.28; %95 GA 1.51-7.14, p=0.003) için bağımsız öngördürücü bulundu. Alıcı işletim karakteristiği analizinde, BNP için 100 pg/ml'lik kesim değerinin eğri altında kalan alanı ve duyarlık/özgüllük değerleri yeniden akım olmaması için sırasıyla 0.741 ve %58.6/%70.3, kalp yetersizliği için 0.822 ve %75/%73.3, ölüm için 0.833 ve %82.5/%69.4 olarak hesaplandı (tümü için, p<0.001).

Sonuç: Başvurudaki yüksek BNP düzeyi, STEMİ hastalarında anjiyografide yeniden akım olmaması, hastaneiçi dönemde akut kalp yetersizliği ve mortalite gelişimi için bağımsız öngördürücüdür. Bu hastaların erken dönem risk tabakalandırılmasında geleneksel risk skorlama sistemlerine eklenebilir.

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Early risk stratification of patients with acute ST-elevation myocardial infarction is important, as timely specific therapeutic approaches may potentially improve the long-term prognosis of high-risk individuals. B-type natriuretic peptide, a neurohormone released from ventricular myocytes in response to acute extension (pressure/volume)[1] has already emerged as an important prognostic marker in patients with STEMI.[2,3] In addition to being an independent predictor of short- and long-term mortality,[3,4] BNP has also been shown to be a significant predictor of no-reflow phenomenon in recent studies on primary percutaneous coronary intervention.[5,6] However, each study identified a different optimal cut-off value for prediction of a number of clinical endpoints. The cut-off value for BNP in healthy individuals is 25 pg/ml[7] and the widely accepted optimal cut-off value for BNP to rule out acute heart failure is 100 pg/ml.[8] At this cut-off value, there is a high diagnostic agreement between diverse BNP assays.[9]

We investigated the in-hospital prognostic value of admission plasma BNP levels and the usefulness of the 100 pg/ml cut-off in predicting multiple clinical endpoints after STEMI.

PATIENTS AND METHODS

Study population

We retrospectively evaluated 992 patients (801 males, 191 females; mean age 56±12 years) who underwent p-PCI for acute STEMI between January 2006 and April 2008. Inclusion criteria were typical ongoing ischemic chest pain for longer than 30 minutes, and ST elevation of at least ≥1 mm in at least two contiguous leads (2 mm for V1-V3) or new-onset left bundle branch block. The study was approved by our hospital ethics committee and all patients gave written informed consent.

Definitions

Preinfarction angina pectoris was defined as cardiac symptoms lasting <30 min and occurring within 48 hours before the onset of infarction. Anemia was defined according to the criteria of the World Health Organization (hemoglobin <13 g/dl for males and <12 g/dl for females).[10] Estimated glomerular filtration rate was calculated according to the MDRD (Modification Diet in Renal Disease) formula.[11] Thrombolysis In Myocardial Infarction (TIMI) risk scores for STEMI were calculated on admission in all the patients.[12] No-reflow was defined as the presence of TIMI ≤2 flow in the absence of residual stenosis, spasm, dissection, or distal embolization. Myocardial blush grade was defined as reported previously (0: minimal or no myocardial blush; 1: dye staining the myocardium with staining persisting through the next injection; 2: dye entering the myocardium but washing out slowly so that it is strongly persistent at the end of the injection; and 3: normal entrance and exit of dye in the myocardium so that it is mildly persistent at the end of the injection).[13] Collateral channels were graded according to the report by Rentrop et al.[14] and good collateral flow was defined as grade 2 or 3. Acute heart failure was defined as the presence of postprocedural pulmonary crackles and alveolar or interstitial edema with radiological evidence, requiring diuretic or inotropic treatment, independent from Killip classification. Reinfarction was defined as the recurrence of typical clinical symptoms and appearance of new electrocardiographic changes with a new elevation in creatine kinase-MB isoform levels >2 times the upper normal limit.

