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Incremental Prognostic Value of C-Reactive Protein and N-Terminal ProB-Type Natriuretic Peptide in Acute Coronary Syndrome

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Background Cardiac biomarkers, including high-sensitivity C-reactive protein (hs-CRP), N-terminal proB-type natriuretic peptide (NT-proBNP) and cardiac troponin-I (Tn-I), have been associated with an adverse outcome in patients with acute coronary syndrome (ACS). Thus, in the present study the incremental prognostic value of these cardiac biomarkers was evaluated for risk stratification of ACS.

Methods and Results The baseline levels of hs-CRP, NT-proBNP and Tn-I were measured in 215 patients (140 males; 65±46 years) with ACS: ST-elevation myocardial infarction (STEMI): 56; non-ST-elevation myocardial infarction (NSTEMI): 98; unstable angina (UA): 61. The patients were retrospectively followed up for a mean of 246 days. There were 24 cardiac events: STEMI: 1, NSTEMI: 6, UA: 6, chronic heart failure: 1, death: 10. The baseline levels of hs-CRP and NT-proBNP were significantly higher in the patients with cardiac events than in those without events. After adjustment for major clinical prognostic factors, hs-CRP and NT-proBNP remained significantly independent predictors for cardiac events. Patients with hs-CRP level >3.5 mg/L and NT-proBNP level >500 pg/ml had an 11-fold higher risk for cardiac events than those with hs-CRP level ≤3.5 mg/L and NT-proBNP level ≤500 pg/ml.

Conclusion The combination of both cardiac markers has an incremental value in the risk stratification of patients with ACS. (*Circ J* 2006; **70:** 1379 – 1384)

Key Words: Acute coronary syndrome; B-type natriuretic peptide; C-reactive protein; Prognosis

Acute coronary syndrome (ACS) encompasses a continuum of cardiac ischemic events, ranging from unstable angina (UA) with no biochemical evidence of myocardial necrosis to acute myocardial infarction (MI) with or without ST-elevation. Patients presenting with chest pain or similar symptoms suggestive of ACS currently account for about 20% of all visits to the medical emergency department[1] Thus, for patients who experience chest pain, noninvasive tests are useful in the diagnosis, management and prediction of prognosis of ACS. Appropriate risk stratification of patients with ACS is important for effective treatment according to risk categories. Recently, biochemical markers, including troponin-I (Tn-I), high-sensitivity C-reactive protein (hs-CRP) and N-terminal proB-type natriuretic peptide (NT-proBNP), have become available for the additional evaluation of risk stratification in ACS patients. Increased levels of Tn-I, hs-CRP and NT-proBNP are respectively associated with higher rates of recurrent ischemic cardiac events. In fact, these biomarkers reflect the different pathophysiological pathways in myocardial ischemia. The NT-proBNP is a cardiac neurohormone that is synthesized in the ventricular myocardium and released in response to ventricular wall stretching[2] and it is used as a useful marker for left ventricular (LV) overload and prognosis in patients with chronic heart failure (CHF). An elevation of Tn-I is a marker of myocardial damage and hs-CRP is a sensitive circulating marker of inflammation and can simply be a surrogate of atherosclerosis burden. In recent studies[3–5] an association between the level of these biomarkers and the risk of future cardiovascular events has been discussed for patients with ACS. Thus, we studied retrospectively the prognostic implications of elevations of Tn-I, NT-proBNP and hs-CRP across the entire spectrum of ACS. Moreover, a combined prediction for analysis of cardiac events was carried out to evaluate a multi-marker strategy for the individualization of risk stratification.

