Additive prognostic value of NT-proBNP over TIMI risk score in intermediate-risk patients with acute coronary syndrome

Akut koroner sendromlu orta riskli hastalarda NT-proBNP'nin TIMI risk skoruna prognostik katkısı

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Objectives: We evaluated the prognostic value of N-terminal pro-brain natriuretic peptide (NT-proBNP) for further risk stratification of intermediate-risk patients with non-ST elevation acute coronary syndromes (NSTE-ACS).

Study design: The study included 137 intermediate-risk patients (85 men, 52 women; mean age 62±11 years) with ACS, based on the TIMI risk score (scores 3 to 5). Serum NT-proBNP levels were measured 12 hours after the last anginal episode. The patients were divided into four groups according to the following NT-proBNP quartiles: 17-310 pg/ml (n=34), 313-688 pg/ml (n=35), 724-2,407 pg/ml (n=34), and 2,575-24,737 pg/ml (n=34). Primary endpoint of the study was mortality. The mean follow-up was 21.8±7.1 months.

Results: There were 27 deaths (19.7%), 14 of which were in the 4th quartile (4th *vs* 1st, 2nd, and 3rd quartiles: p=0.02, p=0.01, and p<0.01, respectively). The first three quartiles did not differ significantly in this respect. In Kaplan-Meier analysis, patients in the 4th quartile had the lowest cumulative survival (log rank test, 4th *vs* 1st, 2nd, and 3rd quartiles: p=0.041, p=0.026, and p=0.009, respectively). NT-proBNP level was significantly higher in nonsurvivors than in survivors (p=0.01). In univariate analysis, mortality was also associated with the TIMI risk score, ejection fraction, and age. Patients who died were older (65.6±11.9 years *vs* 60.7±11.0 years; p=0.048) and had a lower ejection fraction (46.3±11% *vs* 54.1±9.8%; p<0.001) than patients who survived. Mortality rates corresponding to TIMI risk scores of 3, 4, and 5 were 25.9%, 29.6%, and 44.4%, respectively (p=0.58 for TIMI 3 *vs* 4; p=0.001 for TIMI 3 *vs* 5; p=0.013 for TIMI 4 *vs* 5). Cox proportional hazards regression analysis showed that only TIMI risk score was an independent predictor of mortality (hazard ratio 2.3, 95% confidence interval 1.4-3.8, p=0.001).

Conclusion: NT-proBNP has an additive predictive value over TIMI risk score in predicting long-term mortality in intermediate-risk patients with ACS.

Key words: Angina, unstable; biological markers; coronary disease; natriuretic peptide, brain; prognosis; risk assessment.

Amaç: N-terminal pro-beyin natriuretik peptid (NT-proBNP) düzeyinin, orta riskli olarak sınıflandırılmış, ST yükselmesi olmayan akut koroner sendromlu (NSTE-AKS) hastalarda daha ileri risk derecelendirmesine katkısı araştırıldı.

Çalışma planı: Çalışmaya TIMI risk skoruna göre orta riske (skor 3-5) sahip, NSTE-AKS'li 137 hasta (85 erkek, 52 kadın; ort. yaş 62±11) alındı. Son angina atağının 12. saatinde alınan kan örneklerinde serum NT-pro BNP düzeyi ölçüldü ve hastalar NT-proBNP düzeyine göre dört çeyreğe (kuartil) ayrıldı: 17-310 pg/ml (n=34), 313-688 pg/ml (n=35), 724-2,407 pg/ml (n=34) ve 2,575-24,737 pg/ml (n=34). Hastalar çalışmanın birincil sonlanım noktası olan mortalite açısından ortalama 21.8±7.1 ay takip edildi.

