Original Article

Development of a machine learning model to predict the risk of late cardiogenic shock in patients with ST-segment elevation myocardial infarction

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Background: The in-hospital mortality of patients with ST-segment elevation myocardial infarction (STEMI) increases to more than 50% following a cardiogenic shock (CS) event. This study highlights the need to consider the risk of delayed calculation in developing in-hospital CS risk models. This report compared the performances of multiple machine learning models and established a late-CS risk nomogram for STEMI patients.

Methods: This study used logistic regression (LR) models, least absolute shrinkage and selection operator (LASSO), support vector regression (SVM), and tree-based ensemble machine learning models [light gradient boosting machine (LightGBM) and extreme gradient boosting (XGBoost)] to predict CS risk in STEMI patients. The models were developed based on 1,598 and 684 STEMI patients in the training and test datasets, respectively. The models were compared based on accuracy, the area under the curve (AUC), recall, precision, and Gini score, and the optimal model was used to develop a late CS risk nomogram. Discrimination, calibration, and the clinical usefulness of the predictive model were assessed using C-index, calibration plotd, and decision curve analyses.

Results: A total of 2282 STEMI patients recruited between January 1, 2016 and May 31, 2020, were included in the complete dataset. The linear models built using LASSO and LR showed the highest overall predictive power, with an average accuracy over 0.93 and an AUC above 0.82. With a C-index of 0.811 [95% confidence interval (CI): 0.769–0.853], the LASSO nomogram showed good differentiation and proper calibration. In internal validation tests, a high C-index value of 0.821 was achieved. Decision curve analysis (DCA) and clinical impact curve (CIC) examination showed that compared with the previous score-based models, the LASSO model showed superior clinical relevance.

Conclusions: In this study, five machine learning methods were developed for in-hospital CS prediction. The LASSO model showed the best predictive performance. This nomogram could provide an accurate prognostic prediction for CS risk in patients with STEMI.

Keywords: Machine learning; cardiogenic shock (CS); ST-segment elevation myocardial infarction (STEMI); least absolute shrinkage and selection operator (LASSO)

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Introduction

Cardiogenic shock (CS) is the most common cause of in-hospital death in patients with acute myocardial infarction (AMI), occurring in approximately 5–10% of patients. Up to 70% of CS cases can be attributed to AMI (1,2). Mortality among patients with AMI-complicated CS remains high despite early revascularization. ST-segment elevation myocardial infarction (STEMI) is the most severe type of AMI, with poor prognosis and high mortality (3,4). In China, a recent survey suggests that admission rates (per 100,000) for cases of STEMI has increased approximately 4-fold, from 4.6 to 18.0 in men, and 1.9 to 8.0 in women, between 2001 and 2011 (5).

Studies have suggested that the in-hospital mortality of STEMI patients increases to more than 50% after a secondary CS event, especially within 30 days (6). In addition, STEMI-related complications represent a huge medical and economic burden. Some believe that the high mortality rate and the high incidence of complications in STEMI patients are related to the lack of early effective prevention and intervention measures (7). The lag in intervention has been attributed to delayed first medical contact (FMC), the lack of valuable predictive markers, and the inability of traditional scoring scales to provide accurate predictions. Considering the risk of CS and its many related risk factors, an accurate clinical prediction tool must be developed to accurately predict the occurrence of CS. The main risk factors resulting in the death of STEMI patients including older age, previous MI, renal dysfunction, cardiogenic shock, anterior MI, out-of-hospital cardiac arrest, non-reperfused patients. Several risk scores have been developed in the last 20 years to stratify patients hospitalized with acute coronary syndromes (ACS) (8). The most commonly used score is the Global Registry of Acute Coronary Events (GRACE) risk model, which uses eight variables and applies to the entire spectrum of ACS (9). The Brittany Regional Infarction Observatory (ORBI) study provided a scoring system to identify STEMI patients with impending CS following percutaneous coronary intervention (PCI) (10). However, these risk scores were developed by traditional regression methods, and the use of procedural characteristics in the prediction model may cause a delay in calculating the risk while awaiting the results. Thus, in many cases, the shock develops before the risk can be assessed.

Machine learning is a multidisciplinary field involving artificial intelligence, computational complexity theory, that can be characterized by system self-improvement. Based on machine learning methods and admission variables, a nomogram model may improve performance for STEMI patients who may have CS after admission. To the best of our knowledge, this is the first study to use machine learning algorithms to establish an accurate and easy method for predicting the occurrence of STEMI using readily available features on admission. Different machine learning methods for late CS prediction were compared. We present the following article in accordance with the TRIPOD reporting checklist (11) (available at https://dx.doi.org/10.21037/atm-21-2905)

Methods

Patients

All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). Research approval was obtained from the Ethics Committee of the Affiliated Hospital of Zunyi Medical University (approval No. KLL[2020]0144). Patient written informed consent was waived due to the retrospective nature of the study. Patients were recruited from the Affiliated Hospital of Zunyi Medical University between January 2016 and May 2020 (*Figure 1*) according to the STEMI criteria of the European Society of Cardiology (ESC) [2017] (8).

Outcomes

The primary outcome was in-hospital CS defined as systolic blood pressure ≤90 mmHg for more than 30 minutes following the exclusion of hypovolaemia, with clinical evidence of hypoperfusion (cool extremities or a urine output of <30 mL/h and a heart rate ≥60 beats/min) or the requirement for mechanical left ventricular support to correct the condition (12). Late CS was defined as CS developed in the ward. Patients with CS on admission were excluded.

Candidate predictors

Demographic data, disease, electrocardiographic data, laboratory parameters on admission, and in-hospital events were collated from the patient's medical records. Baseline characteristics, demographics (age and gender), risk factors (hypertension, diabetes, current smoking, family history),

