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Original Article

Risk stratification and prognostic value of grace and timi risk scores for female patients with non-st segment elevation acute coronary syndrome

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Abstract: Aim: To investigate the value of Global Registry of Acute Coronary Events (GRACE) and Thrombolysis in Myocardial Infarction (TIMI) risk scores for risk stratification and prognosis in female patients with non-ST segment elevation acute coronary syndrome (NSTE-ACS). Methods: Non-elderly (<65 years) and elderly (≥65 years) female patients with NSTE-ACS (totally 869 cases) were enrolled in this study. The patients were further divided into low, intermediate and high-risk groups according to their GRACE and TIMI scores. Patients were followed up for 1 year to record the mortality and incidence of major adverse cardiac events (MACE). Differences in mortality and MACE incidence between the two scoring systems were compared by the area under the ROC curve. Results: The area under ROC curve corresponding to the mortality and MACE incidence in any period by the GRACE scoring system was significantly larger than the TIMI scoring system in the elderly patients ($P<0.05$). Mortality and MACE incidence increased in parallel with the scores. Risk ratio values of Cox regression analysis based on GRACE and TIMI scores were greater than 1 ($P<0.001$). Conclusion: Both GRACE and TIMI were adoptable in clinical risk stratification and prognosis of female patients with NSTE-ACS at different age groups. GRACE showed better accuracy than the TIMI scores.

Keywords: GRACE, TIMI, female patients, non-ST segment elevation acute coronary syndrome

Introduction

Non-ST segment elevation acute coronary syndrome (NSTE-ACS), including unstable angina and non-ST-segment elevation myocardial infarction (NSTEMI), is the most common clinical type of coronary heart disease with high mortality [1]. Accordingly, correct diagnosis and early treatment are critical to improve clinical outcomes in patients with NSTE-ACS. The occurrence of serious cardiovascular adverse outcomes varies considerably in ACS patients with different clinical characteristics, electrocardiogram (ECG), and enzyme markers. Risk stratification may be helpful for the planning of early treatment strategy with percutaneous intervention or drugs. However, the accuracy of dichotomy risk stratification such as normal or elevated troponin, normal or abnormal ECG is insufficient for prognosis evaluation.

Global Registry of Acute Coronary Events (GRACE) and Thrombolysis in Myocardial Infarction (TIMI) risk scores have been widely used for prognosis predicting in patients with ACS [2-5]. They are based on the clinical data obtained from large-scale clinical trials and other studies. Several independent variables of clinical predictors have been screened out. Risk stratification and prognosis of patients are assessed by sum of the variable scores [6-9]. However, there have been limited Chinese ACS populations included in the GRACE and TIMI studies. Whether GRACE score or TIMI score can be used for risk stratification and prognostic evaluation in Chinese female patients with NSTE-ACS is not clear. Potential variability between the two scoring systems on risk stratification and prognosis evaluation at different age has rarely been reported. Hence, the aim of this study was to assess the prognostic value of

GRACE and TIMI risk scores in Chinese female patients with NSTE-ACS at different ages.

Materials and methods

Patients

This retrospective study included 1136 female patients were diagnosed with NCTE-ACS between January 2010 to January 2012 at the General Hospital of Chinese PLA. The inclusion criteria was chest pain >20 minutes with coronary angiography within 72 h. Patient without complete information or follow-up data were excluded. All patients provided informed written consent. This study was approved by the Ethics Committee of our hospital. Clinical data for GRACE and TIMI scores and follow-up data within 30 days, 6 months and 1 year after the onset of each patient was collected.

Clinical characteristics

A complete medical history was obtained from all subjects, including hypertension, diabetes, and cardiovascular disease (recurrent ischemic angina, nonfatal myocardial infarction, cardiogenic death, new-onset or aggravated heart failure and new-onset severe arrhythmias). Body mass index (BMI) was calculated by using the formula of weight (kg)/height (m^2). Laboratory examination including serum sodium, potassium, creatinine, uric acid, blood urea nitrogen (BUN), total plasma cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), blood glucose and creatine kinase (CK), creatine kinase isoenzyme (CK-MB) and troponin T (TnT). ECG examination and myocardial injury marker determination were also performed.

