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High-Sensitivity Troponin I Assay for Differential Diagnosis of New-Onset Myocardial Infarction in Patients with Acute Decompensated Heart Failure

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Purpose: Acute decompensated heart failure (ADHF) caused by ischemic heart disease is associated with higher mortality and requires immediate diagnosis. Recently, novel methods to diagnose non-ST elevation myocardial infarction (NSTEMI) using high-sensitivity cardiac troponin have been applied. We compared the clinical utility of high-sensitivity troponin I (hS-TnI), delta troponin I, and other traditional methods to diagnose NSTEMI in patients with ADHF.

Materials and Methods: This retrospective cross-sectional study was conducted to analyze patients with ADHF who underwent hS-TnI evaluation of 0–2-h protocol in our emergency department. Patients were grouped according to a diagnosis of NSTEMI.

Results: A total of 524 ADHF [ADHF with NSTEMI, n=109 (20.8%)] patients were enrolled in this analysis. The mean values of hS-TnI (ng/mL) in the ADHF with and without NSTEMI groups were 2.44±5.60 and 0.25±0.91, respectively. Multivariable analysis revealed that regional wall-motion abnormality, T-wave inversion/hyperacute T wave, and initial and delta hS-TnI were predictive factors for NSTEMI. Laboratory values related to cardiac biomarkers, including hS-TnI [odds ratio (OR) (95% confidence interval, CI): 2.18], and the delta hS-TnI [OR (95% CI): 1.55] were significant predictors of NSTEMI. Moreover, receiver operating characteristic analysis showed that the areas under receiver operating characteristic curves for electrocardiographic abnormalities, initial hS-TnI, and delta hS-TnI were 0.794, 0.802, and 0.773, respectively.

Conclusion: For diagnosis of suspected NSTEMI in patients with ADHF, initial hS-TnI assay has similar predictive value as ischemic changes on electrocardiogram and superior predictive value than delta hS-TnI calculated by the 0–2-h protocol.

Key Words: Myocardial infarction, heart failure, biomarker, troponin I

INTRODUCTION

Heart failure is an emerging cause of mortality and morbidity in the Republic of Korea. The estimated prevalence of heart failure in the general population of Korea was 1.53% in 2013 and is expected to increase to 3.35% in 2040.[1] In the United States, 15.5 million cardiac-care visits related to heart failure were recorded between 1992 and 2001, with an average annual increase of 18500 visits.[2] Acute decompensated heart failure (ADHF) is defined as a sudden aggravation of symptoms or signs in patients with compensated heart failure.[3] ADHF is often encountered by clinicians in the emergency room and requires immediate treatment at the time of diagnosis. There are various causes of heart failure, including hypertensive heart disease, valvular heart disease, and cardiomyopathies.[4] Ischemic heart disease is a major cause of heart failure.[5,6] Patients with heart failure due to ischemic heart disease have a high mortality risk and require appropriate management, including coronary interventions.[6-8] To reduce mortality risk in these patients, clinicians need to determine whether patients with heart failure have ischemic heart disease.[9]

Based on findings on an electrocardiogram (ECG), patients

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with ST-elevation myocardial infarction (STEMI) should be immediately treated with coronary interventions or fibrinolysis. However, in patients with non-ST-elevation myocardial infarction (NSTEMI), it may be difficult to determine appropriate management because of the wide spectrum of electrocardiographic findings, including temporary ST elevation, ST depression, T-wave inversion, and even the absence of an ischemic ECG wave.[10] Moreover, various symptoms in ADHF patients with NSTEMI can induce misdiagnosis and delay proper management, if these patients are not specifically evaluated for NSTEMI.

In 2009, high-sensitivity cardiac troponin was introduced into clinical practice and replaced standard cardiac troponin for early diagnosis of acute myocardial infarction.[11,12] In the literature, high-sensitivity cardiac troponin has been reported to facilitate quantification of cardiomyocyte injury secondary to cardiac insults, and values of high-sensitivity cardiac troponin have been shown to be strongly correlated with prognosis in patients with heart failure.[13,14] Therefore, troponin is the preferred cardiac biomarker for clinicians to diagnose myocardial infarction.[15] However, cardiac troponin can be elevated in acute or chronic heart failure without new-onset myocardial ischemia due to various mechanisms, such as apoptosis and autophagy.[16] Elevations in cardiac markers in ADHF patients may reflect hemodynamic stress or myocardial injury due to neurohormonal, inflammatory, or biochemical damage.[17]