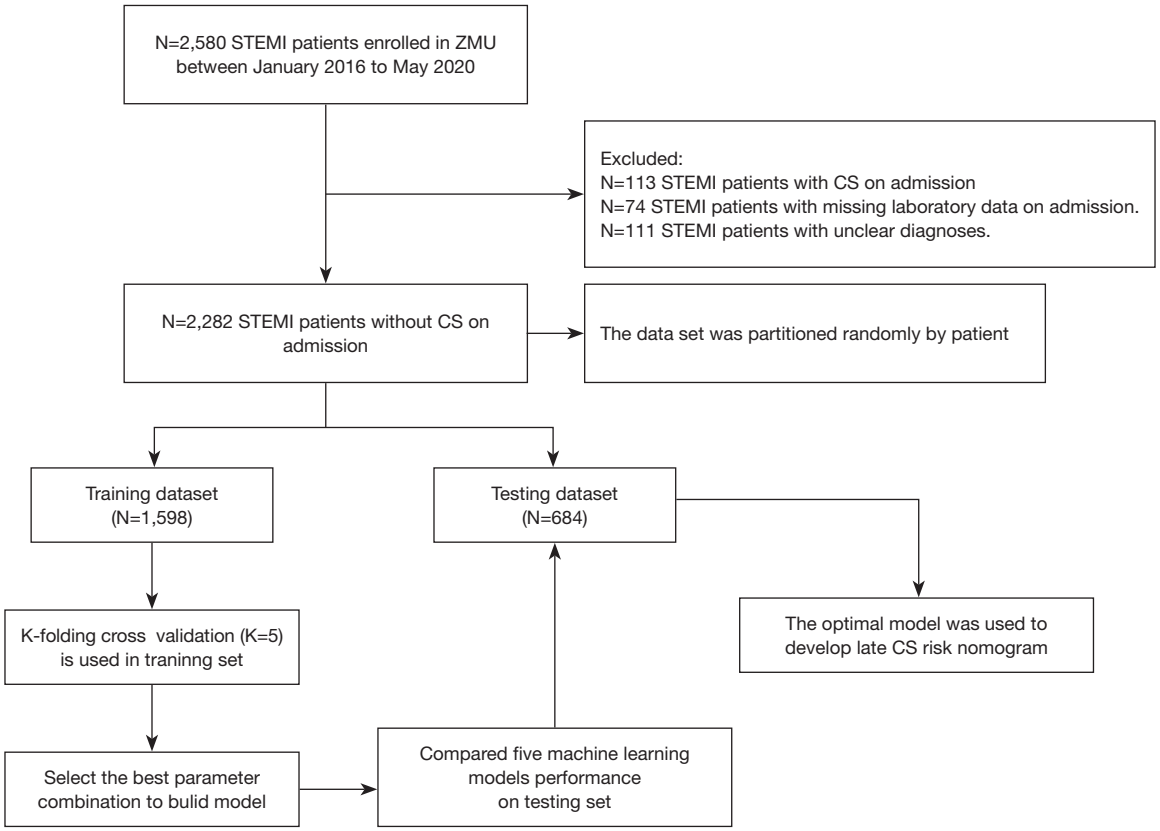

Figure 1 A flow diagram showing the study process. Training and test dataset generation, model training and performance evaluation. A total of 2,282 patients were recruited in the current study. The data were preprocessed and randomly divided into a training set (70%) and a test set (30%), maintaining similar proportions for the two classes proportions in each set. In the training set, k-fold cross-validation (k=5) was used. STEMI, ST-segment elevation myocardial infarction; CS, cardiogenic shock.

non-weekday admission (NWDS), delay (defined as patient FMC >12 hours), medical history [previous stroke, previous chronic kidney disease (CKD)], and electrocardiogram (ECG) findings (inferior, anterior, right ventricular, other) were all recorded from our electronic database. Patients with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 for more than three months were defined as having CKD, where the eGFR was calculated for all patients using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation (13). The dataset was randomly partitioned into the training set and a test set. Based on TRIPOD reporting guidelines, the rule of thumb for sample size is to have at least 10 outcome events per variable (EPV). Assessment of predictors in our study has be done without knowledge of the participant's outcome. A single investigator assessed all demographic information and clinical data and was blinded to the outcome.

Missing data

Complete case data were collected from the electronic health records (EHRs) and analyzed. All variables can be queried in the EHRs. Some patients were excluded as they refused the candidate predictor laboratory test.

Statistical analysis

CS risk prediction models were bases on five machine learning methods, namely, logistic regression (LR), light gradient boosting machine (LightGBM), extreme gradient boosting (XGBoost), support vector machine (SVM), and least absolute shrinkage and selection operator (LASSO) regression. All numbers listed initially with each hyperparameter were considered default values. Continuous variables are presented as medians, and categorical variables are presented as absolute counts and percentages (n, %).

To determine the variables associated with CS risk and to create a predictive model using these variables, machine learning methods and LR analyses were employed. The discriminative abilities of the machine learning models were evaluated and the hyperparameters were tuned by calculating the area under the curve (AUC), accuracy, recall, precision, and the Gini coefficient. The optimal model was used to determine the best combination of variables and develop a nomogram. The variables selected by the best model were manually removed by trial and error to obtain as accurate a model as possible with the smallest number of variables. Five-fold cross-validation (CV) with the training cohort was employed with different randomization schemes. A multivariable LR model was created for comparison by using the variables identified by the best model. Calibration curves were determined as for the best model. These characteristics are described as odds ratios (OR) with 95% confidence intervals (CI) and P values. The CI of Harrell's concordance index was obtained by creating 1,000 bootstrap samples from the entire dataset and replicating the estimation process. The calibration curve was used to analyze the agreement between the nomogram and ideal observations. Decision curve analysis (DCA) was conducted to assess the clinical usefulness of the predictive nomograms by quantifying the net benefits at different threshold probabilities. All analyses were conducted with the statistical packages R version 4.0.2 and Python 3.7.

Results

Model selection

In this study, 1,598 and 684 STEMI patients, including 117 and 53 patients with CS records, were included in the training and test datasets, respectively (*Table 1*). The distributions of these variables are shown in Table S1 (variable correlation heatmap in Figure S1). Among the individuals included in the training dataset, the median age was 64 years [interquartile range (IQR) 53, 73], 75% were male, and 9% had CKD. *Table 2* presents the accuracy, AUC, recall, precision, and Gini coefficient values of the logistic, LASSO, LightGBM, XGBoost, and SVM models with the training and test datasets in predicting CS. The accuracy and AUC with the test dataset show the performance of the developed models. The linear models, LASSO and LR, showed the highest overall predictive power, with average accuracy and AUC above 0.93 and 0.82, respectively, and similar models produced similar results. However, the feature selection method was not applied in the logistic model, therefore, the LASSO regression method with regularization was adopted. Generally, the LightGBM and XGBoost algorithms showed better performance with the training and test datasets. However, the LASSO model had the highest AUC and accuracy (0.822 and 0.931, respectively) with the test dataset (Figure S2). This indicated that LightGBM and XGBoost may encounter more serious overfitting problems compared to other algorithms. In binary classification, LASSO regression may have greater accuracy and demonstrate more convenient advantages compared to other algorithms (Figures S3,S4).

Predictors of in-hospital CS by the LASSO model selection

Of the 33 initial demographic, disease, and lifestyle characteristics, 8 potential indicators based on 2,282 patients were ultimately retained and included in the LASSO regression model with nonzero coefficients (Figure S5). These characteristics included age, CKD, shock index (SI, define as ratio of HR to SBP), delay, white blood cell (WBC) count, hemoglobin (HB), aspartate aminotransferase (AST), and lactic acid dehydrogenase (LDH) (Table S2).

LASSO risk nomogram model building

A model that incorporated the above independent predictors was developed and presented as a nomogram (*Figure 2A*). The nomogram results for patient #6 are illustrated by mapping its values to the covariate scales. The estimated probability of late CS after admission was 0.352 (*Figure 2B*).

Performance of the LASSO risk nomogram model

In this cohort, the nomogram calibration curve for the prediction of CS risk in STEMI patients demonstrated good agreement (*Figure 3A*). The C-index for the prediction nomogram was 0.811 (95% CI: 0.769–0.853) for the cohort and 0.821 following bootstrapping validation, indicating intense discrimination by the model. The output of the LASSO nomogram model thus indicated a strong predictive ability. The AUCs calculated for each of the risk models for late CS following admission are shown in *Figure 3B*. The highest performance of the LASSO risk model demonstrated its improved predictive accuracy (AUC =0.811) over the simple-ORBI model (based only on admission variables in the ORBI score; AUC =0.756), a

Table 1 Characteristics of the patients in the training and test datasets

Characteristics	Total (n=2,282)	Training dataset (n=1,598)	Test dataset (n=684)	P value
Group, n [%]				0.788
Noncardiogenic shock	2,112 [93]	1,481 [93]	631 [92]	
Cardiogenic shock	170 [7]	117 [7]	53 [8]	
Gender, n [%]				0.484
Female	598 [26]	426 [27]	172 [25]	
Male	1,684 [74]	1,172 [73]	512 [75]	
Age, [IQR], y	64.0 [53.0, 73.0]	64.0 [53.0, 72.0]	64.0 [54.0, 73.0]	0.643
Inferior wall, n [%]				0.93
No	1,326 [58]	930 [58]	396 [58]	
Yes	956 [42]	668 [42]	288 [42]	
Anterior wall, n [%]				0.404
No	1,073 [47]	761 [48]	312 [46]	
Yes	1,209 [53]	837 [52]	372 [54]	
Other, n [%]				0.797
No	2,224 [97]	1,556 [97]	668 [98]	
Yes	58 [3]	42 [3]	16 [2]	
Right ventricular, n [%]				0.972
No	2,250 [99]	1,575 [99]	675 [99]	
Yes	32 [1]	23 [1]	9 [1]	
Nonworking days, n [%]				0.783
No	1,426 [62]	1,002 [63]	424 [62]	
Yes	856 [38]	596 [37]	260 [38]	
Hypertension, n [%]				0.346
No	1,155 [51]	798 [50]	357 [52]	
Yes	1,127 [49]	800 [50]	327 [48]	
Diabetes mellitus, n [%]				0.686
No	1,872 [82]	1,307 [82]	565 [83]	
Yes	410 [18]	291 [18]	119 [17]	
Smoker, n [%]				0.634
No	839 [37]	582 [36]	257 [38]	
Yes	1,443 [63]	1,016 [64]	427 [62]	
Stroke, n [%]				0.828
No	2,144 [94]	1,503 [94]	641 [94]	
Yes	138 [6]	95 [6]	43 [6]	

