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Prognostic Value of Serum Biomarkers in Association with TIMI Risk Score for Acute Coronary Syndromes

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Summary

Background: Markers of neurohormonal activation and inflammation play a pivotal role in non-ST-elevation acute coronary syndromes (NSTE-ACS).

Hypothesis: We hypothesized that other biochemical markers could add prognostic value on Thrombolysis In Myocardial Infarction (TIMI) risk score to predict major cardiovascular events in patients with NSTE-ACS.

Methods: In a cohort of 172 consecutive patients with NSTE-ACS, TIMI score was assessed in the first 24 h, and blood samples were collected for measurement of N-terminal pro-brain natriuretic peptide (NT-proBNP), high-sensitivity C-reactive protein, CD40 ligand, and creatinine. Major clinical outcomes (death and cardiovascular hospitalization) were accessed at 30 days and 6 months. Multivariate logistic regression was applied to identify markers significantly associated with outcomes and, based on individual coefficients, an expanded score was developed.

Results: Of 172 patients, 42% had acute myocardial infarction. The unadjusted 30-day event rate increased with age (odds ratio [OR] = 1.03; 95% confidence interval [CI] 1.00–1.06), creatinine (OR = 2.4; 1.4–4.1), TIMI score (OR = 1.6; 1.2–2.2), troponin I (OR = 3.4; 1.5–7.7), total CK (OR = 2.7; 1.2–6.1), and NT-proBNP (OR = 2.9; 1.3–6.3) levels. In multivariate analysis, TIMI risk score, creatinine, and NT-proBNP remained associated with worse prognosis. Multimarker Expanded TIMI Risk Score [TIMI score + (2 × creatinine [in mg/dl]) + (3, if NT-proBNP > 400 pg/ml)] showed good accuracy for 30-day (c statistic 0.77; $p < 0.001$) and 6-month outcomes (c statistic 0.75; $p < 0.001$). The 30-day event rates according to tertiles of expanded score were 7, 26, and 75%, respectively ($p < 0.01$).

Conclusion: In NSTE-ACS, baseline levels of NT-proBNP and creatinine are independently related to cardiovascular events. Both markers combined with TIMI risk score provide a better risk stratification than either test alone.

Key words: acute coronary syndrome, risk stratification, brain natriuretic peptide, creatinine, inflammation, prognosis

Introduction

Risk assessment plays an important role in the management of patients with acute coronary syndromes, enhancing health care quality and efficiency by allowing evidence-based treatments to be targeted at patients who are most likely to benefit from their use.[1–3]

Patients with non-ST-elevation acute coronary syndromes (NSTE-ACS) constitute a population at high risk for the development of major cardiac events.[4] Recently, a new risk stratification strategy using multiple serologic markers has been shown to offer incremental prognostic value.[5, 6] Other noninflammatory biomarkers, such as brain natriuretic peptide (BNP) and its N-terminal fraction (NT-proBNP), have also been studied in this population;[7] however, to date most published data come from post-hoc analyses of randomized controlled trials. Additional assessment of the prognostic utility of a multimarker-integrated approach is required, particularly in heterogeneous populations of consecutive patients admitted with ACS.[8]

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This study aims to evaluate the incremental value of inflammatory and neurohumoral markers in the prediction of cardiac events in patients presenting with NSTE-ACS and to compare this multimarker strategy with the Thrombolysis In Myocardial Infarction (TIMI) risk score in clinical practice.

Methods

Patient Population

A prospective cohort of 172 consecutive patients with a clinical diagnosis of NSTE-ACS admitted to a coronary care unit (CCU) at a teaching hospital from April 2003 to November 2003 was studied. Eligibility criteria included patients presenting with clinical diagnosis of NSTE-ACS within 24 h from symptom onset. Patients who presented with acute chest pain, eletrocardiographic (ECG) abnormalities, and elevated serum markers of myocardial injury, in whom hospital admission and management assumed a principal diagnosis of ACS, were included. The diagnosis of myocardial infarction (MI) was based on the redefined acute MI (AMI) classification proposed by the Joint European Society of Cardiology and American College of Cardiology Committee for the Redefinition of Myocardial Infarction.[9] According to the redefined criteria for the diagnosis of a recent or evolving AMI, a diagnosis of AMI was made if there was a typical increase followed by a gradual fall in troponin or a faster increase followed by a fall in creatine kinase (CK)-MB in combination with at least one of the following: (1) ischemic symptoms, (2) development of pathological Q waves in the ECG, or (3) ECG changes suggestive of ischemia (ST-segment elevation or depression).