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Methods

Patients

Between June 2003 and June 2004, we studied 215 patients admitted to the cardiology department with a diagnosis of ACS for their angina pain. The eligible patients were >30 years of age with 1 or more episodes of typical angina pain lasting >5 min and at least one of the following signs of ischemia: electrocardiogram (ECG) suggestive of ischemic change (elevated or depressed ST-segment or T-wave inversion), or positive Tn-I test. The index event was classified as (1) UA if Tn-I values were not detected on admission and serially every 6 h for 24 h after arrival; (2) non-ST segment

Table 1 Baseline Characteristics of 215 Patients With or Without MACE

	Patients with MACE (n=24)	Patients without MACE (n=191)	p value
Mean age (years)	67±12	65±49	0.787
Sex (M/F)	11/13	129/62	0.042
Tn-I (ng/ml)	30.97±63.54	26.68±69.00	0.772
NT-proBNP (pg/ml)	8,479±9,155	1,483±3,108	0.001
Log NT-proBNP	8.38±1.83	5.91±1.54	0.001
hs-CRP (mg/L)	21.6±3.47	6.1±1.26	0.040
Hypertension (%)	12 (50%)	78 (41%)	0.397
Diabetes (%)	10 (42%)	36 (19%)	0.016
Smoking (%)	9 (38%)	112 (59%)	0.079
Ejection fraction (%)	45.86±13.18	54.49±11.44	0.006
History of IHD (%)	9 (38%)	45 (24%)	0.142
History of CHF (%)	1 (4%)	7 (4%)	1.000
Total cholesterol	193.87±46.88	183.49±42.48	0.277
Triglycerides	128.96±77.63	117.26±85.69	0.534
LDL-cholesterol	132.32±35.57	117.80±33.84	0.056
HDL-cholesterol	37.85±10.89	46.87±32.27	0.186
Diagnosis			
STEMI	6 (25%)	50 (26%)	1.000
NSTEMI	16 (67%)	82 (43%)	0.031
UA	2 (8%)	59 (31%)	0.028
No. of coronary revascularizations	15/24 (62.5%)	100/191 (52.4%)	0.391

MACE, major adverse cardiac events; Tn-I, troponin-I; NT-proBNP, N-terminal proB-type natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein; IHD, ischemic heart disease; CHF, congestive heart failure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non ST-segment elevation myocardial infarction; UA, unstable angina.

elevation MI (NSTEMI) if maximal values of Tn-I exceeded the decision limit (99th percentile of the values for a reference control group) on at least one occasion without ST segment elevation; or (3) ST segment elevation MI (STEMI) if there was a positive Tn-I level with ST segment elevation on ECG. We excluded patients who did not satisfy these inclusion criteria, such those with as non-coronary artery disease or neurosis. The study protocol was approved by the ethics committee of the hospital and written informed consent was given by each patient.

Clinical Characterization and Cardiovascular Risk Factors

At study entry, a thorough medical history was recorded for all the patients, including age, sex, blood pressure and risk factors. The classical risk factors, such as hypertension, diabetes mellitus, smoking or previous stroke, were investigated from medical records, directly from the patient, or both.

Laboratory Analysis

Peripheral blood samples for NT-proBNP and hs-CRP were obtained on admission by direct vein puncture. The hs-CRP level was measured by particle-enhanced immunoturbidimetry, with a lower limit detection of 0.02 mg/L (Roche Diagnostics), and the NT-proBNP concentration measured using an electrochemiluminescence immunoassay on a Modular Analytics E170 (Roche Diagnostics). The Tn-I levels were measured on admission and serially every 6 h to detect the presence of myocardial injury using an enzyme immunoassay based on the sandwich principle (Dimension; Dade Behring); the lower detection limit of this assay is 0.04 ng/ml. The highest value of Tn-I before performing percutaneous coronary angiography was determined in all patients, because elevated Tn-I level is thought to reflect a high risk of cardiac events. The analytic range of NT-proBNT extended from 5 to 35,000 pg/ml. The plasma levels of triglyceride and cholesterol were determined using standard laboratory techniques.

Table 2 MACE During Follow-up Period

Clinical event	No. of patients	%
STEMI	1	0.5
NSTEMI	6	2.8
UA	6	2.8
CHF	1	0.5
Death	10	4.7
Total	24	11.2

Abbreviations see in Table 1.

