Value of hs-cTnT, sST2, and Lp-PLA2 in the classification of acute coronary syndrome

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Abstract. The present study aimed to assess the value of high-sensitivity cardiac troponin T (hs-cTnT), soluble suppression of tumorigenicity 2 protein (sST2) and lipoprotein-associated phospholipase A2 (Lp-PLA2) in the classification of acute coronary syndrome (ACS). A total of 236 patients diagnosed with ACS were enrolled in this retrospective study and were further divided into the non-ST-segment-elevation (NSTE)-ACS group (n=183) and ST-segment elevation myocardial infarction (STEMI) group (n=53). The three biomarkers (hs-cTnT, sST2 and Lp-PLA2) were measured by electrochemiluminescence. The diagnostic performance of each biomarker in differentiating ACS subtypes was evaluated through receiver operating characteristic curve analysis. The DeLong test was applied to compare the discriminatory abilities of the different markers. The binary logistic regression model was employed to analyze the factors influencing ACS classification. The levels of hs-cTnT and sST2 in males were significantly higher in the STEMI group than in the NSTE-ACS group (P<0.05). hs-cTnT [odds ratio (OR)=1.010, 95% CI: 1.007-1.014] and sST2 (OR=1.022, 95% CI: 1.011-1.033) were identified as good predictors for distinguishing STEMI from NSTE-ACS, whereas Lp-PLA2 (P=0.470) was not a suitable biomarker to discriminate between the two types of ACS. Additionally, the diagnostic efficacy of hs-cTnT [area under curve (AUC=0.861)] and the combination of hs-cTnT and sST2 (AUC=0.863) was higher than that of sST2 alone (AUC=0.833, P<0.05). In conclusion, these findings illustrated that hs-cTnT and sST2 are promising biomarkers to classify patients with ACS. Compared with sST2 alone, hs-cTnT and its combined detection demonstrate superior diagnostic efficiency in identifying ACS.

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Introduction

Acute coronary syndrome (ACS) refers to cardiac acute ischemic syndrome, caused by thrombosis, resulting from the rupture or erosion of unstable atheromatous plaques in the coronary arteries (1). It is classified into non-ST-segment elevation myocardial infarction (NSTEMI), STEMI and unstable angina pectoris (UA) (1,2). In clinical settings, UA and NSTEMI present with similar clinical manifestations and electrocardiographic (ECG) features, such as ST-segment depressions and T-wave inversion, and are thus together considered as non-ST-segment-elevation (NSTE)-ACS (3). Both STEMI and NSTEMI are characterized by myocardial injury or necrosis, typically indicated by significantly elevated levels of cardiac biomarkers, such as troponin I (TnI) and troponin T (TnT) (4,5). Compared with patients with NSTEMI**,** patients with STEMI more frequently exhibit complete occlusion of the culprit artery, a higher incidence of transmural ischemia, a larger infarcted myocardial area and worse short-term diagnosis compared with patients with NSTEMI (2).

Globally, STEMI is the single most common cause of sudden death (4,6). It accounts for 1.8 million deaths annually (20% of all deaths) in Europe alone, with a decreasing trend in its relative incidence and a concomitant rise in the incidence of NSTE-ACS (4). According to published data, the incidence of ACS varies by age and sex. In individuals younger than 60 years, ACS occurs 3 to 4 times more frequently in males than in females, whereas females constitute the majority of patients over the age of 75 (4). The risk of myocardial infarction (MI) has been extensively studied and numerous factors, including increased body-mass index, low-density lipoproteins, C-reactive protein (CRP), diabetes, hypertension, smoking and hyperlipidemia are regarded as being associated with increased susceptibility to MI (7,8). Patients typically present with symptoms such as chest pain, epigastric pain, radiating pain to the neck or shoulder, and shortness of breath (6,9,10). Acute myocardial infarction (AMI) has the highest mortality

rate within hours of onset, and early diagnosis and treatment initiation are key interventions for patients with ACS (6). Notably, the 12-lead ECG and cardiac troponins (cTn) are the primary diagnostic tools for AMI (6,11). However, only 5% of patients who present with acute chest pain and undergo ECG are diagnosed with STEMI (6). In addition, troponin is used to evaluate NSTE-ACS in patients with chest pain without pre-hospital ST-segment elevation. Most of these patients are found to have negative troponin levels and are subsequently diagnosed with unstable angina, indicating that troponin may not be an optimal biomarker for NSTE-ACS (6,12).

