

# Development and Validation of a 90-day Mortality Prediction Nomogram for AMI Patients: A Retrospective Cohort Study

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## Research Article

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# Abstract

**Background:** The purpose of this study was to identify the factors influencing the 90-day mortality of acute myocardial infarction(AMI) patients, and to establish a prognostic model for these patients based on the MIMIC-III database.

**Methods:** Retrospective study methods were used to collect AMI patient data that met the inclusion criteria from the MIMIC-III database. Variable importance selection was determined using the random forest algorithm. Multiple logistic regression was used to determine AMI-related risk factors, with the results represented as a nomogram.

**Results:** The baseline scores for the training and validation groups were very flat, and indicators for developing risk-model nomograms were obtained after random forest and multiple logistic regression. The AUC of the risk model was the highest (0.826 and 0.818 in the training and validation groups, respectively) . The Hosmer-Lemeshow goodness-of-fit test and standard curve both produced very consistent results. Both the NRI and IDI values indicated that the risk model had significant predictive power, and DCA results indicated that the risk model had good net benefits for clinical application.

**Conclusions:** The results of this study indicated that age, troponinT, VT, VFI, MI\_his, APS-III, bypass, and PCI were risk factors for 90-day mortality in AMI patients. Interactive nomograms could provide intuitive and concise personalized 90-day mortality predictions for AMI patients.

## Introduction

Acute myocardial infarction (AMI) is a serious type of coronary heart disease that is a serious threat to human health and survival. Reports suggest that more than 8 million lives are threatened by AMI each year[1, 2]. These reports highlight the significance of studying the prognosis of AMI patients, which can promote timely medical interventions and improve the prognosis of these patients, reducing the economic burden and other negative impacts of AMI on patient's families and wider society.

The current prognostic scoring system for AMI patients is not comprehensive. For example, the current scoring system of coronary heart disease is the Global Registry of Acute Coronary Events (GRACE)[3, 4], which analyzes the unstable angina pectoris in acute coronary syndrome and acute non-ST segment elevations to evaluate risk of myocardial infarction. The GRACE Score cannot clearly predict all types of AMI, since prognosis prediction of AMI patients cannot be applied completely. Other medical scores, such as the Acute Physiology Score (APS-III)[5] and the Sequential Organ Failure Assessment (SOFA) score[6, 7], have not been adapted for AMI patients.

The present study was based on a large sample from the Medical Information Mart for Intensive Care III (MIMIC-III) database[8, 9], a large critical medical database, which was used to develop a new predictive nomogram to independently predict the 90-day mortality, and provide treatment guidance and prognosis improvement for AMI patients.

# Materials And Methods

## Data source

Our data were extracted from the free open-access MIMIC-III database (version 1.4) , which contains more than 40,000 ICU patients at the Beth Israel Deaconess Medical Centre in the US between June 2001 and October 2012.

## Study population and data extraction

Data were collected from patients who were first admitted to the ICU (if there were multiple admissions for the same patient) and diagnosed with AMI according to the ICD-9. Those younger than 18 years or for whom more than 5% of the required data were missing were excluded from this study.

The official MIMIC-III tutorial was used to build the database with PostgreSQL (version 13.0, PostgreSQL Global Development Group) and structured query language(SQL) was used to extract data. The extracted variables were age, sex, meanHR(mean heart rate) , SysBP(systolic blood pressure) , labevents parameters[e.g., creatine kinase(CK) , creatine kinase isoenzymes(CK\_MB), lactate dehydrogenase (LDH), troponinT, aspartate transaminase(AST), creatinine, international normalized ratio(INR), platelets, prothrombin time(PT), activated partial thromboplastin time (APTT) or anion gap(AG)] , complications (Hypertension, Obesity, congestive heart failure) , atrial fibrillation(AFI) , atrial flutter(AFL) , ventricular fibrillation(VFI) , ventricular tachycardia(VT) , atrioventricular block(AVB) , previous history of myocardial infarction(MI\_his) , intervention-associated information[e.g., percutaneous coronary intervention(PCI) , heart bypass surgery(bypass) , or intra-aortic balloon pump(IABP)] , aspirin, clopidogrel, atorvastatin, or streptokinase use or not(e.g., drug use) , and scoring system used[e.g., Sequential Organ Failure Assessment (SOFA) , Acute Physiology Score III(APS-III) , Similar Global Registry of Acute Coronary Events Score(similar GRACE Score)] .

## Statistical analyses

Univariate analyses were applied to all variables in our study. The Shapiro-Wilk test was used to assess the distributions of variable. Continuous variables that did not conform to a normal distribution were represented by median values and interquartile ranges, and Kruskal-Wallis rank-sum or Mann-Whitney U tests were used to compare them. All classified variables were expressed as numerals or percentages and compared using chi-square or Fisher's exact tests.

Random forests were used to select or exclude variables for the model. Multivariate logistic regression analysis was used to develop predictive models. The aim of the nomogram was to predict the probability of 90-day mortality in AMI patients. To develop and verify the model, AMI patients were randomly divided into training and validation groups, at a ratio of 7:3.

The discriminability of the nomogram was evaluated using the area under the receiver operating characteristic curve (AUC) , which was also used to identify which model was better at predicting AMI. The Hosmer-Lemeshow goodness-of-fit test ( $P>0.05$ ) and calibration plots were used to calibrate the nomogram. Integrated discrimination improvement(IDI) and net reclassification improvement(NRI) values were calculated to estimate model differentiation. Decision curve analysis(DCA) was used to predict the clinical effectiveness and net benefits of the model.