Table 1 (*continued*)

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Characteristics	Total (n=2,282)	Training dataset (n=1,598)	Test dataset (n=684)	P value
CKD, n [%]				0.352
No	2,060 [90]	1,436 [90]	624 [91]	
Yes	222 [10]	162 [10]	60 [9]	
Delay, n [%]				0.143
FMC ≤12 hours	1,716 [75]	1,216 [76]	500 [73]	
FMC >12 hours	566 [25]	382 [24]	184 [27]	
WBC, [IQR], $\times10^9$/L	10.5 [8.2, 13.3]	10.5 [8.2, 13.2]	10.4 [8.2, 13.4]	0.737
Neutrophil, [IQR], $\times10^9$/L	8.3 [5.8, 11.0]	8.3 [5.8, 11.0]	8.1 [5.9, 11.0]	0.96
Shock index, [IQR]	0.6 [0.5, 0.7]	0.6 [0.5, 0.7]	0.6 [0.5, 0.7]	0.704
NLR, [IQR]	6.2 [3.7, 10.5]	6.3 [3.7, 10.5]	6.1 [3.7, 10.1]	0.367
PLR, [IQR]	157.0 [109.4, 224.8]	158.1 [111.2, 229.8]	153.3 [106.1, 212.7]	0.084
MLR, [IQR]	0.5 [0.4, 0.8]	0.5 [0.4, 0.8]	0.5 [0.4, 0.8]	0.653
SIRI, [IQR]	4.2 [2.3, 7.3]	4.2 [2.3, 7.4]	4.1 [2.4, 7.1]	0.872
SII, [IQR]	1,248.5 [705.2, 2,167.0]	1,269.3 [710.2, 2,200.2]	1,212.2 [701.2, 2,051.6]	0.251
HB, [IQR], g/L	137.0 [123.0, 150.0]	137.0 [123.0, 151.0]	137.0 [122.0, 150.0]	0.925
RBC, [IQR], $\times10^{12}$/L	4.5 [4.0, 4.9]	4.5 [4.0, 4.9]	4.5 [4.0, 4.9]	0.744
PLT, [IQR], $\times10^9$/L	203.0 [167.0, 248.0]	205.0 [169.0, 249.0]	200.0 [163.0, 246.0]	0.177
ALT, [IQR], U/L	31.0 [21.0, 48.0]	30.5 [20.0, 48.0]	32.0 [21.0, 49.0]	0.284
AST, n [%]				0.876
<500 U/L	2,217 [97]	1,552 [97]	665 [97]	
500–1,000 U/L	45 [2]	31 [2]	14 [2]	
≥1,000 U/L	20 [1]	15 [1]	5 [1]	
GGT, [IQR], IU/L	34.0 [22.0, 58.0]	34.0 [22.0, 58.0]	34.0 [21.0, 59.0]	0.655
CK, [IQR], U/L	480.0 [174.0, 1,335.5]	479.5 [174.2, 1,329.2]	481.5 [173.5, 1,350.5]	0.96
CKMB, [IQR], U/L	51.5 [24.0, 124.0]	51.0 [24.0, 123.0]	52.5 [24.0, 128.0]	0.85
LDH, [IQR], U/L	373.0 [264.2, 596.8]	371.5 [265.2, 584.0]	381.0 [263.0, 617.8]	0.642
HBDH, [IQR], U/L	263.0 [173.0, 461.0]	258.5 [173.2, 456.0]	272.0 [169.8, 477.2]	0.63
CTnT, [IQR], ng/L	796.1 [203.2, 2,563.0]	809.0 [212.2, 2,563.0]	778.2 [179.2, 2,564.2]	0.495
BNP, [IQR], pg/mL	883.7 [227.2, 2,632.0]	881.7 [236.6, 2,718.5]	885.9 [209.0, 2,522.8]	0.392

Values are expressed as medians with IQR for continuous data. Other values are presented as numbers and percentages. CKD, chronic kidney disease; FMC, first medical contact; WBC, white blood cell; Shock index, ratio of HR to SBP; PLR, ratio of platelets to lymphocytes; NLR, ratio of neutrophils to lymphocytes; MLR, ratio of monocytes to lymphocytes; SIRI, systemic inflammatory response index; SII, systemic inflammatory reaction index; HB, hemoglobin; RBC, red blood cell; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; CK, creatine kinase; CKMB, creatine kinase MB; LDH, lactate dehydrogenase; HBDH, hydroxybutyrate dehydrogenase; CTnT, cardiac troponin T; BNP, brain natriuretic peptide; IQR, interquartile ranges.

Table 2 A comparison of the model performances with the training and test datasets

Model	Training dataset					Test dataset				
	Acc	AUC	Recall	Precision	Gini	Acc	AUC	Recall	Precision	Gini
LR	0.934	0.826	0.203	0.686	0.653	0.937	0.823	0.308	0.696	0.645
LASSO	0.927	0.803	0.085	0.556	0.605	0.931	0.822	0.212	0.647	0.643
XGBoost	1	1	1	1	1	0.927	0.782	0.25	0.541	0.566
LightGBM	1	1	1	1	1	0.928	0.803	0.25	0.565	0.606
SVM	0.928	0.767	0.042	0.833	0.535	0.927	0.778	0.077	0.667	0.557

LR, logistic regression; LASSO, least absolute shrinkage and selection operator; XGBoost, extreme gradient boosting; LightGBM, light gradient boosting machine; SVM, support vector regression; Acc, accuracy; AUC, area under the curve.

model based on GRACE (AUC =0.778), and a model based on the admission SI (AUC =0.645). The prediction model was further evaluated by DCA and the clinical impact curve (CIC; *Figure 3C*,*D*). The results demonstrated that the LASSO model provided a substantial net clinical benefit over the simple-ORBI model, GRACE model, and the admission SI model for relevant decision thresholds. For a decision threshold of 10% in-hospital CS risk, the LASSO nomogram model identified 20 additional cases compared to the other models, without identifying any false positive cases in a population of 1,000 patients.

Discussion

As the prognosis in patients with CS is grave and evidence-based treatment is limited among patients with fulminant CS, the identification of patients in a pre-CS state may be important (14). In this study, five machine learning models were used to predict CS risk in STEMI patients. Although LightGBM and XGBoost showed the highest AUC and accuracy in the training dataset, those in the test dataset are the most important for constructing a predictive model for an early warning system in clinical practice. Among the models constructed, the LASSO method (accuracy =0.931, AUC =0.822, recall =0.212, precision =0.647, Gini coefficient =0.643) achieved the best performance for CS prediction with the test dataset (*Table 2*, Figure S2). The LASSO model had a stronger explanatory ability and applicability than the other models. LASSO regression results in a full shrinkage of a subset of variables, which effectively operates as a form of variable selection and results in a more stable model that produces a better predictor, particularly when applied to external datasets (15). To date, nomograms have been widely used in the prognostic analysis of tumors and other medical conditions (16). Nomograms rely on a user-friendly digital interface, high accuracy, and a clear interpretation of prognosis to aid clinical decision-making (17). This study is the first to evaluate the efficacy of of multiple machine learning models and select the optimal model with which to construct a nomogram and apply it to the risk prediction of STEMI patients developing late CS following admission.