In addition, according to the fourth universal definition of myocardial infarction, the presence of ischemic damage should not be judged based on elevated cardiac troponin levels.[18] Therefore, it is necessary to discriminate the actual presence of myocardial infarction in ADHF patients with elevated cardiac troponin levels, which has necessitated new cutoff variables and methods of troponin measurement to exclude myocardial infarction in patients with heart failure. Recently, novel methods comprising 0–1 or 0–2-h protocols to diagnose NSTEMI by using high-sensitivity cardiac troponin have been introduced and have found wider application.[19-21]

We conducted this study to comparatively evaluate the clinical utility of high-sensitivity troponin I (hS-TnI, 0–2-h protocol) against other diagnostic tools for diagnosing NSTEMI in patients with ADHF.

MATERIALS AND METHODS

Study design and setting

This retrospective, cross-sectional, single-center study analyzed information from consecutive patients with ADHF who visited the emergency department (ED) of Wonju Severance Christian Hospital, Wonju, Gangwon-do, Republic of Korea, between August 2018 and March 2019. The institution has a regional emergency medical center, and approximately 45000 patients visit the ED per year. All patients who complained of chest pain, shortness of breath, or generalized edema underwent medical history-taking and physical examination by emergency-care physicians. We defined inclusion criteria for patients with ADHF as follows: 1) new or worsening symptoms or signs of dyspnea, fatigue, or edema that led to unscheduled hospital admission, with 2) the represented symptoms presumed to be related to a reduced left ventricular function.[22] Myocardial infarction was diagnosed according to the consensus definition of the Joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation Task Force for the fourth Universal Definition of Myocardial Infarction. We defined myocardial injury as cardiac troponin elevation above the 99th percentile upper normal limit, possibly acute if there was a rise and/or fall of cardiac troponin values. In contrast, we diagnosed myocardial infarction based on the presence of acute myocardial injury with at least one of the following: 1) clinical presentations of myocardial ischemia, 2) new ECG changes suggesting ischemia, 3) pathologic Q waves, 4) evidence of newly developed non-viable myocardium or regional wall-motion abnormality (RWMA) by imaging (i.e., echocardiography), and 5) evidence of a coronary thrombus by angiography.[18] Moreover, we defined new-onset NSTEMI as acute myocardial infarction without ST segment elevation on electrocardiographic presentation. The area of infarction was presumed or identified using a combination of electrocardiographic changes, left ventricular wall motion abnormalities on transthoracic echocardiography (TTE), and coronary angiographic findings.

We included results of simultaneous laboratory tests for hS-TnI and other parameters. Bedside echocardiography was conducted in patients suspected of ADHF with elevated cardiac enzymes, pulmonary edema, or pretibial pitting edema, and echocardiographic images were digitally stored on the server of the Digital Cardiac Archiving & Communication System (GP&P Co., Ltd. Seoul, Republic of Korea). This study was approved by the Institutional Review Board of Wonju Severance Christian Hospital, Yonsei University (approval number: CR319099). Because this study was a retrospective review, the need for informed consent was waived.

Study enrollment

We included patients who were finally diagnosed with ADHF in the patient group based on a review of their electronic medical records. Patients were excluded based on the following criteria: 1) age less than 18 years; 2) diagnosis with STEMI; and 3) missing data on hS-TnI. We diagnosed acute myocardial infarction in the patient group with ADHF based on the fourth universal definition of myocardial infarction and confirmed the final diagnosis through a review of medical records, including information on coronary angiography, ECG, hS-TnI, and TTE (Fig. 1).

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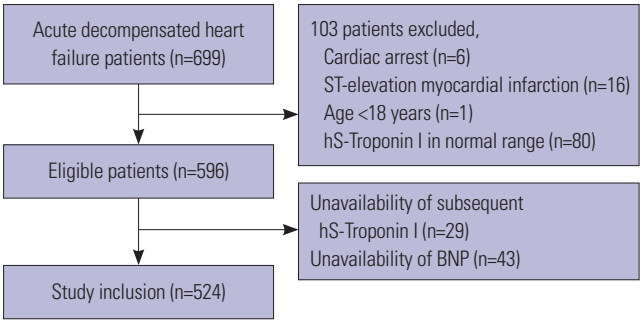

Fig. 1. Study inclusion flow chart. BNP, B-type natriuretic peptide.