During logistic regression and model development, missing values were identified using multiple interpolation. R software (version 4.0.3) was used for all statistical analyses. P values less than 0.05 (in two-sided tests) were considered to be significant.

## Results

### Characteristics of AMI patients

After screening of inclusion and exclusion criteria, the final sample for the study was 4610 patients, of which 894 had died within 90 days (Table 1) . The only index that differed significantly between the two groups was AG. Among the 1383 patients in the modeling group, 76 (5.5%) had a previous history of myocardial infarction and 488 (35.3%) had undergone PCI.

Table1

Charateristics of patients with AMI

Variables(N=4610)	training group(N=1383)	validation group(N=3227)	P value
<b>age (years)</b>	71.00 [60.00, 79.00]	70.00 [60.00, 79.00]	0.329
<b>AST(IU/L)</b>	43.00 [26.00, 98.00]	42.00 [25.00, 101.00]	0.731
<b>troponinT(ng/mL)</b>	1.10 [0.33, 3.45]	1.19 [0.35, 3.32]	0.740
<b>CK(IU/L)</b>	315.00 [86.00, 755.50]	260.00 [84.00, 770.00]	0.884
<b>CK-MB(ng/mL)</b>	9.00 [7.00, 64.50]	9.00 [7.00, 65.00]	0.377
<b>INR</b>	1.20 [1.10, 1.40]	1.20 [1.10, 1.40]	0.669
<b>platlet(k/uL)</b>	236.00 [183.00, 299.00]	234.00 [185.00, 295.00]	0.661
<b>PT(s)</b>	13.50 [12.70, 15.00]	13.50 [12.70, 14.90]	0.806
<b>APTT(s)</b>	32.30 [26.70, 54.10]	31.70 [26.40, 50.90]	0.110
<b>AG(mEq/L)</b>	16.00 [13.00, 18.00]	15.00 [13.00, 18.00]	0.026
<b>SOFA</b>	4.00 [2.00, 6.00]	4.00 [2.00, 6.00]	0.878
<b>APS-III</b>	40.00 [29.00, 54.00]	40.00 [29.00, 53.00]	0.646
<b>sex=Male/Female</b>	898/485 (64.9/35.1)	2081/1146 (64.5/35.5)	0.788
<b>complications</b>			
Hypertension = 0/1	754/629 (54.5/45.5)	1701/1526 (52.7/47.3)	0.273
Obesity = 0/1	1329/54 (96.1/3.9)	3069/158 (95.1/4.9)	0.146
congestive heart failure = 0/1	742/641 (53.7/46.3)	1649/1578 (51.1/48.9)	0.115
<b>AFI = 0/1</b>	986/397 (71.3/28.7)	2291/936 (71.0/29.0)	0.859
<b>AFL = 0/1</b>	1359/24 (98.3/1.7)	3147/80 (97.5/2.5)	0.130
<b>VFI = 0/1</b>	1323/60 (95.7/4.3)	3079/148 (95.4/4.6)	0.757
<b>VT = 0/1</b>	1253/130 (90.6/9.4)	2939/288 (91.1/8.9)	0.615
<b>AVB = 0/1</b>	1332/51 (96.3/3.7)	3112/115 (96.4/3.6)	0.863
<b>MI_his = 0/1</b>	1307/76 (94.5/5.5)	3059/168 (94.8/5.2)	0.720
<b>IABP = 0/1</b>	1348/35 (97.5/2.5)	3129/98 (97.0/3.0)	0.388
<b>drug use = 0/1</b>	682/701 (49.3/50.7)	1582/1645 (49.0/51.0)	0.872
<b>PCI = 0/1</b>	895/488 (64.7/35.3)	2025/1202 (62.8/37.2)	0.217
<b>bypass = 0/1</b>	1055/328 (76.3/23.7)	2435/792 (75.5/24.5)	0.574
<b>LDH(IU/L)</b>			0.096

<109	8 (0.6)	6 (0.2)	
109-245	455 (32.9)	1013 (31.4)	
245-1000	826 (59.7)	2014 (62.4)	
1000-5000	86 (6.2)	173 (5.4)	
>5000	8 (0.6)	21 (0.7)	
<b>Creatinine(mg/dL)</b>			>0.999
0.00-0.39	100 (7.2)	211 (6.5)	
0.40-0.79	162 (11.7)	378 (11.7)	
0.80-1.19	124 (9.0)	250 (7.7)	
1.20-1.59	259 (18.7)	587 (18.2)	
1.60-1.99	531 (38.4)	1338 (41.5)	
2.00-3.99	203 (14.7)	455 (14.1)	
≥4.00	4 (0.3)	8 (0.2)	
<b>meanHR(min<sup>-1</sup>)</b>			0.096
<50	5 (0.4)	10 (0.3)	
50-69	245 (17.7)	601 (18.6)	
70-89	699 (50.5)	1676 (51.9)	
90-109	331 (23.9)	767 (23.8)	
110-140	103 (7.4)	173 (5.4)	
<b>SysBP(mmHg)</b>			>0.999
<80	6 (0.4)	22 (0.7)	
80-99	183 (13.2)	375 (11.6)	
100-119	725 (52.4)	1691 (52.4)	
120-139	376 (27.2)	899 (27.9)	
140-159	79 (5.7)	211 (6.5)	
160-190	14 (1.0)	29 (0.9)	
<b>status = 0/1</b>	1099/284 (79.5/20.5)	2617/610 (81.1/18.9)	0.208