The study was in accordance with Declaration of Helsinki; the Ethics Committee of our institution approved the study, and all patients signed written informed consent.

Data Collection

Patients were assessed using a standardized questionnaire that included data from clinical history, physical examination, laboratory examinations, and hospital management. The ECG was performed routinely on admission and repeated daily during CCU stay. Blood samples were drawn on average 12 h after admission to measure serum levels of high-sensitivity C-reactive protein (hs-CRP), soluble CD40 ligand (CD40L) and NT-proBNP. Additional blood samples were routinely collected 6, 12, and 24 h after admission to measure CK, CK-MB, and troponin I.[10] The TIMI risk score was assessed by the CCU clinical staff and registered in the database.[11]

Laboratory Analysis

Blood samples were collected and serum was stored in aliquots at −70º C. This serum was used to measure NT-proBNP and CD40L. The concentration of NT-proBNP was measured with a sandwich immunoassay (Elecsys 2010, Roche Diagnostics, Indianapolis, Ind., USA), CD40L was measured by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minn., USA),[12] and hs-CRP was measured by immunonephelometry using intensifying particles (Dade Behring, Newark, Del., USA). Attending physicians and investigators were blinded to the test results until the study was completed. Troponin I levels were determined using chemiluminescence immunometric assay (Immulite Turbo®, Diagnostic Products Corp., São Paulo, Brazil), with a recommended reference limit of 1.0 ng/ml.

Outcomes

All patients were followed for 180 days or until death. A trained team performed follow-up by telephone interview. Prespecified primary endpoint was a combination of death and hospitalization for cardiac causes at 30 and 180 days. Hospitalization for cardiac cause was defined as hospitalization for new episodes of prolonged resting chest pain, dyspnea, or need of revascularization procedure.

Statistical Analysis

All results for continuous variables are expressed as means ± standard deviation (SD), and skewed variables are expressed as median and interquartile range (IQR). The cutoff point for NT-proBNP was 400 pg/ml, established by a receiver-operating characteristic (ROC) curve corresponding to the highest likelihood ratio for 180-day mortality rate. The cutoff points for hs-CRP and CD40L were determined by sample distribution tertiles.

Univariate logistic regression was used to determine the variables associated with the composite endpoint of death or hospitalization for cardiac causes at 30 and 180 days. Multivariate logistic regression was performed to evaluate the independent value of each biomarker alone. The models were created based on variables associated with the study endpoint, as well as on clinically relevant characteristics described in the literature. Based on parameter estimates from the final multivariate model, a modified score was developed. The chi-square test was used to test the association between the new score and study endpoints.

In all tests, a two-sided p value < 0.05 was considered statistically significant. All analyses were performed with SPSS software version 10.0 (Statistical Package for Social Sciences, Chicago, Ill., USA).

Results

Baseline Characteristics

The study population consisted of 172 consecutive patients (mean age 62.0 ± 12.7 years, 47.7% male) admitted with NSTE-ACS (Table I). Of these, 84% presented with angina class IIIB according to Braunwald's classification. Non-ST-elevation myocardial infarction (NSTEMI) occurred in 42.4% of the patients. According to the TIMI risk score, 16.3, 55.2, and 28.5% of patients were classified as low, intermediate, and high-risk, respectively.

TABLE I Baseline characteristics of patients admitted with non-ST-elevation acute coronary syndromes (n=172)

Age, years	62.0 ± 12.7
Gender (male)	82 (48)
CHD risk factors	
Diabetes mellitus	59 (30)
Hypertension	149 (87)
Hypercholesterolemia	109 (63)
Previous myocardial infarction	71 (41)
Previous revascularization	68 (40)
TIMI Risk Score	
Low (0–2)	28 (16)
Intermediate (3–4)	95 (55)
High (5–7)	49 (29)
ST-segment depression	55 (32)
Non-ST-elevation MI	72 (42)
Angiography	
Nonsignificant coronary stenosis	14 (11)
Multiarterial lesions	79 (46)

Data expressed as n (%) and mean ± standard deviation for continuous variables.

Abbreviations: CHD = coronary heart disease, TIMI = Thrombolysis In Myocardial Infarction, MI = myocardial infarction.

The median creatinine level was 0.9 mg/dl (IQR 0.8–1.19 mg/ml), and 0.6 ng/ml (0.5–2.9 ng/ml) for troponin I. For hs-CRP, the median was 5 mg/l (1–15 mg/l). Baseline median levels for NT-proBNP and CD40L were 275.6 pg/ml (46.5–1208.5 pg/ml) and 0.1 µg/l (0.0–0.8), respectively.