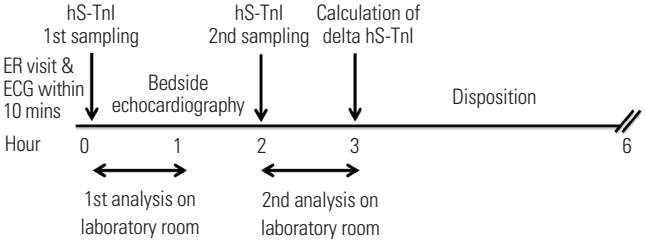

Fig. 2. High sensitivity troponin I (hs-TnI) evaluation process by the 0–2-h protocol in the emergency department since 2015. ER, emergency room; ECG, electrocardiogram.

General evaluation and measurement of high-sensitivity troponin I and delta troponin I in the emergency department

The routine protocol for management in our ED included intensive monitoring, including ECG, oxygen saturation, blood pressure, laboratory tests, including cardiac biomarkers, and bedside echocardiography. Blood samples from patients were routinely tested. Since 2015, hS-TnI was measured using the Siemens Atellica IM High-Sensitivity Troponin I Assay (Siemens Healthineers, Erlangen, Germany) at ED arrival and 2 h later.[23] Each result of hS-TnI was confirmed by primary physicians within approximately 1 h after serial sampling. Patients with hS-TnI values under the reference range (<0.045 ng/mL) were classified as having no significant myocardial damage. For the analysis, we also calculated the difference between initial and 2-h values of hS-TnI, which we defined as delta-troponin I (Fig. 2). Well-trained emergency physicians conducted emergency TTE (EPIQ7 Ultrasound systems, Philips Medical System, Andover, MA, USA) for rapid differential diagnosis of acute coronary artery disease. Physicians performing TTE had completed an official training program based on the American Society of Echocardiography guidelines and had performed at least 300 TTE studies under supervision.[24]

If necessary, all patients were placed on appropriate management regimens to control decompensated heart failure, including intravenous or sublingual nitroglycerin, intravenous furosemide, and supplemental oxygen. Dual antiplatelet therapy, such as aspirin and P2Y12 receptor inhibitors, were included to manage acute coronary disease.

Analysis of electrocardiogram

We obtained ECGs recorded in patients with complaints of chest pain, dyspnea, or generalized edema within 10 minutes of presentation in the emergency room and retrospectively analyzed these records. We divided ECGs into five groups. 1) Non-ischemic ECG group: no evidence of ischemia in ECG or no interval change between the previous and fresh ECG study, which included patients with atrial arrhythmias and left ventricular hypertrophy, which have a low association with myocardial ischemia; 2) other abnormalities or non-specific ST/T group: minimal ST depression (<1 mV) and isolated T-wave inversion not definable as a deeply inverted T wave (Wellen syndrome, type B),[25] which included patients with a non-specific ST wave and T wave that did not satisfy the criteria for the other groups; 3) biphasic T-wave abnormality, revealing positive and negative biphasic morphology in leads V2 to V4 (Wellen syndrome, type A);[26] 4) deeply inverted T wave with large amplitude (>5 mV) and T-wave inversion in precordial leads,[26,27] with the hyperacute T wave defined as a broad-based, symmetric T wave with a large amplitude;[28] and 5) ST depression, defined as a descended ST segment of more than 0.1 mV.[29] On the final diagnosis, all patients classified with STEMI or equivalents were excluded from enrollment.

Analysis of transthoracic echocardiography

Emergency physicians conducted emergency TTE for the evaluation of ADHF patients in the ED. We mainly identified the presence of RWMA through echocardiographic examination. To evaluate a new-onset RWMA, we reviewed and compared the patient's previous transthoracic echocardiographic records. Moreover, we calculated the left ventricular ejection fraction (LVEF) by the modified Simpson's method as the standard measurement method or the Teicholtz method, if the modified Simpson's method was not possible.[30]

We divided these echocardiography records into three groups: 1) No RWMA group, normal systolic function of all LV walls; 2) RWMA group, hypokinesia or akinesia compatible with coronary territory; 3) and non-specific RWMA group, hypokinesia or akinesia of LV mid-segments, such as in stress-induced cardiomyopathy,[31] which included patients without interval change from the previous echocardiographic study.

