

Machine Learning-Based Mortality Prediction of 90-Day Discharge in Acute Coronary Syndrome Patients

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Abstract

Background

This study aims to develop and validate a novel mortality prediction model to forecast the 90-day mortality risk for patients with ACS (Acute Coronary Syndrome) after discharge.

Methods

We selected 1359 patients from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database as our study cohort and collected 32 clinical indicators within the first 24 hours of their admission. By randomly assigning these patients to a training group and a validation group (with a ratio of 0.65:0.35), we used Least Absolute Shrinkage and Selection Operator (LASSO) regression and bidirectional stepwise logistic regression to identify 7 key variables. Based on these variables, we constructed a mortality prediction model. To evaluate the model's accuracy and reliability, we plotted the Receiver Operating Characteristic (ROC) curve, calculated the Area Under the Curve (AUC), sensitivity, and specificity, and performed calibration analysis, including plotting calibration curves, calculating Brier scores, and conducting Hosmer-Lemeshow goodness-of-fit tests. Additionally, through Decision Curve Analysis (DCA) and comparison with current clinical scoring systems, we further assessed the clinical utility of our model.

Results

Age, SOFA (Sepsis-related Organ Failure Assessment), APS III (Acute Physiology Score III), AG(Anion Gap), RR(Respiratory rate), INR(International normalized ratio), and BUN(Bun urea nitrogen) were identified as independent predictors of 90-day mortality risk. The model demonstrated good diagnostic performance in both the training and validation groups, with AUC values of 0.842 and 0.855, respectively. The Hosmer-Lemeshow test results indicated a good fit for both datasets, with P-values of 0.1626 and 0.4008. The Brier scores were 0.107 for the training set and 0.103 for the validation set, indicating the model's good predictive performance. Compared to existing scoring systems (SOFA, APSIII), DCA showed that our model could provide a higher net benefit in clinical applications.

Conclusion

We identified seven clinical indicators including age, SOFA, APSIII, AG, RR, INR, and BUN as independent prognostic factors for predicting the 90-day all-cause mortality in patients with ACS after discharge. This model can assist ICU physicians to quickly make preliminary clinical decisions for ACS patients in clinical practice.

1 Introduction

ACS (Acute Coronary Syndrome) is a significant category of cardiovascular diseases, including unstable angina, non-ST segment elevation myocardial infarction, and ST-segment elevation myocardial infarction. Cardiovascular diseases are among the leading causes of death worldwide, with nearly half of these deaths attributed to ischemic heart disease¹⁻³. Despite significant advancements in the treatment of ACS, precise risk assessment and management for this condition remain crucial. Global cardiovascular disease experts and researchers are dedicated to developing and validating various scoring tools to aid physicians in making more scientific and accurate decisions in clinical practice. Currently, the Global Registry of Acute Coronary Events (GRACE) score is one of the most widely applied tools used to estimate the risk of death for patients during hospitalization and the subsequent six months⁴⁻⁶. In addition, in China, the CPACS scoring system has been developed to predict the risk of in-hospital mortality for ACS patients⁷. Although there is no clear research indicating that risk assessment scores or clinical prediction rules are superior to the judgment of clinical physicians, determining the level of risk in the initial assessment is crucial for guiding patient management⁸.

Although traditional methods have played a role in risk assessment, they have certain limitations, particularly when it comes to handling large-scale data and identifying complex patterns. In recent years, with the rapid development of AI (Artificial Intelligence) technologies, particularly ML (Machine Learning) and DL (Deep Learning), they have shown tremendous potential in medical data analysis, disease pattern recognition, and patient prognosis prediction^{9,10}. Machine learning models demonstrate greater flexibility and personalization when handling medical data. They can seamlessly integrate newly discovered important features and adapt to incomplete datasets. In comparison to traditional scoring systems, these models emphasize personalized medicine more, as during the training process, they tend to prioritize patient data that is similar to the information being evaluated¹¹. These advanced technologies can train algorithms by analyzing large-scale historical datasets, thereby assisting doctors in more accurately identifying high-risk patients and making correct clinical decisions. For instance, a three-year follow-up study covering over two thousand patients with ACS developed a mortality risk prediction model tailored for Chinese patients¹². In a parallel study by Sherazi¹³ and colleagues, researchers developed a model that predicts the risk of mortality one year after hospital discharge for patients with ACS. This predictive model utilizes data from the Korean Acute Myocardial Infarction Registry (KAMIR). Utilizing the National Cardiovascular Disease Database (NCVD) of Malaysia, models that combine DL and ML technologies have also been employed to stratify the in-hospital mortality risk of Asian ACS patients¹⁴. This further confirms the significant value of AI in enhancing the management efficiency of cardiovascular diseases.

Although previous research has thoroughly explored the in-hospital all-cause mortality rates of ACS patients, studies on their early post-discharge mortality are relatively scarce. The novelty of our research lies in focusing on the assessment of the risk of death within 90 days after discharge for ACS patients. Previous studies have shown that ischemia and renal insufficiency are significant factors contributing to

the increased risk of mortality within 60 to 90 days after discharge for patients with heart failure¹⁵. Bjurman C¹⁶ and other researchers have confirmed the importance of risk assessment for patients in the emergency department suspected of having ACS with high baseline levels of high-sensitivity cardiac troponin T (hs-cTnT). They discovered that patients who had hs-cTnT levels greater than 14 ng/L at discharge had a significantly increased risk of death in the subsequent 90 days. These studies show that the period from patient discharge to 90 days is extremely critical. Not only might patients experience complications that did not occur during their hospital stay, but it is also a crucial period for their recovery. With this purpose in mind, we have developed a machine learning-based model aimed at improving the accuracy of predicting mortality within 90 days after discharge for ACS patients. We expect this machine learning-based model to provide more accurate support for clinical decisions, thereby improving patient management and prognosis.

2 Materials and Methods

2.1 Research subjects and outcomes

This study is a retrospective observational study based on the MIMIC-IV database. The MIMIC-IV database (Medical Information Mart for Intensive Care-IV) is freely accessible, the database encompasses clinical data of over 50,000 ICU patients from Beth Israel Deaconess Medical Center in Boston, Massachusetts, from 2008 to 2019. The MIMIC-IV database, launched in June 2022 as version 2.0, introduces a suite of enhancements over the previous MIMIC-III. These upgrades include comprehensive updates to laboratory markers and medication records, as well as the incorporation of vital sign recordings and more detailed patient scoring systems like the SOFA and SAPS II scores¹⁷. By the Health Insurance Portability and Accountability Act (HIPAA), any identifiable patient information has been de-identified to protect privacy¹⁸. Therefore, this study did not require patient consent or ethics approval. The member of our team (Xinyi Zhang) has the authority to access the database and is responsible for data extraction (Authorization code: 10320923).

2.2 Inclusion Criteria

This study extracted patient data from the MIMIC-IV database that met the criteria for ACS as defined in the 10th revision of the International Classification of Diseases (ICD-10 codes I21 or I20). Exclusion criteria included patients under the age of 18 and those with ICU stays of less than 24 hours. Additionally, for patients with multiple ICU admissions, only the data from their first ICU admission was considered. The endpoint event of the study was all-cause mortality within 90 days post-discharge, with patients categorized into deceased and surviving groups for subsequent analysis.

2.3 Research method

2.3.1 Data extraction and processing

We used SQL language to extract data on ACS patients, selecting a total of 37 variables. These include SOFA, age, gender, Body Mass Index (BMI), underlying diseases, complete blood count, lactate, cardiac enzyme studies, biochemistry, and vital signs, among others. All vital signs and laboratory-related indicators are the first values obtained after patient admission. Due to a missing rate of greater than 30% for troponins, CKMB, ProBNP, blood albumin, and oxygen saturation index, these were excluded. The flow chart of the patient selection process is shown in Figure 1.

Figure 1 Flowchart of patients selection.

2.3.2 Data Grouping

We used a random stratified sampling method to divide the data of 1,359 patients into a training set and a validation set. Specifically, 65% of the patient data was randomly selected as the training set for model training and optimization. The remaining 35% of the patient data was used as the validation set to assess the accuracy and generalizability of the model. All data extracted from the database were compared between the survival and death groups as well as between the training and validation sets.

2.3.3 Construction and Validation of a Nomogram

We first conducted Lasso regression to select variables with non-zero coefficients, specifically using the Least Absolute Shrinkage and Selection Operator (LASSO) regression to screen for predictive factors of mortality within 90 days post-discharge. Following cross-validation, variables were retained when lambda was at its optimal value. These variables were then included in a bidirectional stepwise regression to choose a Logistic model with the lowest AIC value. The Hosmer-Lemeshow test assessed the model's goodness-of-fit. Statistically significant parameters were used to construct a Nomogram. For model validation and assessment, we plotted ROC curves on both the training and validation sets to compare the discriminative abilities of the SOFA, APS III, and the model based on AUC, exploring the model's mechanism by analyzing its sensitivity and specificity. Calibration curves evaluated the consistency between actual and predicted incidences. DCA determined the model's clinical net benefit, comparing it simultaneously with the net benefits of commonly used ICU scores SOFA and APS III. The model's predictive accuracy was comprehensively assessed using Brier scores.