Nonnormal continuous variables were presented as median[IQR]. Categorical variables were presented as number(precentage ). Abbreviations: AST, aspartate transaminase; CK, creatine kinase; CK-MB, creatine kinase isoenzymes; INR, international normalized ratio; PT, prothrombin time; APTT, activated partial thromboplastin time; AG, anion gap; SOFA, sequential organ failure assessment;

APSIII, acute physiology score III; AFI, atrial fibrillation; AFL, atrial flutter; VFI, ventricular fibrillation; VT, ventricular tachycardia; AVB, atrioventricular block; MI\_his, previous history of myocardial infarction; IABP, intra-aortic balloon pump; drug use, aspirin, clopidogrel, atorvastatin, or streptokinase use or not; PCI, percutaneous coronary intervention; bypass, heart bypass surgery; LDH, lactate dehydrogenase; meanHR, mean heart rate; SysBP, systolic blood pressure.

## Variable selection and nomogram development

Figure 1 shows the process and results of the random forest feature selection, which identified that the following 19 risk factors affected the prognosis of AMI patients: APS-III, bypass, age, PCI, AG, PT, INR, LDH, AST, troponinT, CK, platelets, congestive heart failure, APTT, MI\_his, CK\_MB, AFI, VT, and VFI. Multivariate logistic regression analysis was conducted on these risk factors, and this results are listed in Table 2. We developed our new risk model by identifying eight significant risk factors using multivariate logistic regression analysis. An interactive nomogram was developed based on this model for predicting the 90-day mortality of AMI patients (Figure 2) .

Table 2

The results of multivariate logistic regression

	OR	2.5%	97.5%	P value
<b>age (years)</b>	1.04	1.03	1.06	<0.001
<b>APSIII</b>	1.03	1.03	1.04	<0.001
<b>bypass</b>	0.18	0.12	0.25	<0.001
<b>PCI</b>	0.30	0.23	0.39	<0.001
<b>AG(mEq/L)</b>	1.01	0.99	1.04	0.235
<b>PT(s)</b>	1.02	1.00	1.05	0.088
<b>INR</b>	0.93	0.80	1.07	0.373
<b>LDH(IU/L)</b>				
<109	Ref.			
109-245	0.47	0.07	4.54	0.461
245-1000	0.78	0.12	7.47	0.805
1000-5000	1.38	0.20	13.69	0.756
>5000	2.29	0.26	27.12	0.475
<b>troponinT(ng/mL)</b>	1.07	1.03	1.11	<0.001
<b>platlet(k/uL)</b>	1.00	1.00	1.00	0.895
<b>congestive heart failure</b>	1.10	0.88	1.36	0.399
<b>APTT(s)</b>	1.00	1.00	1.00	0.634
<b>MI_his</b>	1.58	1.04	2.37	0.028
<b>CK-MB(ng/mL)</b>	1.00	1.00	1.00	0.174
<b>AFI</b>	1.03	0.82	1.30	0.774
<b>VT</b>	1.59	1.13	2.24	0.008
<b>VFI</b>	1.70	1.05	2.71	0.027
Abbreviations: APSIII, acute physiology score III; bypass, heart bypass surgery; PCI, percutaneous coronary intervention; AG, anion gap; PT, prothrombin time; INR, international normalized ratio; LDH, lactate dehydrogenase; APTT, activated partial thromboplastin time; MI_his, previous history of myocardial infarction; CK-MB, creatine kinase isoenzymes; AFI, atrial fibrillation; VT, ventricular tachycardia; VFI, ventricular fibrillation.				

Based on the GRACE Score table, we extracted and processed all variables except ST segment reduction to produce a similar GRACE Score and this results are listed in Table 3.

Table 3

The results of similar GRACE Score by multivariate logistic regression

	OR	2.5%	97.5%	P value
<b>age(years)</b>				
<30	Ref.			
30-39	0.37	0.03	9.46	0.468
40-49	1.23	0.17	25.79	0.858
50-59	1.16	0.16	23.89	0.896
60-69	2.23	0.32	45.48	0.484
70-79	3.93	0.57	79.93	0.233
80-89	6.07	0.88	123.39	0.117
<b>meanHR(min<sup>-1</sup>)</b>				
<50	Ref.			
50-69	0.66	0.13	5.11	0.642
70-89	0.66	0.13	5.10	0.645
90-109	1.10	0.22	8.46	0.918
110-140	1.19	0.23	9.36	0.849
<b>SysBP(mmHg)</b>				
<80	Ref.			
80-99	0.22	0.06	0.67	0.013
100-119	0.08	0.02	0.24	<0.001
120-139	0.07	0.02	0.22	<0.001
140-159	0.10	0.03	0.32	<0.001
160-190	0.07	0.01	0.30	<0.001
<b>Creatinine(mg/dL)</b>				
0.00-0.39	Ref.			
0.40-0.79	0.68	0.46	1.00	0.052
0.80-1.19	0.59	0.38	0.92	0.019
1.20-1.59	0.38	0.26	0.56	<0.001
1.60-1.99	0.25	0.17	0.37	<0.001
2.00-3.99	0.30	0.19	0.47	<0.001