Clinical risk scores

GRACE scores at admission were calculated according to the following indexes: 7 age, heart rate, systolic blood pressure, serum creatinine, Killip classification, cardiac arrest, cardiac biomarkers, and ST segment changes. The theoretical score range is 2-383 points. Patients were divided into three groups based on the scores: the low-risk group (0 to 133 points), intermediate-risk group (134 to 200 points) and high-risk group (>200 points).

TIMI scores were calculated based on the following indexes as previously described: [9] (1) Aged ≥65 years; (2) At least three risk factors for coronary heart disease; (3) Previous coronary artery stenosis ≥50%; (4) ECG showed ST segment changes >0.05 mV; (5) Severe angina pectoris (at least 2 times of outset within the last 24 h); (6) Aspirin intake in the last week; (7) Elevated myocardial infarction markers. Patients were divided into three groups according to TIMI scores at admission: the low-risk group (0 to 2 points), intermediate-risk group (3 to 5 points) and high-risk group (5 to 7 points).

Follow-up data collection

Follow-up data were obtained by clinical review or telephone interviews. Cardiovascular events within 30 days, 6 month and 1 year were recorded. New-onset severe arrhythmia was defined as the following: II or III degree atrioventricular block, ventricular tachycardia, ventricular fibrillation, frequent premature ventricualr contraction (PVC), and atrial fibrillation. More than one occurrence is recorded as one case of arrhythmic events.

Statistical analysis

Statistical analysis was performed using SPSS 13.0 software (SPSS, Chicago, IL). Categorical data were expressed as percentages. Patients who lost to follow-up were regarded as censored data. Rank sum test was used to evaluate the correlation between the risk scores and cardiovascular events. Chi-square test for R × C table was used for comparison of mortality and the incidence of MACE in patients of different risk groups based on the two scoring systems. Kaplan-Meier survival curve and COX regression analysis were also performed to analyze the prognostic value of the two scoring system. The pharmacological anamnesis and percutaneous coronary intervention were also included in the COX regression analysis. To evaluate the discrimination of GRACE and TIMI scores on the incidence of MAGE, area under the ROC curve (AUC) was computed. Differences on AUC were tested by paired *t* test. $P<0.05$ was considered statistically significant.

Results

Clinical characteristics and risk stratification

A total of 869 patients (average age: 69.7±12.8 years) were enrolled in the study. The non-elderly group and the elderly group included

Table 1. Clinical characteristic of female patients with NSTE-ACS based on GRACE risk scores (n=869)

	Non-elderly group (n=462)			Elderly group(n=407)			Total
	Low-risk	Intermediate-risk	High-risk	Low-risk	Intermediate-risk	High-risk	
Age (year), mean±SD	48.03±7.09	54.15±6.71	61.08±8.65	67.39±9.34	72.15±5.22	79.37±6.81	64.7±10.6
Heart rate, mean±SD	77.56±10.38	78.42±9.41	89.81±8.74	75.52±9.39	82.8±11.64	87.3±10.67	79.18±11.83
Systolic pressure (mmHg)	142.7±23.5	128.6±25.95	127.4±29.8	146.7±22.4	141.2±24.8	155.4±26.9	137.9±28.1
Creatinine (mg/dl)	0.79±0.23	1.03±0.31	1.18±0.56	0.84±0.25	1.14±0.40	1.21±0.47	1.08±0.39
Killip > I (%)	15.4	20.2	37.3	28.9	45.6	86.1	42.7
ST segment elevation (%)	23.5	37.8	95.4	34.1	56.2	84.7	34.6
Myocardial injury markers (%)	92.0	94.7	98.3	94.2	91.6	95.5	96.4
Cardiovascular events (%)	2.6	30.1	75.3	5.7	40.5	82.2	39.8

Table 2. Distribution of patients in each risk group at different ages based on risk scores (n=869)

	GRACE	TIMI
Non-elderly group		
Low-risk	163 (35.3%)	140 (30.3%)
Intermediate-risk	208 (45.0%)	236 (51.1%)
High-risk	91 (19.7%)	86 (18.6%)
Elderly group		
Low-risk	112 (27.5%)	127 (31.2%)
Intermediate-risk	165 (40.5%)	82 (20.1%)
High-risk	130 (32.0%)	198 (48.7%)