Abbreviations:

AHF	*Acute heart failure*
AUC	*Area under curve*
BNP	*B-type natriuretic peptide*
CK	*Creatine kinase*
eGFR	*Estimated glomerular filtration rate*
LV	*Left ventricular*
p-PCI	*Primary percutaneous coronary intervention*
STEMI	*ST-elevation myocardial infarction*
TIMI	*Thrombolysis In Myocardial Infarction*

Study protocol

All patients received 300 mg chewable aspirin and a loading dose of 300-600 mg clopidogrel on admission and 70 U/kg intravenous standard heparin before the procedure. Use of glycoprotein IIb/IIIa inhibitor (tirofiban, 10 μg/kg bolus followed by 0.15 μg/kg/min intravenous infusion) was left to the discretion of the primary operator. All p-PCI procedures were performed by experienced interventional cardiologists through the femoral approach with a 7 Fr guiding catheter. The lesions were passed by a 0.014 inch guidewire. In patients with a baseline TIMI ≥1 flow, primary angioplasty was performed with or without stenting based on the primary operator's discretion. Nonionic contrast medium iohexol was used in all the procedures (Omnipaque, GE Healthcare Bio-Sciences). After the procedure, all patients were followed-up in the coronary intensive care unit until clinical stabilization was established. All patients received 300 mg/day aspirin and 75 mg/day clopidogrel during in-hospital stay.

ST-segment resolution was calculated as the sum of ST-segment elevation on admission minus the sum of ST-segment elevation 60 min after p-PCI divided by the sum of ST-segment elevation on admission, and a value of >70% was defined as successful reperfusion (complete resolution).[15] Postprocedural transthoracic echocardiography (Vingmed, Vivid 3 or Vivid 5, GE, Hortan, Norway) was performed during in-hospital period. Left ventricular ejection fraction was calculated using the biplane Simpson's method.

All coronary hemodynamic data were recorded, stored off-line, and analyzed by two independent investigators. Coronary lesions were evaluated in at least two nonforeshortened angiographic views at the end-diastolic phase. Lesions >50% were labeled as hemodynamically significant. Pre- and postprocedural TIMI flows, collateral flow (Rentrop), infarct-related artery, severity of the lesions, and the number of diseased vessels were noted.

Laboratory tests

Peripheral blood samples for BNP were obtained before p-PCI using direct venipuncture of the antecubital vein, collected into EDTA tubes, and sent to laboratory immediately. The samples were centrifuged at 3500 g for five minutes. B-type natriuretic peptide was measured with the use of the immunoassay method on an ADVIA Centaur-XP device (Siemens Medical Solutions, Germany) using the kits of ADVIA Centaur BNP assay (Bayer Diagnostics, Tarrytown, New York). This technique has previously been described elsewhere.[9] The measurable range of the BNP assay was 2.0 to 5,000 pg/ml. The ADVIA Centaur BNP assay had a within run coefficient of variation of 1.8 to 4.3% and a total coefficient of variation of 2.3 to 4.7% at concentrations of 29.4 to 1,736.0 pg/ml. Baseline hemogram parameters, urea, creatinine, CK, CK-MB, and troponin I levels were obtained on admission. Blood samples for CK, CK-MB, and troponin I were obtained every six hours until peak levels were reached and repeated daily thereafter. Hemogram parameters, urea, and creatinine levels were also evaluated daily.

Statistical analysis

Continuous variables with normal and non-normal distribution were expressed as mean±SD and median (interquartile range), respectively. Categorical variables were expressed as percentages. Group means for continuous variables with normal and non-normal distribution were compared using the independent samples t-test and Mann-Whitney U-test, respectively. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. The Spearman correlation test was used for correlation analysis. Multivariate logistic regression analysis was used to identify the independent predictors of elevated BNP (≥100 pg/ml). In order to evaluate whether BNP was an independent predictor of death, AHF, and no-reflow, stepwise multivariate logistic regression analysis was performed for each endpoint. All variables showing a significance level of <0.10 in univariate analysis were included in the model. B-type natriuretic peptide was initially included in the models as a continuous variable and then as a dichotomous variable based on the established cut-off level. Finally, receiver operating characteristic curve analysis was used to identify the area under curve and to determine the specificity and sensitivity of the 100 pg/ml cut-off level in prediction of no-reflow, AHF, and death. A two-tailed *p* value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were processed using the SPSS 11.5 statistical software package.