Events and Follow-up

The development of clinical events was defined as a composite of cardiac death, new or recurrent MI, rehospitalization for worsening UA, and new or worsening CHF. Patients were followed up for a maximum of 436 days, with an average follow-up period of 246±138 days. The follow-up was performed by reviewing the medical records in the outpatient clinic and/or telephone interviews.

Statistical Analysis

The data analyses were performed with the Statistical Package for Social Science (SPSS for Windows 12.0, Chicago, IL, USA) software. The baseline demographic and laboratory information are presented as mean ± standard deviation for the continuous variables and frequencies for the discrete variables. The categorical variables were analyzed using a chi-square test and the continuous variables were analyzed using an unpaired t-test. The NT-proBNP was log-transformed to reduce the effect of extreme values because the relationship between NT-proBNP levels and the endpoint was not linear. Therefore, NT-proBNP was logarithmically transformed before entering the analysis in order to perform the multiple analyses requiring a normal distribution. A receiver-operating characteristics (ROC) curve analysis was used to determine the cut-off values for the cardiac biomarkers as regards prediction for cardiac events during the follow-up period. Univariate and multivariate Cox regression analyses were used to evaluate the prognostic value of the parameters, and also were performed using conventional risk factors, Tn-I, NT-proBNP and hs-CRP variables, so that sequential models were developed to examine the incremental prognostic value. Incremental factors added to the model at each step was considered significant when the difference in the log-likelihood associated with each model corresponded to $p<0.05$. In addition, cardiac event-free survival was determined according to the Kaplan-Meier method. The p-values were 2-sided, and $p<0.05$ was considered to be significant.

Results

Baseline Characteristics and Clinical Outcomes

The study consisted of 215 patients: 56 patients (26.0%) had STEMI, 98 (45.6%) had NSTEMI, and 61 (28.4%) had UA. The mean age of the patients was 65±46 years, and 75 (34.9%) were females. During the mean follow-up period of 246 days, 24 patients (11.2%) experienced cardiac

Table 3 Cox Regression Analysis for MACE

	Univariate analysis		*Multivariate analysis*	
	Hazard ratio (95%CI)	*p value*	*Hazard ratio (95%CI)*	*p value*
Age	*1.00 (0.994–1.007)*	*0.822*	*1.00 (0.986–1.016)*	*0.922*
Sex	*2.57 (1.148–5.729)*	*0.022*	*2.60 (0.627–10.791)*	*0.188*
Hypertension	*1.42 (0.637–3.159)*	*0.392*	*1.85 (0.720–4.740)*	*0.202*
Diabetes	*2.67 (1.184–6.006)*	*0.018*	*0.89 (0.351–2.274)*	*0.814*
Smoking	*0.44 (0.193–1.011)*	*0.053*	*2.08 (0.471–9.186)*	*0.334*
Diagnosis	*0.76 (0.440–1.296)*	*0.309*	*0.52 (0.226–1.185)*	*0.119*
Tn-I	*1.00 (0.995–1.005)*	*0.972*	*1.00 (0.991–1.004)*	*0.495*
NT-proBNP	*1.00 (1.000–1.000)*	*<0.001*	*1.00 (1.000–1.000)*	*0.031*
Log NT-proBNP	*2.48 (1.822–3.363)*	*<0.001*	*2.19 (1.397–3.437)*	*0.001*
hs-CRP	*1.22 (1.104–1.345)*	*<0.001*	*1.36 (1.155–1.591)*	*<0.001*
LDL-cholesterol	*1.01 (0.999–1.022)*	*0.073*	*1.01 (0.999–1.030)*	*0.061*
Ejection fraction	*0.94 (0.913–0.974)*	*<0.001*	*0.95 (0.911–0.993)*	*0.024*
Coronary revascularization	*1.17 (0.509–2.669)*	*0.717*	*1.10 (0.411–2.929)*	*0.852*

CI, confidence interval. Other abbreviations see in Table 1.