2.4 Statistical analysis

All data processing and statistical analyses were conducted using R. For variables with less than 30% missing data, we imputed continuous variables using the mean and categorical variables using the mode. Comparisons of count data between groups were performed using the Chi-squared test or Fisher's exact test and presented as counts (percentages) [n (%)]. Quantitative data were described

using different statistical methods according to their distribution: means $\pm$ standard deviation ($\bar{x} \pm s$) for normally distributed data, and medians (interquartile ranges) [M (P25, P75)] for skewed data, with independent sample t-tests and Kruskal-Wallis H tests used for intergroup comparisons, respectively. In R, the "glmnet" package was used for LASSO regression analysis; the "caret" package was utilized for dataset splitting (to create training and test sets) and to perform cross-validation; logistic regression was carried out using the "glm" function; the "rms" package was used to construct nomograms, build calibration curves, and directly calculate Brier scores; the "pROC" package was responsible for drawing ROC curves and calculating AUC values; the "ResourceSelection" package was used for goodness-of-fit tests, and the "rmda" package for decision curve analysis. A p-value of less than 0.05 was considered statistically significant.

2.5 Ethics approval and consent to participate

The MIMIC-IV database received approval from the Institutional Review Boards of both Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology. All identifiable health information within the database has been anonymized, thus negating the necessity for individual patient consent. The study's procedures adhered strictly to the pertinent guidelines and regulations.

3 Outcome

3.1 Baseline analysis of clinical data of ACS patients in the training set and validation set

In our study, a total of 1,359 patients were included. Within the training dataset, the 90-day overall mortality rate for ACS patients was 17.31% (n=228), with most patients being white (63.24%), a relatively higher proportion being male (66.86%), and a significant number being overweight (with a BMI > 23.9) (88.35%). A higher prevalence of chronic congestive heart failure (57.69%) was noted, and a considerable proportion of patients developed varying degrees of AKI during their ICU stay (84.05%). The clinical characteristics of the entire study population are presented in Table 1.

Data are expressed as median (IQR), or n (%). Analysis of variance (or the Kruskal-Wallis test) and Chi-square (or Fisher's exact) tests were used for comparisons among groups. Statistical significance (P<0.05).

APS III, Acute Physiology Score III; CCI, Charlson Comorbidity Index; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; BMI, Body Mass Index; AG, Anion Gap; Scr, Serum Creatinine; BUN, Blood Urea Nitrogen; MBP, Mean Blood Pressure; AKI, Acute Kidney Injury; RR, Respiratory Rate; HR, Heart Rate. MT, malignant tumor; INR, International Normalized Ratio.

3.2 Feature selection and model development

We selected the 32 clinical features as independent variables for the study and utilized the LASSO regression method for the analysis. By employing 10-fold cross-validation, we ascertained the optimal value of λ (lambda. min) and identified 24 variables with non-zero coefficients. These variables include age, SOFA, CCI, APS III, SAPS II, Scr, BUN, AG, K⁺, Ca²⁺, PLT, Hb, T, RR, MBP, INR, PT, race, congestive heart failure, chronic lung disease, MT, cerebrovascular disease, BMI, and gender. Variables with non-zero coefficients from the LASSO regression results are shown in Table 2. Figures 2 and 3 respectively depict the variable selection path and the cross-validation plot.

This table shows the 24 variables with non-zero coefficients in the lasso regression.

APS III, Acute Physiology Score III; CCI, Charlson Comorbidity Index; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; AG, Anion Gap; Scr, Serum Creatinine; BUN, Blood Urea Nitrogen; MBP, Mean Blood Pressure; AKI, Acute Kidney Injury; RR, Respiratory Rate; HR, Heart Rate. MT, malignant tumor, INR, International Normalized Ratio.

The trend lines of coefficients illustrate the association between 32 characteristics and mortality within 90 days. Coefficient trend lines describe the relationship between 32 features and 90-day mortality.

Selection of the parameter (lambda) for deviance in LASSO regression is determined using both the minimum criterion and the 1 standard error rule.

Table 3 summarizes the results of the logistic regression analysis conducted on the training dataset. Further selection through bidirectional stepwise logistic regression, using the minimum AIC (Akaike Information Criterion) as the standard, included the following 10 variables: age ([OR: 1.053, 95% Confidence Interval [CI]: 1.03–1.077), $P < 0.001$; SOFA (OR: 1.091, 95% CI: 1.01–1.178), $P = 0.026$; CCI (OR: 1.081, 95% CI: 0.972–1.198), $P = 0.146$; APS III (OR: 1.023, 95% CI: 1.008–1.037), $P = 0.002$; Scr (OR: 0.768, 95% CI: 0.577–0.985), $P = 0.052$; BUN (OR: 1.02, 95% CI: 1.008–1.034), $P = 0.001$; AG (OR: 1.086, 95% CI: 1.026–1.149), $P = 0.004$; RR (OR: 1.064, 95% CI: 1.028–1.101), $P < 0.001$; INR (OR: 1.662, 95% CI: 1.205–2.316), $P = 0.002$. Race (Black/African American) (OR: 0.808, 95% CI: 0.112–7.867), $P = 0.841$; Race (white) (OR: 2.483, 95% CI: 0.495–19.739), $P = 0.319$; Race (other) (OR: 3.061, 95% CI: 0.591–24.842), $P = 0.227$. Among these predictors, race is a categorical variable, while the rest are continuous variables.

These variables were then included in a bidirectional stepwise regression to choose a Logistic model with the lowest AIC value.

APS III, Acute Physiology Score III; APS III, Acute Physiology Score III; CCI, Charlson Comorbidity Index; Scr, Serum Creatinine; BUN, Blood Urea Nitrogen; AG, Anion Gap.

We ultimately selected 7 significant variables with a P-value of less than 0.05 to construct the predictive model. These are: "Age", "SOFA", "APS III", "Urea Nitrogen", "AG", "RR", and "International Normalized Ratio". Based on this model, we constructed a nomogram to predict the 90-day mortality rate for patients with ACS, as shown in Figure 4. A line is drawn upward from the point axis to connect each predictor in the predictor line plot to a specific point. The "Total Points" axis is used to display the sum of the points

for each variable. The plotted “Total Points” axis is then directly connected to the probability axis via a vertical line to determine the probability of 90-day post-discharge outcomes for ACS patients.

As depicted in Figure 5, our predictive model scored an AUC (Area Under the Receiver Operating Characteristic Curve) of 0.842 on the training set (with a 95% confidence interval of 0.809-0.875) and an AUC of 0.855 on the validation set (with a 95% confidence interval of 0.815-0.894). Concurrently, we evaluated our model against traditional scoring systems such as APsIII and SOFA. The AUC values for these systems on the training set were 0.779 and 0.678 respectively (Figure 6), and on the validation set, they were 0.801 and 0.692 respectively (Figure 7). These results indicate that our model may outperform these traditional scoring systems in terms of predictive performance. Utilizing the Youden Index, we identified 0.16 as the optimal cut-off point in the training set, corresponding to a sensitivity of 80.4% and a specificity of 75.1%. For the validation set, the cut-off was set at 0.109, with a sensitivity of 92% and specificity of 67%, suggesting good generalizability of the model to both the training and validation sets. Regarding calibration, the curves showed a reasonable fit for both the training set (Figure 8) and the validation set (Figure 9), with Hosmer-Lemeshow test P-values of 0.1626 and 0.4008 respectively, indicating no statistical significance and good agreement between the predicted and observed values. Furthermore, Brier scores were 0.107 for the training set and 0.103 for the validation set, demonstrating the accuracy of the model. DCA curves have been plotted for both sets, where our model is represented by the red line. It demonstrates a higher net benefit across the full range of risk thresholds compared to established scoring systems such as SOFA and APS (Figure 10 and Figure 11).

4 Discussion

We developed a risk prediction model for 90-day mortality after discharge in ACS patients using nomograms. Nomograms are commonly used tools for evaluating prognosis in oncology and medical fields. Compared to traditional staging, nomograms allow for rapid calculations through a user-friendly digital interface. With their higher accuracy and more understandable prognostic outcomes, nomograms can be seamlessly integrated to assist in clinical decision-making¹⁹. Through LASSO regression and bidirectional stepwise logistic regression, we identified independent risk factors for mortality within 90 days after discharge in ACS patients. These are SOFA, APsIII, INR, BUN, AG, RR, and age. To our knowledge, this is the first study to construct a risk factor prediction model for all-cause mortality within 90 days of discharge for ACS patients using the MIMIC-IV database. In this study, we incorporated the SOFA and the APsII as independent risk factors. These are two of the most commonly utilized assessment scales in the ICU to evaluate the degree of organ dysfunction and the severity of the condition in ICU patients. The SOFA²⁰ was established following a consensus conference in 1994, with the purpose of creating a scoring system "to quantitatively and objectively describe the extent of organ function impairment/failure in a group of patients or in an individual patient over time as objectively as possible.". The SOFA, as a widely used scoring tool in the ICU, provides clinicians with critical information regarding the severity of cardiovascular patients' conditions and the potential for deterioration in clinical practice²¹. The research by Moreno et al. indicates that the initial SOFA upon ICU admission is an

effective tool for quantifying the degree of organ dysfunction or failure at the time of admission, with significant clinical application value²². The study by Yang et al.²³ found that SOFA is an important risk factor affecting the prognosis of elderly patients undergoing cardiac surgery. Our research further confirms the utility of the SOFA as an independent risk factor in predictive models. In this way, the model can more accurately predict the risk level of ACS patients at the time of ICU admission, thereby guiding clinicians to closely monitor high-risk patients. The inclusion of APS III significantly improved the model's predictive accuracy for the risk of death within 90 days after discharge for patients with ACS. This finding is consistent with the research of Markgraf R²⁴ et al., who indicated that, when using a 50% decision threshold, the APACHE III scoring system could classify patients' clinical outcomes with an overall accuracy of 85%. This underscores the practical value of APS III in quantifying changes in the acute physiological status of critically ill patients and in predicting short-term prognosis. For the performance evaluation of the predictive model, we employed ROC curve and DCA curve analyses. The ROC curve is derived by calculating the sensitivity and specificity of the model at each possible cutoff point, then plotting sensitivity against 1-specificity. This curve can be used to select the optimal cutoff value for model prediction outcomes, assess the diagnostic accuracy of the model, and compare the efficacy of different models²⁵. The Area Under the ROC Curve (AUC) reflects the overall level of model prediction accuracy. Our model demonstrated an AUC value higher than that of traditional scoring systems (SOFA and APS III), which signifies the superior discriminative ability of the model we developed. The DCA curve is a statistical method used to evaluate whether a model is useful in supporting clinical decisions and which model can lead to the best decisions²⁶. In our study, by comparing the net benefits under different threshold conditions of the DCA curve, the results showed that our model provided a net benefit that surpassed traditional scoring systems in terms of clinical decision support. This finding highlights the potential value of our model in practical clinical application.