In this sizeable homogeneous cohort of STEMI patients without CS on admission, we developed and validated a new predictive tool that uses 8 variables, including 4 patient-related variables and 4 laboratory-related variables, to predict the development of in-hospital CS after admission. Integrating risk factors for age, disease, and laboratory measurements into an easy-to-use nomogram helps the individualized prediction of late CS development in patients with STEMI via the creation of a risk nomogram. The internal validation of the model showed good differentiation and calibration capability. In particular, our high C-index from the internal validation indicated that the nomogram can be used extensively and accurately because of the reasonably large sample size used in its construction. In agreement with previous studies (18-20), approximately 5–10% of STEMI patients in this study presented with CS. Recent analyses indicated that older age, diabetes mellitus, stroke, treatment delays, anterior STEMI, heart rate, systolic blood pressure, cardiac arrest, elevated glycemia, and impaired renal function were associated with the development of in-hospital CS (14,21-24). In this current study, the risk factors for CS in STEMI patients were determined to be age, CKD, SI, delay, and laboratory measurements including WBC, HB, AST, and LDH. Moreover, in the recently published ORBI risk score study, which included 9,046 STEMI patients, older age, SI, and longer delays between symptoms were also predictors

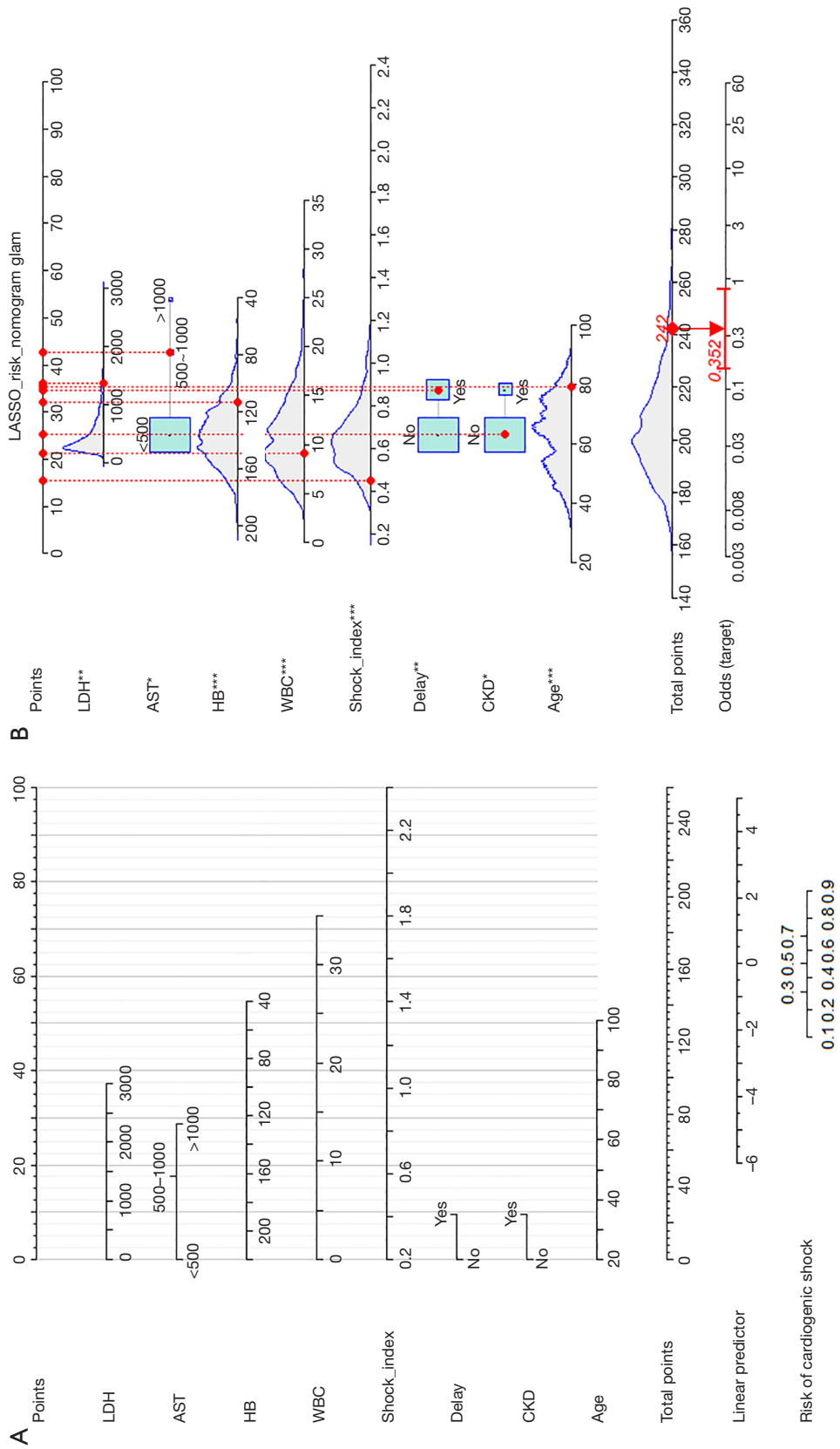

Figure 2 LASSO risk model that incorporated the 8 independent predictors was developed and presented as a nomogram. (A) Proposed CS nomogram; (B) the nomogram results for patient #6 are illustrated by mapping the values to the covariate scales. The incidence estimated for late CS after admission is 0.352. * , P<0.05; ** , P<0.01; *** , P<0.001. CS, cardiogenic shock; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; HB, hemoglobin; WBC, white blood cell; CKD, chronic kidney disease.