≥4.00	NA	NA	NA	0.959
<b>congestive heart failure</b>	1.22	0.99	1.50	0.060
<b>PCI</b>	0.38	0.29	0.49	<0.001
<b>MI_his</b>	1.70	1.14	2.50	0.008
<b>AST(IU/L)</b>	1.00	1.00	1.00	0.484
<b>LDH(IU/L)</b>	1.00	1.00	1.00	<0.001
<b>CK(IU/L)</b>	1.00	1.00	1.00	0.660
<b>CK-MB(ng/mL)</b>	1.00	1.00	1.00	0.032
<b>troponinT(ng/mL)</b>	1.08	1.05	1.12	<0.001
Abbreviations: meanHR, mean heart rate; SysBP, systolic blood pressure; PCI, percutaneous coronary intervention; MI_his, previous history of myocardial infarction; AST, aspartate transaminase; LDH, lactate dehydrogenase; CK, creatine kinase; CK-MB, creatine kinase isoenzymes.				

## Nomogram performance

AUCs were used to evaluate the differences between our risk model and similar GRACE Score, APS-III, and SOFA as shown in Figure 3. Our risk model had the highest AUC values (0.826 and 0.818 in the training and validation groups, respectively) .

Pair-wise AUC comparisons of the different models revealed all P values to be less than 0.001, indicating that there were statistically significant differences in the predictive ability between the different models.

## Nomogram calibration

The Hosmer-Lemeshow goodness-of-fit test revealed a high consistency between the prediction and observation probabilities of the training (chi-square=16.91, P=0.051) and validation groups (chi-square=11.72, P=0.230) . The calibration diagram also revealed good consistency between the predicted and observed results of the training and validation groups (Figure 4) .

The NRI values for the risk model in the training group were 0.29 (95% CI=0.13–0.37) , 0.70 (95% CI=0.59–0.82) , and 0.59 (95% CI=0.50–0.69) versus the similar GRACE Score, SOFA, and APS-III models, respectively; the corresponding values in the validation group were 0.32 (95% CI=0.05–0.41) , 0.51 (95% CI=0.34–0.73) , and 0.45 (95% CI= 0.31–0.61) .

Similarly, the IDI values for the risk model in the training group were 0.05 (95% CI=0.04–0.07, P<0.001) , 0.15 (95% CI=0.13–0.16, P<0.001) , and 0.10 (95% CI=0.09–0.11, P<0.001) versus the GRACE, SOFA, and APS-III models, respectively; the corresponding values in the validation group were 0.06 (95% CI=0.03–

0.09,  $P < 0.001$ ) , 0.12 (95% CI=0.09–0.15,  $P < 0.001$ ) , and 0.07 (95% CI=0.05–0.08,  $P < 0.001$ ) . These results indicate that the nomogram developed in this study exhibits improved prediction ability compared with the other models.

## Clinical application

The DCA plots indicated the high clinical net benefit of our risk model and demonstrated its clinical applicability and impact on clinical decision-making (Figure 5) .

## Discussion

AMI is a serious threat to human health and mortality worldwide, and has a high incidence rate with an ongoing tendency to increase[10-12]. All patients with AMI should receive short-term risk assessments as soon as possible after admission, which we aimed to provide with 90-day mortality risk prediction models that guide the treatment and prognosis of patients.

The most widely used scoring system is the GRACE Score[3, 5, 13], but there are many limitations to this system. First, it was established and validated between 1999 and 2003, and the characteristics of AMI patients and treatment regimens are constantly changing. Second, the GRACE Score also considers patients with ST-segment depression, but the type of AMI is far more than this. Similarly, other widely used clinical scoring systems such as APS-III and SOFA are not specific to AMI, and cannot be generalized to the risks and prognosis predictions of all AMI patients.

Based on the lack of an accurate scoring system for AMI patients, 4610 patients and 30 risk factors relating to AMI were selected using sample data from the MIMIC-III database[14-18]. Using a random forest[19] selection method identified 19 risk factors that had been identified in the multivariate logistic regression analysis[20]. We concluded that there were eight independent risk factors for AMI, and our new risk prediction model was developed using these eight factors, which were then drawn into a nomogram that provides accurate, simple, and intuitive predictions[21-23]. The new model indicated that there were six variables in the following order of increasing risk: age, APS-III, troponin T, MI\_his, VT, and VFI. This suggests that AMI patients with advanced age, poor acute physiological status, elevated troponin T, previous history of myocardial infarction, VT, and VFI had a higher risk of death at 90 days after diagnosis, and should be a priority for timely interventions and treatments. The application of early PCI and bypass surgery can somewhat reduce the risk of 90-day mortality in AMI patients, which is conducive to their treatment and for improving their prognosis[24, 25]. In addition, the factors used to develop our risk model are readily available and can be routinely collected from historical records, strengthening the clinical application value of our prediction model.

We conducted a comprehensive evaluation of our developed prognostic model. We extracted most of the risk factors in the GRACE Score, constructed our own GRACE Score, and extracted additional APS-III and SOFA scores to compare the four models to better assess the predictive power of the new model. This

analysis revealed that many variables with similar GRACE Scores were not statistically significant after the multiple logistic regression analysis, such as age and meanHR after GRACE scale classification, AST, and CK, also indicating that the GRACE Score is not applicable to AMI patients.

The AUC values of the new model before and after internalization verification were 0.826 and 0.818, respectively, which are far higher than the AUC values of the other three comparison models. The P values from AUC pairwise comparisons were all less than 0.001, indicating that the predictive efficacy varied between the different models, and that the new model had improved ability in distinguishing the 90-day mortality of AMI patients. The Hosmer-Lemeshow goodness-of-fit test and calibration plots further indicated that the model was consistent with the data.