RESULTS

Baseline characteristics of the patients are shown in Table 1. Baseline BNP levels ranged from 4.30 to 1,357 pg/ml with a median of 73 (interquartile range 37-138) pg/ml. In 334 patients (33.7%), BNP levels were elevated. Patients with elevated BNP levels on admission were older and had prolonged transfer to hospital. Moreover, the frequencies of comorbid conditions such as diabetes, hypertension, renal dysfunction, anemia, and anterior myocardial infarction, Killip class ≥2, and right/left bundle branch block on admission were significantly higher in patients with elevated BNP levels (Table 1).

Predictors of elevated BNP levels on admission

In correlation analysis, baseline BNP levels were positively correlated with age (r=0.24, p<0.001), pain-to-door time (r=0.28, p<0.001), TIMI risk score (r=0.40, p<0.001), and peak CK level (r=0.38, p<0.001), and negatively correlated with eGFR (r=-0.25, p<0.001), postprocedural LV ejection fraction (r=-0.44, p<0.001), preprocedural TIMI flow (r=-0.30, p<0.001), and postprocedural TIMI flow (r=-0.29, p<0.001). In multivariate logistic regression analysis, age, diabetes mellitus, pain-to-door time, eGFR, multivessel disease, culprit left anterior descending artery, proximal lesion site, and baseline TIMI ≤1 flow were identified as independent predictors of elevated BNP levels on admission (Table 2).

Table 1. Clinical and procedural data of the patients

	Overall (n=992)		BNP ≥100 pg/ml (n=334)		BNP <100 pg/ml (n=658)		
	n	%	n	%	n	%	*p*
Age (years) / Mean±SD	56±12		60±12		55±11		**<0.001**
Gender							**0.001**
Male	801	80.6	249	74.6	552	83.9	
Female	191	19.3	85	25.5	106	16.1	
Hypertension	446	45.0	174	52.1	272	41.3	**0.002**
Diabetes mellitus	242	24.4	113	33.8	129	19.6	**<0.001**
Hypercholesterolemia	397	40.0	120	35.9	277	42.1	0.071
Current smoker	506	51.0	137	41.0	369	56.1	**<0.001**
Previous myocardial infarction	71	7.2	30	9.0	41	6.2	0.14
Previous coronary artery bypass grafting	32	3.2	10	3.0	22	3.3	0.91
Preinfarction angina pectoris	209	21.1	65	19.5	144	21.9	0.42
Pain to door time (min) / Median (interquartile range)	140 (80-240)		195 (110-290)		120 (70-210)		**<0.001**
Pain to balloon time of >4 hours	321	32.4	165	49.4	156	23.7	**<0.001**
Killip class ≥2	194	19.6	109	32.6	85	12.9	**<0.001**
Cardiogenic shock	66	6.7	49	14.7	17	2.6	**<0.001**
Bundle branch block on admission	58	5.9	40	12.0	18	2.7	**<0.001**
Estimated glomerular filtration rate <60 ml/min/1.73m^2	88	8.9	59	17.7	29	4.4	**<0.001**
Baseline BNP (pg/ml) / Median (interquartile range)	73 (37-138)		202 (135-327)		45 (27-72)		**<0.001**
Baseline anemia	257	25.9	109	32.6	148	22.5	**0.001**
Anterior myocardial infarction	531	53.5	217	65.0	314	47.7	**<0.001**
TIMI risk classification / Median (interquartile range)	2 (1-4)		3 (2-5)		2 (1-3)		**<0.001**
Previous drug use							
Aspirin	114	11.5	39	11.7	75	11.4	0.98
Angiotensin converting enzyme inhibitor	234	23.6	82	24.6	152	23.1	0.66
Beta-blocker	138	13.9	50	15.0	88	13.4	0.55
Statin	219	22.10	61	18.3	158	24.0	**0.047**
Multivessel disease	407	41.0	164	49.1	243	36.9	**<0.001**
Infarct-related artery							
Left anterior descending artery	534	53.8	216	64.7	318	48.3	**<0.001**
Circumflex artery	117	11.8	38	11.4	79	12.0	0.85
Right coronary artery	319	32.2	72	21.6	247	37.5	**<0.001**
Baseline TIMI 2/3 flow	244	24.6	41	12.3	203	30.9	**<0.001**
Rentrop grade 2/3	46	4.6	11	3.3	35	5.5	0.16
Tirofiban use	498	50.2	161	48.2	337	51.2	0.40
Stent use	920	92.7	302	90.4	618	93.9	0.06
Proximal lesion site	583	58.8	245	73.4	338	51.4	**<0.001**
Final TIMI 3 flow	852	85.9	253	75.8	599	91.0	**<0.001**
Myocardial blush grade 3 (787 patients)	316	40.2	67	23.6	249	49.5	**<0.001**
ST resolution >70%	543	54.7	127	39.0	416	67.0	**<0.001**
Peak creatine kinase (IU/l)	1843 (970- 3308)		2970 (1511-4235)		1459 (866-2507)		**<0.001**
Postprocedural ejection fraction (%) / Mean±SD	46±9		41±9		49±7		**<0.001**
Significant mitral regurgitation	18	1.8	13	3.9	5	0.8	**0.001**
In-hospital diuretic use	189	19.1	121	36.2	68	10.3	**<0.001**
Furosemide (mg/dl) / Median (interquartile range)	40 (20-60)		60 (40-80)		40 (20-60)		**0.008**