Statistical analysis

To compare the characteristics of ADHF patients with and without NSTEMI, the independent two sample t-test or Mann–Whiney U test were used for continuous variables, based on the normality assumptions from the Kolmogorov-Smirnov test. The chi-square test was used to compare categorical variables. Univariate logistic regression analyses were conducted to test the association between NSTEMI and age, sex, smoking, past history, systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, temperature, oxygen saturation, Glasgow Coma Scale score, ECG, echocardiography, and

laboratory values. For multivariable analysis, logistic regression analysis was applied to the variables that showed a statistical difference in univariate analysis. The Hosmer-Lemeshow goodness-of-fit test was used to assess the suitability of the models. Discrimination of diagnostic measures was assessed using the area under receiver operating characteristic (ROC) curves (AUC). Analyses were conducted using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA) and the R Statistical Package (version 3.5.1; Institute for Statistics and Mathematics, Vienna, Austria; www.R-project.org).

RESULTS

Baseline characteristics of the patients

The baseline characteristics of all patients are presented in Table 1. Among 524 patients (with NSTEMI, n=109; without NSTEMI, n=415), there were no significant differences in sex, age, and smoking history in the two groups. Among comorbidities, diabetes was more frequent and atrial fibrillation was less frequent in patients with NSTEMI. There was no difference in other medical characteristics, vital signs, or symptom onset time. The admission rate into intensive care units was significantly higher in the ADHF patients with NSTEMI than that in the ADHF patients without NSTEMI. There were no significant differences in 30-day mortality rates between the ADHF patients with and without NSTEMI.

Table 1. Baseline Characteristics of the Enrolled Patients

	ADHF with NSTEMI (n=109)	ADHF without NSTEMI (n=415)	*p* value
Male sex	55 (50.5)	180 (43.4)	0.186
Age (yr)	76.2±12.2	76.6±12.5	0.766
Smoking			0.295
Smoker	11 (10.1)	27 (6.5)	
Ex-smoker	18 (16.5)	57 (13.7)	
Past history			
Hypertension	64 (58.7)	264 (63.6)	0.347
Diabetes	51 (46.8)	148 (35.7)	0.033
Hyperlipidemia	10 (9.2)	52 (12.5)	0.334
Chronic kidney disease	25 (22.9)	94 (22.7)	0.950
Coronary arterial occlusive disease	25 (22.9)	106 (25.5)	0.576
Valvular heart disease	34 (32.1)	130 (33.8)	0.744
Atrial fibrillation	7 (6.5)	76 (18.4)	0.003
Initial vital signs			
Systolic blood pressure (mm Hg)	138±33	138±34	0.854
Diastolic blood pressure (mm Hg)	82±22	80±22	0.582
Pulse rate (beat/min)	96±25	92±28	0.115
Respiratory rate (beat/min)	22±4	21±4	0.224
Temperature (°C)	36.6±0.8	36.7±0.8	0.338
Oxygen saturation (%)	82±31	85±28	0.292
Symptom onset time (h)	28.6±33.7	32.1±37.1	0.420
Disposition			
ICU admission	33 (30.3)	85 (20.5)	0.029
Death within 30 days	6 (5.5)	29 (7.0)	0.581

ADHF, acute decompensated heart failure; NSTEMI, non-ST-elevation myocardial infarction; ICU, intensive care unit.

Clinical evaluation for the diagnosis of NSTEMI

Findings from the ECG, TTE, and laboratory results to diagnose NSTEMI in ADHF patients are summarized in Table 2. In the ADHF patients diagnosed with NSTEMI, 73 patients (68.2%) had abnormal ECG findings: non-specific ST-T wave changes in 21 (19.6%), biphasic T-wave abnormality in 5 (4.7%), T-wave inversion or hyperacute T wave in 32 (29.9%), and ST depression in 15 (14.0%). In comparison, only 159 (39.5%) of ADHF patients without myocardial infarction had abnormal findings, including ST depression or various T-wave changes.

While analyzing TTE, there was a significant difference in mean LVEF between ADHF patients with and without NSTEMI (mean±SD 35±12 vs. 43±15, respectively). In the ADHF with NSTEMI group, 9 patients (8.3%) were identified with no RWMA and 88 patients (80.7%) had clearly identifiable RWMA. However, 12 patients (11.0%) had nonspecific RWMA, and there were subtle findings or no differences when compared with previous TTE examinations. In the ADHF without NSTEMI group, 295 patients (71.1%) had no RWMA, and 32 patients (7.7%) had RWMA. Moreover, 61 patients (14.7%) had nonspecific RWMA with subtle findings or no difference when compared with previous examinations, and 27 patients (6.5%) were not evaluated.