We also used NRI, IDI, and DCA to assess whether the newly developed prognostic model performed well and its clinical usability[26]. Our results indicated that the new model was better than the other three models for both groups. DCA indicated that the new model also had greater clinical net benefits than the other three models, and can be better applied to clinical decision-making.

As expected, this study had some limitations. First, it had a retrospective design, and so prospective confirmatory studies are required. Second, only internal validation was used in this study, with external validation from other institutions providing further validation of our nomogram. Third, multiple logistic regression was used in this study, and it may be necessary to add time variables to further verify the accuracy of the results.

## **Conclusions**

Through random forests and multivariate logistic regression analysis on our large data sample from the MIMIC-III database, we identified eight independent risk factors for 90-day mortality in AMI patients. We developed a nomogram model based on this, and used AUC, Hosmer-Lemeshow goodness-of-fit test, calibration plots, NRI, IDI, and DCA to evaluate the prediction effectiveness of the new model. The new model could be useful in improving the prognosis of AMI patients.

## **Declarations**

## **Contributors**

Concept: J.L., Z.D., R.Y.. Design: J.L., R.Y.. Data collection or processing: R.Y., W.M.. Analysis or interpretation: R.Y., W.M., L.Z., T.H. and D.H.. Literature search: J.L., Z.D., R.Y. and S.Z.. Writing: R.Y. and all authors controls.

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## Availability of data and material

The MIMIC III database (version 1.4) is publically available from <https://mimic.physionet.org/>. Any researcher who adheres to the data use requirements is permitted access to the database.

## Competing interests

None declared.

## Patient consent for publication

Not required.

## Ethics approval and consent to participate

The MIMIC-III database has received ethical approval from the Institutional Review Boards of both Beth Israel Deaconess Medical Center (Boston, MA, USA) and the Massachusetts Institute of Technology (Cambridge, MA, USA). All data are de-identified in this database to remove patients' information, and the requirement for individual patient consent is not indispensable.

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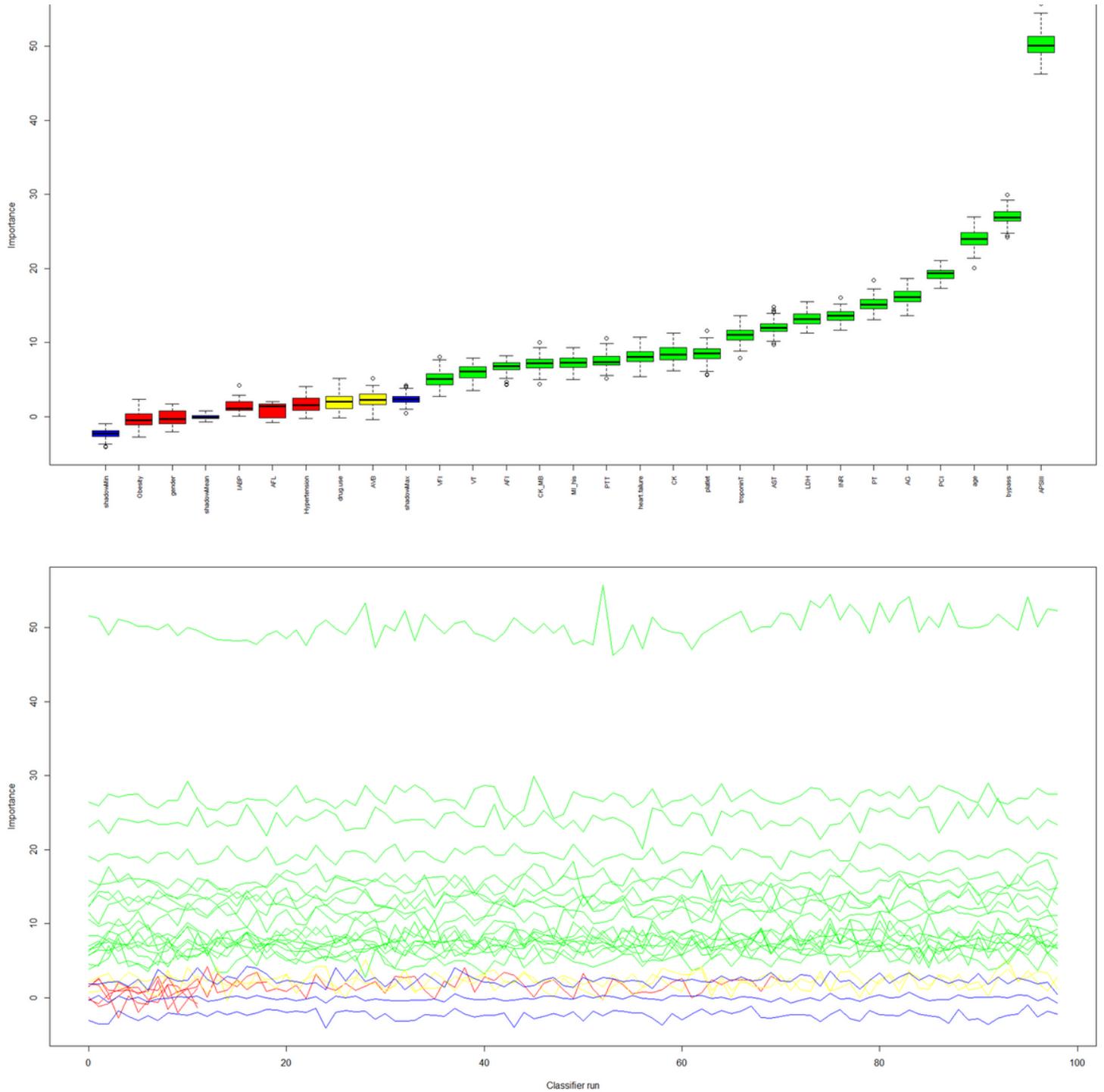
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# Figures