In our study, we found that the risk of death within 90 days after discharge for patients with ACS correspondingly increased with age. This is consistent with the views of Avezum A²⁷ et al., who believe that the higher in-hospital mortality rate among elderly patients with ACS is related to their not receiving evidence-based treatments widely. This perspective is also supported by a large-scale study covering 25 countries in Europe and the Mediterranean basin, which further confirmed the significantly increased risk of death for elderly patients when experiencing heart failure, as well as the fact that patients over the age of 65 make up the vast majority in the proportion of deaths. This highlights the importance of improving the quality of treatment and care for elderly patients to enhance their survival rates²⁸. In our study, gender was not found to be an independent risk factor, which is contrary to the findings of Ogbu I²⁹ et al., who discovered a significant correlation between gender and in-hospital mortality in patients with ACS, with females having a higher risk of death than males. Another study indicates that the untimely diagnosis of female ACS patients results in delayed treatment, thus increasing both in-hospital and long-term mortality rates³⁰. We speculate that this discrepancy may be due to the fact that observing prognoses over a shorter time frame may not be sufficient to reveal the long-term impacts of gender. Future research that conducts a more detailed analysis of gender factors will help to clarify the role of

gender in clinical decision-making and provide more personalized treatment plans for male and female patients with ACS.

BUN is a significant risk factor for mortality within 90 days post-discharge for patients with ACS. BUN is a key prognostic indicator for patients with ACS, and its significance may exceed that of creatinine levels³¹. The elevation of BUN not only reflects the balance between the production and excretion of urea but is also closely related to the reabsorption of urea regulated by antidiuretic hormone and angiotensin-II, which is particularly critical in water regulation³². Kirtane AJ et al.³³ similarly found that in patients with unstable coronary artery syndrome who have normal or mildly decreased GFR, the increase in BUN is closely associated with an increase in mortality rate. This relationship may be due to reduced circulatory blood volume and decreased renal blood flow caused by heart failure, subsequently affecting renal function and resulting in elevated BUN levels³⁴. These findings underscore the importance of monitoring and assessing BUN levels in managing ACS patients, especially in clinically evaluating patients' prognostic risks.

We found that the AG was also a significant risk factor in this study. The study indicates that lactate and ketone ions account for 62% of the increase in AG. In animal studies and patients with heart failure (HF) or ACS, significant increases in metabolism, enhanced sympathetic nervous system activity, accelerated glycolysis, and the association between elevated lactate levels and improved bioenergy supply have been observed³⁵. These studies suggest that the accumulation of organic acid ions may be a mechanism, implying that higher AG levels may lead to more severe coronary artery disease and heart failure³⁶. Research conducted domestically has also confirmed a positive correlation between AG levels and the occurrence of Major Adverse Cardiovascular Events (MACE) during a 1-year follow-up period in patients with ACS, indicating that AG has high clinical value in early prognosis prediction for ACS patients³⁷. Monitoring AG levels in ACS patients not only helps in understanding the patients' metabolic status but also provides clinicians with a valuable tool to assess patients' cardiac function and the risk of coronary artery disease.

We also found that in patients with ACS, an increase in INR value is associated with an increased risk of patient mortality. In the study by Delgado G. E. et al.³⁸, the researchers found a positive correlation between increased INR and mortality rates among patients with coronary artery disease who did not receive oral anticoagulant therapy, as well as among patients without coronary artery disease, after excluding cases treated with coumarin-class drugs. Elevated INR is an independent predictor of all-cause mortality in patients with ADHF—Acute Decompensated Heart Failure—who are not receiving anticoagulant therapy, reflecting coagulation abnormalities and liver dysfunction, possibly through systemic inflammation, neurohormonal activation, and venous congestion³⁹. Therefore, we can consider that strengthening the protection of vital organ functions is crucial in the management of ACS patients. This means that close monitoring and support of cardiac pump function and liver function are necessary in order to alleviate complications and improve treatment outcomes.

Because it is simple and easy to observe, the RR is considered one of the indicators for identifying the severity of a patient's condition. Eick et al.⁴⁰ pointed out in their 2018 study that patients with a higher RR at night have a significantly increased mortality rate during their hospital stay and within the following two years. A study from China confirmed that the resting RR at admission combined with the GRACE score has important clinical application value for risk stratification in ACS patients, and can be used for early warning of the risk of short-term death⁴¹. Therefore, by closely monitoring the RR, a simple and low-cost method, high-risk ACS patients can be identified early, thereby providing them with more focused monitoring and treatment.

Despite this, our study still has certain limitations. On one hand, crucial laboratory indicators such as troponin I, proBNP, and the myocardial enzyme spectrum, as well as data on infection sites and medication use, were not included in our study. This may impact the integrity and accuracy of the model. On the other hand, although our study includes large-scale data from over a thousand patients, the retrospective design itself may introduce selection bias, limiting the generalizability of our conclusions. Lastly, future research should consider integrating external study results, such as validating the universality of the predictive model with multicenter data, and exploring the integration of these tools into mobile applications, wearable devices, and personal computer software, aiming to provide clinicians and patients with a more convenient and efficient decision support system.

5 Conclusion

In this study, we identified seven clinical indicators including age, SOFA, APSIII, AG, RR, INR, and BUN as independent prognostic factors for predicting the 90-day all-cause mortality in patients with ACS after discharge. Based on these indicators, we developed a new predictive model which has been validated to demonstrate good accuracy in assessing the risk of death. This model can assist ICU physicians to quickly make preliminary clinical decisions for ACS patients in clinical practice.

Declarations

Author contributions

Conception and design: X.Y. Zhang and M.R. Lin. Administrative support: J.D. Lin and F. Deng. Provision of study materials or patients: X.Y. Zhang, M.R. Lin, and X.Y. Guo. Collection and assembly of data: X.Y. Zhang and X.Y. Guo. Data analysis and interpretation: X.Y. Zhang and M.R. Lin. Manuscript writing: All authors. Final approval of manuscript: All authors.

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Data Availability

The data used in this study comes from the Medical Information Mart for Intensive Care IV (MIMIC-IV) Clinical Database¹⁸. To gain access to these datasets, one must submit a request to PhysioNet⁴². For details on how to request access, visit www.physionet.org. The collection of patient information and creation of the research resource was reviewed by the Institutional Review Board at the Beth Israel Deaconess Medical Center, who granted a waiver of informed consent and approved the data sharing initiative.

Competing interests

The authors affirm that no commercial or financial interests that might be perceived as a conflict of interest influenced the conduct of this research.

Author Contribution

Conception and design: X.Y. Zhang and M.R. Lin. Administrative support: J.D. Lin and F. Deng. Provision of study materials or patients: X.Y. Zhang, M.R. Lin, and X.Y. Guo. Collection and assembly of data: X.Y. Zhang and X.Y. Guo. Data analysis and interpretation: X.Y. Zhang and M.R. Lin. Manuscript writing: All authors. Final approval of manuscript: All authors.

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Tables

Tabel 1: The clinical characteristics of the whole study population.