In clinical practice, patients with suspected ACS are often directly admitted to emergency departments (EDs). Yet, the majority of these patients are not ultimately diagnosed with ACS and could be managed at general care centers to avoid unnecessary ED congestion, costs and time delays (5,13). To solve this problem, numerous biomarkers, such as high-sensitivity cTn (hs-cTn), N-terminal prohormone of brain natriuretic peptide (NT-proBNP), hsCRP and D-dimer, have been clinically applied for risk stratification based on major adverse cardiac events (MACE), enabling appropriate treatment decisions and timely, safe discharge (9-12). In addition, numerous studies have evaluated the diagnostic and prognostic value of emerging biomarkers, including soluble suppression of tumorigenicity 2 protein (sST2), which is a biomarker for cellular stress and injury (14-16), hs-cTnT, a biomarker of MI (5,9,13) and lipoprotein-associated phospholipase A2 (Lp-PLA2), a biomarker of plaque inflammation (8,10,17), in the classification and risk stratification of ACS. Elevated serum levels of sST2 have been shown to independently predict future heart failure, cardiovascular events and mortality (18), while increased hs-cTnT levels are associated with a higher risk of MACE (9). Lp-PLA2 has demonstrated limited utility as a standalone biomarker for cardiovascular events, but it could offer additional prognostic information when assessed at a time-point significantly distant from the acute coronary event (8).

The diagnosis of STEMI and NSTE-ACS determines the choice and timing of ACS treatment and management (17). However, the diagnostic, prognostic and classificatory value of reported biomarkers in ACS remains largely undetermined. Published studies reported inconsistent results for various kinds of biomarkers in ACS classification. A total of 11 biomarkers, such as ST2 protein and fibroblast growth factor, have been reported to exhibit elevated concentrations in STEMI and NSTEMI, respectively, and may effectively differentiate between these two MI types. However, these findings lack clinical reliability due to their reliance on registry data (2). Patients with NSTE-ACS with high sST2 levels had a ~3-fold higher risk of cardiovascular disease (CVD) and heart failure (HF) compared to patients with STEMI within the following year (15). The upper reference limits, as well as age and sex-based thresholds for these 11 biomarkers and other biomarkers in ACS classification is still uncertain (15,19). Therefore, assessing the performance of these biomarkers for distinguishing STEMI and NSTEMI is most important in the management of patients with ACS. Of them, the hs-cTnT, sST2 and Lp-PLA2 biomarkers are most focused on in clinical practice; therefore, the present study investigated the role of these three emerging biomarkers in the classification of ACS.

Patients and methods

Patients. A total of 1,236 patients with suspected ACS encountered at Nanjing First Hospital (Nanjing, China) between January 2022 and December 2022 were enrolled in the present study. Eligible patients were identified according to the following inclusion and exclusion criteria. The inclusion criterion was patients suspected of having ACS by clinical doctors based on their clinical symptoms, such as chest pain and dyspnea. The exclusion criteria were as follows: i) Non-cardiological chest pain or dyspnea; ii) combined malignant tumor disease; iii) cases complicated with infectious diseases; and iv) coexisting immune system diseases. All coronary angiograms (CAG) were independently reviewed by two cardiologists and a diagnosis of ACS was established based on a combination of clinical symptoms, ECG changes, cardiac biomarkers and CAG findings indicating significant stenosis (≥50%) in one or more coronary arteries, following the diagnostic criteria recommended by the European Society of Cardiology guidelines (20-22). This retrospective study was approved by the Institutional Review Board of Nanjing First Hospital (approval no. KY20250714-KS-01), which waived the requirement for individual patient consent. Finally, a total of 183 patients (150 with UA and 33 with NSTEMI) were diagnosed as having NSTE-ACS, and 53 patients were diagnosed with STEMI. The patient inclusion flow-chart is shown in Fig. 1. Among the 263 patients included, 175 (74.15%) were male and 61 (25.85%) were female. The median age was 59 years (range, 31-91 years).

Instruments and reagents. Heparin-anticoagulated peripheral blood and serum samples were collected for hs-cTnT detection, which was detected with an electrochemiluminescence analyzer (Cobas e411; Roche Diagnostics) and non-anticoagulated samples were used to obtain serum for the detection of sST2 and Lp-PLA2 via chemiluminescence analyzers (CL2000; Beijing Leadman; and 411; Nanjing Norman, respectively).