On chest radiographic findings, pulmonary edema was more frequent in the ADHF patients with NSTEMI than in the ADHF patients without NSTEMI (61.5% vs. 47.2%). There was no difference in the prevalence of cardiogenic shock in each group. We confirmed that only 110 patients underwent coronary angiogram, while 414 patients did not undergo the procedure. A coronary angiogram was not performed in some patients due to various reasons, such as old age, disagreement about the procedure, chronic kidney disease, and absence of indications for interventional treatment. Of the 110 patients, 57 culprit lesions were identified as NSTEMI. Considering the onset of symptoms, culprit lesions in 11 of the ADHF patients without NSTEMI were not classified as acute lesions.

There were no significant differences between NSTEMI and non-NSTEMI groups in hemoglobin and white blood cells that could be identified as laboratory markers possibly associated with the worsening of clinical symptoms. However, C-reactive protein was significantly elevated in the ADHF group without NSTEMI. As a biomarker of heart failure, the level of B-type natriuretic peptide was higher in all patients than the upper limit of the normal reference range, but was more significantly elevated in ADHF patients with NSTEMI. The cardiac biomarkers associated with myocardial infarction, creatine kinase MB (CK-MB) and hS-TnI, were significantly higher in the ADHF with NSTEMI group. However, delta hS-TnI, which is

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the difference between hS-TnI in the 0–2-h protocol, did not show a significant difference between the two groups.

Prediction of NSTEMI in ADHF patients

We conducted univariate analysis of basic and clinical factors to determine their associations with the diagnosis of NSTEMI in ADHF patients. Baseline factors, including age, sex, smoking history, and past history of most comorbidities, were not significantly different, although a past history of diabetes [odds ratio (OR) (95% confidence interval, CI): 1.59 (1.04–2.43), p=0.034] was a significant factor associated with NSTEMI diagnosis. In this study, no prior history of atrial fibrillation [OR (95% CI): 0.31 (0.14–0.69), p=0.004] was also a significant factor associated with NSTEMI diagnosis. Presumed ischemic ECG findings [OR (95% CI): 3.30 (2.09–5.19), p<0.001] were significant predictors of NSTEMI. Compared to normal movement in echocardiography, the findings with RWMA [OR (95% CI): 46.62 (25.64–84.76), p<0.001] were also significant predictors of NSTEMI.

Table 2. Clinical Findings for Diagnosis of NSTEMI

	ADHF with NSTEMI (n=109)	ADHF without NSTEMI (n=415)	*p* value
ECG			<0.001
No ischemic changes on ECG	34 (31.8)	244 (60.4)	
Presumed ischemic ECG findings	73 (68.2)	159 (39.6)	
Other abnormality/ non-specific ST/T	21 (19.6)	76 (18.9)	
Biphasic T abnormality	5 (4.7)	16 (4.0)	
T inversion/hyperacute T wave	32 (29.9)	53 (13.2)	
ST depression	15 (14.0)	14 (3.5)	
Echocardiography*			<0.001
No RWMA	9 (8.3)	295 (71.1)	
Nonspecific RWMA or no interval change	12 (11.0)	61 (14.7)	
RWMA (compatible coronary lesion)	88 (80.7)	32 (7.7)	
Left ventricular ejection fraction, (%)	35±12	43±15	<0.001
Pulmonary edema (on chest radiograph)	67 (61.5)	196 (47.2)	0.008
Cardiogenic shock	8 (7.3)	23 (5.6)	0.483
Coronary angiography			<0.001
No culprit lesion	9 (8.3)	33 (8.0)	
Presence of culprit lesion	57 (52.3)	11 (2.7)	
Not implemented	43 (39.5)	371 (89.4)	
Killip classification			
I	22 (20.2)	-	
II	15 (13.8)	-	
III	64 (58.7)	-	
IV	8 (7.3)	-	
Laboratory values			
Hemoglobin (g/dL)	11.3±2.4	11.6±2.5	0.342
White blood cell ($\times 10^3$/L)	9.8±5.0	9.6±17.0	0.854
C-reactive protein (mg/dL)	3.52±5.33	4.79±7.26	0.044
Creatinine (mg/dL)	2.66±3.04	2.10±2.15	0.073
Creatinine clearance rate (mL/min)	45.85±30.62	51.00±48.21	0.173
B-type natriuretic peptide (pg/mL)	1769.0±1522.7	1207.3±1214.9	0.001
CK-MB (ng/mL)	9.97±22.77	3.66±4.49	0.005
hS-TnI (ng/mL)†	2.44±5.60	0.25±0.91	<0.001
Delta hS-TnI (ng/mL)	1.99±12.08	0.31±1.40	0.184

ADHF, acute decompensated heart failure; NSTEMI, non-ST elevation myocardial infarction; ECG, electrocardiogram; hS-TnI, high-sensitivity troponin I; RWMA, regional wall-motion abnormality; CK-MB, creatine kinase MB.
*27 of ADHF patients without NSTEMI were not evaluated, †Normal reference range: 0–0.045 ng/mL.