Table 2. The results of multivariate logistic regression analysis showing independent predictors of elevated BNP levels (≥100 pg/ml) on admission

	Odds ratio	95% Confidence interval	*p*
Age (for every 10-year increase)	1.26	1.07 - 1.48	**0.005**
Diabetes mellitus	1.55	1.08 - 2.21	**0.016**
Pain-to-door time (for every 1-hour delay)	1.17	1.09 - 1.26	**<0.001**
Estimated glomerular filtration rate (for every 10-ml/min/m^2 decrease)	0.87	0.79 - 0.95	**0.002**
Multivessel disease	1.49	1.10 - 2.02	**0.009**
Culprit left anterior descending artery	2.18	1.57 - 3.03	**<0.001**
Proximal lesion site	1.74	1.25 - 2.42	**0.001**
Baseline TIMI ≤1 flow	2.59	1.74 - 3.87	**<0.001**

Baseline BNP levels and in-hospital cardiovascular events

Admission BNP levels were significantly higher in patients who subsequently developed angiographic no-reflow (median; interquartile range: 164; 87-326 *vs.* 65; 33-122 pg/ml, p<0.001), AHF (median; interquartile range: 238; 99-414 *vs.* 61; 33-109 pg/ml, p<0.001), and in-hospital death (median; interquartile range: 321; 129-564 *vs.* 69; 34-124 pg/ml, p<0.001) compared to patients who did not experience these complications. Comparison of in-hospital cardiovascular events based on the cut-off level of BNP is shown in Table 3. Compared to patients who developed in-hospital cardiovascular events and had a baseline BNP level of <100 pg/ml, the frequencies of angiographic no-reflow (24.3% *vs.* 9%), death (15.6% *vs.* 1.7%), and AHF (32.3% *vs.* 5.5%) were significantly higher (p<0.001 for all), and length of hospital stay was significantly longer in patients having high BNP levels (p<0.001). The frequencies of reinfarction and target vessel revascularization did not differ significantly between the two BNP groups (p>0.05).