Variables	Total (n = 1359)	Alive (n = 1131)	Died (n = 228)	P value for alive vs dead	Training set (n = 884)	Validation set (n = 475)	P value for train vs validate
Severity scores							
CCI, Mean $\pm$ SD	6.21 $\pm$ 2.65	5.87 $\pm$ 2.56	7.90 $\pm$ 2.45	<.001	6.29 $\pm$ 2.63	6.06 $\pm$ 2.70	0.118
Sofa, M (Q ₁ , Q ₃)	5.00 (3.00, 7.00)	5.00 (2.00, 7.00)	7.00 (5.00, 10.00)	<.001	5.00 (2.00, 7.00)	5.00 (3.00, 7.00)	0.762
APSOIII, M (Q ₁ , Q ₃)	39.00 (29.00, 51.50)	36.00 (28.00, 47.00)	54.00 (44.00, 66.25)	<.001	39.00 (29.75, 52.00)	38.00 (29.00, 50.00)	0.371
SAPS II: , M (Q ₁ , Q ₃)	37.00 (29.00, 45.00)	35.00 (28.50, 42.00)	44.50 (38.00, 54.00)	<.001	37.00 (30.00, 45.00)	36.00 (29.00, 43.50)	0.157
Laboratory results							
Lac, M (Q ₁ , Q ₃), mmol/L	1.70 (1.20, 1.92)	1.60 (1.20, 1.92)	1.92 (1.58, 3.00)	<.001	1.80 (1.20, 1.92)	1.70 (1.30, 1.92)	0.584
Scr, M (Q ₁ , Q ₃), mg/dL	0.90 (0.70, 1.10)	0.80 (0.70, 1.07)	1.00 (0.80, 1.42)	<.001	0.90 (0.70, 1.10)	0.82 (0.70, 1.10)	0.646
BUN, M (Q ₁ , Q ₃), mg/dL	20.00 (15.00, 34.00)	19.00 (14.00, 28.00)	34.00 (22.00, 51.50)	<.001	20.00 (15.00, 34.00)	20.00 (15.00, 34.00)	0.325
AG, M (Q ₁ , Q ₃)	15.00 (13.00, 18.00)	15.00 (13.00, 17.00)	18.00 (15.00, 21.00)	<.001	15.00 (13.00, 18.00)	15.00 (13.00, 18.00)	0.278
AST, M (Q ₁ , Q ₃), U/L	47.00 (25.00, 146.32)	42.00 (23.50, 146.16)	87.50 (39.75, 207.25)	<.001	47.00 (26.00, 146.32)	48.00 (24.50, 146.32)	0.534
K ⁺ , M (Q ₁ , Q ₃), mmol/L	4.20 (3.90, 4.60)	4.20 (3.90, 4.50)	4.40 (3.90, 4.90)	<.001	4.20 (3.90, 4.60)	4.20 (3.90, 4.60)	0.788
Na ⁺ , M (Q ₁ , Q ₃), mmol/L	139.00 (136.00, 141.00)	139.00 (137.00, 141.00)	137.00 (134.75, 140.00)	<.001	139.00 (136.00, 141.00)	139.00 (136.00, 141.00)	0.561
Ca ²⁺ , M (Q ₁ , Q ₃), mmol/L	8.70 (8.30, 9.20)	8.80 (8.30, 9.20)	8.50 (8.10, 9.00)	<.001	8.70 (8.30, 9.20)	8.70 (8.30, 9.10)	0.394

WBC, M (Q ₁ , Q ₃), 10 ⁹ /L	10.00 (7.60, 13.30)	9.70 (7.40, 12.85)	11.75 (8.70, 15.80)	<.001	10.20 (7.70, 13.43)	9.60 (7.50, 13.00)	0.156
Hb, Mean ± SDs,g/L	11.82 ± 2.30	12.02 ± 2.28	10.83 ± 2.12	<.001	11.87 ± 2.30	11.73 ± 2.30	0.297
Plt, M (Q ₁ , Q ₃), 10 ⁹ /L	203.00 (166.00, 254.00)	204.00 (166.00, 254.50)	198.50 (156.50, 252.50)	0.157	201.00 (165.00, 253.00)	205.00 (167.00, 256.00)	0.304
RDW, M (Q ₁ , Q ₃), %	13.70 (13.00, 14.80)	13.60 (12.90, 14.60)	14.60 (13.40, 15.90)	<.001	13.70 (13.00, 14.80)	13.70 (13.10, 14.90)	0.99
INR, M (Q ₁ , Q ₃)	1.20 (1.10, 1.30)	1.10 (1.10, 1.20)	1.30 (1.20, 1.52)	<.001	1.10 (1.10, 1.30)	1.20 (1.10, 1.30)	0.729
Pt, M (Q ₁ , Q ₃), s	12.50 (11.60, 13.80)	12.30 (11.50, 13.30)	13.70 (12.70, 16.85)	<.001	12.40 (11.60, 13.80)	12.50 (11.60, 13.80)	0.811
PTT, M (Q ₁ , Q ₃), s	41.90 (30.35, 68.90)	40.90 (30.20, 64.85)	44.35 (30.80, 92.28)	0.008	42.10 (30.48, 70.88)	41.20 (30.20, 66.15)	0.392
Vital signs							
T, M (Q ₁ , Q ₃), °C	36.56 (36.39, 36.89)	36.61 (36.39, 36.89)	36.56 (36.39, 36.89)	0.607	36.61 (36.39, 36.89)	36.56 (36.39, 36.89)	0.946
RR, M (Q ₁ , Q ₃), Bpm	18.00 (15.00, 22.00)	17.00 (15.00, 20.50)	21.00 (17.00, 24.00)	<.001	17.00 (15.00, 22.00)	18.00 (16.00, 22.00)	0.238
MBP M (Q ₁ , Q ₃), mmHg	81.00 (71.00, 92.00)	81.00 (71.00, 93.00)	79.00 (69.00, 88.00)	0.076	81.00 (71.00, 92.00)	80.00 (71.00, 92.00)	0.646
HR, M (Q ₁ , Q ₃), Bpm	81.00 (74.00, 92.00)	80.00 (73.00, 90.00)	87.00 (74.75, 100.25)	<.001	81.00 (74.00, 92.00)	81.00 (73.50, 90.00)	0.425
Comorbidities							
Congestive heart failure, n (%)				<.001			0.204
NO, (n, %)	592 (43.56)	533 (47.13)	59 (25.88)		374 (42.31)	218 (45.89)	
Yes, (n, %)	767 (56.44)	598 (52.87)	169 (74.12)		510 (57.69)	257 (54.11)	
Chroniclungdisease, n (%)				0.077			0.864

NO, (n, %)	1078 (79.32)	907 (80.19)	171 (75.00)		700 (79.19)	378 (79.58)
Yes, (n, %)	281 (20.68)	224 (19.81)	57 (25.00)		184 (20.81)	97 (20.42)
MT, n (%)				<.001		0.444
NO, (n, %)	1315 (96.76)	1104 (97.61)	211 (92.54)		853 (96.49)	462 (97.26)
Yes, (n, %)	44 (3.24)	27 (2.39)	17 (7.46)		31 (3.51)	13 (2.74)
Cerebrovascular disease, n (%)				0.008		0.622
NO, (n, %)	1187 (87.34)	1000 (88.42)	187 (82.02)		775 (87.67)	412 (86.74)
Yes, (n, %)	172 (12.66)	131 (11.58)	41 (17.98)		109 (12.33)	63 (13.26)
AKI, n (%)				<.001		0.81
0, (n, %)	211 (15.53)	198 (17.51)	13 (5.70)		141 (15.95)	70 (14.74)
1, (n, %)	260 (19.13)	237 (20.95)	23 (10.09)		173 (19.57)	87 (18.32)
2, (n, %)	574 (42.24)	502 (44.39)	72 (31.58)		366 (41.40)	208 (43.79)
3, (n, %)	314 (23.11)	194 (17.15)	120 (52.63)		204 (23.08)	110 (23.16)
Demographics						
BMI, n (%)				0.322		0.652
BMI< 18.5	8 (0.59)	6 (0.53)	2 (0.88)		4 (0.45)	4 (0.84)
18.5≤ BMI≤ 23.9	150 (11.04)	119 (10.52)	31 (13.60)		99 (11.20)	51 (10.74)
BMI≥23.9	1201 (88.37)	1006 (88.95)	195 (85.53)		781 (88.35)	420 (88.42)
Race, n (%)				0.287		0.061
Asian	26 (1.91)	22 (1.95)	4 (1.75)		19 (2.15)	7 (1.47)

Black/African American	85 (6.25)	77 (6.81)	8 (3.51)		58 (6.56)	27 (5.68)	
White	834 (61.37)	687 (60.74)	147 (64.47)		559 (63.24)	275 (57.89)	
Other	414 (30.46)	345 (30.50)	69 (30.26)		248 (28.05)	166 (34.95)	
Gender, n (%)				0.043	0.554		
Female, (n, %)	458 (33.70)	368 (32.54)	90 (39.47)		293 (33.14)	165 (34.74)	
Male, (n, %)	901 (66.30)	763 (67.46)	138 (60.53)		591 (66.86)	310 (65.26)	
Age, M (Q ₁ , Q ₃), years	70.97 (62.56, 78.61)	69.79 (61.62, 76.71)	77.87 (69.64, 85.78)	<.001	71.22 (63.44, 78.75)	70.56 (60.56, 78.37)	0.096

Data are expressed as median (IQR), or n (%). Analysis of variance (or the Kruskal-Wallis test) and Chi-square (or Fisher's exact) tests were used for comparisons among groups. Statistical significance (P<0.05).

APS III, Acute Physiology Score III; CCI, Charlson Comorbidity Index; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; BMI, Body Mass Index; AG, Anion Gap; Scr, Serum Creatinine; BUN, Blood Urea Nitrogen; MBP, Mean Blood Pressure; AKI, Acute Kidney Injury; RR, Respiratory Rate; HR, Heart Rate. MT, *malignant tumor*; INR, *International Normalized Ratio*.