There were no significant differences between the two groups in initial laboratory values, including hemoglobin, white blood cells, and C-reactive protein, for the prediction of NSTEMI. However, laboratory values related to cardiac biomarkers, including CK-MB [OR (95% CI): 1.08 (1.04–1.12), p<0.001] and initial hS-TnI [OR (95% CI): 1.70 (1.39–2.09), p<0.001], were significant predictors for NSTEMI. Moreover, delta hS-TnI [OR (95% CI): 1.13 (1.00–1.28), p=0.048] was a valuable predictor for the diagnosis of NSTEMI (Table 3).

Multivariable analysis showed the following characteristics to be predictive factors for a diagnosis of NSTEMI: previous history of diabetes [OR (95% CI): 2.83 (1.06–7.56), p=0.038], RWMA on echocardiography [OR (95% CI): 29.79 (10.96–80.99), p< 0.001], initial hS-TnI [OR (95% CI): 2.18 (1.13–4.23), p=0.021], and delta hS-TnI [OR (95% CI): 1.55 (1.05–2.28), p=0.027] (Table 3). Moreover, subgroup analysis of ADHF patients with or without chronic kidney disease was also performed. Initial hS-TnI [OR (95% CI): 24.05 (1.42–406.51), p<0.028] was the only significant predictor of NSTEMI in patients with chronic kidney disease (Supplementary Tables 1, 2, and 3, only online). However, RWMA on echocardiography [OR (95% CI): 27.35 (10.27–72.82), p<0.001] was the only significant predictor of NSTEMI in patients without chronic kidney disease (Supplementary Tables 4, 5, and 6, only online).

To estimate the predictive power for NSTEMI in ADHF patients, ROC analysis revealed the following AUC values for various diagnostic factors: echocardiographic abnormalities, 0.906 (95% CI 0.864–0.938); ECG abnormalities, 0.794 (95% CI 0.740–0.841); initial hS-TnI, 0.802 (95% CI 0.749–0.848); and delta hS-TnI, 0.773 (95% CI 0.718–0.823).

Echocardiographic abnormalities showed the highest predictive power, while the other diagnostic predictors, including single electrocardiographic abnormality, increased initial hS-TnI, and increased delta hS-TnI, showed no significant differences in diagnostic benefits for NSTEMI in patients with ADHF (Fig. 3). The cutoff value of hS-TnI was 0.104 ng/mL, with a sensitivity of 75.9% and specificity of 68.1%, to distinguish NSTEMI among ADHF patients. However, the cutoff value of delta hS-TnI was 0.235 ng/mL, with a sensitivity of 35.5% and specificity of 76.1%.

Table 3. Univariate and Multivariable Logistic Regression Analysis of the Relationship between Acute Myocardial Infarction and Clinical Characteristics