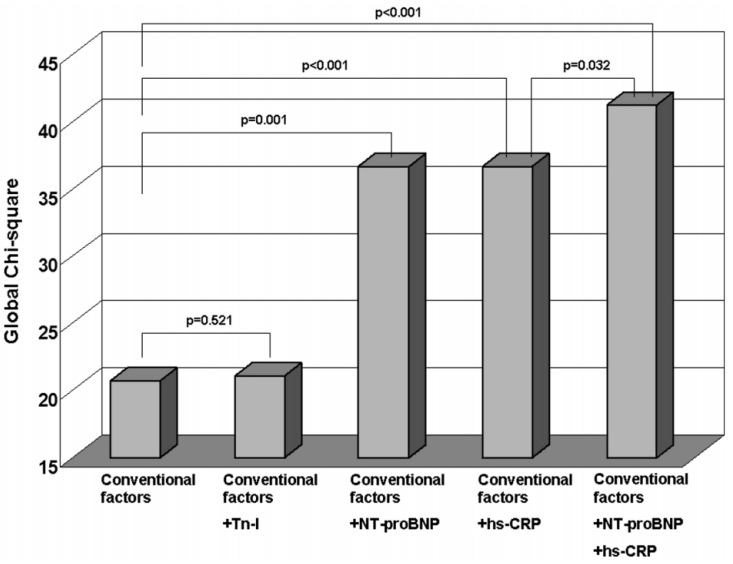

Fig 1. Incremental prognostic value of the conventional risk factors, Tn-I, NT-proBNP and hs-CRP, by Cox proportional-hazards model, presented as a global chi-square value. hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal proB-type natriuretic peptide; Tn-I, troponin-I.

events and 10 of them (4.7%) died, 8 from cardiac causes and 2 cerebrovascular accidents (stroke and hemorrhage); 5 deaths occurred in hospital. Of the remainder 13 patients (6%) had a recurrent ischemic event (subsequent MI: 7, recurrent UA: 6), and 1 (0.5%) had severe heart failure. Univariate analysis revealed that the patients who experienced cardiac events were more often female, more likely to have a history of diabetes, had higher levels of hs-CRP and NT-proBNP, more likely to have NSTEMI than UA, and had a lower LV ejection fraction (LVEF) (Tables 1,2). However, no significant differences were found between the patients with or without further cardiac events as regards age, Tn-I level, history of hypertension and smoking, and the cholesterol level.

NT-ProBNP, Tn-I and hs-CRP

The baseline NT-proBNP level (Table 1) was significantly higher in the individuals experiencing cardiac events than in those who did not (8,479 vs 1,483 pg/ml; p=0.001). In addition, there was a significant trend towards a higher level of hs-CRP (Table 1) in the patients with cardiac events (21.6 vs 6.1 mg/L; p=0.040). The NT-proBNP level was also moderately correlated with the LVEF (r=–0.440, p<0.001) and hs-CRP level (r=0.279, p<0.001). However, the level of Tn-I did not differ between the 2 groups (31.0 vs 26.7 ng/ml; p=0.772). The univariate and multivariate predictors of cardiac events are listed in Table 3. In a Cox regression analysis that included NT-proBNP, hs-CRP, Tn-I, age, sex, hypertension, diabetes, smoking, cholesterol, LVEF and diagnosis, NT-proBNP (p=0.031), hs-CRP (p< 0.001) and the LVEF (p=0.024) remained as independent predictors of cardiac events. With regard to the incremental value, the value of NT-proBNP and hs-CRP, not Tn-I, added incremental prognostic value to conventional risk factors. The global chi-square value showed improvement with an increment of 16 after adding NT-proBNP, 16 after adding hs-CRP and 20 after adding the NT-proBNP + hs-CRP levels (Fig 1).