Bulgular: Yirmi yedi (%19.7) ölümle karşılaşıldı: bunların 14'ü dördüncü çeyrekte idi (4. çeyreğe göre 1, 2, 3. çeyrekler için sırasıyla p=0.02, p=0.01 ve p<0.01). Ölümler açısından ilk üç çeyrek arasında anlamlı farklılık görülmedi. Kaplan-Meier analizinde en düşük kümülatif sağkalım yine dördüncü çeyrekte görüldü (4. çeyreğe göre 1, 2, 3. çeyrekler için sırasıyla, log rank testi, p=0.041, p=0.026 ve p=0.009). NT-proBNP düzeyi ölen hastalarda, yaşayanlardan anlamlı derecede yüksekti (p=0.01). Tekdeğişkenli analizde, mortalite ayrıca TIMI risk skoru, ejeksiyon fraksiyonu ve yaş ile de ilişkili bulundu. Ölen hastalar, yaşayanlardan daha ileri yaştaydı (ort. yaş 65.6±11.9 ve 60.7±11.0; p=0.048) ve ejeksiyon fraksiyonu daha düşüktü (%46.3±11 ve %54.1±9.8; p<0.001). TIMI risk skoru 3, 4, 5 olan hastalarda mortalite oranı sırasıyla %25.9, %29.6 ve %44.4 bulundu (TIMI 3-4 için p=0.58; TIMI 3-5 için p=0.001; TIMI 4-5 için p=0.013). Cox oransal risk analizinde sadece TIMI risk skoru mortalite için bağımsız öngördürücü olarak bulundu (risk oranı 2.3, %95 güven aralığı 1.4-3.8, p=0.001).

Sonuç: Orta riskli AKS hastalarında NT-proBNP, uzun dönem mortalitenin öngörülmesinde TIMI risk skoruna ek bilgi sağlamaktadır.

Anahtar sözcükler: Angina, kararsız; biyolojik belirteç; koroner hastalık; natriüretik peptid, beyin; prognoz; risk değerlendirmesi.

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Unstable coronary artery disease, i.e., unstable angina and non-ST elevation myocardial infarction, is the most common cause of admission to coronary care units, accounting for 60-70% of all admissions due to acute coronary syndromes (ACS).[1,2] Patients with non-ST elevation acute coronary syndromes (NSTE-ACS) constitute a heterogeneous group that varies widely regarding the severity of the underlying coronary artery disease (CAD), prognosis, and response to treatment. Risk stratification of patients with NSTE-ACS is mandatory to initiate appropriate medical and invasive therapies. Among several scoring systems proposed to assess this heterogeneous group, the TIMI risk score is one of the most frequently used systems.[3] Patients with the highest risk for subsequent events usually benefit the most from an intensified pharmacological treatment and early mechanical intervention.[4-6] On the other hand, it is often difficult to further improve the prognosis of low-risk patients, and these patients usually benefit more from a conservative management presenting a lower risk for side effects. However, for intermediate-risk patients, it is still not clear which would benefit more from invasive therapies or from a conservative strategy.

Brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) have shown promise for risk stratification of patients with NSTE-ACS.[7-13] In NSTE-ACS, high levels of these markers have been associated with a two- to three-fold greater risk for death at 10 months.[8] In this study, we hypothesized that NT-proBNP could be used to identify a higher-risk subgroup among intermediate-risk ACS patients.

PATIENTS AND METHODS

Patient selection. Between June 2004 and June 2006, a total of 168 patients were admitted to the cardiology department of our hospital, a tertiary center, with the diagnosis of NSTE-ACS. Of these, 31 patients (18.5%) were lost to follow-up. The remaining 137 patients (85 men, 52 women; mean age 62±11 years) comprised the study group. Baseline clinical characteristics of the patients are shown in Table 1.

Inclusion criteria were as follows: *(i)* the presence of typical cardiac ischemic chest pain and/or ECG changes including ST-segment depression or T-wave inversion associated with chest pain, and/or *(ii)* raised troponin I levels (>0.04 ng/ml), and *(iii)* a TIMI risk score of 3 to 5.

