The ratio of N-terminal pro-B-type natriuretic peptide to troponin I for differentiating acute coronary syndrome

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Original Contribution

Abstract

Introduction: It is difficult to differentiate whether coronary or non-coronary causes in patients with elevated troponin I (TnI) in emergency department (ED). The aim of this study was to develop a clinical decision tool for differentiating a coronary cause in the patients with elevated TnI.

Methods: This was a retrospective observational study that enrolled consecutive ED patients. Patients were included in the study if they were ≥16 years of age, had admitted through ED with a medical illness, and TnI levels at initial evaluation in the ED were ≥0.2 ng/mL. Patients diagnosed with ST elevation myocardial infarction or congestive heart failure were excluded. Coronary angiography, electrocardiogram, laboratory results, echocardiography, and clinical characteristics were analyzed.

Results: Among the included 1441 patients, 603 and 838 patients were categorized into an acute coronary syndrome (ACS) group and non-acute coronary syndrome (non-ACS) group, respectively. The ratio of N-terminal pro-B-type natriuretic peptide (NT-proBNP) to TnI was significantly higher in the non-ACS group compared to the ACS group. The AUC of NT-proBNP/TnI (0.805, 95% CI, 0.784-0.826) was significantly superior to that of NT-proBNP/creatinine kinase-MB, TnI, and NT-proBNP. The patients of the non-ACS group with high levels of TnI and BNP showed more critically ill manifestation at the time of presentation and higher mortality.

Conclusion: NT-proBNP/TnI may help to distinguish medical patients with elevated TnI whether the elevated TnIs were caused from ACSs or from conditions other than ACS.

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1. Introduction

Troponin-I (TnI) is the most preferred cardiac biomarker for the diagnosis of myocardial infarction. Specifically, the diagnosis of non-ST elevation myocardial infarction (NSTEMI) exclusively depends on an elevation of this cardiac biomarker in blood [1,2]. Elevated TnI levels can be seen in non-coronary cardiac problems (such as heart failure, arrhythmias, perimyocarditis, and stress-induced cardiomyopathy) and non-cardiac problems (such as pulmonary thromboembolism, sepsis, renal failure, neurological diseases, severe hemorrhage, and many other conditions) [3-7]. Elevated troponins without coronary etiology have been described in numerous studies. Elevation of Troponins were observed in 32 to 50% of patients with pulmonary thromboembolism [8], in 32 to 49% of patients with perimyocarditis [9], 52 to 55% of patients in acute heart failure [10], and 36 to 85% of patients in sepsis [11]. Elevated TnI levels have even occurred in up to 30% of healthy athletes [12]. This clinical circumstance has been described in various terms such as elevated troponin without coronary etiology, non-coronary troponin elevation, or elevated troponin unrelated to an acute myocardial infarction (AMI). By third universal definition of myocardial infarction, these hypertrponinemias without ST segment elevation on electrocardiogram (ECG) fall into type 2 myocardial infarction (MI) [11]. Type 2 MI is myocardial infarction secondary to an ischemic imbalance. In instances of myocardial injury with necrosis where several conditions other than coronary artery disease (CAD) contributes to an imbalance between myocardial oxygen supply and/or demand.

TnI tests have been widely implemented in most emergency departments (ED) as a routine diagnostic process in patients with symptoms suggestive of acute coronary syndromes [13]. However, it is difficult to differentiate whether coronary or non-coronary causes in patients with elevated TnI in emergency department. In addition, there are no current guidelines for diagnostic or therapeutic strategies in these patients with TnI elevation and a low suspicion of acute coronary events.
Therefore, emergency physicians can inevitably progress to additional and essentially time- and cost-wasting investigations that include echocardiography, coronary computed tomography, or cardiac magnetic resonance imaging. In a recent study, the ratio of B-type natriuretic peptide to troponin T was shown to discriminate stress cardiomyopathy from AMI [14]. We applied the ratio of B-type natriuretic peptide to Tnl for patients in whom Tnl level was elevated, and the clinical decision of whether or not they had an ACS was ambiguous.