**Figure 1**

Feature selection and ranking by Random Forest. The plot above shows boxplot of all the attributes plus minimum, average and maximum shadow score. Variables having boxplot in green are important variables confirmed by Random Forest. if boxplots are in red, it indicates that they were rejected. Yellow

color of boxplot indicates they are tentative; the plot above shows history of decisions of rejecting or accepting features by Random Forest in 100 Boruta function runs.

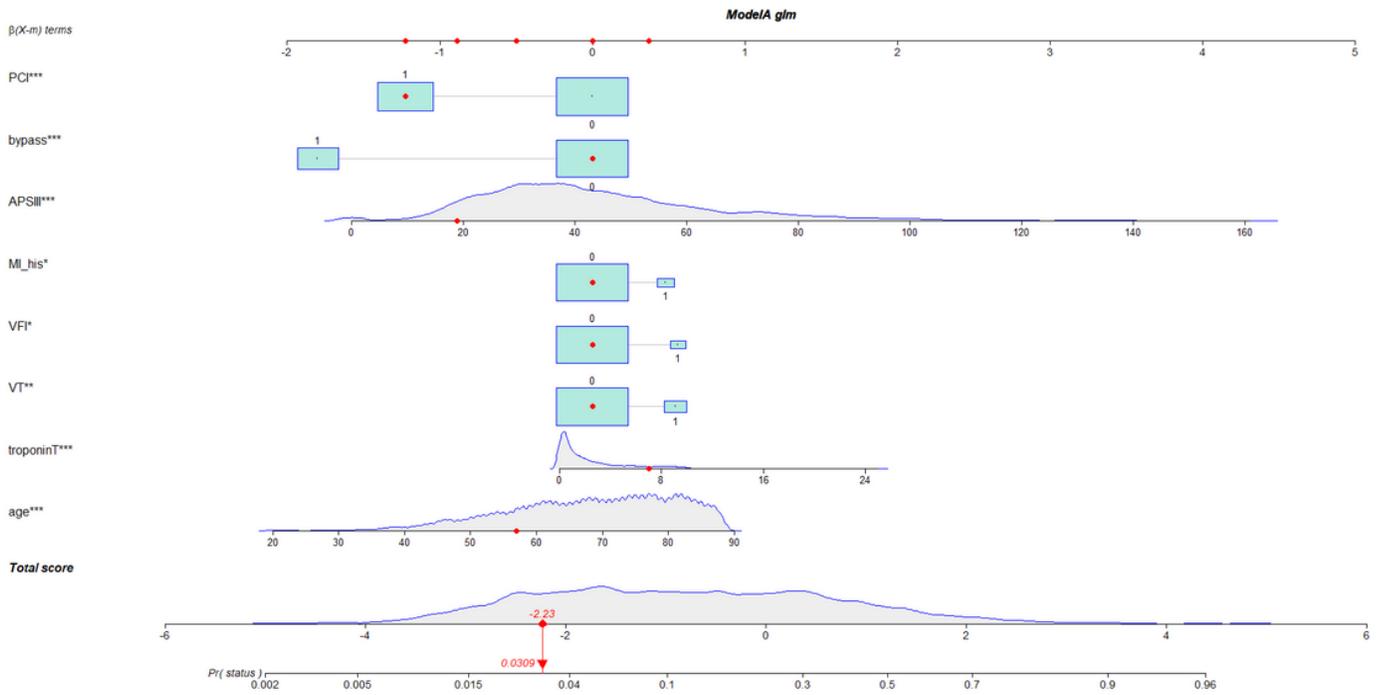
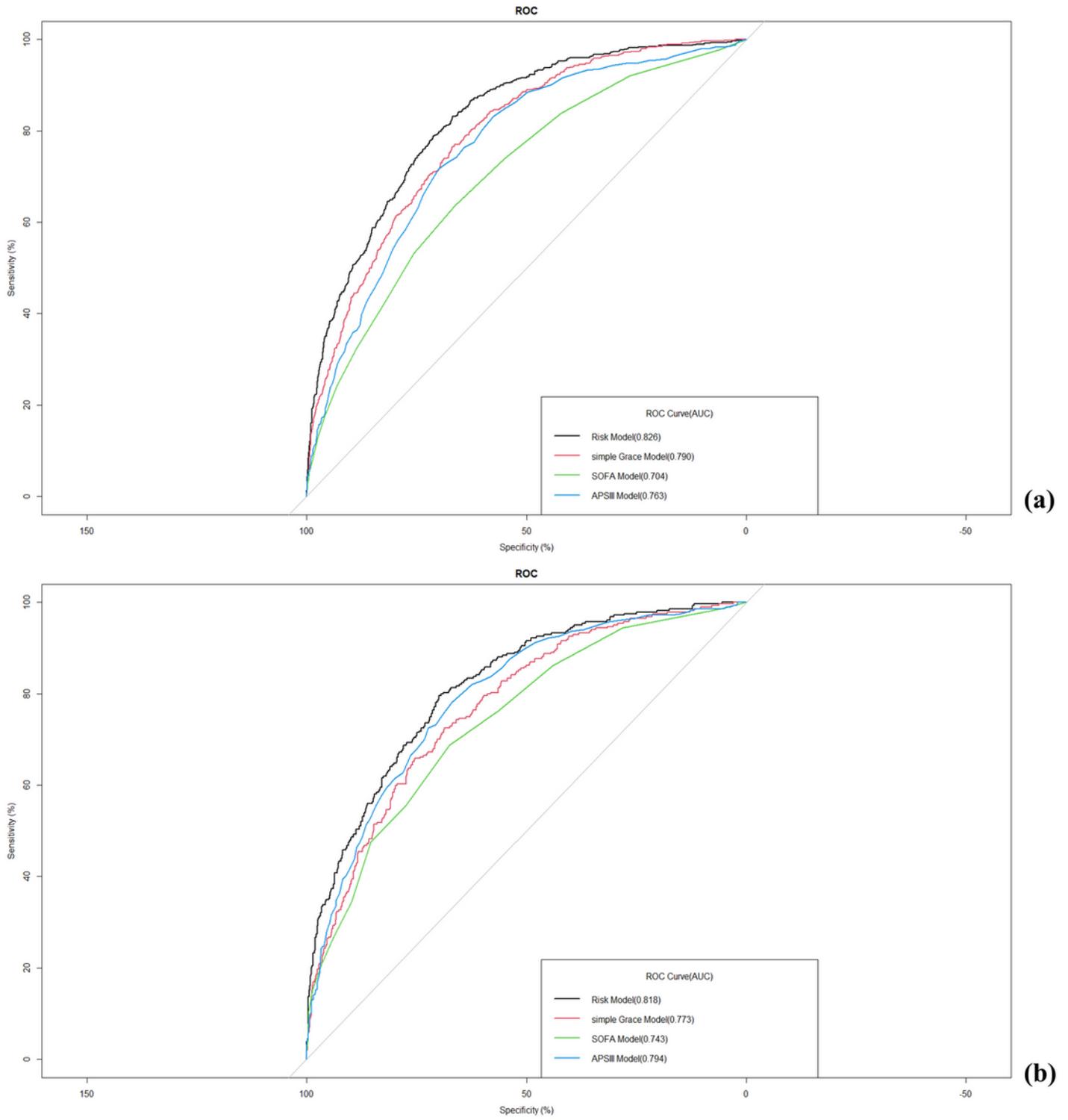