The TIMI risk score for each patient was the sum of seven variables, assigned 1 point for each existing variable: age ≥65 years, ≥3 risk factors for coronary artery disease, use of aspirin within the past 7 days, known coronary artery stenosis ≥50%, ≥2 episodes of angina within the past 24 hours, ST-segment deviation, and elevated cardiac biomarkers. In patients without a prior coronary angiogram to conclude coronary artery stenosis, 1 point was accorded to a history of myocardial infarction or coronary revascularization as suggested by the authors of the TIMI risk score.[14,15]

As the release of NT-proBNP is markedly increased in patients with heart failure due to diastolic dysfunction or systolic dysfunction, and in patients with severe renal impairment,[16] patients presenting with heart failure symptoms or signs, with a previous history of heart failure, or those with a serum creatinine level >2 mg/dl were excluded to eliminate these confounding factors.

All patients received standard treatment as recommended for ACS including aspirin, clopidogrel, low-molecular weight heparin, glycoprotein IIb/IIIa inhibitors, ACE inhibitors, beta-blockers, and statins as appropriate.[17] Patients were submitted to coronary angiography (CAG) and/or revascularization at the discretion of the treating physician, taking the related guidelines into consideration.[17] Angiographic data were recorded. Severe stenosis was defined as 70% or more stenosis in one of the three major coronary arteries (i.e. left anterior descending, circumflex, and right coronary arteries) or 50% or more stenosis of the main coronary artery.

The study was approved by the local research ethics committee and all patients gave informed consent to participation.

Follow-up. After admission, complete physical examination was performed and blood chemistry was assessed. The patients were evaluated by two-dimensional and Doppler echocardiography for left ventricular function on the second day of admission.

Table 1. Baseline clinical characteristics of the patients

	n	%	Mean±SD
Age			61.7±11.3
Male	85	62.0	
Female	52	38.0	
Hypertension	69	50.4	
Diabetes mellitus	40	29.2	
Hypercholesterolemia	76	55.5	
Smoking	56	40.9	
Horizontal ST depression	87	63.5	
Coronary artery disease	61	44.5	
Troponin I (>0.04 ng/ml)	112	81.8	
NT-proBNP (pg/ml)			2209±3739

Patients were followed up for a mean of 21.8±7.1 months on the basis of outpatient visits or telephone contact. We defined the primary endpoint as mortality from all causes.

Measurement of blood NT-proBNP levels. NT-proBNP levels are subject to marked dynamic changes in patients with NSTE-ACS.[18] Natriuretic peptides rise continuously during the first 24 hours after the onset of ischemia.[19] A recent meta-analysis demonstrated that the prognostic value of natriuretic peptide measurement was similar when blood was obtained at the time of first patient contact or in the following hours or days after admission.[20] In order to standardize NT-proBNP levels, blood samples were collected 12 to 18 hours after the last anginal episode. Blood samples were drawn into standard sampling tubes. All samples were centrifuged within one hour at 2,000 rpm for 20 minutes. Serum and plasma were obtained and stored at -20 ºC and all samples were processed within six months after sampling using the Roche Diagnostic NT-proBNP assay on an Elecsys 2010 analyzer.

Statistical analysis. Patients were categorized into quartiles according to the NT-proBNP levels. Continuous variables were presented as mean ± standard deviation or median, as appropriate, and categorical variables as percentages. Differences in categorical baseline variables between the NT-proBNP quartiles were evaluated with the chi-square test or Fisher's exact test. Differences in continuous variables between the NT-proBNP quartiles were evaluated with one-way analysis of variance and further with post hoc procedures. Differences between the survival and non-survival groups were analyzed by an unpaired t-test or Mann-Whitney U-test for continuous variables as appropriate, and chi-square test for categorical variables. Correlations between two continuous variables were sought using the Pearson correlation coefficient or Spearman rank correlation coefficient if variables were not normally distributed. Association of various variables with mortality was assessed using the Cox proportional hazards model. Cumulative survival rates were calculated using the Kaplan-Meier method and the differences were determined using the log-rank test. Data were analyzed using the SPSS (version 14.0) statistical package, and a p value of less than 0.05 was considered to be statistically significant.