Pharmacologic treatment during hospitalization consisted of aspirin in 94% of patients, clopidogrel in 88%, heparin in 95%, beta blockers in 79%, angiotensin-converting enzyme inhibitors in 62%, statins in 82%, and glycoprotein IIbIIIa receptor blockers in 19%. Twenty-six percent of the study population underwent percutaneous coronary revascularization and 12% coronary artery bypass surgery during hospitalization.

Outcomes during Follow-Up

Thirty-day mortality was 7.0%, and 19.2% were hospitalized for cardiac causes or died during this period. Within 6 months, these outcomes rates doubled, increasing to 11.6 and 42.4%, respectively.

Baseline characteristics associated with 30-day risk of combined endpoint in univariate analysis were age, creatinine, TIMI risk score, troponin I, total CK, and NT-proBNP (Table II). Variables associated with 6-month risk of combined events in univariate analysis were similar and included in addition previous AMI and ST-segment depression ≥ 1 mm. There was no association between hs-CRP and CD40L with short- and medium-term cardiac risk.

In multivariate analysis, creatinine, TIMI risk score, and NT-proBNP were independently associated with 30-day outcomes. Adjusted odds ratios increased 1.41 times for every point of the TIMI risk score, 2.18 times per mg/dl of creatinine, and 2.65 times for NT-proBNP > 400 ng/ml on admission. Within 6 months, the same variables showed a similar association with the primary outcome. To establish a practical tool for physicians, a simplified mathematical model using each variable's risk coefficient, expressed as its rounded odds ratio, was developed:

$$[\text{TIMI score} + (2 \times \text{creatinine [in mg/dl]}) + (3, \text{if NT-proBNP} > 400 \text{ pg/ml})]$$

The accuracy of each independent variable for short- and long-term outcomes is described in Table III. Overall, individual accuracy varied from 0.60 to 0.70 and was greater for the TIMI risk score and creatinine. In this model, predictive value increased significantly when all variables were included: to 0.77 (0.68–0.86) in short-term and to 0.75 (0.68–0.83) in medium-term follow-up.

Area under ROC curve for multivariate model for prediction of short-term events is illustrated in Figure 1. As expected, the area for the expanded score is greater than curves representing each variable alone and TIMI risk score for both outcomes.

There was a statistically significant association between the expanded score and 30-day combined outcome (chi-square = 31.9; $p < 0.001$) and 6-month endpoint (chi square = 25.3; $p < 0.001$) (Fig. 2). In both cases, higher-risk categories for the expanded score correlated with development of more events. When patients were stratified according to both TIMI risk and expanded score, results were independent and additive, especially for the moderate- and high-risk groups (Fig. 3). For both 30-day and 180-day outcomes, patients with low TIMI risk scores did not benefit from further risk stratification by the expanded score. However, patients in the intermediate TIMI risk group (20% risk for events at 30 days) could be divided into three categories according to the expanded score, with event rates ranging from 11 to 75%.

Discussion

The results of the present study demonstrate that a multimarker approach combining creatinine, NT-proBNP, and TIMI risk score adds prognostic information to that conveyed by the TIMI risk score alone in assessing cardiovascular outcomes in a prospective "real world" cohort. We used an integrated assessment strategy in which the TIMI risk score was a central tool, reflecting contemporary cardiology practice. Adding NT-proBNP and creatinine in the first 24 h after admission improved prognostic accuracy. When patients were stratified according to both the TIMI risk score and the modified one, results were independent and additive, especially for moderate- and high-risk groups.

B-type natriuretic peptide is a circulating cardiac hormone released mainly by the ventricles in response to increased wall stress.[13] It has been recently shown that BNP and NT-proBNP levels can provide independent predictive information on mortality when obtained within the first few days after an episode of ACS.[13–15] The results of this study, using the composite end-

TABLE II Risk factors associated with 30-day death and/or hospitalization for cardiac causes