462 and 407 cases, respectively. Each group was divided into three subgroups by different risk level based on GRACE scores. The clinical characteristics of the enrolled patients are summarized in **Table 1**. Distribution of patients in each risk group at different ages based on risk scores are shown in **Table 2**. Based on the obtained GRACE scores, 35.3%, 45% and 19.7% of the non-elderly patients were assigned to low, intermediate and high-risk groups, respectively, which was similar with the results based on TIMI scores (30.3%, 51.1% and 18.6%, respectively). However, 27.5%, 40.5% and 32.0% of the elderly patients were assigned to low, intermediate and high-risk groups, respectively, based on GRACE scores, which was inconsistent with the results based on TIMI scores (31.2%, 20.1% and 48.7%, respectively). These results indicated that TIMI risk scores showed different results in risk stratification between non-elderly and elderly patients.

Survival analysis

Data from patients who lost follow-up were included and was regarded as censored data for further prognosis analysis by survival analysis. As shown in **Figures 1** and **2**, a significant difference was shown on Kaplan-Meier curve according to GRACE score and TIMI score between the elderly and non-elderly groups (P<0.001). Significant differences were also shown on MACE between the elderly and non-elderly groups (P<0.001). Risk ratio (RR) values of Cox regression analysis based on GRACE and TIMI scores were greater than 1 (P<0.001).

AUC of mortality and MACE incidence of different groups scored by GRACE and TIMI

In the non-elderly group, larger AUC of MACE incidence within 30 days was shown by GRACE scores than that by TIMI scores (**Figure 3**; **Table 3**). No significant difference in AUC of mortality and MACE incidence was shown within the other two periods. In the elderly group, larger AUC of mortality and MACE incidence were shown by GRACE scores compared with TIMI scores. Take the elderly group as a whole, AUC of the mortality of different period and MACE incidence in GRACE scoring system were significantly larger than TIMI scoring system (P<0.001). However, the two scoring system did not show significant difference in the elderly group (P=0.147). This finding indicated that for the same group of patients, GRACE scores may suggest higher risk or poor prognostic than TIMI scores.

Discussion

In this study, we investigated the values of GRACE and TIMI scores for risk stratification and prognosis in female patients with NSTE-ACS at different ages. Our findings showed that mortality and MACE incidence increased in parallel with the scores. The two scoring system