RESULTS

Patients were categorized into quartiles according to the NT-proBNP levels, which were 17-310 pg/ml (1st quartile, n=34), 313-688 pg/ml (2nd quartile, n=35), 724-2,407 pg/ml (3rd quartile, n=34), and 2,575-24,737 pg/ml (4th quartile, n=34). Table 2 shows baseline characteristics according to the quartiles. Patients in the highest quartile were older and exhibited a higher female ratio (p<0.001). Local wall motion abnormality was more frequent (p=0.008) and ejection fraction tended to decrease (p<0.001) in the upper quartiles. There were no significant differences between the quartiles with regard to troponin level, TIMI risk score (3 to 5), history of coronary artery disease, cardiovascular risk factors (hypertension, diabetes, hypercholesterolemia, smoking), or treatment at discharge. However, a separate analysis taking NT-proBNP as a continuous variable showed a positive correlation between troponin I and NT-proBNP levels (r=0.336, p<0.001).

Of the study group, 118 patients (86.1%) underwent coronary angiography. Baseline angiographic findings are presented in Table 2. NT-proBNP level was correlated with the extent of CAD (r=0.236, p=0.01). NT-proBNP levels were significantly higher in patients with three-vessel disease (1,849 ng/ml) than in patients with single- (564 ng/ml) or two-vessel (477 ng/ml) disease (p=0.009 and p=0.002, respectively). Three-vessel disease was significantly more prevalent in the 4th quartile compared to the other quartiles (p=0.01). After CAG, 48 patients (40.7%) underwent percutaneous coronary intervention, one of which was unsuccessful, 34 patients (28.8%) underwent coronary artery bypass grafting (CABG) surgery, and 36 patients (30.5%) were treated medically. In the latter group, 13 patients had noncritical atherosclerotic lesions, 15 patients had significant stenosis that were not suitable for revascularization, and eight patients refused surgery or died before the planned date of surgery. Nineteen (13.9%) patients were not submitted to CAG and revascularization due to comorbidities and advanced age (n=10), patient's refusal to invasive strategy (n=6), and lack of social security (n=3). These patients were older (70.5±11.6 *vs* 60.5±10.8; p<0.001) and had significantly higher NT-proBNP levels compared to those undergoing CAG (3,518 ng/ml *vs* 605 ng/ml; p<0.001). Baseline NT-proBNP levels according to the revascularization status of the patients are given in Table 3.

Concerning the TIMI risk score, 60 patients (43.8%) met three variables, 50 patients (36.5%) met four variables, and 27 patients (19.7%) met five variables. Patients with a TIMI risk score of 5 had higher NT-proBNP levels than those with a TIMI

Table 2. Baseline characteristics and angiographic data according to the quartiles