		Univariate analysis		Multivariate analysis	
Characteristics	n (%)	Odds ratio (95% CI)	p Value	Odds ratio (95% CI)	p Value
Gender					
Female	14 (16.7)	1			
Male	19 (24.4)	1.61 (0.74; 3.48)	0.227		
Age, years		1.03 (1.00; 1.06)	0.040		
Diabetes mellitus					
No	21 (19.8)	1			
Yes	12 (21.4)	0.91 (0.41; 2.01)	0.808		
Previous MI					
No	15 (15.8)	1			
Yes	18 (26.9)	1.96 (0.90; 4.24)	0.088		
Previous revascularization					
No	28 (19.6)	1			
Yes	5 (26.3)	1.47 (0.49; 4.41)	0.495		
Creatinine, mg/dl		2.42 (1.41; 4.13)	0.001	2.18 (1.33;3.57)	0.002
TIMI Risk Score		1.61 (1.18; 2.20)	0.003	1.41 (1.01;1.97)	0.045
ST-segment depression ≥ 2 mm					
No	27 (18.8)	1			
Yes	12 (66.7)	2.17 (0.75; 6.29)	0.155		
Troponin I					
<1 ng/ml	11 (12.0)	1			
≥1 ng/ml	22 (31.9)	3.45 (1.54; 7.73)	0.003		
CK-MB					
<10 U/l	18 (17.6)	1			
≥10 U/l	15 (25.0)	1.55 (0.72; 3.38)	0.264		
Hs-CRP (tercis)					
≤ 2.7 mg/l	15 (25.4)	1			
2.8–9.0 mg/l	6 (12.2)	0.41 (0.014; 1.15)	0.091		
> 9.0 mg/l	12 (22.2)	0.84 (0.35; 2.00)	0.690		
NT-proBNP					
≤ 400 pg/ml	12 (13.0)	1	1		
> 400 pg/ml	21 (30.0)	2.86 (1.29; 6.32)	0.010	2.65 (1.07; 6.55)	0.035
CD40L (tercis)					
≤ 0.00 mg/l	17 (27.9)	1			
0.01–0.47mg/l	6 (12.8)	0.45 (0.11; 1.81)	0.261		
≥ 0.48 mg/l	10 (18.5)	0.12 (0.01; 1.03)	0.054		

Abbreviations: CI = confidence interval, MI = myocardial infarction, TIMI = Thrombolysis In Myocardial Infarction, CK-MB = creatine kinase-MB, Hs-CRP = high-sensitivity C-reactive protein, NT-proBNP = N-terminal pro brain natriuretic peptide, CD40L = CD40 ligand.

TABLE III Prognostic performance of the NT-proBNP, creatinine, TIMI risk score and Expanded TIMI Risk Score

	30-Day death and/or hospitalization for cardiac cause					
	Maximum point				95% CI	
Variables	Specificity	Sensitivity	Area	p Value	Inferior limit	Superior limit
NT-proBNP	66.7	62.0	0.609	0.054	0.478	0.740
Creatinine	48.5	86.0	0.717	0.000	0.616	0.818
TIMI risk score	48.5	75.2	0.652	0.007	0.548	0.755
Multimarker Expanded TIMI Risk Score [a]	81.8	62.8	0.768	< 0.001	0.676	0.859

[a] Expanded score = TIMI+2 × creatinine (mg/dl) + 3 × NT-proBNP (=1, if higher than > 400 pg/ml).
Abbreviations as in Tables I and II.

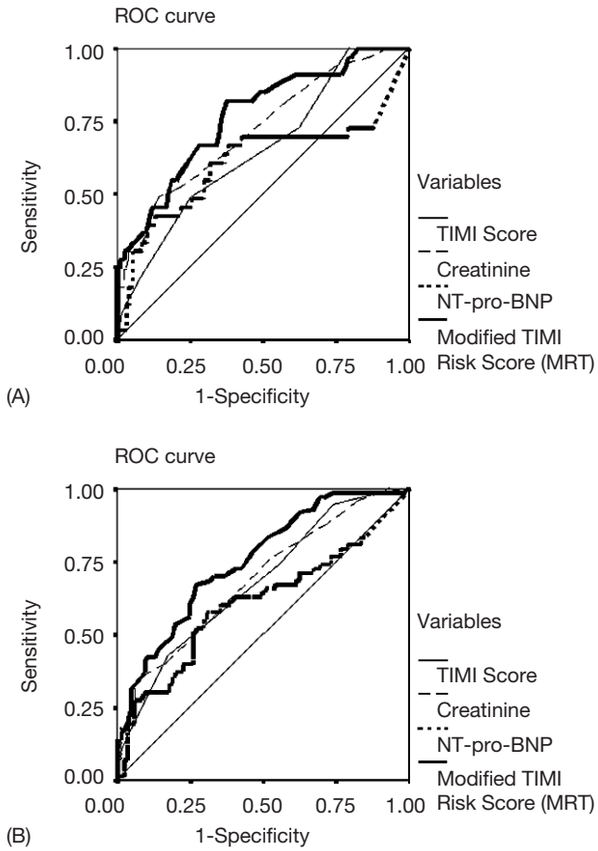

FIG. 1 Receiver-operating characteristic (ROC) curve of 30-day (A) and 6-month (B) combined outcome of death and hospitalization for cardiac causes. Abbreviations as in Tables I and II.