The aim of this study was to develop a clinical decision tool for distinguishing the etiology in patients with elevated Tnl (whether coronary or non-coronary), and to describe the clinical characteristics of patients with non-coronary hypertrponinemia (NCH).

2. Methods

2.1. Study design and setting

This was a single-center, retrospective, observational cohort study that analyzed consecutive patients who visited the emergency department of our Hospital, which is a tertiary hospital located in urban area from September 1, 2013 to October 31, 2016. The annual ED census ranged from 32,000 to 35,000 patients. This study was approved by our hospital institutional review board.

2.2. Participants

Patients were included in the study if they were ≥16 years of age and presented with a medical illness and for whom the physician ordered cardiac biomarkers, which included creatinine kinase-MB (CK-MB), Tnl, and NT-proBNP at the first encounter. In addition, patients were included if they met the criteria of a serum Tnl level of ≥0.2 ng/mL and were admitted to the hospital after ED management. Patients with ST elevation myocardial infarction (STEMI) were excluded because the diagnosis of STEMI is not derived from the evaluation of biomarkers. We also excluded patients who were diagnosed with heart failure because those patients were readily diagnosed by clinical manifestations, radiologic and echocardiographic findings, and blood tests.

2.3. Measurements and data collection

Data were collected from the ED registry following the standard format of the National Emergency Department Information System (NEDIS) of our nation and the electronic medical records (EMR) system of our hospital. Extracted data from the ED registry included age, gender, physiological parameters at the time of presentation to the ED, and the patient’s category (e.g., disease, injury, and others). Physiological parameters and patient category were entered by the triage nurse at the time of presentation to the ED. The National Early Warning Score (NEWS) was calculated for each patient. The applicability of the NEWS in patients presenting to ED has been previously validated in many studies [15,16]. During the study period, five full-time emergency physicians attended in rotation and decided to order the biomarkers when patients’ symptoms suggested acute coronary syndrome, non-coronary cardiovascular etiologies, pulmonary problems, shock, or critical illness of unclear cause. Simultaneously available laboratory results of creatinine kinase-MB (CK-MB), Tnl, and NT-proBNP were collected. The biomarkers were measured by an electrochemiluminescence immunoassay technique using the Roche Cobas 8000 analyzer (Roche diagnostics, Rotkreuz ZG, Switzerland) during the study period. The final diagnosis at the time of discharge as well as the patient’s outcome were collected from the discharge note and the final diagnosis section indicated on the EMR. All the discharge notes and final diagnoses were entered by attending physicians and were then examined by certified professional health information managers. All diagnoses were documented following the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10). We called type 2 MI without significant coronary occlusion “non-acute coronary syndrome (ACS)” group in the presenting study. The primary outcome was the diagnosis of non-ACS at discharge that was confirmed by CAG, ECC, laboratory results, echocardiography, and clinical manifestation. We used a new cohort (606 consecutive patients with same inclusion criteria between November 1, 2016 and December 21, 2017) for validation of our final prediction model.

2.4. Statistical analysis

We divided MIs into ACS group that need coronary procedures and non-ACS group that need treatment of another illness. Among the demographic, physiological, and laboratory data, statistically significant parameters were assigned to independent variables with Tnl, NT-proBNP, the ratio of NT-proBNP to CK-MB (NT-proBNP/CK-MB), and the ratio of NT-proBNP to Tnl (NT-proBNP/Tnl), respectively. Then, the bundels of independent variables were entered into a multivariate logistic regression where the diagnosis of non-ACS group at time of discharge was the dependent variable. The adjusted odds ratios of Tnl, NT-proBNP, NT-proBNP/CK-MB and NT-proBNP/Tnl were calculated. Areas under the receiver operating curve (AUC) of NT-proBNP/Tnl was compared with the AUCs for Tnl, NT-proBNP, NT-proBNP/CK-MB and NT-proBNP/Tnl. The sensitivity and specificity of NT-proBNP/Tnl were obtained from the receiver operating characteristic (ROC) curve, and the cutoff were chosen at the point that the Youden’s index showed the maximum value. Additionally, we selected two supplementary cut-offs where sensitivity or specificity reached 95%, and established four strata based on the cutoffs for easier clinical implementation. The non-ACS group was stratified into 12 subgroups based on the ICD-10. The differences of NT-proBNP/Tnl between each subgroup were compared with Kruskal-Wallis tests, which included a post hoc analysis using Mann-Whitney U tests that established p values using a Bonferroni correction.