	1st quartile (n=34)		2nd quartile (n=35)		3rd quartile (n=34)		4th quartile (n=34)		
	%	Mean±SD	%	Mean±SD	%	Mean±SD	%	Mean±SD	*p*
Age (years)		57.1±11.5		59.4±9.6		61.3±11.1		69.0±9.4	**<0.001**
Women	11.5		19.2		26.9		42.3		**<0.001**
Hypertension	58.8		48.6		55.9		67.6		0.45
Diabetes mellitus	17.6		34.3		29.4		35.3		0.35
Hyperlipidemia	47.1		65.7		52.9		55.9		0.46
Smoking	52.9		42.9		44.1		25.3		0.09
Aspirin the last 7 days	67.6		60.0		50.0		44.1		0.22
ST-segment depression	55.9		68.6		55.9		73.5		0.31
Known coronary artery disease	41.2		57.1		47.1		32.4		0.20
Anginal attacks (n≥2)	88.2		60.0		64.7		41.2		**0.001**
Troponin I (ng/ml)		1.2±3.4		1.4±1.8		3.6±7.5		2.2±2.3	0.10
TIMI risk scoring									0.31
TIMI 3	47.1		40.0		47.1		41.2		
TIMI 4	47.1		37.1		32.4		29.4		
TIMI 5	5.9		22.9		20.6		29.4		
Ejection fraction (%)		57.5±6.8		54.9±9.0		48.8±12.1		48.9±10.7	**<0.001**
Local wall motion abnormality	35.3		54.3		70.6		70.6		**0.008**
Treatment at discharge									
Aspirin	100.0		97.1		97.1		97.1		0.79
Beta-blocker	79.4		82.9		85.3		85.3		0.90
ACE inhibitor	82.4		74.3		88.2		79.4		0.51
Statin	58.8		77.1		67.6		76.5		0.30
Nitrate	70.6		71.4		67.6		61.8		0.82
Calcium channel blocker	8.8		22.9		5.9		5.9		0.07
Angiographic findings (n=118)									
Extent of coronary artery disease									**0.01**
No severe stenosis	17.6		3.0		10.7		9.1		
1-vessel disease	41.2		27.3		50.0		18.2		
2-vessel disease	29.4		48.5		28.6		13.6		
3-vessel disease	11.8		21.2		10.7		59.1		
Left main coronary artery disease	2.9		6.1		3.6		0		0.69

risk score of 3 or 4 (for TIMI 5 *vs* 3: 2,024 ng/ml *vs* 729 ng/ml, p=0.013; for TIMI 5 *vs* 4: 2,024 ng/ml *vs* 634 ng/ml, p=0.011).

Adverse events. During the follow-up period, there were 27 (19.7%) deaths, two of which (1.5%) occurred during hospital stay. One of the in-hospital deaths occurred after CABG surgery. Mortality rates were higher in patients who were not submitted to CAG and revascularization, in patients who refused CABG surgery, and in those awaiting the time of surgery (p<0.001; Table 3).

According to the NT-proBNP quartiles, there were five deaths (14.7%) in the 1st quartile, five deaths (14.3%) in the 2nd quartile, three deaths (8.8%) in the 3rd quartile, and 14 deaths (41.2%) in the 4th quartile. Mortality was significantly higher in the 4th

Table 3. Mortality rates and baseline NT-proBNP levels according to the revascularization status of the patients

	n	Mortality	%	*p*	NT-proBNP (ng/ml)*	*p*
Percutaneous coronary intervention (+)	47	4	8.5	0.000	510	0.000
Coronary artery bypass grafting (+)	34	2	5.9		634	
Medical treatment after coronary angiography						
Noncritical stenoses or lesions not suitable for revascularization†	29	4	13.8		750	
Refused CABG surgery	8	6	75.0		2,204	
Conservative strategy	19	11	57.9		2,774	

†One patient with unsuccessful PCI is included in this group. *Median values.

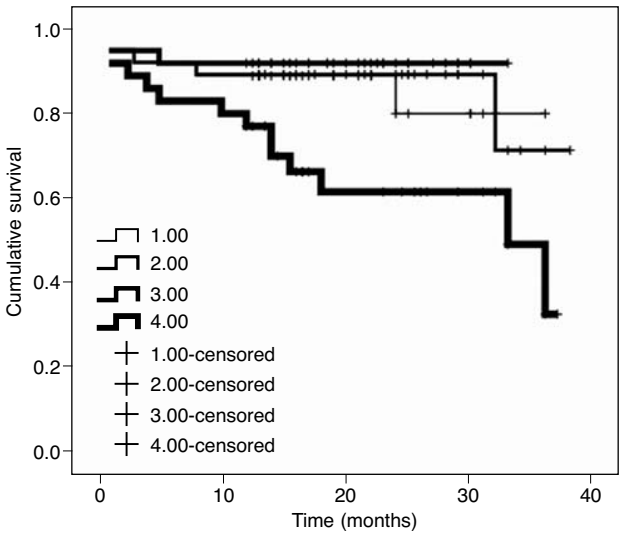

Figure 1. Survival functions.

quartile (for 1st *vs* 4th quartile: p=0.02; for 2nd *vs* 4th quartile: p=0.01; for 3rd vs 4th quartile: p<0.01), but the first three quartiles did not differ significantly in this respect.