Prognostic value of baseline BNP levels

In univariate analysis, BNP≥100 pg/ml was found to be a strong predictor of no-reflow (OR 3.25, 95% CI 2.25-4.68), AHF (OR 8.25, 95% CI 5.49-12.40), and in-hospital mortality (OR 10.84, 95% CI 5.57-21.09) (for all p<0.001). Other univariate predictors of no-reflow, AHF, and death are summarized in Table 4. In multivariate analysis, when BNP (for every 10 pg/ml increase) was included in the model as a continuous variable, it was found to be an independent predictor of no-reflow (OR 1.06, 95% CI 1.04-1.09, p<0.001), AHF (OR 1.07, 95% CI 1.04-1.11, p=0.004) and mortality (OR 1.08, 95% CI 1.05-1.12, p<0.001). When BNP was included in the model as a dichotomous variable according to the laboratory cut-off level of 100 pg/ml, it was found to be a strong independent predictor of no-reflow (OR 1.83, 95% CI 1.22-2.74, p=0.003), AHF (OR 2.67, 95% CI 1.55-4.58, p<0.001), and in-hospital mortality (OR 3.28, 95% CI 1.51-7.14, p=0.003). Other independent predictors of no-reflow, AHF, and death are shown in Table 4.

Table 3. In-hospital cardiovascular events

	Overall (n=992)		BNP ≥100 pg/ml (n=334)		BNP <100 pg/ml (n=658)		
	n	%	n	%	n	%	*p*
No-reflow	140	14.1	81	24.3	59	9.0	**<0.001**
Acute heart failure	144	14.5	108	32.3	36	5.5	**<0.001**
Death	63	6.4	52	15.6	11	1.7	**<0.001**
Reinfarction	15	1.5	6	1.8	9	1.4	0.80
Target vessel revascularization	20	2.0	8	2.4	12	1.8	0.71
Hospital stay (days) / Median (interquartile range)	5 (3-6)		5 (4-7)		4 (3-6)		**<0.001**

In receiver operating characteristic curve analysis, AUC of BNP and the sensitivity and specificity of the laboratory cut-off value (100 pg/ml) for in-hospital cardiovascular events were as follows: for no-reflow, AUC=0.741, 95% CI 0.698-0.783, sensitivity=58.6%, specificity=70.3%); for AHF, AUC=0.822, 95% CI 0.785-0.860, sensitivity=75%, specificity=73.3%; and for in-hospital mortality, AUC=0.833, 95% CI 0.773-0.889, sensitivity=82.5%, specificity=69.4%) (p<0.001 for all, Fig. 1a-c) . There was no difference between the AUCs of BNP and TIMI risk scoring system with respect to prediction of in-hospital mortality (p=0.11) (Fig. 1c).

Mortality rates during early hospital period were 1.1% and 19.5% in patients with a TIMI risk score of <4 and ≥4, respectively. When both TIMI risk score and BNP levels were taken into consideration, in-hospital mortality increased from 0.4% (TIMI risk score <4 and BNP <100 pg/ml) to 28.9% (TIMI risk score ≥4 and BNP ≥100 pg/ml).

DISCUSSION

This retrospective study confirms that admission plasma BNP level is an important and independent prognostic marker that predicts angiographic no-reflow, AHF, and death during early in-hospital period in patients treated with p-PCI for acute STEMI. Furthermore, this study demonstrates the clinical usefulness of the previously established cut-off value (100 pg/ml) of BNP in prediction of multiple clinical endpoints and early risk stratification of patients after STEMI.

Table 4. Univariate and multivariate analysis for predictors of no-reflow, heart failure, and death*