Statistical analysis. All statistical analyses were performed using SPSS 20.0 software (IBM Corp.). The Kolmogorov-Smirnov test was used to assess the normality of the measurement data. The measurement data in accordance with the normal distribution were presented as the mean ± standard deviation. Student's t-test was used to compare the groups. Non-normally distributed measurement data were expressed as the median (interquartile range) and the Mann-Whitney U-test was used to analyze differences between groups. Enumeration data were expressed as n (%) and the χ^2 test was used for intergroup comparison. Univariate logistic regression model was conducted to evaluate the impact of individual factors on ACS classification. The Hosmer-Lemeshow test was performed to evaluate the fit of the regression model. Receiver operating characteristic (ROC) curves were plotted to calculate the diagnostic value of individual and combined biomarkers for ACS classification. Furthermore, the DeLong test (23) was applied to compare the AUCs of different biomarkers. A two-sided $P<0.05$ was considered to indicate statistical significance.

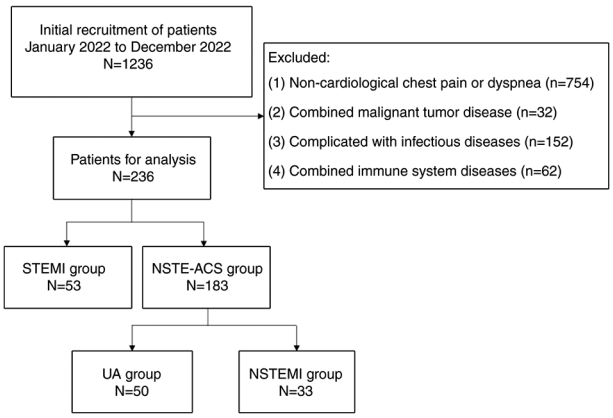

Figure 1. Patient inclusion flow chart. NSTE-ACS, non-ST-segment-elevation acute coronary syndrome; NSTEMI, non-ST-segment elevation myocardial infarction; UA, unstable angina pectoris.

Results

Characteristics of patients. There was a significant difference in gender distribution between STEMI (males/females=46:7) and NSTE-ACS (males/females=129:54) cases (χ^2=5.697, P=0.017), as shown in Table I. However, no significant difference was observed in age between the two groups (STEMI: 63.60±12.90 years vs. NSTE-ACS: 65.25±11.39 years, P=0.369). The levels of hs-cTnT [STEMI: median 1,641.00 ng/l (interquartile range 288.15-4193.50 ng/l) vs. NSTE-ACS: median 17.08 ng/l (interquartile range 9.62-166.10 ng/l), P<0.001; cut-off value 524 ng/l) and sST2 [STEMI: median 53.17 ng/ml (interquartile range 28.47-154.87 ng/ml) vs. NSTE-ACS: median 16.92 ng/ml (interquartile range 12.50-25.01), P<0.001; cut-off value 29.27 ng/ml) were significantly higher in the STEMI group compared to the NSTE-ACS group; however, no significant difference was found in Lp-PLA2 levels between the two groups [STEMI: median 194.48 ng/ml (interquartile range 141.36-276.59 ng/ml) vs. NSTE-ACS: median 184.26 ng/ml (interquartile range132.05-259.92), P=0.470], as shown in Table I.

Predictive value of hs-cTnT and sST2 in patients with ACS. A univariate logistic regression analysis of the factors influencing the likelihood that the patient had NSTE-ACS or STEMI was conducted, with the presence or absence of STEMI as the dependent variable, and gender, age, hs-cTnT, sST2 and Lp-PLA2 as the independent variables. The results showed that hs-cTnT [odds ratio (OR)=1.010, 95% CI: 1.007-1.014] and sST2 (OR=1.022, 95% CI: 1.011-1.033) were predictors of STEMI, as shown in Table II. The Hosmer-Lemeshow test was performed to evaluate the fit of the regression model and the result (χ^2=11.158, P=0.193) showed no significant difference between the predicted and observed values, suggesting that the model fits the data well for classifying the two ACS groups.

Diagnostic value of hs-cTnT and sST2 in patients with ACS. To further assess the diagnostic value of hs-cTnT and sST2 in distinguishing STEMI from NSTE-ACS, the predictive values for hs-cTnT and sST2 alone and in combination for classification of the two ACS groups were assessed, and the results revealed that hs-cTnT (AUC=0.861, cut-off value=524 ng/l, 95% CI: 0.810-0.902; specificity: 88.52%; sensitivity: 71.70%), sST2 (AUC=0.833, cut-off value=29.27 ng/ml, 95% CI: 0.779-0.878; specificity: 83.06%, sensitivity: 75.47%) and their combination (AUC=0.863, 95% CI: 0.812-0.904; specificity: 91.80%, sensitivity: 71.70%) could serve as diagnostic biomarkers for STEMI, as shown in Table III and Fig. 2. Additionally, the diagnostic efficacy of hs-cTnT (AUC=0.861, P=0.0017) and the combination of hs-cTnT and sST2 (AUC=0.863, P<0.005) was higher than that of sST2 alone (AUC=0.833).