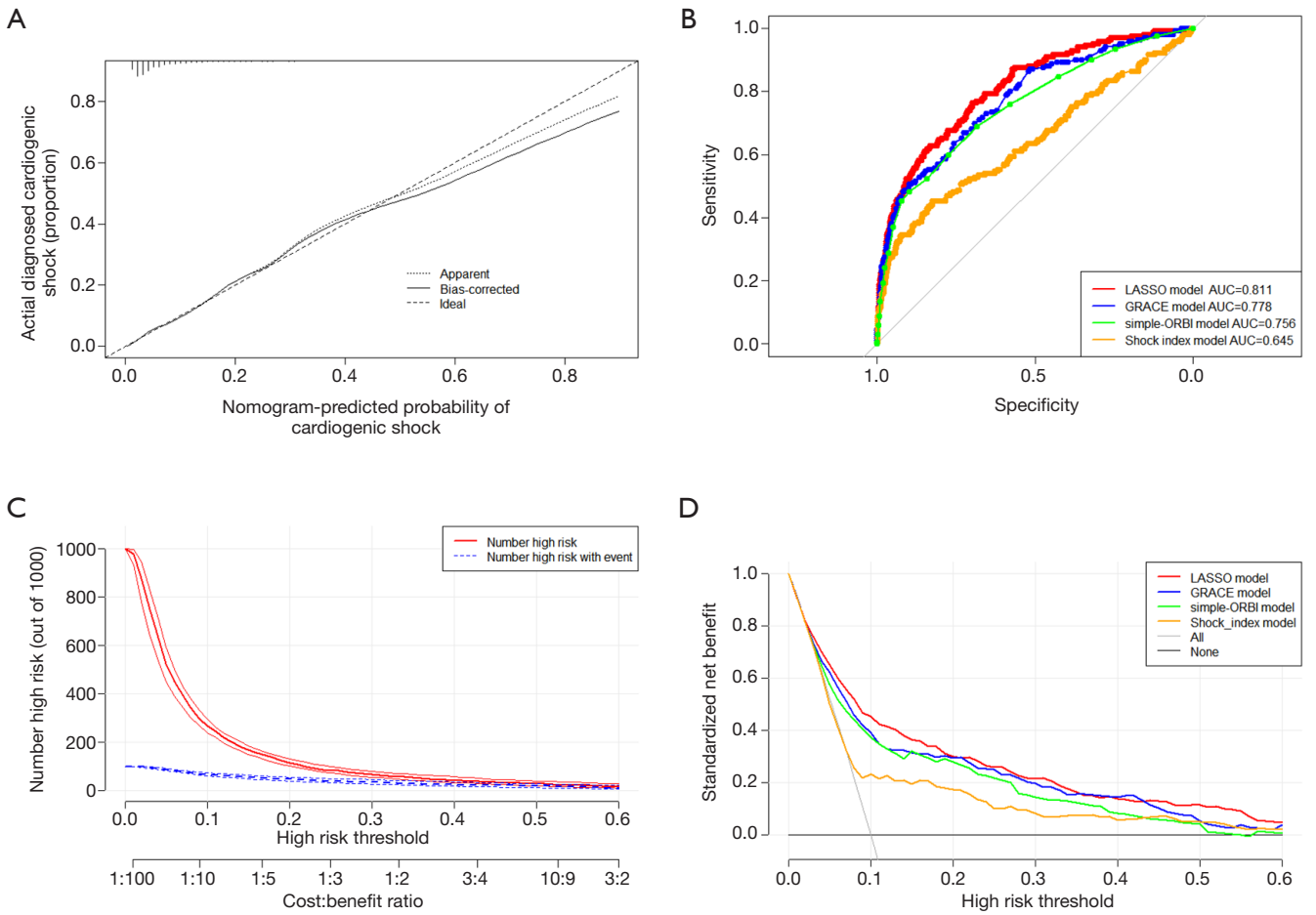

Figure 3 Performance of the LASSO risk nomogram model. (A) Calibration curves for the predictions of the CS nomogram in the cohort. The solid line represents the performance of the nomogram; a closer fit to the diagonal dotted line represents a better prediction. (B) Predictive accuracy of the LASSO model, GRACE model, simple-ORBI model (based only on admission variables in the ORBI score, such as age, previous stroke/TIA, presentation with cardiac arrest, anterior myocardial infarction, FMC delay >90 min, Killip Class II or III, heart rate >90 beats/min, and the combination of systolic blood pressure <125 mmHg and pulse pressure <45 mmHg) and shock index model for late CS. (C) Decision curve analysis for the CS nomogram.The LASSO nomogram model (red) demonstrated an improved net benefit compared with the simple-ORBI model (green), the GRACE model (blue), and a model based on admission shock index (orange). (D) Clinical impact curve for the LASSO nomogram model. The heavy red solid line shows the total number of patients out of 1,000 who would be deemed high risk for each risk threshold. The blue dashed line shows how many of those patients would be true positive cases. CS, cardiogenic shock; LASSO, least absolute shrinkage and selection operator; GRACE, Global Registry of Acute Coronary Events; ORBI, Brittany Regional Infarction Observatory; TIA, transient ischemic attack; FMC, first medical contact.

of CS, which concurs with the prognostic impact of these factors identified in the present analysis.

There is a close relationship between renal and cardiovascular diseases, which may be related to the shared profile of risk factors (25). Compared with normal kidney function in healthy patients, abnormal kidney function in STEMI patients is associated with a greater than 70% increase in the risk of adverse clinical events (26). Chronic renal failure has been defined as a prognostic determinant in STEMI patients complicated with CS (27). CKD is a predisposing factor for renal acidosis and since severe hypotension deteriorates renal perfusion, it exacerbates renal acidosis and plays a prominent role in the vicious cycle encountered in CS patients. Furthermore, the success of PCI has been reported to be low in patients with CKD, and their coronary atherosclerotic plaques tend to have marked

calcification with increased media thickness, particularly in end-stage renal disease patients. In addition, microvascular impairment has been observed in patients with CKD (28,29). In this model, delay refers to an FMC >12 hours. These patients may present with atypical symptoms or a lack of awareness of their condition. At present, the patient delay is the main reason for the total excess time of STEMI ischemia and poor prognosis. Systemic delay can be improved by constructing chest pain centers and training the medical team (30). To minimize patient delay, the public should be made awareness of the common symptoms of AMI and when to call emergency services. The model presented in this study confirmed that SI is a valuable indicator for predicting prognosis in patients with AMI complicated by CS. Previous studies have used SI to predict mortality in the ACS population and have found that an increased SI can predict short-term mortality in patients with STEMI. A SI ≥0.7–0.8 on admission in patients with STEMI was associated with a mortality rate of 16–20%, and the lower the SI, the lower the risk of death (31-34). This study showed that the traditional inflammatory indicators, WBC count and myocardial enzymes (LDH and AST), remain essential in the risk prediction of STEMI and confirmed that anemia might increase the risk among patients after PCI. Pathophysiologically, hemoglobin concentration and blood oxygen saturation decrease in patients with anemia, which leads to an imbalance in the oxygen supply, consumption of cardiomyocytes, and myocardial ischemia. After myocardial ischemia, a reflex causes the activation of the sympathetic nerve and the angiotensin aldosterone system, which leads to a compensatory increase in heart rate and blood volume. This increase leads to an increase in cardiac load and aggravates myocardial ischemia. In addition, vascular inflammation increases in patients with anemia, which can aggravate coronary artery plaques and thrombi.

The machine learning-based nomogram presented in this study has several strengths. First, the nomogram was developed from a largely homogeneous population of STEMI patients analyzed by machine learning with improved model performance over traditional regression methods. This method also results in a superior final prediction model without sacrificing the interpretability of the relationship between risk factors and the outcomes of interest. Second, the assessment of the risk of bias (ROB) is an essential step in any prediction model study. A high ROB will overestimate the model efficacy. The Prediction Model Risk of Bias Assessment Tool (PROBAST) was developed to address the lack of appropriate tools specific to the evaluation of ROB and the applicability of prediction model studies (35). The ROB is low when predictions are made without knowledge of the outcome status. Based on the patient's clinical and laboratory data on admission, the proposed LASSO risk model of late CS was constructed to ensure a low ROB. Additionally, there was no risk of delayed calculation caused by waiting for the procedural results to be available. Third, as previously discussed, to ensure that the outcome was isolated to the predictors, several known risk factors for the development of CS in STEMI were not included in the present study, such as in-hospital treatment (including PCI and coronary artery bypass grafting), diagnostic variables, left ventricular ejection fraction (LVEF), and lactate levels. The inclusion of these factors would have inflated the apparent model performance because they are measured closer in time to the outcome assessment and are likely to be more strongly associated with the outcome. Fourth, the nomogram demonstrated superior clinical benefit compared with the simple-ORBI model (based on ORBI but excluding procedural variables) and the GRACE model, which have been externally validated in the general population for predicting in-hospital late CS (9,10). Finally, the nomogram efficiently addresses a significant clinical need, refining the identification of patients at high risk of CS development on admission, which may be the most suitable time to initiate early adjunctive therapies. This was the first machine learning model developed for this condition using a large sample size, and the results were displayed directly via a nomogram, which can be easily applied in clinical practice. The early prediction of CS has positive clinical importance in the treatment and prognosis of patients with STEMI. Patients at higher risk may benefit from early management, which may prevent iatrogenic shock.

Limitations

There were certain limitations to this current research. First, the data collected only represented a portion of STEMI patients and may not be representative of all STEMI patients. Second, not all possible factors that influence CS were included in the risk factor analyses. For example, glycemia is not routinely recorded in our patients and therefore could not be tested as a potential predictor of CS. Additionally, the influence of other variables, such as insurance and other factors, are not fully understood. Third, although the bootstrap test thoroughly

assessed the robustness of our nomogram, external testing could not be conducted, and the generalizability to other STEMI populations in other regions and countries is unclear. Further investigations using larger populations are warranted to fully evaluate the applicability of this model.

Conclusions

This research established a new nomogram capable of predicting the risk of CS in STEMI patients with good accuracy. This nomogram is a simple and efficient tool that may be implemented on admission in routine clinical practice to identify STEMI patients with a high risk of developing in-hospital CS.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/atm-21-2905). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was locally approved by the Ethics Committee of the Affiliated Hospital of Zunyi Medical University (approval No. KLL[2020]0144). All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). Patient written informed consent was waived due to the retrospective nature of the study.

