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Combined Assessments of Biochemical Markers and ST-Segment Resolution Provide Additional Prognostic Information for Patients With ST-Segment Elevation Myocardial Infarction

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ABSTRACT

Background and Objectives: The prognostic value of biochemical markers and the resolution of ST-segment elevation on electrocardiogram are well established. However, how a combination of these two tools affects the evaluation of risk stratification has not yet been evaluated. **Subjects and Methods:** Between January 2006 and June 2008, 178 consecutive patients treated with primary percutaneous coronary interventions after ST-segment elevation myocardial infarctions (STEMI) were analyzed at two coronary care units. Patients were divided into the following three groups according to ST-segment resolution: complete ($\geq 70\%$ depression of the elevated ST-segment, $n=63$), partial (30% to 70%, $n=90$), and incomplete ($<30\%$, $n=25$). Demographic data, including history, electrocardiography, biochemical markers, initial ejection fraction, and angiographic findings were also evaluated. **Results:** There were 7 deaths, 3 repeated myocardial infarctions, and 17 readmissions for worsening heart failure during six months of follow-up. In a multivariate analysis to predict clinical outcomes, ejection fraction {hazard ratio (HR): 0.83 (0.76-0.91), $p<0.01$ }, high-sensitivity C-reactive protein {HR: 1.15 (1.05-1.26), $p<0.05$ }, and the degree of ST-segment resolution {HR: 0.96 (0.93-0.99), $p<0.05$ } were independently associated with clinical outcomes. According to the Cox-proportional hazards model, the addition of ST-segment resolution markedly improved the prognostic utility of the model containing biochemical markers and ejection fraction. **Conclusion:** Assessment of biomarkers upon admission and ST-segment resolution are strong predictors of clinical outcomes. The combination of these data provides additive information about prognosis at an early point in the disease progression and further improves risk stratification for STEMI. (Korean Circ J 2011;41:372-378)

KEY WORDS: Myocardial infarction; Prognosis; C-reactive protein; N-terminal pro-B-type natriuretic peptide; Electrocardiogram.

Introduction

Early risk stratification is essential in the management of patients with suspected or confirmed acute coronary synd-

rome. Traditionally, risk stratification involves an evaluation of medical history, a physical examination, and electrocardiography (ECG) upon admission. In recent years, additional variables for early risk stratification in patients with ST elevation myocardial infarction (STEMI) have been identified, and include the elevation of cardiac biochemical markers. For example, the myocardial release of troponin I (TnI) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) represent sensitive serum markers for minimal myocardial injury. When present, these markers are associated with an increased likelihood of a cardiac event.¹⁾ The elevation of another marker, high-sensitivity C-reactive protein (hsCRP), upon admission with STEMI is associated with an increased risk of complications both during hospitalization and after discharge.²⁾ These biochemical markers are noninvasive indicators of the risk of

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first or recurrent cardiovascular events and also predict the success of therapeutic and preventive interventions.¹⁾ Thus, several studies have demonstrated the independent prognostic value of elevated TnI, NT-proBNP, or hsCRP at admission in patients with STEMI.³⁻⁹⁾ Additionally, in patients treated for STEMI, early ST-segment resolution has been associated with a better outcome based on improved early infarct-related artery patency, smaller infarct size, and less impairment of left ventricular function.¹⁰⁻¹²⁾

However, the combination of these two early available tools for predicting risk soon after a patient's presentation has not been evaluated. To address these issues, we retrospectively assessed the clinical characteristics and follow-up outcomes of consecutive patients who received primary percutaneous coronary intervention (PCI) after STEMI. The aim of this study was to evaluate the combined effect of using multiple biochemical markers and ST-segment resolution assessments for early risk stratification in patients with STEMI and treated by PCI.