Table 2: Lasso Regression Results for the Training Set

Variable	coefficient
Age	0.966316858
Sofa	0.003931174
CCI	0.003566407
APS III	0.005202393
SAPS II	0.001817838
Scr	0.068336308
BUN	-0.033017951
AG	0.003617608
K ⁺ ,	1.73251E-05
Ca ²⁺ ,	-0.011981595
Plt	0.000544299
Hb	-0.000140722
T	0.006821697
RR	-0.005146894
MBP	0.002870298
INR	0.001353896
Pt	0.036375453
Race	0.000918684
Congestive heart failure	0.025833753
Chronic lung disease	-0.031248347
MT	0.024900857
Cerebrovascular disease	0.066107271
Body mass index	0.032448992
Gender	-0.006125352

This table shows the 24 variables with non-zero coefficients in the lasso regression.

APS III, Acute Physiology Score III; CCI, Charlson Comorbidity Index; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; AG, Anion Gap; Scr, Serum Creatinine; BUN, Blood

Urea Nitrogen;MBP, Mean Blood Pressure; AKI, Acute Kidney Injury; RR, Respiratory Rate; HR, Heart Rate. MT, *malignant tumor*,*INR*,*International Normalized Ratio*.

Table 3: Bidirectional Stepwise Regression Results for the Training Set

Variable	β	OR_CI	P_Value
Age	0.051337943	1.053 (1.03–1.077)	<0.001
Sofa	0.086690375	1.091 (1.01–1.178)	0.026
CCI	0.077626031	1.081 (0.972–1.198)	0.146
APS III	0.022378842	1.023 (1.008–1.037)	0.002
Scr	-0.26420446	0.768 (0.577–0.985)	0.052
BUN	0.020286551	1.02 (1.008–1.034)	0.001
AG	0.082267203	1.086 (1.026–1.149)	0.004
RR	0.061629226	1.064 (1.028–1.101)	<0.001
Inr	0.508235674	1.662 (1.205–2.316)	0.002
Race1Black/African American1	-0.212703736	0.808 (0.112–7.867)	0.841
RACE1White1	0.909468286	2.483 (0.495–19.739)	0.319
Race4Other1	1.118659073	3.061 (0.591–24.842)	0.227

These variables were then included in a bidirectional stepwise regression to choose a Logistic model with the lowest AIC value.

APS III, Acute Physiology Score III; APS III, Acute Physiology Score III; CCI, Charlson Comorbidity Index; Scr, Serum Creatinine; BUN, Blood Urea Nitrogen; AG, Anion Gap.

Figures

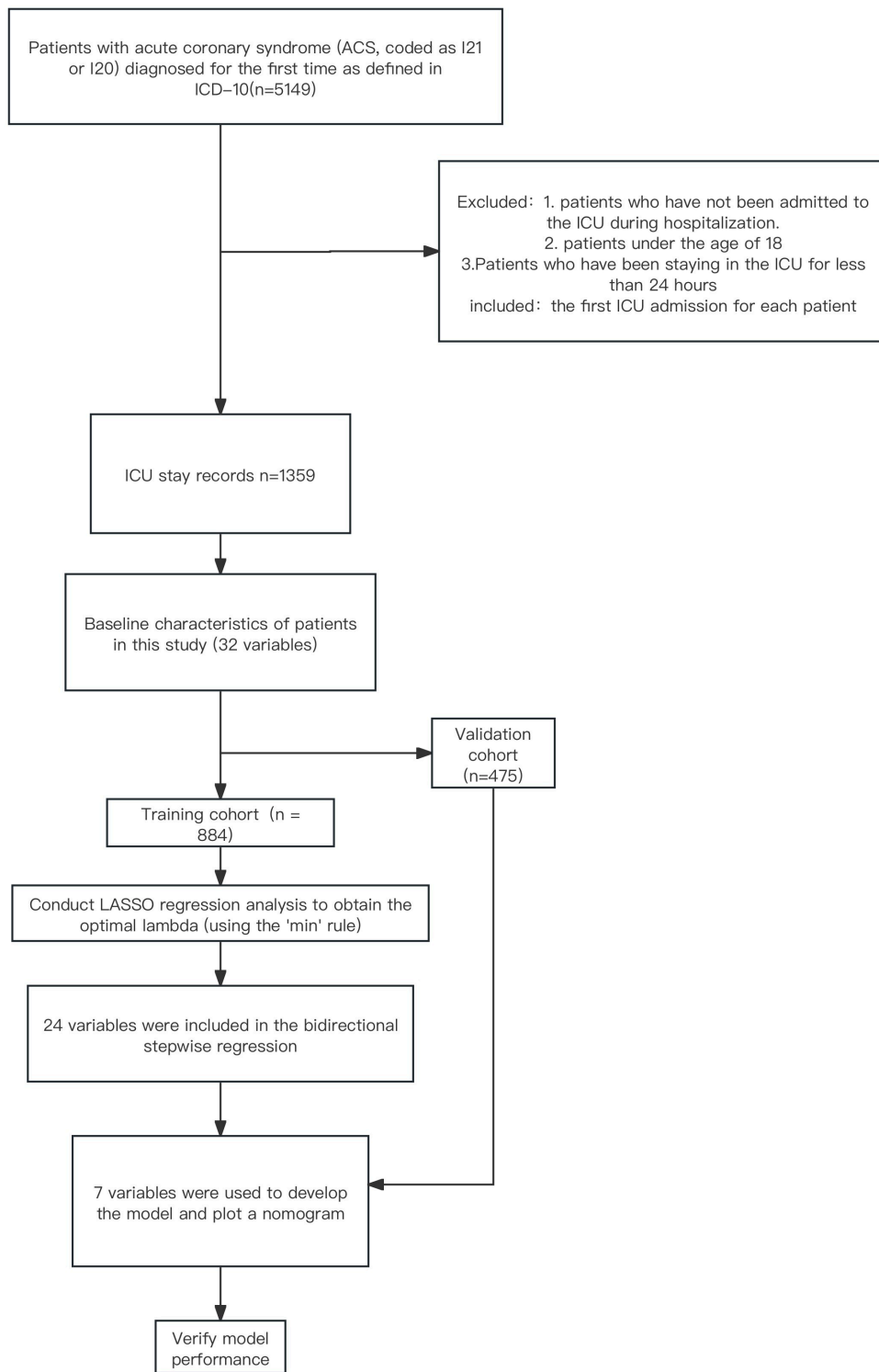


Figure 1

Flowchart of patients selection.