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Performance Metrics

In the current study, the following metrics were applied to evaluate the performance of each model.

i.) True positives (TPs), positive diagnoses classified as positive outcomes.

ii.) False positives (FPs), negative diagnoses classified as positive outcomes.

iii.) True negatives (TNs), negative diagnoses classified as negative outcomes.

iv.) False negatives (FNs), positive diagnoses classified as negative outcomes.

v.) The learning curve, adopted to assess classification performance (*Figure S3*).

vi.) Accuracy, the ability to correctly classify the dataset

$$Accuracy = \frac{TP + TN}{TP + FP + TN + FN} \quad (1)$$

vii.) True positive rate (TPR), or Sensitivity

$$TPR = \mathrm{Re}call = Sensitivity = \frac{TP}{TP + FN} \quad (2)$$

viii.) False positive rate (FPR), or type I error probability

$$FPR = FP/(FP + TN) \quad (3)$$

ix.) True negative rate (TNR), or Specificity

$$Specificity = TNR = \frac{TN}{TN + FP} = 1 - FPR \quad (4)$$

x.) Precision

$$\mathrm{Pr}ecision = \frac{TP}{TP + FP} \quad (5)$$

xi.) Receiver operating characteristic (ROC) curve, a curve determined by plotting TPR and FPR and used for evaluating the model performance.

xii.) Area under the curve (AUC), an index used to evaluate the predictive and classification performance of a model.

xiii.) Gini coefficient, used to measure the performance of a model.

Gini=2*AUC - 1 (6)

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Table S1 Differences between demographic and clinical characteristics of CS and non-CS groups

Variables	Total (n=2282)	Noncardiogenic shock (n=2,112)	Cardiogenic shock (n=170)	P value
Demographic				
Age, median (IQR)	64.0 (53.0, 73.0)	64.0 (53.0, 72.0)	70.0 (62.2, 77.0)	<0.001
Sex, n (%)				<0.001
Female	598 (26)	534 (25)	64 (38)	
Male	1684 (74)	1578 (75)	106 (62)	
Smoker, n (%)				0.021
No	839 (37)	762 (36)	77 (45)	
Yes	1443 (63)	1350 (64)	93 (55)	
NWD on admission, n (%)				0.109
No	1426 (62)	1330 (63)	96 (56)	
Yes	856 (38)	782 (37)	74 (44)	
Delay, n (%)				<0.001
FMC ≥12 hours	1716 (75)	1612 (76)	104 (61)	
FMC <12 hours	566 (25)	500 (24)	66 (39)	
Electrocardiographic data				
Inferior wall, n (%)				
No	1326 (58)	1221 (58)	105 (62)	
Yes	956 (42)	891 (42)	65 (38)	
Anterior wall, n (%)				0.304
No	1073 (47)	1000 (47)	73 (43)	
Yes	1209 (53)	1112 (53)	97 (57)	
Right ventricular, n (%)				0.51
No	2250 (99)	2081 (99)	169 (99)	
Yes	32 (1)	31 (1)	1 (1)	
Other, n (%)				0.009
No	2224 (97)	2064 (98)	160 (94)	
Yes	58 (3)	48 (2)	10 (6)	
Medical history				
Hypertension, n (%)				0.469
No	1155 (51)	1074 (51)	81 (48)	
Yes	1127 (49)	1038 (49)	89 (52)	
Diabetes mellitus, n (%)				0.216
No	1872 (82)	1739 (82)	133 (78)	
Yes	410 (18)	373 (18)	37 (22)	
Stroke, n (%)				0.941
No	2144 (94)	1985 (94)	159 (94)	
Yes	138 (6)	127 (6)	11 (6)	
CKD, n (%)				< 0.001
No	2060 (90)	1926 (91)	134 (79)	
Yes	222 (10)	186 (9)	36 (21)	
Vital signs on admission				
Shock index, median (IQR)	0.6 (0.5, 0.7)	0.6 (0.5, 0.7)	0.7 (0.6, 1.0)	<0.001
HR, median (IQR), beats/min	80.0 (71.0, 90.0)	79.0 (71.0, 90.0)	86.0 (74.2, 105.0)	<0.002
SBP, median (IQR), mmHg	126.0 (110.0, 140.0)	126.0 (111.0, 140.0)	115.0 (99.0, 136.0)	<0.003
DBP, median (IQR), mmHg	80.0 (70.0, 90.0)	80.0 (70.0, 90.0)	75.5 (63.0, 86.0)	<0.004
Laboratory on admission				
WBC, median (IQR), ×109/L	10.5 (8.2, 13.3)	10.4 (8.0, 13.1)	12.4 (9.5, 16.4)	<0.001
Neutrophil count, median (IQR), ×109/L	8.3 (5.8, 11.0)	8.1 (5.7, 10.8)	10.3 (7.4, 13.6)	<0.001
NLR, median (IQR)	6.2 (3.7, 10.5)	6.2 (3.6, 9.9)	8.4 (4.7, 14.1)	<0.001
PLR, median (IQR)	157.0 (109.4, 224.8)	157.4 (110.7, 223.6)	152.4 (95.0, 253.1)	0.681
MLR, median (IQR)	0.5 (0.4, 0.8)	0.5 (0.4, 0.8)	0.6 (0.4, 1.0)	<0.001
SIRI, median (IQR)	4.2 (2.3, 7.3)	4.0 (2.3, 7.0)	6.0 (3.5, 11.2)	<0.001
SII, median (IQR)	1248.5 (705.2, 2167.0)	1234.3 (701.1, 2111.0)	1564.6 (787.9, 2814.4)	0.001
HB, median (IQR)	137.0 (123.0, 150.0)	138.0 (124.0, 151.0)	128.0 (111.0, 142.0)	<0.001
RBC, median (IQR), ×1012/L	4.5 (4.0, 4.9)	4.5 (4.0, 4.9)	4.2 (3.7, 4.7)	<0.001
PLT, median (IQR), ×109/L	203.0 (167.0, 248.0)	204.0 (168.0, 248.0)	195.5 (145.5, 254.8)	0.135
ALT, median (IQR), U/L	31.0 (21.0, 48.0)	30.5 (20.0, 46.0)	43.5 (24.0, 82.0)	<0.001
AST, n (%)				<0.001
<500 U/L	2217 (97)	2073 (98)	144 (85)	
500–1000 U/L	45 (2)	32 (2)	13 (8)	
≥1000 U/L	20 (1)	7 (0)	13 (8)	
GGT, median (IQR), IU/L	34.0 (22.0, 58.0)	34.0 (22.0, 56.0)	44.5 (23.0, 78.2)	0.001
CK, median (IQR),U/L	480.0 (174.0, 1335.5)	470.0 (172.0, 1331.0)	562.0 (259.0, 1350.0)	0.065
CKMB, median (IQR),U/L	51.5 (24.0, 124.0)	51.0 (24.0, 124.0)	65.0 (29.0, 138.0)	0.036
LDH, median (IQR),U/L	373.0 (264.2, 596.8)	363.0 (260.0, 572.0)	555.0 (365.8, 907.0)	<0.001
HBDH, median (IQR),U/L	263.0 (173.0, 461.0)	254.5 (169.0, 443.0)	416.0 (232.8, 674.8)	<0.001
CTnT, median (IQR), ng/L	796.1 (203.2, 2563.0)	753.5 (193.0, 2424.5)	2076.5 (595.8, 4178.5)	<0.001
BNP, median (IQR), pg/mL	883.7 (227.2, 2632.0)	812.5 (201.7, 2335.5)	4332.0 (1082.5, 12196.0)	<0.001
Risk assessment				
GRACE score, median (IQR)	122 (102.0, 142.0)	119.0 (102.0, 139.0)	160.0 (128.0, 193.8)	<0.001
Simple-ORBI, median (IQR)	4.0 (2.0, 7.0)	4.0 (2.0, 6.0)	8.0 (5.0, 12.0)	<0.001

Shock index ratio of HR to SBP; SIRI systemic inflammatory response index; SII systemic inflammatory reaction index; PLR ratio of platelets to lymphocytes, NLR ratio of neutrophils to lymphocytes; MLR ratio of monocytes to lymphocytes; GRACE, Global Registry of Acute Coronary Events score; α-HBDH, α-Hydroxybutyrate dehydrogenase; BNP B-type natriuretic peptides; NWD Non-weekday admission; CKD, Chronic kidney disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, White blood cell; HB, Hemoglobin; RBC, Red blood cell; PLT, Platelet; ALT, alanine aminotransferase; AST Aspartate transaminase; GGT, glutamyl transferase, CK, creatine kinase; CKMB, creatine kinase isoenzymes; LDH, lactate dehydrogenase; CTnT, Cardiac troponin; ORBI, The Brittany Regional Infarction Observatory.