Subjects and Methods

Study participants

Between January 2006 and June 2008, 178 consecutive patients who presented with their first STEMI and were subsequently treated with primary PCI were enrolled in the study, which took place at two coronary care units at the Kyung Hee University Hospital, Seoul, Korea. All patients were treated according to the standard of care for STEMI and underwent primary PCI. The diagnostic work-up in all patients consisted of history, 12-lead ECG, blood chemistries, and a two-dimensional (2D) echocardiography. The inclusion criteria were as follows: 1) presentation within 12 hours of symptom onset; 2) chest pain lasting ≥ 30 minutes and resistant to nitrates; and 3) ≥ 0.2 mV ST-segment elevation in at least two contiguous leads on 12-lead ECG. The exclusion criteria were as follows: 1) prior myocardial infarction, defined by pre-existing pathologic Q-wave; 2) non-ST elevation myocardial infarction; and 3) thrombolytic therapy taken instead of PCI. Patients with infectious disease, collagen disease, malignant disease, or severe hepatic or renal failure were also excluded. Initial clinical demographic data, including Killip classification, symptom-to-balloon times, door-to-balloon times, and pre- and post-thrombolysis in myocardial infarction (TIMI) flow grades were evaluated. All patients included in the study sample provided written informed consent for all procedures and our institutional review board approved this research.

Electrocardiographic and echocardiographic assessment

For all 178 patients, a standard 12-lead ECG was obtained at initial presentation and at 60 minutes after PCI, and was

obtained by investigators blinded to the clinical characteristics and coronary angiography findings of the patients. Using calipers, the sum of the ST-segment elevation 20 ms after the J point was calculated and compared with the baseline ECG. The percent resolution of the ST-segment on ECG was categorized as complete ($\geq 70\%$), partial (30% to 70%), or incomplete ($\leq 30\%$), as originally described by Schroder et al.¹⁰⁾ In all patients, standard echocardiography was performed within one hour after coronary intervention. Left ventricular (LV) ejection fraction (EF) was also assessed.

Biochemical markers

Blood samples used to obtain serum levels of TnI, NT-proBNP, and hsCRP were taken on presentation at the emergency department of each center. Creatine phosphokinase (CK), CK-MB isoenzyme, and TnI levels were measured quantitatively at admission, six hours later, and then twice daily over the first 48 hours. Levels were detected routinely in the laboratory using commercially available assays (Abbott Immunoassay, Abbott Laboratories, Abbott Park, IL, USA). The normal value of TnI in our institution is 0.5 ng/mL. TnI levels ≥ 0.5 ng/mL on admission was used as a serum marker for myocardial ischemia. NT-proBNP and hsCRP levels were also measured quantitatively at admission. NT-proBNP was quantified using a one-step enzyme immunoassay based on electrochemiluminescence technology (Elecys 2010, Roche Diagnostics). Finally, hsCRP was determined with the Hitachi 717 system (Roche Diagnostics).

Follow-up and end points

All study participants underwent the implantation of drug-eluting stents (DES). The choice of the specific type of DES {i.e., sirolimus-eluting (Cypher, Cordis, Johnson & Johnson, Miami Lakes, FL, USA) or paclitaxel-eluting (Taxus, Boston Scientific, Natick, MA, USA) stents} was left to the surgeon's discretion. Patients were prescribed aspirin and clopidogrel for at least six months, regardless of DES type. All participants were followed for at least six months (13.6 ± 3.1 months). The outcome events in this study were all cause mortality, repeated myocardial infarction, and readmission for worsening of heart failure up to six months after PCI.

Statistical analysis

Statistical analysis was performed using the SPSS package for Windows, Version 17.0. Continuous variables are presented as a mean \pm a standard deviation or median, as appropriate, and categorical variables as a percentage. Continuous data were compared using one-way analysis of variance among ST-segment resolution groups. Categorical data were compared using the chi-square test. Correlations between two continuous variables were performed using the Pearson correlation coefficient. A multivariate analysis using forward stepwise

logistic regression was performed to check for independent variables related to major adverse cardiac events (MACE) reported up to six months of follow-up. The overall MACE-free survival rates were calculated using the Kaplan-Meier method, and the differences were determined using the log-rank test. The independent effects of variables on prognosis were calculated using a Cox proportional hazards regression model. Additionally, we performed a univariate and multivariate analysis using a Cox proportional hazards regression model, in which we explored the effects of different combinations of biomarkers on patient prognosis. A $p < 0.05$ was considered statistically significant.