	No-reflow		Heart failure		Death	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Univariate analysis						
Age ≥65 years	2.04 (1.40 - 2.97)	**<0.001**	2.58 (1.79 - 3.72)	**<0.001**	3.52 (2.10 - 5.91)	**<0.001**
Diabetes mellitus	1.45 (0.98 - 2.15)	0.076	3.23 (2.23 - 4.66)	**<0.001**	4.68 (2.77 - 7.89)	**<0.001**
Current smoker	0.59 (0.41 - 0.85)	**0.007**	0.44 (0.30 - 0.63)	**<0.001**	0.20 (0.10 - 0.39)	**<0.001**
Reperfusion time >4 hours	4.34 (2.98 - 6.29)	**<0.001**	3.04 (2.12 - 4.36)	**<0.001**	3.72 (2.20 - 6.31)	**<0.001**
Renal dysfunction†	2.90 (1.76 - 4.78)	**<0.001**	7.59 (4.76 - 12.11)	**<0.001**	11.58 (6.60 - 20.31)	**<0.001**
BNP ≥100 pg/ml	3.25 (2.25 - 4.68)	**<0.001**	8.25 (5.49 - 12.40)	**<0.001**	10.84 (5.57 - 21.09)	**<0.001**
Anemia on admission	1.60 (1.09 - 2.33)	**0.019**	2.62 (1.81 - 3.78)	**<0.001**	3.01 (1.79 - 5.04)	**<0.001**
Baseline TIMI ≤1 flow	7.29 (3.37 - 15.87)	**<0.001**	10.86 (4.42 - 27.02)	**<0.001**	10.75 (2.60 - 43.47)	**<0.001**
Female gender	–		1.93 (1.29 - 2.88)	**0.002**	2.60 (1.51 - 4.46)	**0.001**
Multivessel disease	–		1.92 (1.35 - 2.75)	**<0.001**	2.15 (1.28 - 3.61)	**0.005**
Final TIMI ≤2 flow	–		5.54 (3.70 - 8.30)	**<0.001**	5.41 (3.16 - 9.26)	**<0.001**
Postprocedural LVEF ≤35%	–		40.08 (25.10 - 63.75)	**<0.001**	22.93 (12.41 - 42.38)	**<0.001**
Anterior myocardial infarction	–		3.14 (2.1 - 4.71)	**<0.001**	1.66 (0.98 - 2.84)	0.057
Multivariate analysis						
BNP ≥100 pg/ml	1.83 (1.22 - 2.74)	**0.003**	2.67 (1.55 - 4.58)	**<0.001**	3.28 (1.51 - 7.14)	**0.003**
Baseline TIMI ≤1 flow	5.37 (2.43 - 11.90)	**<0.001**	3.84 (1.37 - 10.77)	**0.01**	–	
Reperfusion time >4 hours	3.36 (2.27 - 4.98)	**<0.001**	–		–	
Renal dysfunction†	–		3.00 (1.44 - 6.25)	**0.003**	3.73 (1.71 - 8.13)	**0.001**
Postprocedural LVEF ≤35%	–		19.23 (10.86 - 34.48)	**<0.001**	11.11 (5.00 - 25.00)	**<0.001**
Diabetes mellitus	–		1.96 (1.12 - 3.42)	**0.018**	–	
Anemia on admission	–		2.08 (1.15 - 3.78)	**0.015**	–	
Final TIMI ≤2 flow	–		2.35 (1.30 - 4.25)	**0.004**	–	
Anterior myocardial infarction	–		1.92 (1.02 - 3.60)	**0.043**	–	

*Univariate analysis includes parameters with p<0.1, and multivariate analysis includes parameters with p<0.05; OR: Odds ratio; CI: Confidence interval; LVEF: Left ventricular ejection fraction; †Estimated glomerular filtration rate <60 ml/min/1.73m^2.