Prediction of Cardiac Events

Fig 2 shows the area under the ROC curves for hs-CRP and NT-proBNP for prediction of cardiac events (0.71: 95% confidence interval (CI), 0.61–0.82 for hs-CRP; 0.86: 95% CI, 0.78–0.95 for NT-proBNP). The optimal values of hs-CRP and NT-proBNP for predicting cardiac events were defined as the concentration with the largest sum of sensitivity plus specificity for each of the curves; as such, for hs-CRP, the optimal concentration was 3.5 mg/L, whereas

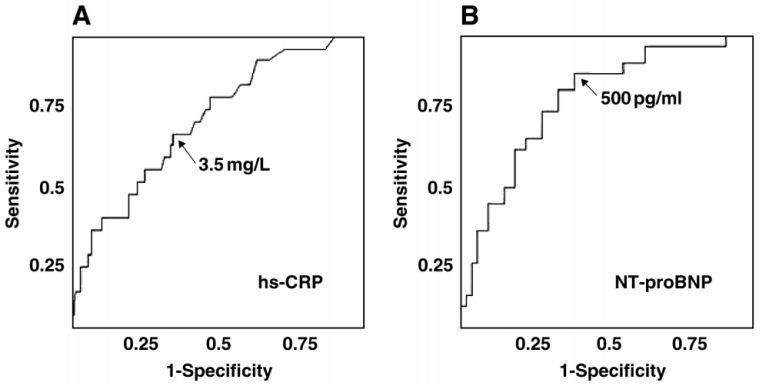

Fig 2. Receiver-operating characteristics curves for hs-CRP (A) and NT-proBNP (B) in patients with and without cardiac events during the follow-up period. hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal proB-type natriuretic peptide.

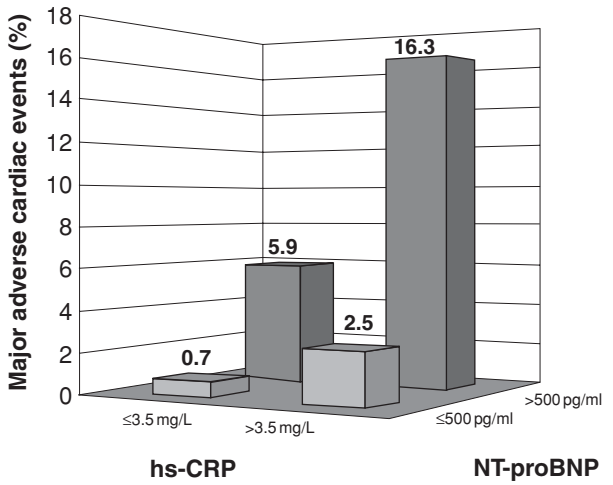

Fig 3. Relationship between cardiac markers and cardiac events in the follow-up period. hs-CRP, high sensitivity C-reactive protein; NT-proBNP, N-terminal proB-type natriuretic peptide.

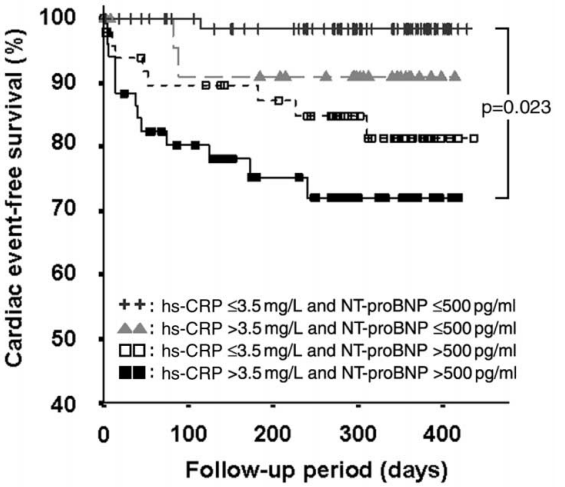

Fig 4. Kaplan-Meier analysis of cardiac event-free survival in patients with acute conronary syndromes stratified into 4 groups based on combinations of the hs-CRP and NT-proBNP levels. hs-CRP, high sensitivity C-reactive protein; NT-proBNP, N-terminal proB-type natriuretic peptide.