Results

Initial clinical characteristics in each ST-segment resolution group

The 178 patients treated with primary PCI were divided into the following three groups according to ST-segment resolution: complete ($n=63$, 59.9 ± 12.3 years, male 81%), partial ($n=90$, 63.9 ± 10.9 years, male 68%), and incomplete ($n=25$, 67.6 ± 13.3 years, male 76%). Baseline characteristics, risk factors, LV EF, and biochemical markers at admission are listed in Table 1. Patients in the incomplete resolution group were older, had worse Killip classifications, and had signifi-

cantly prolonged symptom-to-door times and door-to-balloon times. Risk factors such as diabetes, hypertension, dyslipidemia, smoking history, and ischemic heart disease history were not different among the three groups. There were no significant differences among the groups regarding use of medications, such as aspirin, clopidogrel, beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and statins either during admission or after discharge (data not shown).

Laboratory and echocardiographic findings in each ST-segment resolution group

The LV EF was significantly lower in patients with incomplete resolution (Table 1). Biochemical markers, such as TnI, NT-proBNP, and hsCRP at admission were significantly higher among patients in the incomplete resolution group, and were well correlated with the percent of ST-segment resolution ($r = -0.38$, $p < 0.01$; $r = -0.41$, $p < 0.01$; $r = -0.43$, $p < 0.01$, respectively). However, the maximal values of CK-MB and TnI after PCI were not significantly different among the three groups (data not shown).

Angiographic findings and clinical outcomes

As shown in Table 2, there were no differences among the 3 groups in the number of diseased vessels, location of the cul-

Table 1. Baseline characteristics classified by degree of ST-segment resolution after PCI in patients with ST-segment elevation myocardial infarction

	Complete (n=63)	Partial (n=90)	Incomplete (n=25)	p
Age (year)	59.9 ± 12.3	63.9 ± 10.9	67.6 ± 13.3	<0.05
Male gender (%)	51 (81)	61 (68)	19 (76)	0.18
sBP (mmHg)	129.3 ± 28.8	120.3 ± 35.1	115.0 ± 28.0	0.10
dBP (mmHg)	76.0 ± 14.2	73.5 ± 18.7	68.5 ± 19.7	0.19
Heart rate (beat/min)	73.4 ± 14.8	79.2 ± 23.7	79.6 ± 21.1	0.19
Killip class (more than II) (%)	10 (16)	41 (45)	16 (64)	<0.01
Symptom-to-door times (minute)	209.8 ± 130.8	263.5 ± 171.0	422.3 ± 206.7	<0.01
Door-to-balloon time (minute)	80.6 ± 24.7	96.2 ± 41.3	185.4 ± 74.9	<0.01
Anterior wall MI (%)	34 (54)	48 (53)	15 (60)	0.83
Risk factors (%)				
Diabetes	21 (33)	26 (29)	8 (32)	0.84
Dyslipidemia	21 (33)	24 (27)	6 (24)	0.57
Hypertension	36 (57)	23 (65)	15 (60)	0.56
Smoking	41 (65)	54 (60)	15 (60)	0.75
History of IHD	21 (33)	25 (28)	13 (52)	0.07
Ejection fraction	53.5 ± 9.6	47.3 ± 10.3	40.3 ± 9.9	<0.01
Initial TnI (ng/mL)	2.6 ± 12.8	5.9 ± 16.9	16.3 ± 26.2	<0.01
NT-proBNP (pg/mL)	353.9 ± 723.9	1082.5 ± 2205.1	2035.3 ± 1903.0	<0.01
hsCRP (mg/L)	3.5 ± 7.9	4.9 ± 7.6	9.9 ± 9.8	<0.01