To show the statistical significance between the AUC of NT-proBNP/Tnl and others (Tnl, NT-proBNP, and NT-proBNP/CK-MB), we needed, at least, 229 patients in ACS group and 458 patients in non-ACS group; the ratio of sample sizes in ACS group to non-ACS group was 0.5 in this study population. The sample size was calculated under the assumption that AUC of NT-proBNP/Tnl would reach 0.8 and those of others were 0.75, while type I error were 0.05 and power was 80%.

Independent t-tests, chi-square tests, Fisher’s exact tests and the Mann-Whitney U tests were used to describe demographic and physiological characteristics and laboratory findings. All p values were two-sided, and a value of p < 0.05 was considered statistically significant. Analyses were performed with MedCalc for Windows, version 16.8 (MedCalc Software, Ostend, Belgium).

3. Results

3.1. Characteristics of study subject

Among 1907 eligible patients, patients with STEMI (n = 293) and heart failure (n = 173) were excluded, and 1441 were included in the study. Data missing occurred in heart rate (n = 7, 0.5%), breath rate (n = 7, 0.5%), body temperature (n = 1, 0.1%), peripheral oxygen saturation (n = 9, 0.6%), and NEWS (n = 16, 1.1%). ACS and non-ACS groups contained 603 and 838 patients, respectively. In the ACS group, CAG confirmed the presence of an ACS in 530 patients (87.9%), and other patients were clinically assumed to have an ACS based on the subsequent results of the cardiac biomarkers and echocardiography. In the non-ACS group, 111 patients (13.2%) were underwent CAG. Table 1 summarizes patient demographics, physiological variables, the results of the cardiac biomarkers, and in-hospital mortality between the two groups in derivation cohort. The test characteristics for the validation cohort was shown in Table 2.
All continuous variables showed skewed distribution, exhibited by median [interquartile range] values. Physiologic parameter:

- Systolic blood pressure, mmHg: 130 [110–150]; 120 [100–140]; 0.001
- Heart rate, per minute: 78 [69–91]; 95 [78–113]; 0.001
- Respiratory rate, per minute: 20 [20–20]; 20 [20–24]; 0.001
- Body temperature, °C: 36.5 [36.4–36.7]; 36.7 [36.4–37.2]; 0.001
- Peripheral oxygen saturation, %: 98 [96–99]; 96 [90–98]; 0.001
- Consciousness (alert, %): 576 [95.5]; 645 [77.6]; 0.001
- National early warning score: 2 [0–4]; 6 [2–9]; 0.001

Diagnostic properties of NT-proBNP/TnI for different cutoffs

- Criterion Sensitivity (95% CI) Specificity (95% CI) PPV (95% CI) NPV (95% CI)
- ≥90% 29.19 (25.6–31.0) 94.99 (93.3–96.4) 81.1 (75.6–85.6) 65.1 (63.9–66.1)
- ≥1115 77.11 (73.6–80.4) 73.51 (70.4–76.5) 67.7 (65.0–70.3) 81.7 (79.3–83.9)
- ≥11,000 95.02 (93.0–96.6) 31.98 (28.8–35.3) 50.1 (48.9–51.4) 89.9 (86.1–92.8)