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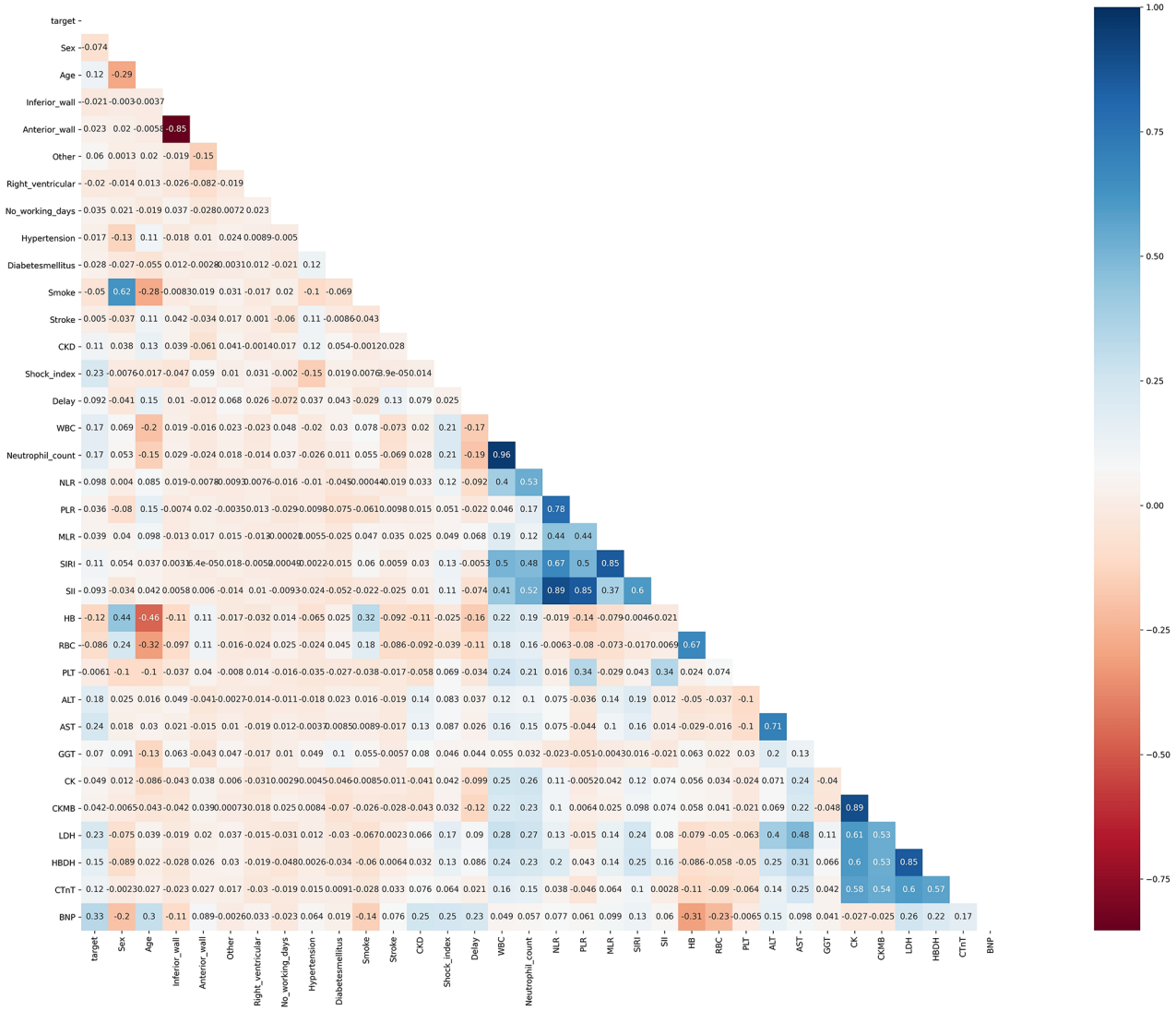

Figure S1 Variable correlation heatmap.

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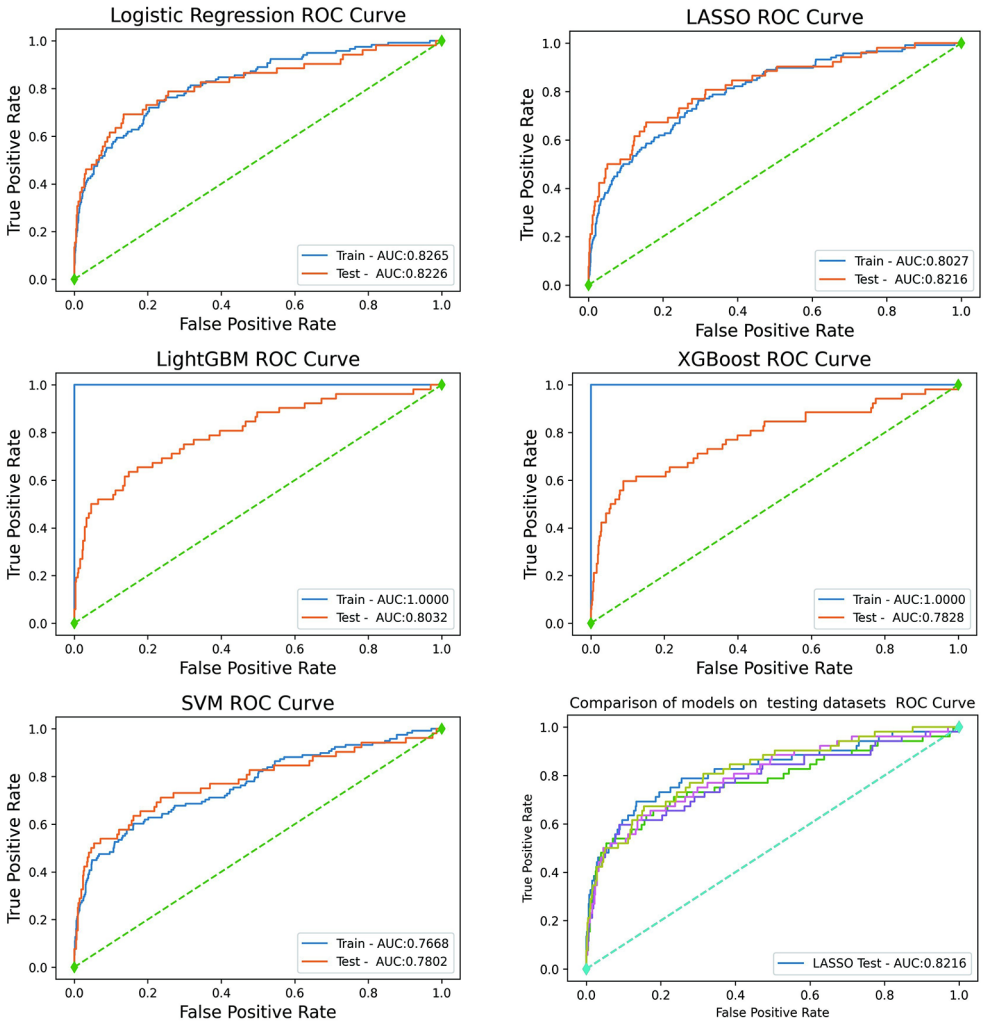

Figure S2 Receiver operating characteristic (ROC) curves of 5 machine learning model performance with the training dataset and the test dataset.