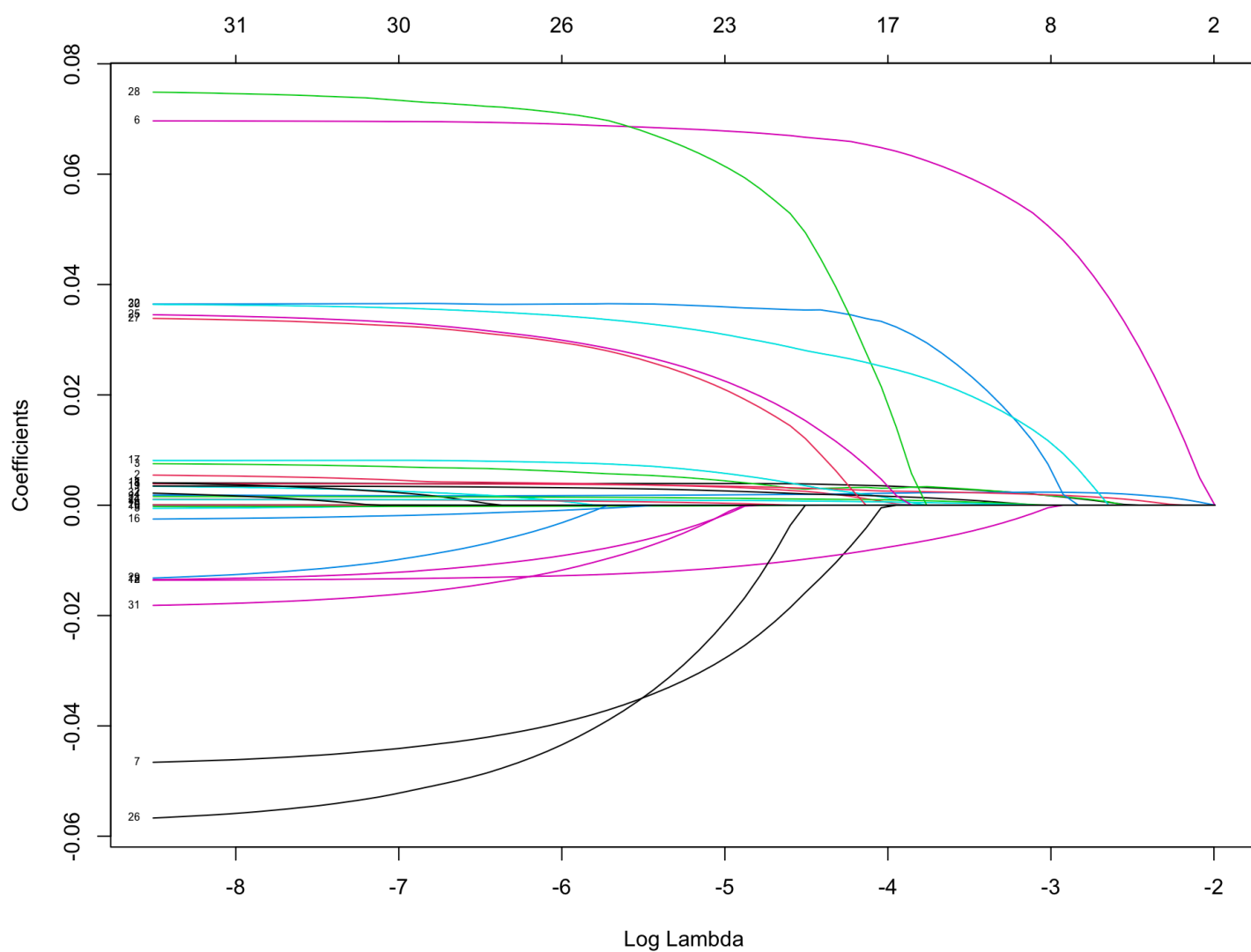


Figure 2

Variable Selection Path Plot

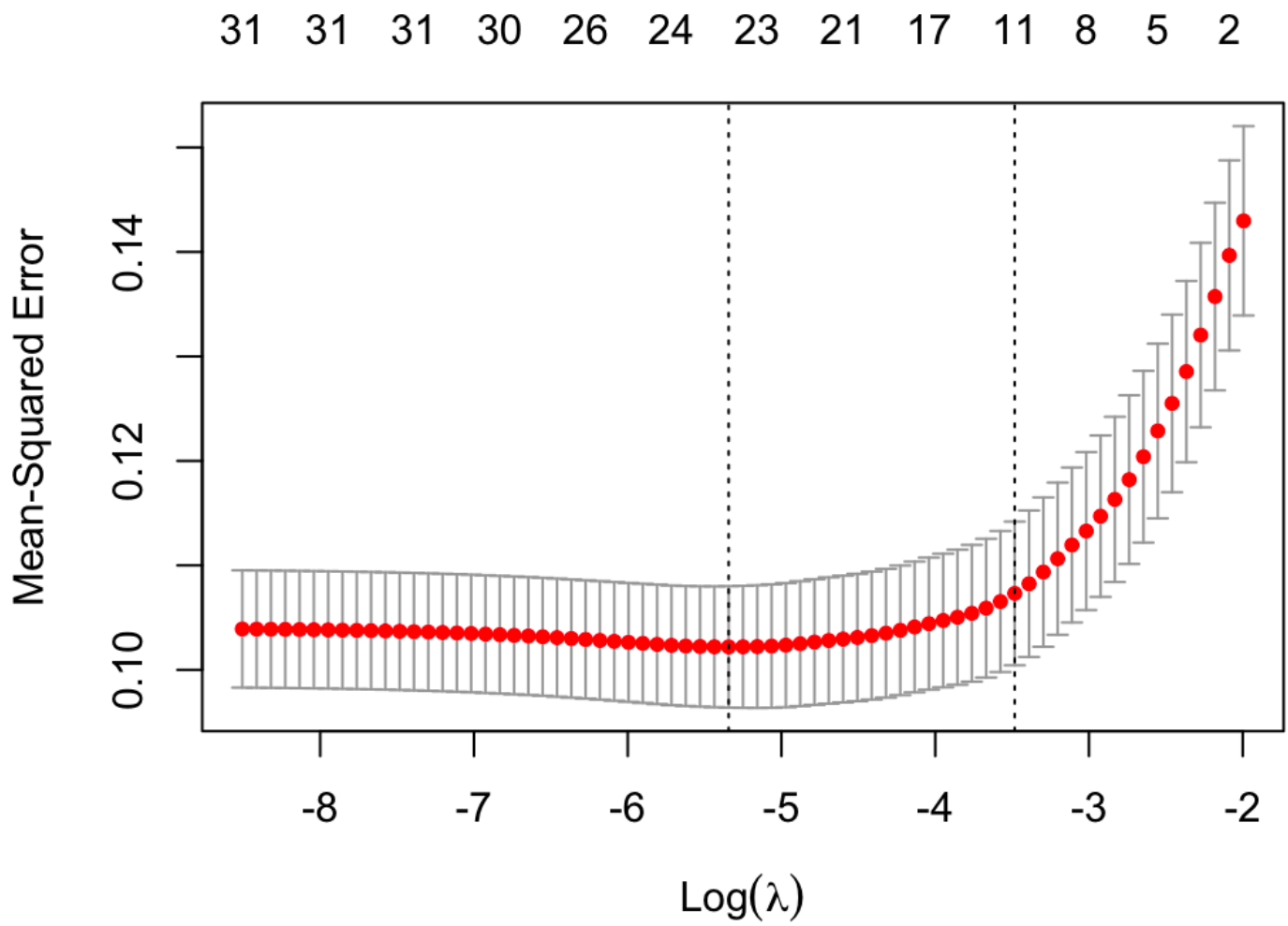


Figure 3

Cross-Validation Plot

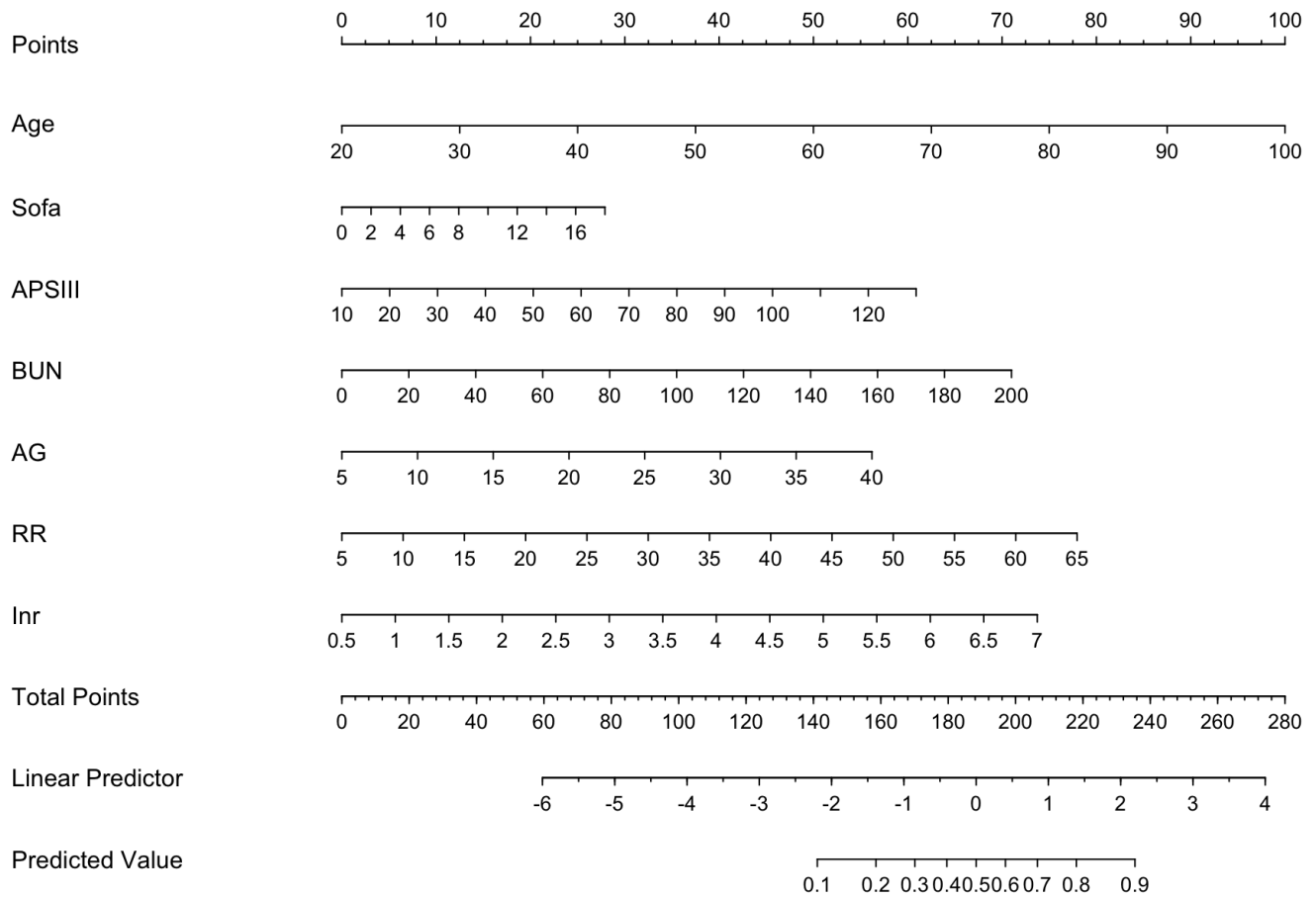


Figure 4

Nomogram used to predict mortality within 90 days after discharge of ACS patients.