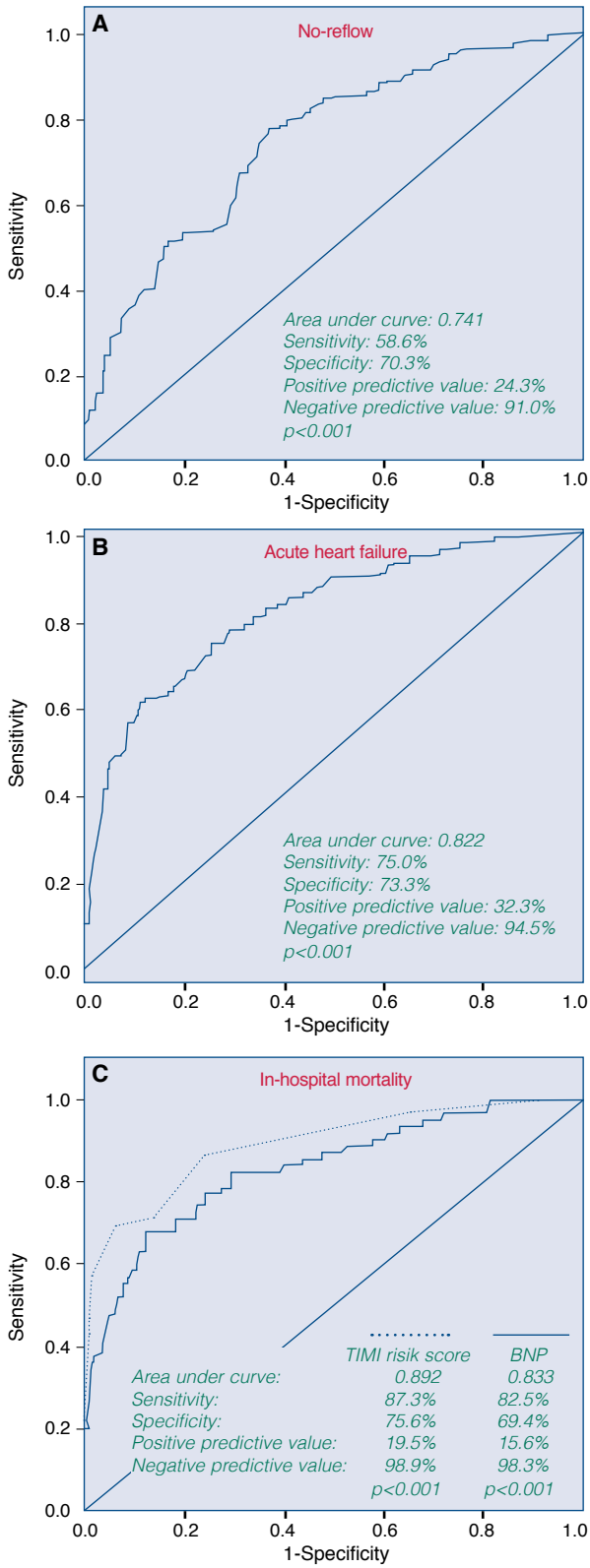

Figure 1. Receiver operating characteristic curves for the ability of BNP (cut-off value 100 pg/ml) to predict **(A)** angiographic no-reflow, **(B)** acute heart failure, and **(C)** (in comparison with TIMI risk score, p=0.11) in-hospital mortality.

No-reflow is a serious complication of p-PCI and is associated with poor short- and long-term prognosis.[16,17] Therefore, utilization of new tools to predict no-reflow is essential for identification of patients at high risk. Grabowski et al.[5] were the first to demonstrate that a high admission BNP level (>100 pg/ml) was a powerful predictor of angiographic no-reflow. Subsequent studies with varying optimal cut-off values confirmed the value of BNP and N-terminal pro-BNP as a predictor of no-reflow.[6,18] Jeong et al.[6] identified the optimal cut-off value of BNP as 90 pg/ml in prediction of no-reflow with positive predictive value of 12% and negative predictive value of 98%. In our study, with the cut-off value of 100 pg/ml, these values were 24.3% and 91%, respectively, for prediction of no-reflow.

The exact mechanism underlying the link between admission BNP level and no-reflow has not been clearly defined. High BNP levels on admission may just be a consequence of overstretched LV due to a larger infarct area which may be related to factors such as prolonged reperfusion time and preprocedural TIMI ≤1 flow. However, in our study, BNP was still a predictor of no-reflow independent from these factors. On the other hand, high BNP levels may reflect mainly the severity of myocardial ischemia. Goetze et al.[19] demonstrated that myocardial ischemia was associated with increased cardiac BNP expression independent from LV functions. Moreover, previous studies demonstrated that BNP levels were higher in patients with more severe coronary artery disease.[20,21] We found that high baseline BNP levels were associated not only with angiographic no-reflow, but also with poor microvascular perfusion evaluated by electrocardiographic ST-segment resolution and myocardial blush grade, in accordance with previous studies that used magnetic resonance imaging.[22,23]