Discussion

The present retrospective study indicated that both sST2 and hs-cTnT demonstrated significant utility in differentiating between STEMI and NSTE-ACS, while Lp-PLA2 was not a valuable biomarker for the classification of the two types of MI. We observed that the circulating levels of hs-cTnT were 96-fold higher in STEMI than that in NSTE-ACS, providing a cut-off value of 524 ng/l to discriminate between the types of MIs. Moreover, the serum levels of sST2 were 3-fold higher in STEMI than in NSTE-ACS, and it could accurately classify the two types of ACS with a cut-off value of 29.27 ng/ml. Of note, hs-cTnT and its combination with sST2 outperformed sST2 alone in terms of diagnostic efficiency in patients with ACS and combined detection of the two markers did not improve the biomarkers' ability to distinguish between the two types of ACS as compared to hs-cTnT alone.

Over decades of standardized cardiovascular disease prevention in developed countries, the incidence of STEMI has decreased significantly, while China has shown a rapid growth trend (24,25). Similar to the present findings, numerous studies have reported higher cases of STEMI in males (63-67%) than in females (30-37%) (26,27). This difference may be due to risk factors such as smoking, diabetes, dyslipidemia, abdominal obesity and hypertension, which are more prevalent in males (28). In addition, estrogen hormone in females offers a temporary premenopausal vascular protection, delaying the onset and severity of atherosclerosis in women contrary to men, though this protection declines post-menopause, allowing for the later onset of ACS events in women. In contrast to the present results, NSTE-ACS has been reported to be predominantly higher in females (29,30), likely due to a higher incidence of diffuse coronary artery disease, microvascular dysfunction and older age at ACS presentation, factors less frequently associated with STEMI's characteristic vessel occlusion (31). These sex-based epidemiological patterns underscore the necessity of gender-tailored strategies for ACS prevention, diagnosis and management.

Various guidelines and expert consensus affirm the diagnostic and therapeutic value of myocardial markers, including creatine kinase isoenzyme and myoglobin (CK-MB), cTnT, cTnI, heart-type fatty acid binding protein, myosin binding protein C and NT-proBNP, in ACS pathophysiology and guiding risk stratification (5,14,32). Despite the critical need to accurately and safely rule out STEMI in patients with NSTE-ACS, the discriminative value of these biomarkers is still unclear. The present study focused on evaluating hs-cTnT, sST2 and Lp-PLA2 for ACS classification. The results indicated that both hs-cTnT and sST2, individually and in

Table I. Comparison of clinical data between NSTE-ACS group and STEMI group.

Group	NSTE-ACS	STEMI	t/χ^2	P-value
Sex (male/female)	129/54	46/7	5.697	0.017
Age, years	65.25±11.39	63.60±12.90	0.234	0.369
hs-cTnT, ng/l	17.08 (9.62-166.10)	1641.00 (288.15-4193.50)	-7.989	<0.001
sST2, ng/ml	16.92 (12.50-25.01)	53.17 (28.47-154.87)	-7.369	<0.001
Lp-PLA2, ng/ml	184.26 (132.05-259.92)	194.48 (141.36-276.59)	-0.723	0.470

Values are expressed as n, the mean ± standard deviation or median (interquartile range). NSTE-ACS, non-ST-segment-elevation acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction; hs-cTnT, high-sensitivity cardiac troponin T; sST2, soluble suppression of tumorigenicity 2 protein; Lp-PLA2, lipoprotein-associated phospholipase A2.

Table II. Results of a univariate logistic regression analysis of the factors associated with the risk of ST-segment elevation myocardial infarction as opposed to non-ST-segment-elevation acute coronary syndrome.

Factor	β	P-value	OR	95% CI
Sex (male/female)	0.242	0.675	1.273	0.412-3.937
Age[a]	-0.038	0.050	0.963	0.928-1.000
hs-cTnT[a]	0.001	<0.001	1.010	1.007-1.014
sST2[a]	0.021	<0.001	1.022	1.011-1.033
Lp-PLA2[a]	-0.002	0.312	0.998	0.995-1.002

[a]A continuous variable. OR, odds ratio; 95% CI, 95% confidence interval; hs-cTnT, high-sensitivity cardiac troponin T; sST2, soluble suppression of tumorigenicity 2 protein; Lp-PLA2, lipoprotein-associated phospholipase A2.