Continuous data are presented as the mean value \pm standard deviation and categorical variables are presented as a percentage. P were calculated from comparisons across the three groups. PCI: percutaneous coronary intervention, sBP: systolic blood pressure, dBP: diastolic blood pressure, MI: myocardial infarction, IHD: ischemic heart disease, TnI: troponin I, NT-proBNP: N-terminal pro-B-type natriuretic peptide, hsCRP: high-sensitivity C-reactive protein

Table 2. Angiographic characteristics and outcomes according to degree of ST-segment resolution after PCI in patients with STEMI

	Complete (n=63)	Partial (n=90)	Incomplete (n=25)	p
Coronary flow before PCI (%)				0.15
TIMI 0 or 1	46 (73)	68 (75)	23 (92)	
TIMI 2 or 3	17 (27)	22 (25)	2 (8)	
Coronary flow after PCI (%)				0.11
TIMI 0 or 1	5 (8)	6 (7)	5 (20)	
TIMI 2 or 3	58 (92)	84 (93)	20 (80)	
No. of diseased vessels (%)				0.48
1	22 (35)	39 (43)	8 (32)	
2	20 (32)	29 (36)	10 (40)	
3	21 (33)	19 (21)	7 (28)	
Culprit artery (%)				0.75
Left main	0 (0)	3 (3)	0 (0)	
LAD	31 (49)	50 (55)	13 (52)	
LCX	6 (9)	5 (5)	2 (8)	
RCA	26 (41)	32 (35)	10 (40)	
Lesion type (%)				0.24
A or B1	14 (22)	14 (15)	2 (8)	
B2 or C	49 (78)	76 (85)	23 (92)	
Target lesion				
Stent diameter	3.2±0.5	3.1±0.3	3.3±0.4	0.15
Stent length	25.5±5.1	26.3±5.2	26.0±5.7	0.67
CCU adm (days)	2.3±1.4	3.3±2.3	3.7±2.9	<0.01
In-hospital mortality (%)	0 (0)	0 (0)	3	<0.01
Overall mortality (%)	0 (0)	1 (1)	6 (24)	<0.01
Re-infarction (%)	1 (1)	1 (1)	1 (4)	0.61
Re-hospitalization due to CHF (%)	2 (3)	9 (10)	6 (24)	<0.01

Continuous data are presented as the mean value±standard deviation and categorical variables are presented as a percentage. P were calculated from comparisons across the three groups. PCI: percutaneous coronary intervention, STEMI: ST-segment elevation myocardial infarction, TIMI: Thrombolysis in Myocardial Infarction, LAD: left descending artery, LCX: left circumflex artery, RCA: right coronary artery, CCU: coronary care unit, CHF: congestive heart failure

pruit artery, type of lesion, or target lesion. Pre- and post-TIMI flow grade 0 or 1 was more commonly observed in the incomplete group, but this finding was not statistically significant. The duration of coronary care unit admission in days was significantly prolonged in the incomplete group (2.3±1.4, 3.2±2.3 and 4.7±2.9, respectively; $p<0.05$). Three (1.7%) patients died before discharge, and another four (2.2%) patients died during the follow-up period. The in-hospital mortality was only in the incomplete group.

The all-cause mortality rate increased stepwise according to ST-segment resolution status (0%, 1%, and 24%, respectively; $p<0.01$). Three patients were re-treated due to repeated infarction, as shown in Table 2. During follow-up, 17 patients were readmitted for worsening congestive heart failure. The readmission rate was 3% (2/63), 10% (9/90), and 24% (6/25) in complete, partial, and incomplete ST resolution groups, respectively ($p<0.01$).