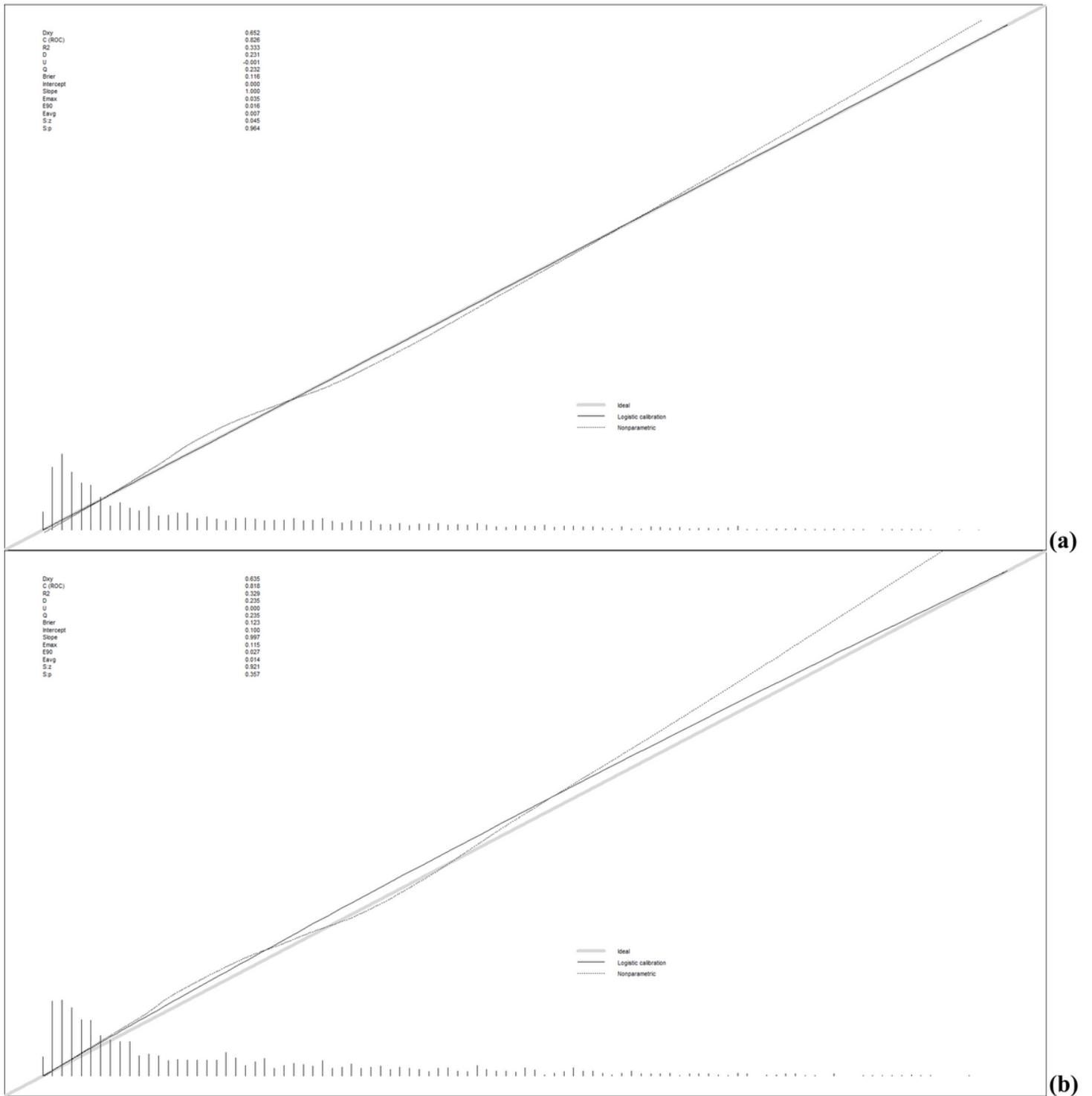
Figure 2

Predictive nomogram for the 90-day mortality of patients with AMI.



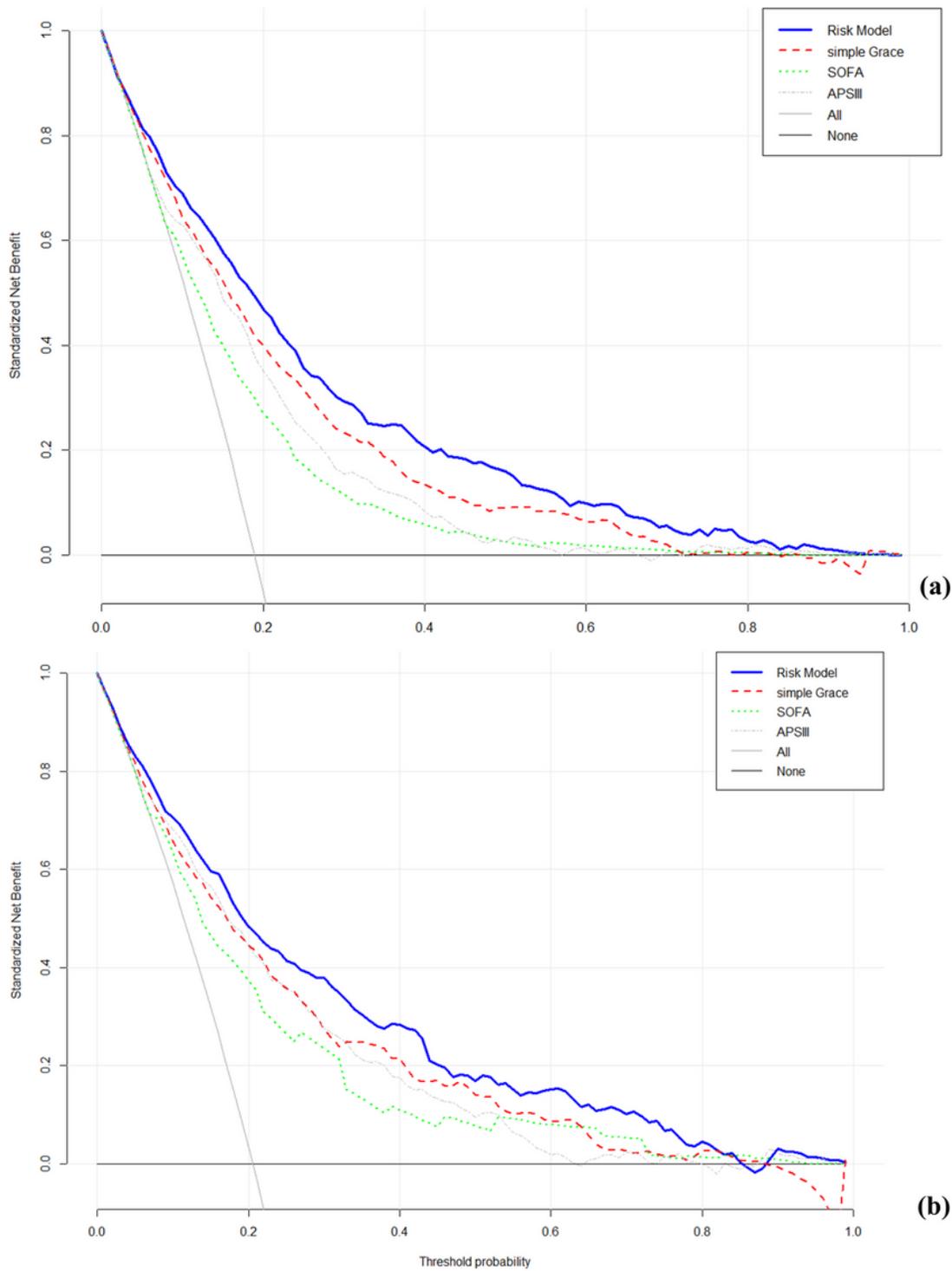
**Figure 3**

ROC curve (a) for the training group; (b) for the validation group. Abbreviations:AUC: area under the ROC curve; ROC: receiver operating characteristic.



**Figure 4**

Calibration plot (a) for the training group; (b) for the validation group.



**Figure 5**

Decision curve analysis of the training group (a) and validation group (b).