	Univariate analysis		Multivariable analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Male sex	1.33 (0.87–2.03)	0.186	2.10 (0.96–1.03)	0.096
Age (yr)	1.00 (0.98–1.01)	0.765	1.00 (0.96–1.03)	0.880
Smoking				
Ex-smoker	1.31 (0.73–2.34)	0.985		
Current smoker	1.69 (0.80–3.54)	0.316		
Past history				
Hypertension	0.81 (0.53–1.25)	0.347		
Diabetes	1.59 (1.04–2.43)	0.034	2.83 (1.06–7.56)	0.038
Hyperlipidemia	0.71 (0.35–1.44)	0.337		
Chronic kidney disease	1.02 (0.62–1.68)	0.949		
Coronary arterial occlusive disease	0.87 (0.53–1.43)	0.576		
Valvular heart disease	0.93 (0.59–1.47)	0.744		
Atrial fibrillation	0.31 (0.14–0.69)	0.004	0.26 (0.04–1.70)	0.159
Systolic blood pressure (mm Hg)	1.00 (0.99–1.01)	0.854		
Diastolic blood pressure (mm Hg)	1.00 (0.99–1.01)	0.581		
Pulse rate (beat/min)	1.01 (1.00–1.01)	0.115		
Oxygen saturation (%)	1.00 (0.99–1.00)	0.293		
Symptom onset time (h)	1.00 (0.99–1.00)	0.444		
Presumed ischemic ECG findings	3.30 (2.09–5.19)	<0.001	2.11 (0.81–5.47)	0.125
RWMA on echocardiography	46.62 (25.64–84.76)	<0.001	29.79 (10.96–80.99)	<0.001
Left ventricular ejection fraction	0.96 (0.95–0.98)	<0.001	1.02 (0.98–1.06)	0.360
Pulmonary edema (on chest radiograph)	1.78 (1.16–2.74)	0.009	1.88 (0.98–5.03)	0.212
Cardiogenic shock	1.35 (0.59–3.10)	0.484		
Laboratory values				
Hemoglobin (g/dL)	0.96 (0.88–1.05)	0.342		
White blood cell ($\times 10^9$/L)	1.00 (0.99–1.01)	0.914		
Creatinine (mg/dL)	1.09 (1.01–1.18)	0.032	0.97 (0.77–1.22)	0.762
Creatinine clearance rate (mL/min)	1.00 (1.00–1.00)	0.281		
C-reactive protein (mg/dL)	0.97 (0.94–1.01)	0.093		
B-type natriuretic peptide (pg/mL)	1.00 (1.00*–1.00)	<0.001	1.00 (1.00–1.00)	0.284
CK-MB (ng/mL)	1.08 (1.04–1.12)	<0.001	0.95 (0.86–1.06)	0.366
Initial hS-TnI (ng/mL)	1.70 (1.39–2.09)	<0.001	2.18 (1.13–4.23)	0.021
Delta hS-TnI (ng/mL)	1.13 (1.00*–1.28)	0.048	1.55 (1.05–2.28)	0.027

OR, odds ratio; CI, confidence interval; RWMA, regional wall-motion abnormality; hS-TnI, high-sensitivity troponin I; ECG, electrocardiogram; CK-MB, creatine kinase MB.
*Statistical significance.

DISCUSSION

This is the first report to compare the predictive power of NSTEMI diagnosis using methods, such as hS-TnI, delta hS-TnI, ECG, and echocardiography, in ADHF patients. Recently, 0–1 or 0–2-h protocols using high-sensitivity troponin in acute chest pain patients have been noted for their clinical feasibility for differential diagnosis of NSTEMI. Nestelberger, et al.[21] reported the 0–2-h protocol using hS-TnI, suggesting that adequate diagnostic triage of NSTEMI is possible with clinical safety and efficacy. However, the feasibility of determining whether the occurrence of NSTEMI in patients with ADHF when hS-TnI is performed according to these protocols has not been precisely elaborated. Therefore, we attempted to identify the initial values and 2-h values of hS-TnI from data of ADHF patients collected over 8 months to confirm the correlation with NSTEMI.

When conducting the 0–1-h protocol with hS-TnI, clinicians have little time to make clinical decisions in the emergency room. As a practical process, we performed the laboratory test according to the 0–2-h protocol to treat suspected patients of acute coronary syndrome. In addition, ECG, echocardiography, and cardiologist consultation within 2 h was undertaken by emergency physicians. Therefore, we selected the 0–2-hour protocol with hS-TnI for the diagnosis of acute myocardial infarction.

Among the diagnostic methods presented in our study, TTE

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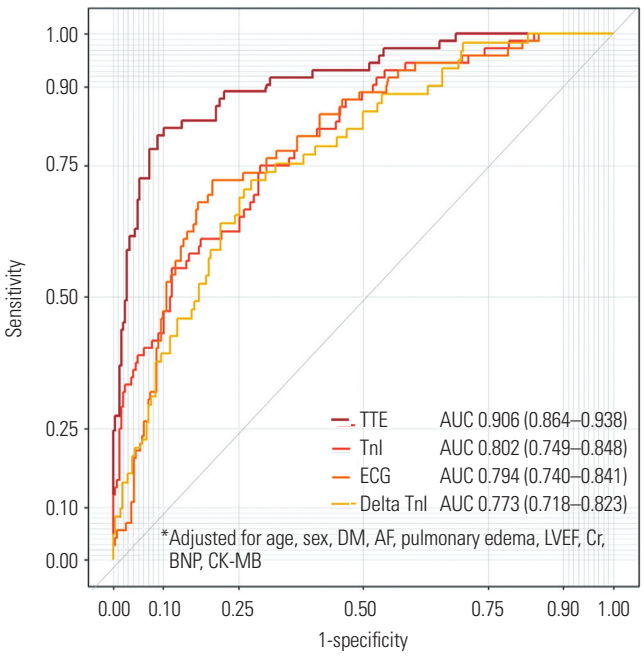