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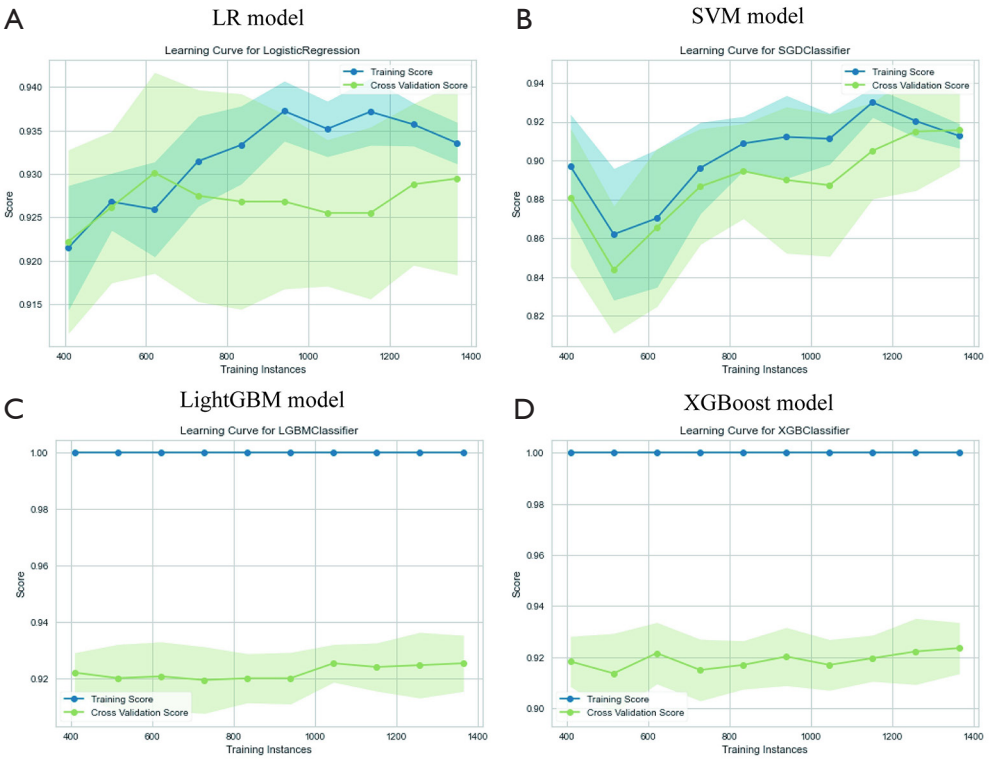

Figure S3 Learning curve for the different models.

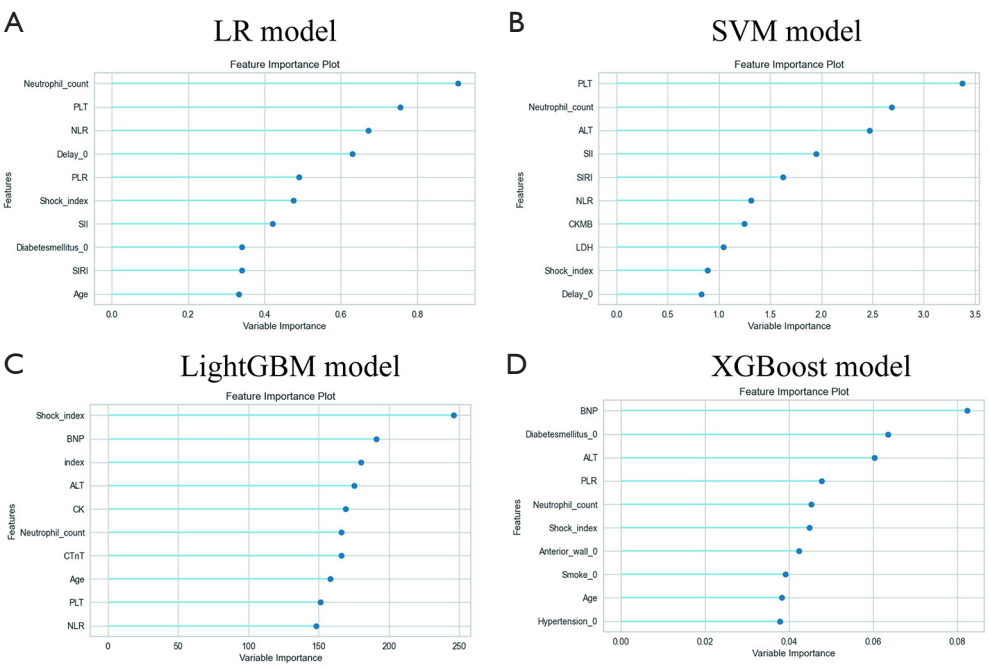

Figure S4 Variable importance size in the different models.

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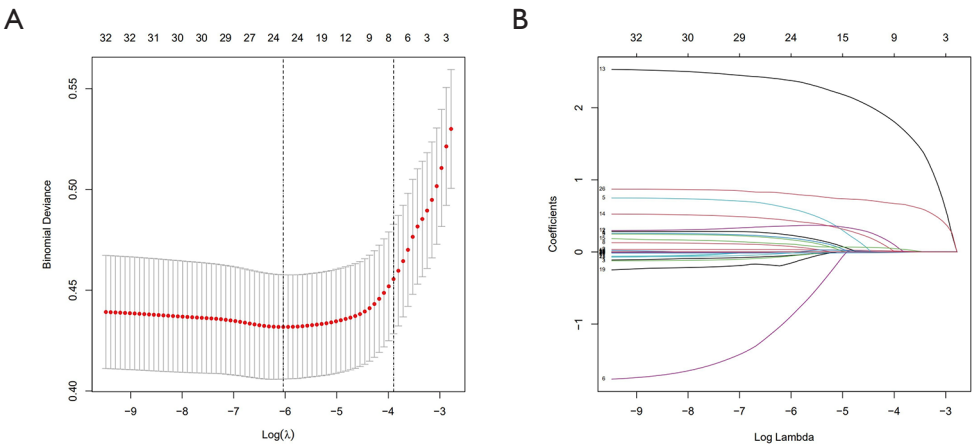

Figure S5 Selection of demographic and clinical features using the least absolute shrinkage and selection operator (LASSO) binary logistic regression model.

Table S2 Prediction factors for CS in STEMI patients

Intercept and variable	β	Prediction model	
		Odds ratio (95% CI)	P-value
(Intercept)	-6.4271	0.0016 (0.0002-0.0115)	P<0.001
Age	0.0345	1.0351 (1.0188-1.0521)	P<0.001
CKD			
No	Reference		
Yes	0.5254	1.6913 (1.0504-2.6568)	0.02606
Delay			
No	Reference		
Yes	0.5191	1.6805 (1.1504-2.4402)	0.00672
Shock index	2.4828	11.9741 (6.0138-23.9791)	P<0.001
WBC	0.1137	1.1203 (1.0769-1.1653)	P<0.001
HB	-0.0166	0.9835 (0.9745-0.9926)	P<0.001
AST			
<500	Reference		
500–1000	0.9568	2.6032 (1.1143-5.8094)	0.02243
>1000	1.5725	4.8185 (1.4578-16.3762)	0.01005
LDH	0.0007	1.0006 (1.0002-1.0011)	0.00463

parameter combinations are exhausted by grid search. Performance evaluation indices such as accuracy, AUC, recall, precision and the Gini coefficient were adopted to assess the average predictive performance of the model. The optimal model was used to develop the late-CS risk nomogram. Shock index ratio of HR to SBP; WBC, white blood cell; HB, hemoglobin; CKD, chronic kidney disease; AST, aspartate transaminase; LDH, lactate dehydrogenase.

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