Previous studies demonstrated that BNP level was related to infarct area and there was a positive correlation between the BNP level and transmural infarct pattern in patients treated with p-PCI.[22,23] We found that bundle branch block, which may also be related to larger infarct area, was more frequent in patients with elevated plasma BNP levels on admission. Furthermore, BNP was found to be an independent predictor of increased long-term collagen turnover and progressive LV dilation.[24,25] Our work contributes to these studies showing an independent strong relationship between elevated admission BNP levels and development of AHF during early in-hospital period. Patients with high admission BNP levels had a six-

fold higher rate of in-hospital AHF than those with lower BNP levels. We found that admission BNP levels were negatively correlated with postprocedural LV ejection fraction and positively correlated with peak cardiac enzyme levels. Accordingly, the incidence of severe mitral regurgitation was higher in patients with elevated BNP levels on admission. These results are in accordance with those of previous studies demonstrating significant association between baseline BNP levels and LV end-diastolic volume index and development of AHF in early postinfarction period.[25,26] In our study, positive predictive value of the cut-off value of BNP for the development of AHF was only 32.3%, whereas negative predictive value was significantly higher (94.5%). The cut-off value of 100 pg/ml had a sensitivity of 75% and a specificity of 73.3% in predicting AHF during early in-hospital period.

Several studies have shown that elevated baseline BNP level in acute myocardial infarction is related with increased in-hospital and long-term mortality.[2-5] In a study investigating the additional benefit of baseline BNP over TIMI risk score, the optimal cut-off value of BNP in predicting 42-day mortality was found to be 331 pg/ml.[27] In a subgroup analysis of the ENTIRE-TIMI 23 trial, baseline BNP was found to be associated with higher 48-hour, 7- and 30-day mortality rates, with an optimal cut-off value of 80 pg/ml.[4] Likewise, Ang et al.[28] found that BNP >80 pg/ml predicted short-term and 10-month adverse cardiovascular events (death and heart failure) independent from echocardiographic parameters (LV ejection fraction and LV hypertrophy). In our study, baseline BNP of ≥100 pg/ml predicted mortality with a sensitivity of 82.5% and specificity of 69.4%. Patients with a baseline BNP level of ≥100 pg/ml had a nine-fold higher rate of in-hospital mortality. Baseline BNP level seems to improve early risk prediction in patients with STEMI, in addition to established risk scoring systems. With the cut-off value of 100 pg/ml, the prognostic value of BNP was as strong as that of TIMI risk score for STEMI (Fig. 1c). Combined use of BNP levels and TIMI risk scoring for prediction of death resulted in increased sensitivity and specificity rates. Among patients with a low TIMI risk score (<4), lower BNP levels were associated with an eight-fold lower mortality rate compared with elevated BNP levels. Likewise, among patients with a TIMI risk score of ≥4, those with lower BNP levels had a 3.5-fold lower mortality rate.

The primary limitation of this study lies in its retrospective and single-center design. It relies on accuracy of the written records. We tried to offset the inherent selection bias of this retrospective study with multiple controls of data analysis. Secondly, serial measurements of BNP levels were not performed. Therefore, the relationship between BNP kinetics and clinical endpoints is not known. Thirdly, the precise estimation of infarct size and the extent of microvascular obstruction was not available. Finally, LV diastolic functions were not evaluated.

In conclusion, elevated BNP level on admission is an independent predictor of angiographic no-reflow, AHF, and mortality during early in-hospital period. In addition to traditional risk scoring systems, admission BNP levels might improve early risk stratification of patients with STEMI.

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Key words: Angioplasty, balloon, coronary; coronary angiography; myocardial infarction; natriuretic peptide, brain; prognosis; risk assessment.

Anahtar sözcükler: Anjiyoplasti, balon, koroner; koroner anjiyografi; miyokart enfarktüsü; natriüretik peptit, beyin; prognoz; risk değerlendirmesi.