Prognostic values of biochemical markers and ST-segment resolution

Using median values, the study sample was divided into two groups according to the initial TnI (median=0.38 ng/mL), hsCRP (median=2.45 mg/L), and NT-proBNP (median=456 pg/mL) levels. Kaplan-Meier curves showing MACE-free-survival based on the biochemical levels and ST-segment resolutions are presented in Fig. 1. There was a significant increased risk of six-month MACE with increasing baseline circulating levels of either TnI (6%, and 23% for lower and higher levels, respectively; $p<0.01$), hsCRP (6%, and 23% for lower and higher levels, respectively; $p<0.01$), or NT-proBNP (10%, and 24% for lower and higher levels, respectively; $p<0.05$). There was also a significant, gradually increased risk of six-month MACE according to the ST resolution status (5%, 12%, and 48% for complete, partial and incomplete ST resolution, respectively; $p<0.01$).

To evaluate the independent contribution of ST-segment

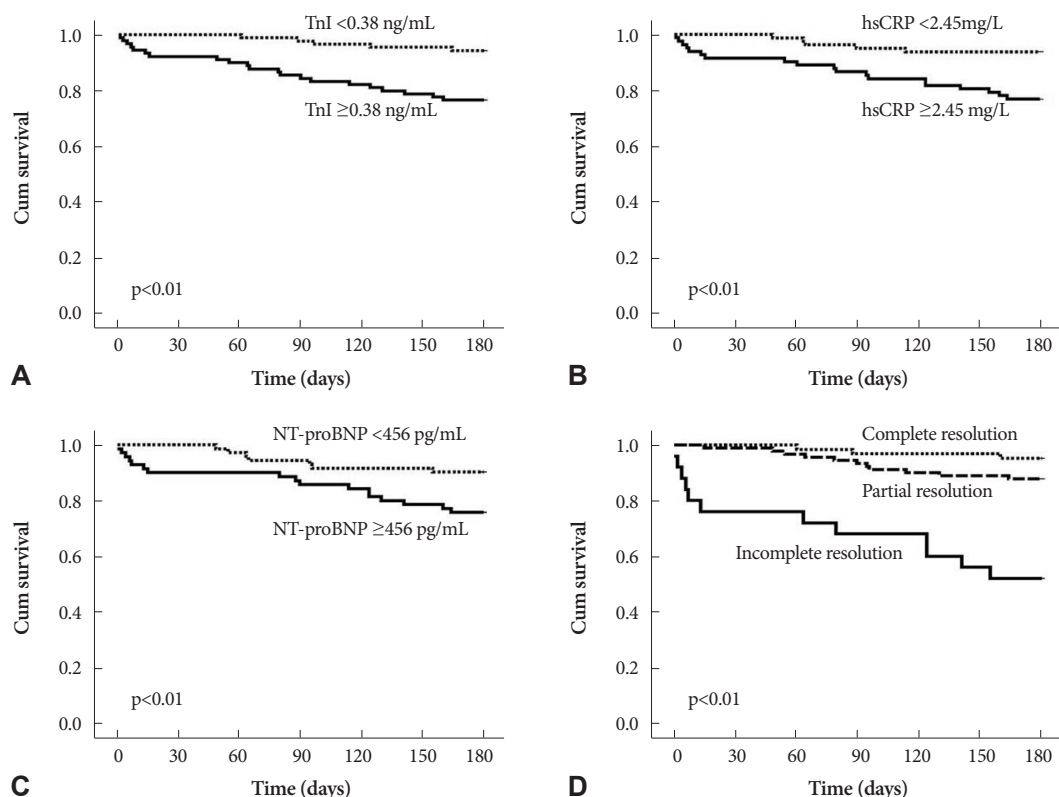


Fig. 1. Kaplan-Meier analysis according to the statuses of TnI (A), hsCRP (B), NT-proBNP (C), and ST resolution (D). Elevated TnI, hsCRP, and NT-proBNP at initial presentation showed a significantly higher number of major adverse cardiac events ($p < 0.01$ for all). Patients presenting with incomplete ST segment resolution, NT had a significantly worse clinical outcome over the 6-month follow-up ($p < 0.01$). TnI: troponin I, hsCRP: high-sensitivity C-reactive protein, NT-proBNP: N-terminal pro-B-type natriuretic peptide.