The Youden’s index showed the biggest at the NT-proBNP/TnI > 1115. Sensitivity and specificity for the cutoff point were 77.11% (95% CI, 73.6–80.4) and 73.51% (95% CI, 70.4–76.5). Sensitivity showed 95% for the cutoff of ≥1,100 (specificity: 31.98%), and specificity 95% for the cutoff ≤90 (sensitivity: 29.19%). The diagnostic properties for the cutoffs were shown in Table 4. The patients were categorized according to the cutoff scores for NT-proBNP/TnI in the ROC curve technique, and the assigned ranges were <90, 90–1115, 1115–11,000, and >11,000. Fig. 1 shows the distribution of the ACS and non-ACS groups at the cutoff ranges that represented the positive and negative predictive values based on the strata. In validation cohort, the AUC of NT-proBNP/TnI (0.774, 95% CI, 0.739–0.807) was significantly superior to that of NT-proBNP/CK-MB (0.737, AUC difference = 0.0367, p = 0.0003; 95% CI, 0.701–0.772), TnI (0.663, AUC difference = 0.0839, p = 0.0002; 95% CI, 0.652–0.727), and NT-proBNP (0.687, AUC difference = 0.868, p < 0.0001; 95% CI, 0.649–0.724). The distribution of the ACS and non-ACS groups at the cutoff ranges was similar to that of derivation cohort (Fig. 2). In addition, we performed a secondary analysis just of the patients (ACS group: 530, non-ACS group: 111) that had cardiac catheterization. The results of secondary analysis are shown in Table 5. Figs. 3, 4 show the distribution of the ACS and non-ACS groups at the cutoff ranges in derivation and validation cohort.

Subgroups of the non-ACS group stratified by diagnosis and NT-proBNP/TnI

Among the non-ACS group (n = 838), diseases of the circulatory system (I category of ICD-10) comprised 14.1% (n = 118) of patients, respiratory diseases (J category of ICD-10) comprised 23.5% (n = 197), genitourinary diseases (N category of ICD-10) comprised 14.2% (n = 119), neoplasms (C category of ICD-10) comprised 10.9% (n = 91), digestive tract diseases (K category of ICD-10) comprised 7.9% (n = 66), infectious diseases (A category of ICD-10) comprised 5.4% (n = 45), and metabolic diseases (E category of ICD-10) comprised 3.9% (n = 33). Among the patients in the non-ACS group who were diagnosed with circulatory diseases in the I category of the ICD-10, arrhythmias...
for 22.7% \( (n = 52) \), pulmonary embolism for 16.2% \( (n = 35) \), and stroke for 13.8% \( (n = 28) \). NT-proBNP/TnI levels in the ACS group were significantly different from all other categories \( (p < 0.001) \) (Fig. 5). The detailed descriptions of disease categories are represented in Supplement 1.

4. Discussion

The main purpose of this study was to develop a clinical decision tool for distinguishing the etiology of elevated TnIs at the time of ED presentation in patients with ambiguous clinical manifestation. In the presenting study, NT-proBNP/TnI was an independent predictor of ACS and was superior to TnI, NT-proBNP, and NT-proBNP/CK-MB. We called type 2 MI without significant coronary occlusion “non-acute coronary syndrome (ACS) group” in the presenting study. Stress-induced cardiomyopathy, also known as Takotsubo cardiomyopathy, may be a possible diagnosis in these patients. The diagnosis of this condition requires typical echocardiographic findings [17]. However, in many patients with an elevated TnI, the echocardiographic findings failed to match the specific criteria. In addition, despite the non-ACS that were confirmed by coronary angiography (CAG) exhibited a very low risk for cardiac death and AMI [18], this angiographic information is mostly unavailable in the ED setting. Therefore, our results can be applied to patients in ambiguous but inescapable situations such as vague symptoms, unstable features, and inconclusive results after ED evaluation.

An elevation of B-type natriuretic peptide is an established marker of left ventricular dysfunction [19]. Troponin are elevated in the setting of membrane leak caused by acute myocardial necrosis, whereas BNP is related to ventricular stress with or without myocardite necrosis [19-21]. It is known that BNP and TnI are increased in both stress induced cardiomyopathy and AMI [21,22]. However, because stress induced cardiomyopathy is a disease primarily causing distention of the ventricles and characterized by reversible myocardial dysfunction without necrosis, a greater increase in BNP compared with troponin has been demonstrated, compared with AMI [21,23-26]. NT-proBNP in heart with normal function is mainly produced in the atrium. However, there is increased ventricular production of NT-proBNP in HF [20]. We excluded patients diagnosed with STEMI and HF because those patients were readily diagnosed by ECG, clinical manifestations, radiologic and echocardiographic findings, and cardiac biomarkers such as TnI or NT-
proBNP. Therefore, the results may be of use in those patients who were known to have normal cardiac function.