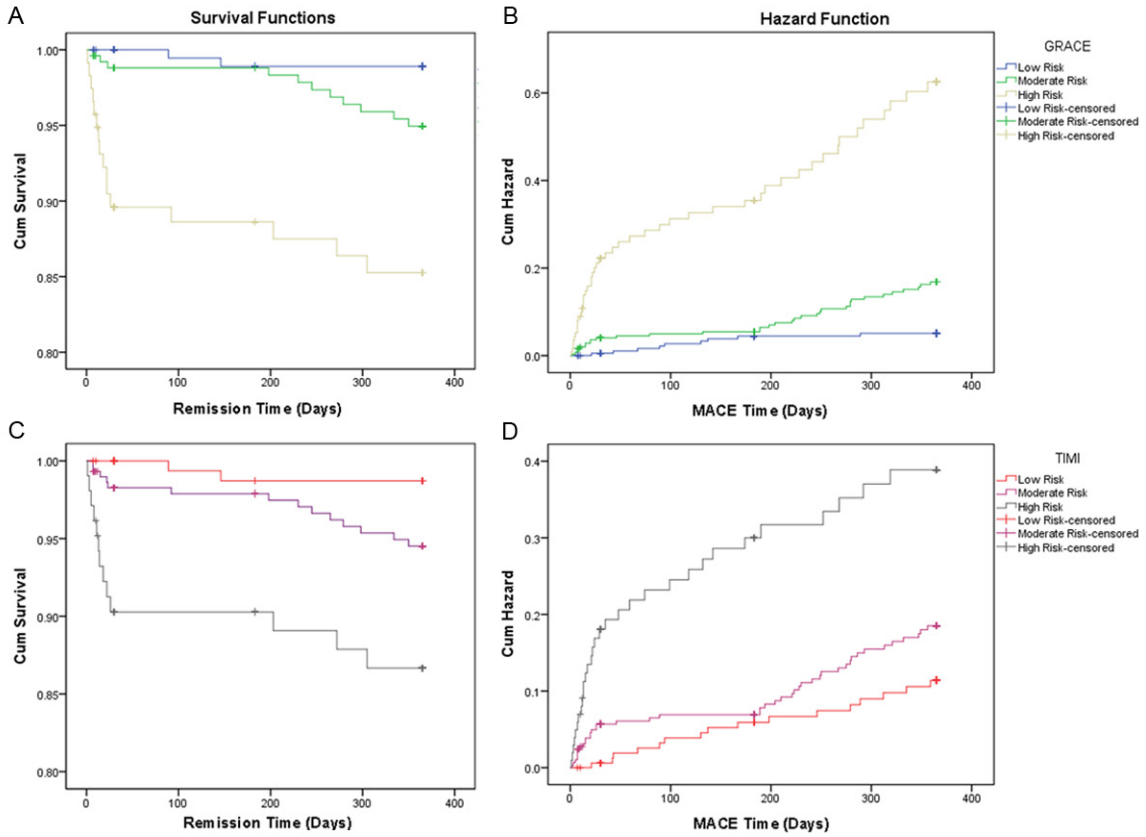

Figure 1. Kaplan-Meier survival curves of remission time and hazard function of MACE time in elderly female patients with NSTE-ACS grouped by GRACE and TIMI scores. Kaplan-Meier curves (A, C): RR value of GRACE score: 3.129, 95% CI: (1.945, 5.035), P<0.001; RR value of TIMI score: 2.174, 95% CI: (1.413, 3.346), P<0.001. Hazard function (B, D): RR value of GRACE score: 2.284, 95% CI: (1.771, 2.945), P<0.001; RR value of TIMI score: 1.909, 95% CI: (1.506, 2.420), P<0.001.

showed significant differences between non-elderly and elderly patients. For all patients enrolled in the study (including patients lost to follow-up), death and MACE were regarded as endpoint events. These findings indicated that there was a guide role of the two scoring systems for prognosis of female patients with NSTE-ACS. Cox regression analysis revealed that RR values of the two scoring system were larger than 1. No obvious difference was observed on non-elderly patients between AUC of GRACE and TIMI scoring models. However, GRACE scores of elderly patients showed larger AUC than that of TIMI scores (P<0.05), which demonstrated better accuracy than TIMI scores in elderly patients.

Coronary risk factors, coronary artery stenosis, ST segment shift and elevated cardiac enzymes are taken into account in TIMI scoring system, which could determine the prognosis of patients more accurately [10-13]. However, TIMI scores are obtained only by presence or absence of prognostic factors without further severity or quantization analysis of the factors, such as levels of age and blood pressure. In addition, many elderly patients are not aware of their blood pressure or diabetes, which may lead to errors during TIMI scoring. The factors described above may cause differences on prognosis between GRACE risk score and TIMI risk score in elderly female patients with NSTE-ACS. Otherwise, comprehensive analysis is performed by GRACE risk scores with many factors including age, heart rate, systolic blood pressure, creatinine, Killip classification, cardiovascular events, myocardial enzyme markers, ECG ST-segment changes and other factors [14, 15]. The indicators are collected by a clinician rather from patient memory. Different scores of aforementioned indicators are given, inducing more accurate scoring. In addition, renal dysfunction is considered one of the factors that indicate a poor prognosis. It has been shown