Table 3. Univariate and multivariate predictors of major adverse cardiac events after ST-segment elevation myocardial infarction

	Univariate analysis		Multivariate analysis	
	p	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)
Age	0.08	1.03 (0.99-1.07)	-	-
Killip class	0.07	2.18 (0.94-5.05)	-	-
Sx-to-balloon time	0.07	1.00 (1.00-1.01)	-	-
Door-to-balloon time	<0.01	1.01 (1.00-1.02)	0.57	1.00 (0.99-1.02)
Ejection fraction	<0.01	0.90 (0.86-0.94)	<0.01	0.83 (0.76-0.91)
Initial TnI	<0.05	1.02 (1.00-1.04)	0.19	1.02 (0.99-1.05)
Initial hsCRP	<0.01	1.09 (1.04-1.14)	<0.05	1.15 (1.05-1.26)
Initial NT-proBNP	<0.05	1.01 (1.00-1.02)	0.93	1.00 (1.00-1.00)
Degree of ST resolution	<0.01	0.96 (0.94-0.98)	<0.05	0.96 (0.93-0.99)

IHD: ischemic heart disease, Sx: symptom, TnI: troponin I, NT-proBNP: N-terminal pro-B-type natriuretic peptide, hsCRP: high-sensitivity C-reactive protein

resolution to the prediction of clinical outcomes after STEMI, multiple regression analysis was performed (Table 3). Variables used for this analysis were age, Killip classification, symptom-to-balloon time, door-to-balloon time, LV EF, TnI, hsCRP, NT-proBNP, and the degree of ST-segment resolution. For multiple regression analysis, univariate analysis was selected for factors showing a $p < 0.05$. The most important predictors of clinical outcomes after STEMI were the LV EF {hazards ratio (HR): 0.83 (0.76-0.91), $p < 0.01$ }, hsCRP {HR: 1.15

(1.05-1.26), $p < 0.05$ }, and the degree of ST-segment resolution {HR: 0.96 (0.93-0.99), $p < 0.05$ }. The additional benefit of using ST-segment resolution to predict cardiac events is shown in Fig. 2. With regard to the incremental value, ST-segment resolution is a good parameter to predict MACE after STEMI. However, the addition of biochemical markers markedly improved the prognostic utility of the model containing ST-segment resolution.

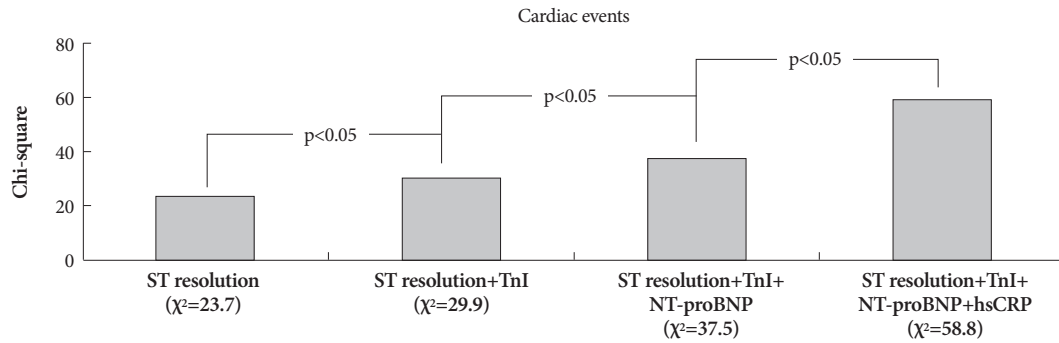


Fig. 2. Prognostic value of a multi-marker approach. The addition of biochemical markers markedly improved the prognostic utility of the model containing ST-segment resolution. TnI: troponin I, hsCRP: high-sensitivity C-reactive protein, NT-proBNP: N-terminal pro-B-type natriuretic peptide.