Table III. Diagnostic value of combined detection of hs-cTnT and sST2 to distinguish ST-segment elevation myocardial infarction from non-ST-segment-elevation acute coronary syndrome.

Variable	Cut-off value	Youden index	Sensitivity, %	Specificity, %	AUC	95% CI	AUC P
hs-cTnT	524 ng/l	0.6022	71.70	88.52	0.861	0.810-0.902	0.0017
sST2	29.27 ng/ml	0.5853	75.47	83.06	0.833	0.779-0.878	-
Combined detection	-	0.6350	71.70	91.80	0.863	0.812-0.904	<0.005

Values are evaluated by the DeLong test. The combined detection is a fitted curve, so have with no specific cut-off value. AUC, area under curve; 95% CI, 95% confidence interval; AUC P, P-value of AUC; hs-cTnT, high-sensitivity cardiac troponin T; sST2, soluble suppression of tumorigenicity 2 protein.

combination, effectively predicted STEMI, whereas Lp-PLA2 showed no utility in ACS classification.

Stimulation expression gene 2 (ST2), a member of the interleukin (IL)-1 receptor family, interacts specifically with and IL-33 (15,16,18). It exists mainly in 2 isoforms: ST2 and ST2L, which is divided into transmembrane forms, and sST2 (14,18). sST2 is a marker of stress and injury of cardiomyocytes (14,15), whose high expression in serum has been reported to independently predict HF, CVD events and death in both STEMI and NSTE-ACS (14,16,18). Numerous studies suggest that sST2, as a marker reflecting myocardial fibrosis, inflammation and oxidative stress, is helpful for risk stratification and prognostic evaluation of patients with HF (33,34). For the application of sST2 in the diagnosis of ACS, the present study established that the biomarker had 3-fold higher expression in STEMI than NSTE-ACS, which is similar to the findings reported by Hjort *et al* (2). This higher level of sST2 in STEMI is attributed to the greater degree of myocardial damage and dysfunction compared to NSTE-ACS (2,15). However, Hjort *et al* (2)'s conclusions were based on registry data and non-quantitative assays with no absolute concentration measurements, limiting direct comparison with the clinically applied cut-offs. Importantly, the present study was conducted using clinical patient's results taken from the hospital's database, enabling for sST2 clinical comparison and STEMI prediction with a cut-off value of 29.27 ng/ml (sensitivity: 75.47%, specificity: 83.06%).

cTnI and -T are proteins that are implicated in actin-myosin interaction, produced and released by cardiomyocytes due to stress or necrosis (35); their elevated levels in peripheral blood indicate cardiomyocyte damage (12,36) and are reported to be

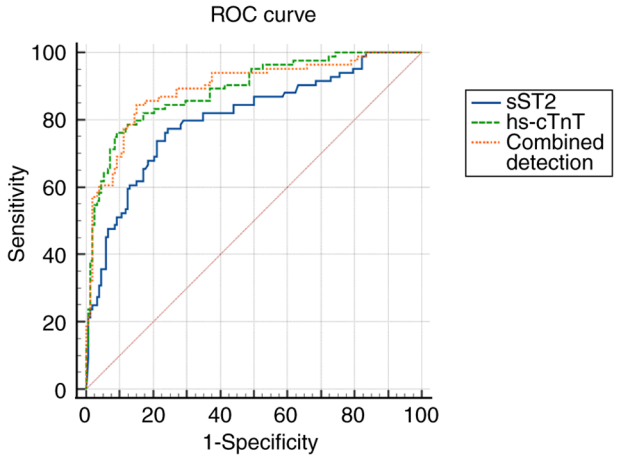

Figure 2. ROC curve showing the diagnostic value of hs-cTnT (AUC=0.861), sST2 (AUC=0.833) and their combination (AUC=0.863) in classifying ACS subtypes. ROC, receiver operating characteristic; AUC, area under the curve; hs-cTnT, high-sensitivity cardiac troponin T; sST2, soluble suppression of tumorigenicity 2 protein.