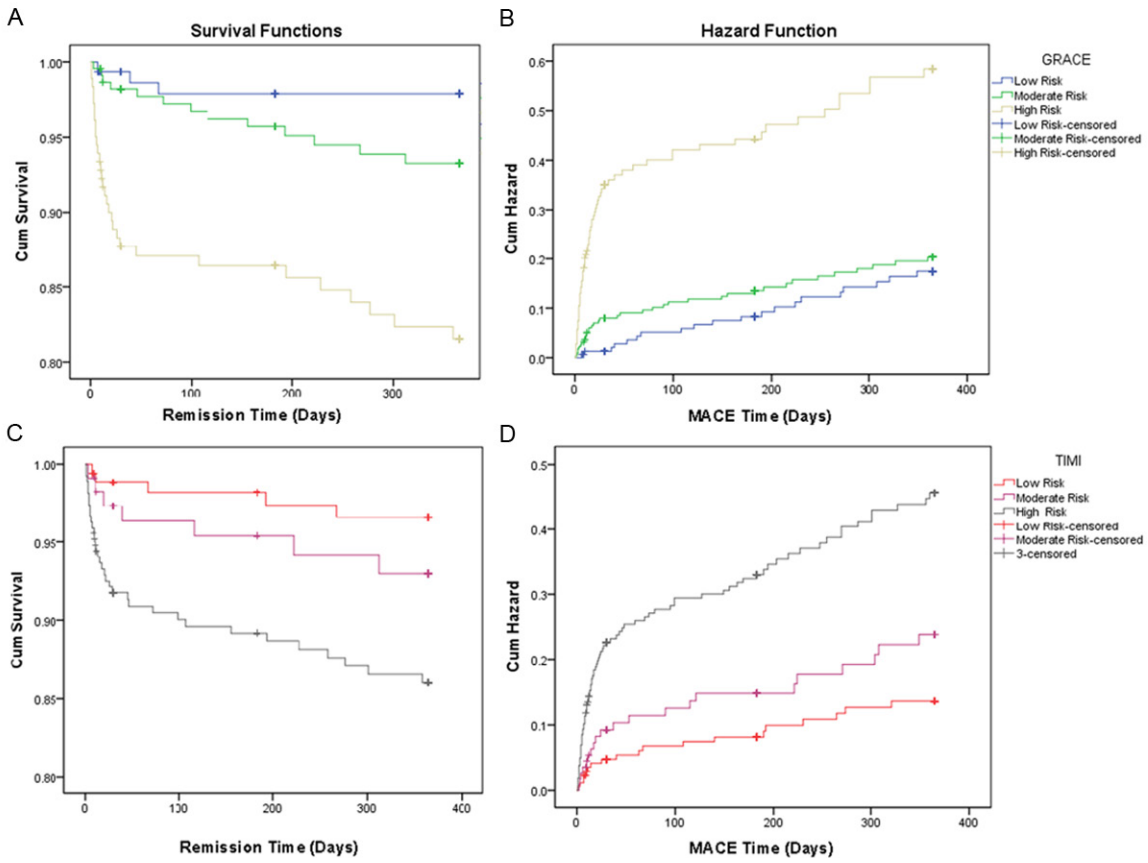

Figure 2. Kaplan-Meier survival curves of remission time and hazard function of MACE time in non-elderly female patients with NSTE-ACS grouped by GRACE and TIMI scores. Kaplan-Meier curves (A, C): RR value of GRACE score: 3.726, 95% CI: (2.101, 6.608), P<0.001; RR value of TIMI score: 3.112, 95% CI: (1.759, 5.506), P<0.001. Hazard function (B, D): RR value of GRACE score: 3.703, 95% CI: (2.790, 5.098), P<0.001; RR value of TIMI score: 2.039, 95% CI: (1.499, 2.774), P<0.001.

that renal dysfunction is an independent risk factor for high mortality of patients with acute coronary syndrome [16, 17]. Moreover, renal dysfunction is more commonly seen in elderly women with NSTE-ACS than the non-elderly women, which may also be an important reason leading to the difference in prognostic effects between GRACE and TIMI risk scores in elderly female patients with NSTE-ACS.

Our study has limitations. Some of the patients were followed up by telephone interview, which may introduce errors. In addition, the follow-up time was only one year and did not cover all the mortality and MACE.

Conclusions

In conclusion, GRACE and TIMI risk scores presented differences in risk stratification and prognosis of female patients with NSTE-ACS. GRACE showed better accuracy than TIMI scores in elderly patients. This study demonstrated the importance of age in risk stratification of female patients with NSTE-ACS.

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Disclosure of conflict of interest

None.