Discussion

In this study, initial TnI, NT-proBNP, and hsCRP plasma levels were higher in the incomplete ST-segment resolution group than in the ST-segment resolution groups, and these elevated biomarkers on admission predicted an adverse prognosis over the following six months, especially among patients who presented with two or three elevated biomarkers. Furthermore, biochemical markers, such as TnI, NT-proBNP, and hsCRP at admission were well correlated with the percent of ST-segment resolution. The combination of these tools improved risk stratification in STEMI.

In agreement with previous studies,¹³⁻¹⁵ elevated levels of TnI, NT-proBNP, and hsCRP were each associated with higher rates of MACE. Among them, only the hsCRP at initial presentation was significantly and independently associated with an adverse prognosis over the next six months. This finding suggests that the inflammatory process associated with myocardial necrosis may be still ongoing when the degree of inflammation in the acute phase increases, as several lines of studies have suggested.¹⁶⁻¹⁸

By contrast, TnI and NT-proBNP were not independent predictors of clinical outcomes. This discrepancy with previous studies is probably explained by the relatively small sample size. However, despite the small sample size, the combination of several these markers allowed for a very good prediction of clinical outcomes in patients with STEMI treated with PCI as shown in Fig. 2. These incremental effects could be explained by the different pathophysiological mechanisms assessed by these three biomarkers in myocardial ischemia, i.e., elevations in troponins indicate myocardial necrosis,^{3,13} NT-proBNP is elevated in response to left ventricular overload,^{8,9} and hsCRP is a marker of inflammation.¹² Multi-marker approaches to rapidly stratify patients and identify those at risk for adverse cardiac outcomes may help in the selection of more intense interventional or pharmacological treatment strategies.

In the present study, ST-segment resolution at 60 minutes was independently associated with six-month MACE, which agrees with the findings of previous studies.^{3,10} Another strong

finding was a positive correlation between ST-segment resolution and the three biochemical makers. We evaluated the association between the initial biochemical makers and partial or incomplete ST-segment resolution. In a multivariate analysis, elevated hsCRP {HR: 6.29 (2.43-16.30), $p < 0.01$ } and elevated NT-proBNP {HR: 3.32 (1.29-8.52), $p < 0.01$ } were independently associated with partial or incomplete ST-segment resolution, but not elevated TnI {HR: 2.47 (0.99-6.20), $p = 0.053$ }. This finding suggests that high burdens of inflammation and ventricular loads may be associated with a lower likelihood of successful epicardial reperfusion. For this reason, the combination of biomarkers and early ST-segment resolution improved risk prediction. Biomarkers at admission and ST-segment resolution at 60 minutes are strong predictors of clinical outcomes, and the combination of them gives additive early information concerning patient prognosis, and further improves risk stratification in STEMI.

There are several limitations to the present study. Only a small number of patients from two centers were enrolled. The possibility of selection bias and low statistical power must therefore be considered when interpreting our findings. However, we demonstrated that elevated levels of biochemical markers were each associated with higher rates of clinical outcomes, as has been demonstrated by previous studies.^{1,7,11,15} We also showed the powerful prognostic value of the combination of biomarkers at admission and ST-segment resolution at 60 minutes.

Another weak point of this study is that it was a retrospective study and we therefore could not control medications use. In this study, medications were chosen by each physician according to each patient's status. Nevertheless, there was no significant difference in medication use among the three groups. We also achieved the purpose of this study by demonstrating improved predictions of clinical outcomes using the two different systems for patients with first STEMI.

Conclusion

Our study suggests an association among high plasma levels of TnI, NT-proBNP, and hsCRP at admission, incomplete

ST segment resolution in patients with STEMI after PCI, and unfavorable clinical outcomes. Multi-directional approaches to risk stratification and treatment of patients with STEMI may improve the outcomes of adverse cardiac events.

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