more sensitive and specific markers of cardiomyocyte injury than CK, its CK-MB and myoglobin, which was once considered the gold standard for myocardial injury (19). However, conventional cTn assays have the drawback of delayed elevation and require serial sampling over 6-9 h, limiting their sensitivity at AMI presentation (19,25). hs-cTn assays were developed to detect low cTn concentrations at or below concentrations corresponding to the 99th percentile value of a normal reference population to enable the diagnosis of an ongoing myocardial injury in stable patients and even seemingly healthy populations (19). Giannitsis *et al* (7) also found that the evaluation of hs-cTnT was a more accurate approach for troponin detection in patients with NSTE-ACS than the conventional cTnT or -I assay. In the present study, a 96-fold higher median value of hs-cTnT in STEMI than in NSTE-ACS was observed, which can be associated with the higher incidence of transmural ischemia and a larger area of infarction in STEMI that increase cardiomyocyte stress, producing more hs-cTnT in response than in patients with NSTE-ACS (2,35,37). hs-cTnT, when used alone and in combination with sST2 showed higher potential to discriminate STEMI compared with sST2 alone. Although the combined model yielded a numerically higher AUC than hs-cTnT alone (0.863 vs. 0.861), DeLong's test showed no statistically significant difference (P=0.849). The estimated ΔAUC (0.002) indicates that any incremental discrimination, if present, is likely very small. Detecting such a modest effect generally requires substantially larger sample sizes and event counts than those yielded in the present study. Accordingly, the current analysis may be underpowered and the absence of statistical significance should not be overinterpreted as evidence of no effect. Future work with larger cohorts and/or external validation is warranted to clarify whether the addition of variables to hs-cTnT provides statistically and clinically meaningful improvement.

Lp-PLA2 is a biomarker of plaque inflammation whose circulating levels are associated with changes in coronary plaque volume (10,17). It has been shown that there is a link between Lp-PLA2 levels and the severity of coronary artery disease (38). Zhao *et al* (39) concluded that a higher serum Lp-PLA2 activity level is associated with a more severe degree of coronary artery disease. Similarly, a study by Möckel *et al* (12) revealed that Lp-PLA2 is an effective independent marker for risk stratification, which proved to be superior to CRP and the Thrombolysis in Myocardial Infarction (TIMI) risk score (12). Lp-PLA2 was reportedly higher in NSTE-ACS than STEMI (40), but its sensitivity and specificity in differentiating between the two ACS subtypes was relatively low (41). Similarly, in the present study, there was no significant difference in Lp-PLA2 serum levels between STEMI and NSTE-ACS, showing low discriminative power. These findings indicate that Lp-LPA2 is only a biomarker of atherosclerotic burden and chronic vascular inflammation rather than acute plaque rupture or myocardial injury, which are critical in distinguishing between STEMI and NSTE-ACS (40,41); hence, it is not an applicable marker in ACS classification.

To the best of our knowledge, the present study is the first retrospective cohort study demonstrating the potential of hs-cTnT and sST2 to discriminate between STEMI and NSTE-ACS, both independently and in combination. However, despite these remarkable findings, the present study has certain limitations. As a single-center retrospective study, it may be subject to inherent biases and limited external validity. No adjustments were made for sociodemographic factors, clinical characteristics or medication use, which may affect the absolute diagnostic power. Notably, this study focused solely on the etiologic classification of ACS and the findings were independent of disease severity. Although NSTE-ACS is clinically diagnosed, the severity of individual cases may vary depending on baseline health conditions. Hence, treatment strategies should be tailored according to risk stratification, which can be guided by established risk scoring systems, such as the Global Registry of Acute Coronary Events risk score and the TIMI risk score (42,43). In addition, a larger sample size or an external validation cohort would be required to confirm whether the observed modest incremental value is statistically significant. Therefore, multicenter studies with larger sample sizes may be recommended to validate the present findings, with or without adjustments for potential confounding factors.

In conclusion, the present findings indicate that cardiac biomarkers, including hs-cTnT and sST2, either individually or in combination, can effectively distinguish patients with STEMI from those with NSTE-ACS.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YW was responsible for software, data collection and writing the manuscript. NL participated in data curation and manuscript writing. CS contributed to data collection and manuscript writing. BH participated in conception, design, and critical review of the manuscript. YPM performed formal analysis and acquired funding. HP designed the study and revised the manuscript. HP and YPM confirmed the authenticity of the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The Ethics Committee of Nanjing First Hospital (Nanjing, China) approved this study (approval no. KY20250714-KS-01).

Patient consent for publication

As this was a retrospective study, patient consent for inclusion was waived.

Competing interests

The authors declare that they have no competing interests.

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