Fig. 3. Receiver operating characteristic curve for predicting NSTEMI with acute decompensated heart failure with each diagnostic method. AUC, receiver operating characteristic curves; NSTEMI, non-ST elevation myocardial infarction; TTE, transthoracic echocardiography; TnI, high-sensitivity troponin I; ECG, electrocardiogram; DM, diabetes; AF, atrial fibrillation; LVEF, left ventricular ejection fraction; Cr, creatinine; BNP, B-type natriuretic peptide; CK-MB, creatine kinase MB.

had the highest predictive power for NSTEMI. However, compared with ECG changes, initial hS-TnI presented nearly similar levels of predictivity for an NSTEMI diagnosis. In fact, there was no difficulty in diagnosing myocardial infarction immediately in emergency centers with specialized medical personnel or well-established diagnostic tools. However, hS-TnI may serve as an alternative choice in diagnostic plans when patients have to be diagnosed in resource-constrained settings or by physicians who are unfamiliar with echocardiography or electrocardiography. We suggest that the diagnosis of NSTEMI in ADHF patients using the delta hS-TnI based on the 0–2-h protocol at such institutions should be applied with caution for clinical feasibility. According to our findings, clinical judgment based on the first value of hS-TnI is more appropriate than the delta hS-TnI of the 0–2-h protocol. Compared with the initial value of hS-TnI, delta hS-TnI was similar or less predictable for evaluating NSTEMI in ADHF patients. In addition, if clinicians consider the time factor during diagnostic strategy in ED, they should rely on initial hS-TnI rather than delta hS-TnI when evaluating acute coronary syndrome among ADHF patients.

Some of the patients included in this study suffered from renal disease, including chronic kidney disease. Depending on renal function, changes in hS-TnI may be affected and may not be properly used as an interference factor for diagnosis. However, with regard to hS-TnI, the results of subgroup analysis of patients with kidney disease were similar to those of all patients in our study (Supplementary Tables 1, 2, and 3, only online). Although the reason for outcomes in patients with chronic kidney disease may require additional consideration, our findings indicate that hS-TnI may also be useful for the diagnosis of NSTEMI in ADHF patients.

A few patients in this study did not have a final diagnosis of NSTEMI despite ischemic changes, such as ST depression in ECG or significant RWMA in echocardiography. It might be presumed that these patients had prior heart lesions without any cardiac examination and visited our institution for the first time. Unlike other studies that are known to be a risk factor for myocardial infarction, specific features of the ADHF patients in our report indicate that diabetes is a unique common factor in NSTEMI.[32] However, the point that the distribution of atrial fibrillation is less frequent is presumed to be a kind of bias that occurred during data collection. The known risk factors for myocardial infarction, hypertension and hyperlipidemia, were not associated with NSTEMI in this analysis. Therefore, we included diabetes, atrial fibrillation, and main laboratory values as an adjusted factor in the ROC analysis model to predict NSTEMI.

This study has several limitations. First, we investigated and analyzed factors associated with NSTEMI in ADHF patients, although other factors known to be related to myocardial infarction were not included in our study. Second, this was retrospective research undertaken at a single center with data gathered in a cross-sectional period, which may have conferred a risk of selection bias. Third, some patients could not immediately access an emergency room after the onset of related symptoms, which may have induced time-related effects in hS-TnI and delta hS-TnI values. Fourth, not all patients underwent coronary angiography, and thus, we could not identify culprit lesions in these patients and presumed new-onset NSTEMI using other diagnostic modalities (Supplementary Table 7, 8, and 9, only online). For this reason, coronary angiography was not included in univariate or multivariable logistic regression analysis. Fifth, ADHF patients enrolled in the study were not clearly distinguished based on new-onset acute heart failure (de novo) type and the acute decompensated chronic heart failure type. Sixth, hS-TnI may not be diagnostically useful for patients with heart failure due to large infarctions but can guide the differential diagnosis of subtle myocardial infarction. Therefore, our results should be generalized with caution, and future diagnostic predictive analysis will be needed for each independent population or type of myocardial infarction.

In conclusion, for diagnosis of suspected NSTEMI in ADHF patients, initial assessment of hS-TnI has similar predictive power as ischemic changes on ECG and superior predictive power than delta hS-TnI calculated by the 0–2-h protocol.

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