for NT-proBNP, it was 500 pg/ml. The sensitivity and specificity in patients with a serum level of hs-CRP >3.5 mg/L were 62.5% and 66.0%, respectively, and in patients with a serum level of NT-proBNP >500 pg/ml they were 87.5% and 55.0%, respectively. The risk of cardiac events increased in those patients with hs-CRP level >3.5 mg/L (p=0.003) and NT-proBNP level >500 pg/ml (p<0.001) (Fig 3). To further analyze the prognostic power of these cardiac biomarkers, 4 groups were defined: (1) hs-CRP ≤3.5 mg/L and NT-proBNP ≤500 pg/ml, n=83; (2) hs-CRP >3.5 mg/L and NT-proBNP ≤500 pg/ml, n=26; (3) hs-CRP ≤3.5 mg/L and NT-proBNP >500 pg/ml, n=52; and (4) hs-CRP >3.5 mg/L and NT-proBNP >500 pg/ml, n=54. Individuals with elevated levels of both biomarkers (group 4) had an 11-fold higher risk of cardiac events than the patients with no elevation of either biomarker (group 1) (hazard ratio 11.8, 95% CI 1.4 to 98.8, p=0.023) (Fig 4).

Discussion

We studied the prognostic value of cardiac markers for adverse outcome in patients with ACS. However, ACS is a heterogenous group, clinically and pathophysiologically, for which reason the prognostic significance of the cardiac biomarkers has not been well evaluated in patients with persistent ST-segment elevation. Thus, we designed a study to evaluate the prognostic information of cardiac marker for the entire spectrum of ACS, focusing on risk stratification particularly. In addition, because the number of patients with STEMI (56 patients) was not enough for distortion of the results, we included them in the present analysis.

The results demonstrate that elevated NT-proBNP and hs-CRP levels provide important and independent information for risk stratification across the entire spectrum of ACS. Elevation of cardiac Tn-I has been reported to be a powerful predictor of an adverse outcome in patients with NSTEMI or UA, and in some patients with STEMI[6,7] but we found no significant differences in the serum Tn-I levels between patients who experienced cardiac events and those who did not. The most important point to consider was that the cardiac Tn-I level, not Tn-T, was measured in the present study, which implies a limitation of the standard cardiac markers. The prognostic value of Tn-I has not been investigated to the same extent as that of Tn-T. In one study, although patients with an elevated Tn-I level were at increased risk of death, the Tn-I level did not offer prognostic information independent of brain natriuretic peptide.[4] Those findings were supported by the results of previous studies that demonstrated that a negative Tn-I is not a reliable indicator of the absence of myocardial damage and does not

indicate a low risk of subsequent cardiac event[8,9] Thus, it remains unclear whether Tn-I has the same prognostic value as Tn-T, although other studies[10,11,12] have shown a higher predictive value for the Tn-T compared with Tn-I. A potential explanation for the lower significance of the Tn-I level in the present study is the relatively small patient sample size, which may account, at least partially, for this discrepancy. However, further investigations are required to determine the degree to which the development of cardiac events is dependent on the severity of the increase in the Tn-I level.

The hs-CRP, as an acute phase reactant, has been used primarily as a marker of systemic inflammation. The activation of inflammation and acute phase reaction appear to play an important role not only in the pathogenesis of atherosclerosis, but also in the initiation of ACS. Verma et al showed that C-reactive protein (CRP) actively participates in both atheromatous lesion formation and plaque disruption![13] In addition, it has been recently reported that the level of CRP may correlate with the number of vulnerable atherosclerotic plaques with superficial foam cells, large necrotic cores and thin-capped atheroma![14] Furthermore, CRP was found to correlate significantly with the extent and severity of coronary artery disease![15] Therefore, it is possible that an elevated level of CRP reflects a more diffuse process of coronary atherosclerosis with a higher plaque burden and increased vascular inflammation, with a higher prevalence of myocardial damage. Thus, in our study, higher levels of hs-CRP had a predictive role for the occurrence of cardiac events in patients with ACS, in accordance with previous findings![16] which revealed that elevation in CRP levels seems to correlate with in-hospital and short-term prognosis. Together with hs-CRP, we also identified that patients with adverse events had a higher tendency for diabetes, as reported by other studies[17–19] that have shown that an increased CRP levels is associated with the insulin resistance syndrome, suggesting that chronic subclinical inflammation may be part of the metabolic syndrome. Moreover, some studies have reported that elevated CRP levels in patients with coronary artery disease are associated with a profound impairment of systemic endothelial vascular reactivity![15] endothelial dysfunction[20,21] and atherogenesis![22]