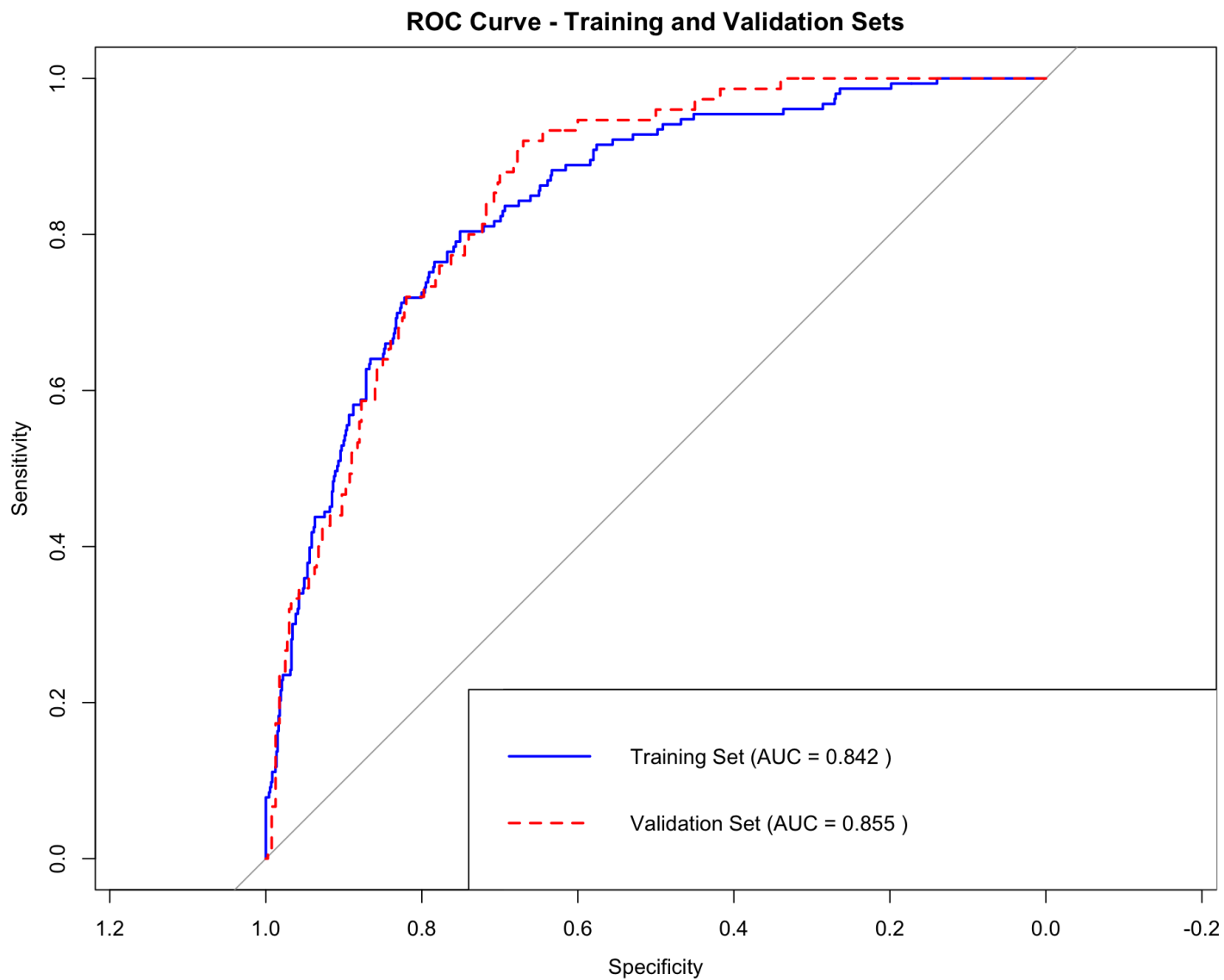


Figure 5

ROC Curves for the Training and Validation Sets

ROC Curves for Training Set

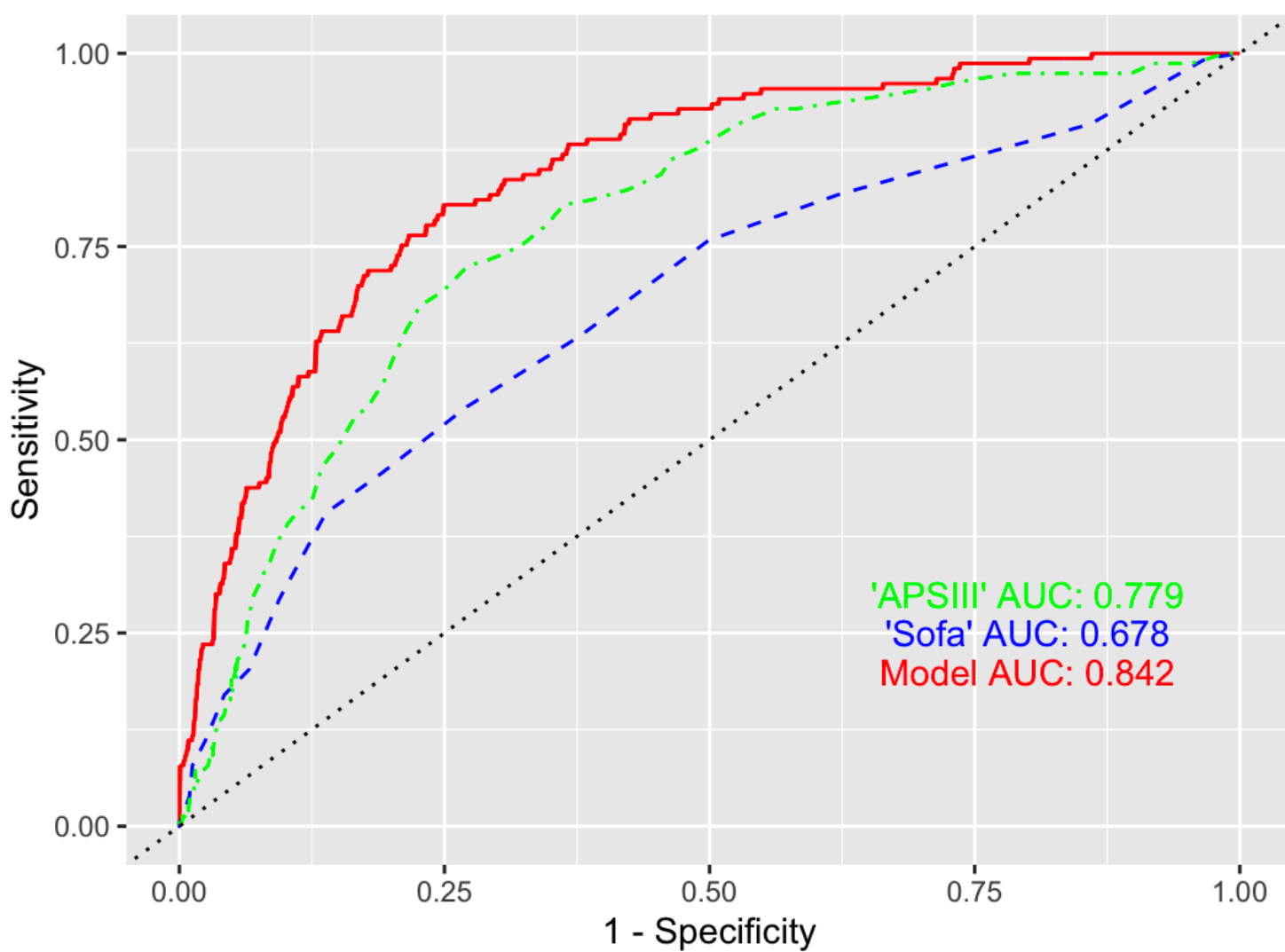


Figure 6

ROC Curves for SOFA, APS III, and the Model on the Training Set

ROC Curves for Validation Set

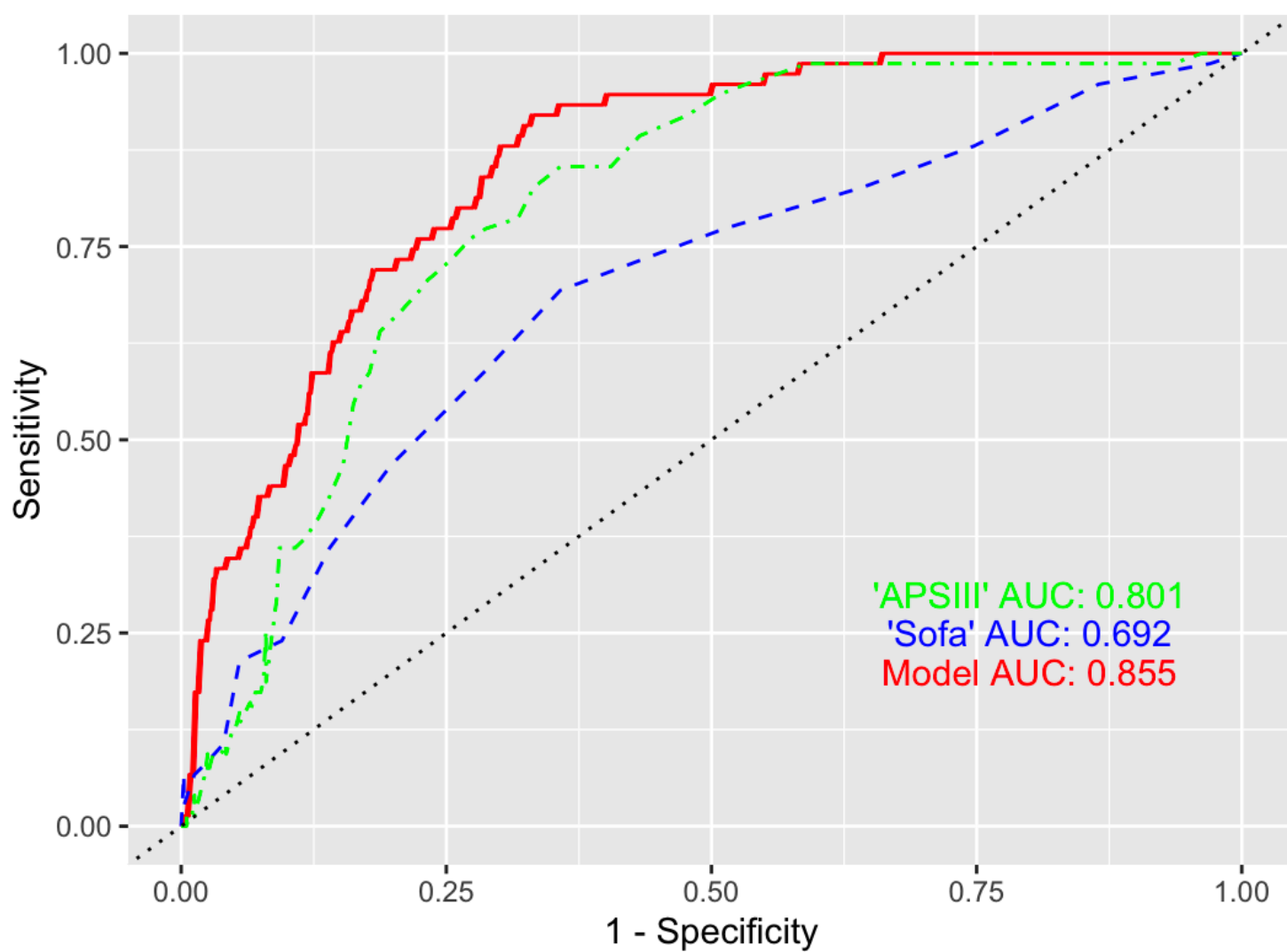


Figure 7