Abbreviations

NSTE-ACS, Non-ST segment elevation acute coronary syndrome; NSTEMI, Non-ST-segment elevation myocardial infarction; MACE, Major adverse cardiac events; GRACE, Global Registry of Acute Coronary Events; TIMI, Thrombolysis in

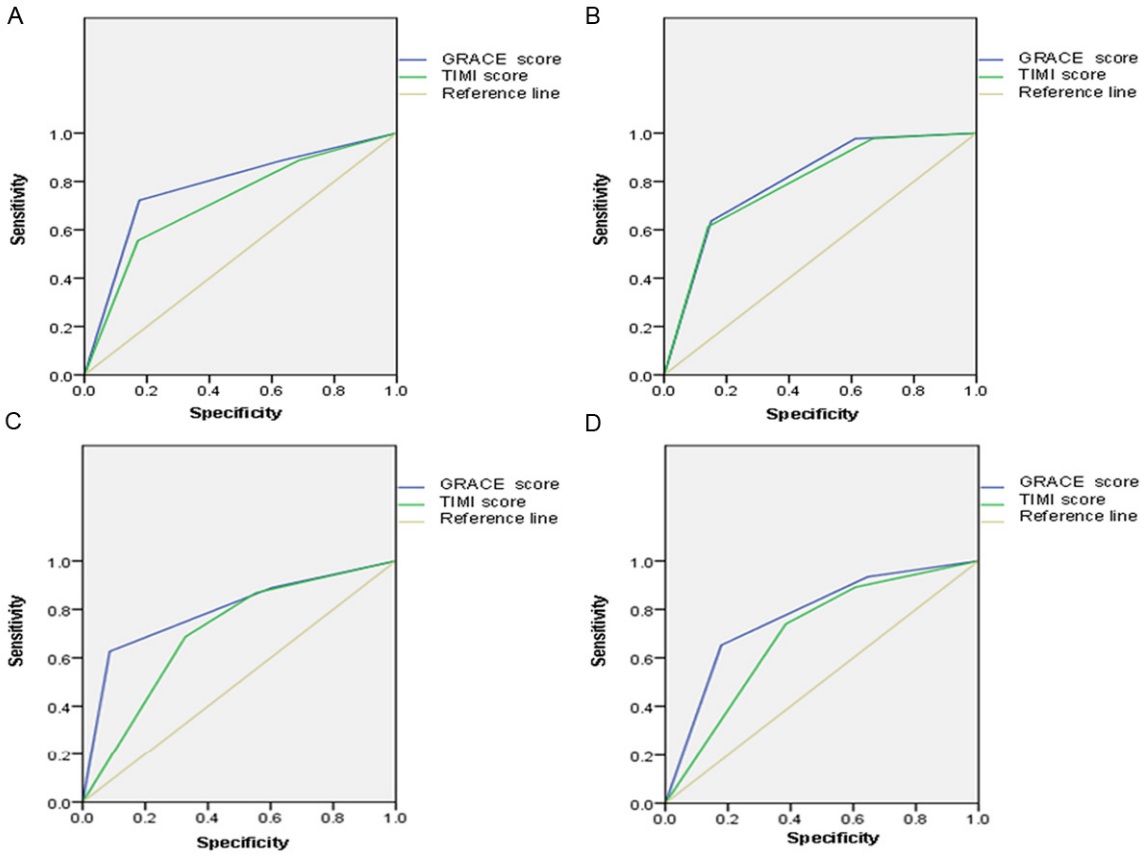

Figure 3. Receiver operator characteristic curves of GRACE and TIMI risk scores for (A) incidence of MACE within 30 days in the non-elderly group, (B) mortality within 1 year in the non-elderly group, (C) incidence of MACE within 6 months in the elderly group, and (D) mortality within 1 year in the elderly group.

Table 3. AUC of mortality and MACE at different time intervals based on GRACE and TIMI risk scores

		Area under ROC curve	
		GRACE	TIMI
Non-elderly group			
Mortality	30 days	0.81	0.68
	6 months	0.78	0.77
	1 year	0.77	0.75
MACE	30 days	0.76	0.75
	6 months	0.79	0.78
	1 year	0.78	0.76
Elderly group			
Mortality	30 days	0.75	0.67
	6 months	0.77	0.71
	1 year	0.79	0.68
MACE	30 days	0.81	0.72
	6 months	0.82	0.73
	1 year	0.78	0.72

In the elderly group, area under the ROC curve (AUC) from GRACE score model was significantly greater than that from TIMI score model (P=0.000148). The non-elderly group showed no obvious difference on AUC from the two score models (P=0.147) (Paired t test).

Myocardial Infarction; BMI, Body mass index; ECG, Electrocardiography; PVC, Premature ventricular contraction; AUC, Area under the ROC curve.

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