We demonstrated NT-proBNP/TnI values in disease categories in the non-ACS group. All categories showed significant differences from the ACS group. In previous studies, kidney and respiratory diseases, pulmonary embolism, malignancies, and cerebral strokes were shown to be associated with elevations of TnI and NT-proBNP levels [27-31]. We also aimed to describe the clinical characteristics of patients with elevated TnI unrelated to an ACS. Basal characteristics and in-hospital mortality of the two groups were very different. The patients of the non-ACS group with high levels of TnI and BNP showed more critically ill manifestation at the time of presentation and higher mortality. These observations were similar to those from several previous studies that showed that high levels of TnI and BNP were associated with significantly higher mortality in non-ACS patients [32,33]. Therefore, this study can provide a biochemical diagnostic tool for the differentiation of patients with a NCH from those patients with an ACS.

As the NT-proBNP/TnI might be a useful but imperfect tool in the clinical decision-making process, we introduced two supplementary cutoffs (NT-proBNP/TnI at 90 and 11,000, at 95% sensitivity and specificity) as well as the traditional one. This clinical insight would be more helpful with additional information from the ECG, echocardiography, radiologic results and other laboratory findings in various clinical settings. To the best of our knowledge, this is the first study to deduce a biochemical diagnostic tool for the differentiation of patients with a NCH from those patients with an ACS.

This study has some limitations. First, this was a retrospective, single-center study, so generalization of the results should be cautious. Second, selection bias was inevitable because patients visited from or transferred to our hospital came from a relatively small area of approximately 60 km in radius. However, because our hospital is the only

<table>
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<th>AUC difference</th>
<th>p</th>
<th>95% CI</th>
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<tr>
<td>NT-proBNP/CK-MB</td>
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<td>0.665-0.738</td>
<td>0.00292</td>
<td>0.8178</td>
<td>-0.0219-0.0278</td>
</tr>
<tr>
<td>TnI</td>
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<td>0.588-0.664</td>
<td>0.0789</td>
<td>0.0155</td>
<td>0.0150-0.0143</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>0.640</td>
<td>0.601-0.677</td>
<td>0.0658</td>
<td>0.0050</td>
<td>0.0199-0.112</td>
</tr>
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</table>

AUC differences were compared to NT-proBNP/TnI.

**Table 5**  
Area under receiver operating characteristic curve of NT-proBNP/TnI, NT-proBNP/CK-MB, TnI, and NT-proBNP in derivation cohort that had cardiac catheterization.

CI, confidence interval.

**Fig. 3.** The distribution of the ACS and non-ACS groups at the cutoff ranges in derivation cohort (ACS group: 530, non-ACS group: 111) that had cardiac catheterization.

**Fig. 4.** The distribution of the ACS and non-ACS groups at the cutoff ranges in validation cohort (ACS group: 332, non-ACS group: 274) that had cardiac catheterization.
tertiary care center in the area, patients with suspected acute coronary syndrome or those who were critically ill almost always present to our ED. Third, we conducted this study with patients who presented to the ED, so severity scoring systems based on ICU admission could not be used to describe the severity profiles of the patients, this might interfere the generalization of results from the presenting study. Fourth, not all the ACSs were confirmed with CAG, and a final diagnosis that was dependent on the clinical assumption could be potentially erroneous. Fifth, because of relatively small number of validation cohort, statistical power for validation was limited. Sixth, reference values for NT-proBNP, Troponin I in each hospital may be different. Therefore, there is no absolute cutoff value and may vary from hospital to hospital. Each hospital would give a different ratio, so a ratio may not be generalizable in most cases.

5. Conclusion

Among medical patients in whom etiology of TnI elevation was ambiguous, NT-proBNP/TnI can be a good predictor in differentiating patients with NCH from those with ACS. In addition, patients with NCH at the time of ED presentation might be more seriously ill compared to patients with other disease. In some cases, NT-proBNP/TnI can be a good predictor in differentiating patients with NCH from those with ACS. In addition, patients with NCH at the time of ED presentation might be more seriously ill compared to patients who were diagnosed with ACS.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2018.08.035.

Competing interests

No authors have any competing interests to declare.

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References