Kaplan-Meier curves showing the relationship between the cumulative survival and NT-proBNP quartiles are presented in Fig. 1. Patients in the 4th quartile had the lowest cumulative survival (log rank test, p=0.041 for 4th *vs* 1st quartile; p=0.026 for 4th *vs* 2nd quartile; p=0.009 for 4th *vs* 3rd quartile). NT-proBNP level was significantly higher in nonsurvivors than in survivors (3,241 *vs* 619 ng/ml; p=0.01).

In univariate analysis, mortality was also associated with the TIMI risk score, ejection fraction, and age. Patients who died were older than patients who survived (65.6±11.9 years *vs* 60.7±11.0 years; p=0.048). Based on the TIMI risk score, there were seven deaths (25.9%) in patients with a score of 3, eight deaths (29.6%) in patients with a score of 4, and 12 deaths (44.4%) in patients with a score of 5. Patients with a TIMI risk score of 5 had a higher mortality rate than patients with scores of 4 or 3 (p=0.58 for TIMI 3 *vs* 4; p=0.001 for TIMI 3 *vs* 5; p=0.013 for TIMI 4 *vs* 5). Ejection fraction was lower in patients who died than those who survived (46.3±11% *vs* 54.1±9.8%; p<0.001).

Cox proportional hazards regression analysis that included baseline variables that were associated with mortality in univariate analysis showed that only TIMI risk score was an independent predictor of mortality (HR 2.3, 95% confidence interval 1.4-3.8, p=0.001; p values for NT-proBNP quartiles, age, and ejection fraction were 0.066, 0.052, and 0.074 respectively).

DISCUSSION

In the present study, the role of NT-proBNP for further risk stratification was investigated in patients with NSTE-ACS having an intermediate-risk profile (TIMI risk score of 3 to 5). Mortality in the 4th BNP quartile was significantly higher than the lower quartiles and patients who died had significantly higher NT-proBNP levels than patients who survived.

Several studies have shown that there is a strong and independent association between BNP or NT-proBNP levels and mortality in NSTE-ACS.[7-13] Although the results of this study were in line with previous studies with respect to the association between mortality and NT-proBNP, our data demonstrated that the degree of this association was not so strong among NSTE-ACS patients having an intermediate risk profile. Some explanations for this discrepancy may be offered. First of all, patients were selected after being categorized with the TIMI risk score and only those having a risk score of 3 to 5 were included. Therefore, patients were already assigned to an intermediate-risk group by a scoring system validated by large clinical trials.[3] Secondly, in the majority of previous studies, higher BNP levels were found to be related to comorbidities such as age, hypertension, diabetes mellitus, and hypercholesterolemia.[21] The reason for the strong association between BNP level and mortality in unstable CAD is not fully understood, but one reason may be that BNP level also increases in the presence of comorbidities which are all associated with a worse prognosis.[21] In our study, there were no differences between the NT-proBNP quartiles with respect to major cardiovascular risk factors (i.e., hypertension, diabetes mellitus, hypercholesterolemia, smoking, and known CAD), which might have reduced the strength of association between NT-proBNP and mortality. Thirdly, in this prospective observational study, some patients underwent revascularization and some patients did not. One of the suggested pathophysiologic mechanisms underlying the increase in BNP levels during ACS is the severity of ischemic insult.[21] Therefore, timely performed revascularization may have reduced the prognostic power of high NT-proBNP level and the strength of association between mortality and NT-proBNP.