point of death and hospitalization for cardiac causes, reinforce the value of NT-proBNP levels to predict short- and medium-term cardiovascular outcomes. Early NT-proBNP elevations can reflect the consequence of repeated episodes of ischemia. However, peak values of BNP may reflect the severity of ischemic injury rather than the extent of myocardial necrosis.[16–18] Bazzino *et al.* showed additive value of NT-proBNP over TIMI risk score and the American College of Cardiology/American Heart Association (ACC/AHA) ACS classification.[19] In their study, the cutoff point for NT-proBNP was very close to median levels detected in our population.

Traditional measurements of renal function, such as serum creatinine and estimation of creatinine clearance, carry independent prognostic information for patients with NSTE-ACS.[20] Our results confirm creatinine as an independent prognostic tool, with an expressive odds ratio for 180-day outcome.

In this study, we were unable to identify any association between elevated hs-CRP or CD40L with major cardiovascular endpoints on 180-day follow-up. The assay for this test is not yet validated for clinical use, and this may contribute to the lack of correlation. Similar results were published in 1,773 consecutive patients hospitalized for NSTE-ACS.[21]

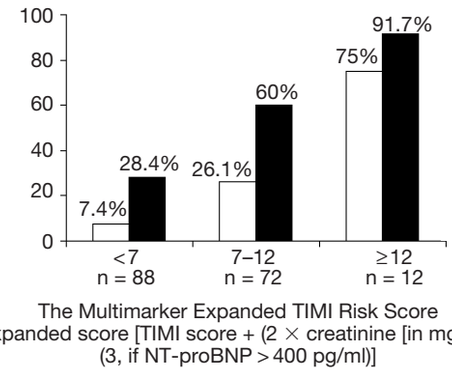

FIG. 2 Combined outcome of death and hospitalization for cardiac cause according to the Expanded score. P for trend < 0.001 for both outcomes. □ = 30-day, = ■ 180-day combined outcome. Abbreviations as in Table II.

Only troponin I was independently associated with the combined endpoint of death or (re)AMI. High-sensitivity CRP levels were only associated with the secondary endpoint of overall mortality.

Platelets, and their expression of CD40L, have recently been recognized as important players in the inflammatory response.[22–24] Researchers analyzed serum levels of CD40L in 1,088 randomized patients during the c7E3 Anti Platelet Therapy in Unstable Refractory angina (CAPTURE) study,[25] identifying high-risk patients and those who would benefit most from abciximab use.[12] Other studies failed to show prognostic correlation between NSTE-ACS and CD40L, and this new marker is still not available for clinical use. Antiplatelet drugs such as clopidogrel can reduce soluble CD40L expression, thus affecting serum levels.[26] The majority of our patients received 300 mg of clopidogrel on admission, which could have lowered CD40L serum levels, affecting its predictive capacity.

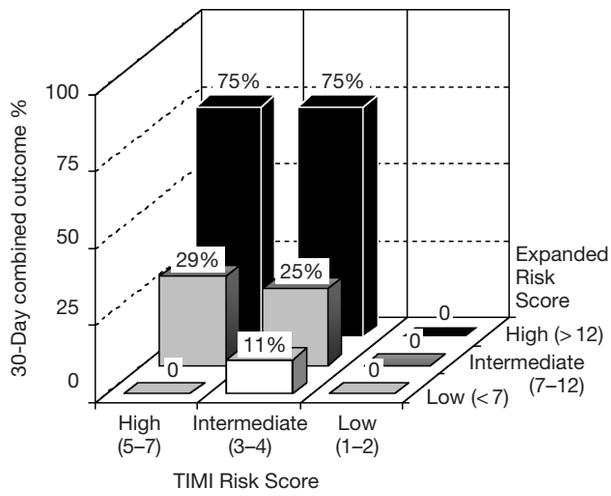

FIG. 3 Combined outcome of death and hospitalization for cardiac cause according to the Thrombolysis In Myocardial Infarction (TIMI) Risk Score and Expanded TIMI Risk Score.

Conclusion

Findings from our study confirm the additive prognostic value of serum markers associated with the TIMI risk score. An expanded score, adding NT-proBNP and creatinine, significantly improves prognostic accuracy. Although a well-constructed prediction model may perform adequately within its own derivation cohort, it needs to be validated in other cohorts and across the whole spectrum of ACS.

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