The NT-proBNP is a circulating cardiac hormone that is mainly released from the ventricle in response to increased stretch or wall tension[23,24] Therefore, NT-proBNP has been widely used as a simple and useful marker for LV overload, such as LV dysfunction or LV hypertrophy, and for prognosis in patients with CHF. Previous studies[25–27] have demonstrated that after MI, an elevated NT-proBNP level is associated with a lower LVEF and an increased risk of heart failure or death. Recently, NT-proBNP has been shown to provide significant prognostic information across the entire spectrum of ACS[28] and the present results extend these findings to patients with STEMI. We found that an elevated NT-proBNP level and the LVEF had useful prognostic value in predicting the risk of cardiac events. Moreover, NT-proBNP even remained significantly predictive of cardiac events for those patients with a preserved LVEF ≥50% (p=0.037, data not shown). The present study showed that the patients with a baseline level of NT-proBNP >500 pg/ml (sensitivity=87.5%, specificity=55.0%) were at higher risk of cardiac events. The explanation for the higher cut-off values of NT-proBNP in this study may have be the inclusion of patients with STEMI, because STEMI would have a significant role in the great rise of NT-proBNP level in response to ischemic severity, as has been speculated in previous studies![25,29] Cardiac ischemia causes the release of NT-proBNP in proportion to the extent and severity of the ischemic insult![9] and NT-proBNP is higher in patients with UA than in those with stable angina or healthy control subjects![25] Thus, ischemic injury would likely cause transient LV systolic and diastolic dysfunction, leading to increased LV end-diastolic wall tension, which would be a trigger for releasing of NT-proBNP, even in the absence of myocardial necrosis or overt LV dysfunction.

The present study also sought to evaluate whether the concurrent assessment of NT-proBNP and hs-CRP as cardiac biomarkers is useful for predicting cardiac events in patients with ACS. Our data show that the levels of NT-proBNP and hs-CRP provide significant incremental prognostic information over that provided by the conventional clinical risk factors. Binary cut-points were also investigated to assist in a rapid decision-making process. The patients with elevated levels of both cardiac markers on admission had higher rates of cardiac events than the patients with normal levels. In a multivariate analysis, when correcting for a large number of clinical risk factors, elevated levels of NT-proBNP and hs-CRP were identified as independent predictors of cardiac events. Accordingly, the present results reveal that a simultaneous increase in both markers identifies a subset of cases with a high probability of cardiac events during the follow-up period. Thus, simultaneous assessment of these biomarkers would be more useful in predicting the cardiac events than the respective value of each biomarker, providing complementary prognostic information. Moreover, this simple evaluation using a combination of biomarkers would help the clinician determine the risk stratification for cardiac events.

Study Limitations

Not all the patients were followed up completely: the follow-up rate was approximately 85%. Thus, a complete follow-up study is required. The number of patients was so small that the lack of association with prognosis of some of the studied variables should be interpreted cautiously. In a number of previous reports[4,9,28] the mean age of patients with cardiac events is older than those without cardiac events; however, the difference in the mean age of the 2 groups was not significant in the present study. Also, the Tn-I level did not reach significance in this study, although other studies have shown a prognostic value of Tn-I for patients with ACS. Another limitation is that blood samples for NT-proBNP were not obtained serially from admission. In patients with acute MI, the level of NT-proBNP is significantly increased on admission, peaks twice and then decreases gradually![30] Thus, in the present study, we could not examine the time course of plasma NT-proBNP levels in response to ACS. In addition, this study was retrospective and thus lacked detail information on coronary angiography and follow-up medication, both of which are important factors for subsequent cardiac events, although we did evaluated the major factors affecting the level of cardiac markers.

In conclusion, elevated levels of hs-CRP and NT-proBNP on admission would appear to have an independent prognostic value and the combination of both cardiac markers might have an incremental value in the risk stratification of patients with ACS.

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