NT-proBNP is released in response to increased intraventricular pressure or wall tension. Levels of NT-proBNP correlate with left ventricular dilatation, remodeling, and dysfunction in patients presenting with acute myocardial infarction.[22,23] Hence, it seems that elevated BNP levels reflect a greater degree of

myocardial dysfunction and are associated with a greater risk for death. However, association between elevated NT-proBNP levels and mortality has been found to be independent of heart failure or left ventricular ejection fraction.[7,8,11,13,24] Elevated levels of natriuretic peptides have been documented in patients with ACS in the absence of detectable myocardial necrosis.[20] These data indicate that mechanisms other than left ventricular dysfunction play a role in NT-proBNP elevations in ACS. Several studies have suggested that elevated BNP levels may be a marker of the extent and severity of ischemia. Brain natriuretic peptide levels have been shown to increase transiently after exercise in patients with stable angina pectoris and correlate with the size of ischemic territory during nuclear stress imaging.[25] Sadanandan et al.[24] demonstrated that elevated BNP levels in patients with NSTE-ACS were associated with a tighter culprit lesion diameter stenosis. Palazzuoli et al.[26] found that patients with 3- or 4-vessel disease had higher BNP levels than patients with 1- or 2-vessel disease among patients with stable angina pectoris and NSTE-ACS with preserved systolic function. Our results are in accordance with these studies. In our study, 3-vessel disease was significantly more prevalent in the 4th quartile, and patients with 3-vessel disease had significantly higher NT-proBNP levels than patients with 1- or 2-vessel disease.

In accordance with the previous studies, segmental wall motion abnormality was more prevalent and ejection fraction was lower in the upper quartiles, both of which might reflect permanent left ventricular dysfunction secondary to myocardial necrosis or temporary left ventricular dysfunction secondary to acute ischemic insult, with its magnitude related to the size of the jeopardized myocardium.

The TIMI risk score was developed and adapted for patients with unstable angina.[3] The usefulness of this score has been validated by the results of the PRISM-PLUS and TACTICS-TIMI 18 trials.[8,15] These studies indicated that a positive troponin test, among all other variables, was the most important predictor of outcome and imposed therapeutic implications.[27] Additional biomarkers have been investigated to increase the predictive accuracy of the score. Tello-Montoliu et al.[28] investigated the role of NT-proBNP, C-reactive protein (CRP), troponin T, and D-dimer in improving the predictive accuracy of the TIMI risk score in patients with NSTE-ACS. Troponin T, CRP and NT-proBNP were all predictors of adverse events. In all patient groups with a low, moderate or high risk profile based on the TIMI risk score, the presence of two or three elevated biomarkers increased the event rate twofold in comparison with no or one elevated biomarker. They also found positive correlations between these biomarkers. In our study, the only independent predictor of mortality was the TIMI risk score. High NT-proBNP levels were associated with mortality. However, there was no association between mortality and troponin I elevation. This may be explained by the relatively small number of patients without troponin I elevation (n=25, 18.3%), which might have reduced the discriminative value of troponin I for prediction of mortality between the two groups. On the other hand, we found a positive correlation between NT-proBNP and troponin I, which can be explained by the infarct size. We feel that incorporation of CRP, in addition to NT-proBNP, into the TIMI risk score might have improved the prognostic accuracy of the TIMI risk score.

In conclusion, these data suggest that increased NT-proBNP level is a weak-moderate predictor of long-term mortality and has an additive prognostic value over TIMI risk score in ACS patients with an intermediate risk profile. NT-proBNP is also associated with the extent and severity of myocardial ischemia in this group of patients.

Study limitations. In this prospective observational study, some patients underwent percutaneous coronary intervention, some patients had CABG, and some only had medical therapy. Revascularization time also varied among patients especially in those whose revascularization procedure was surgery scheduled at a later time than the index event. These differences might have affected event rates. The number of patients was also small; thus, the association of the studied variables with the prognosis should be interpreted cautiously.

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