ROC Curves for SOFA, APS III, and the Model on the Validation Set

Calibration Curve for Training Set

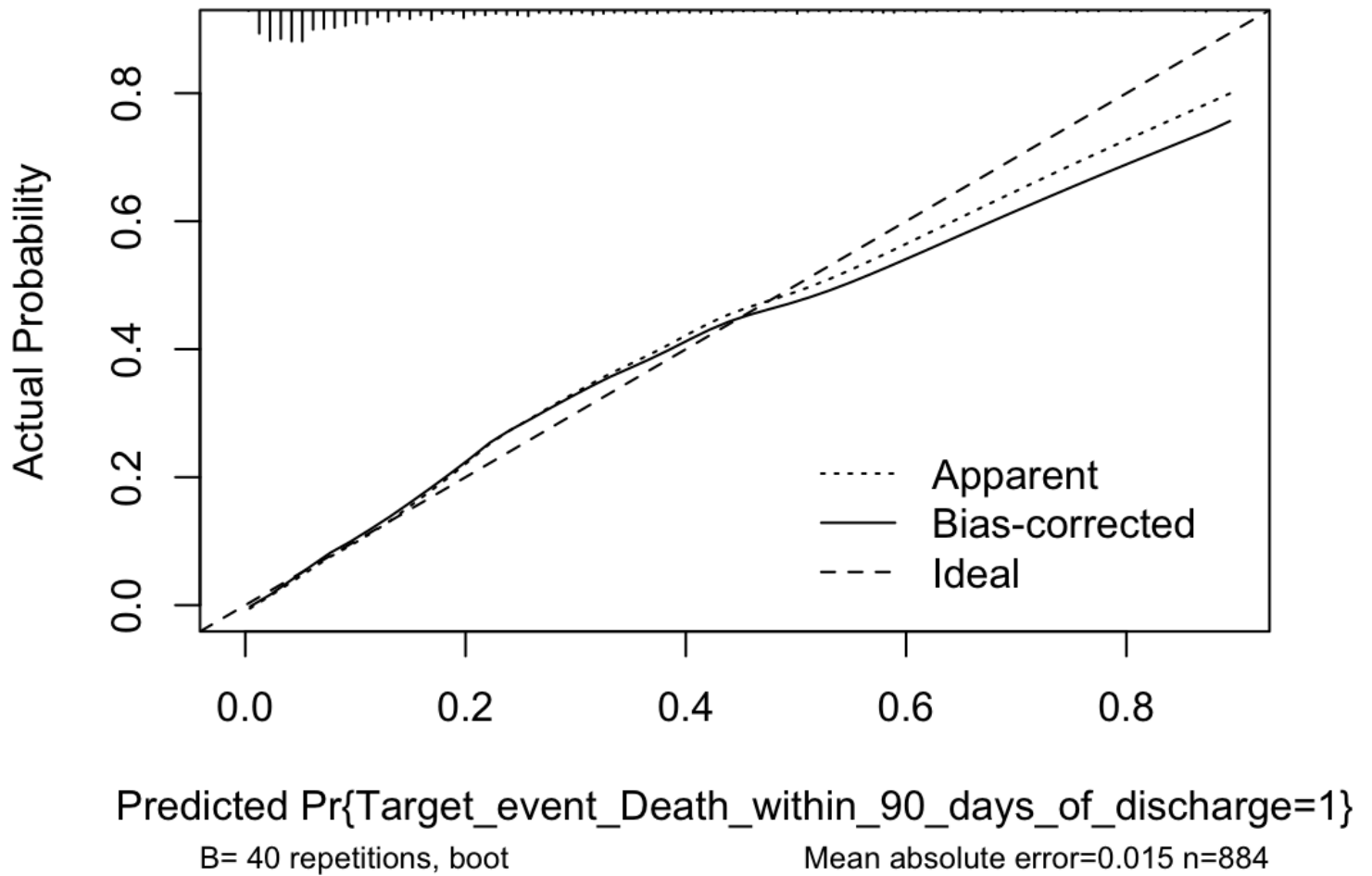


Figure 8

Calibration Curve for the Training Set

Calibration Curve for Validation Set

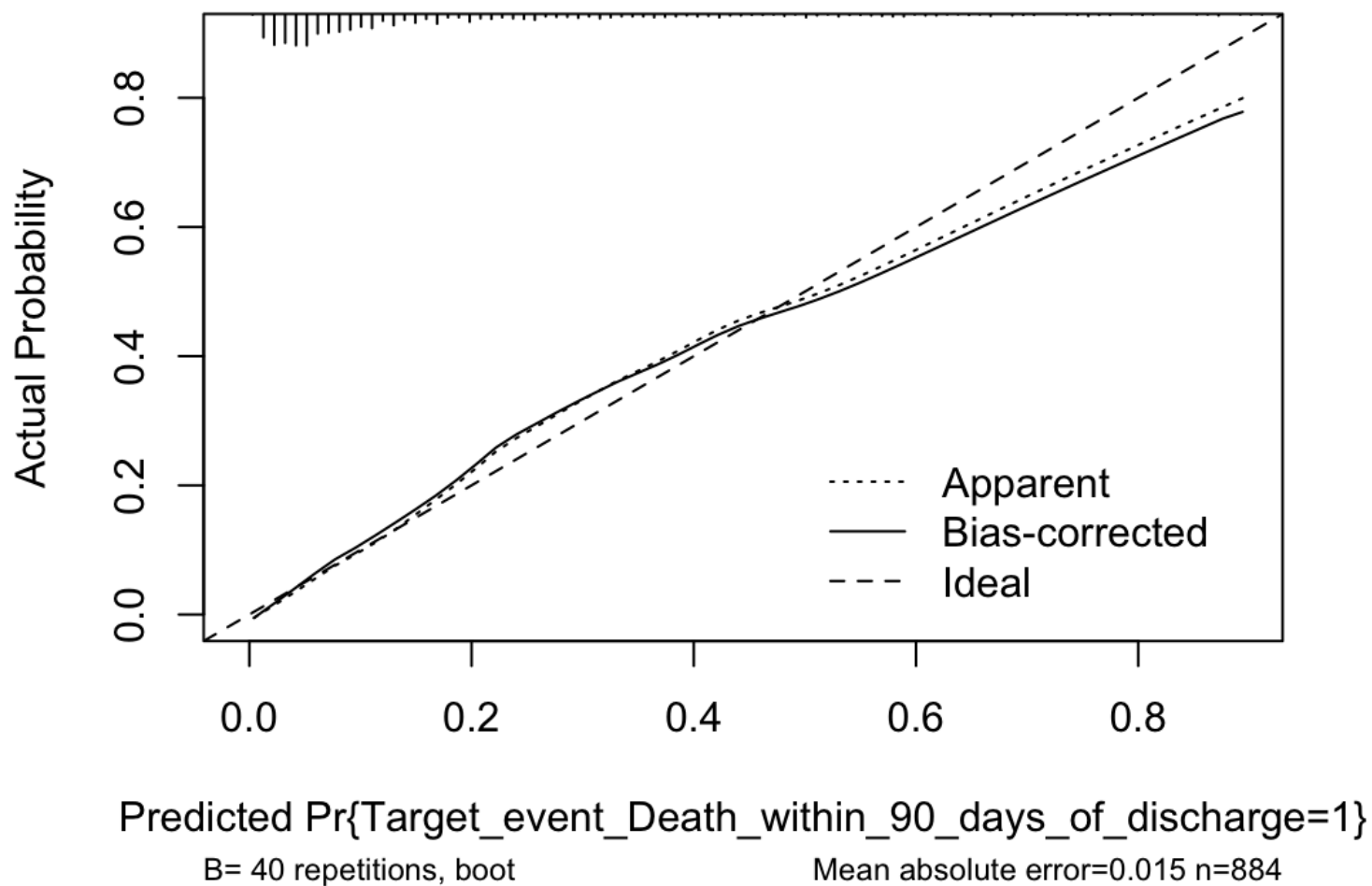


Figure 9

Calibration Curve for the Validation Set

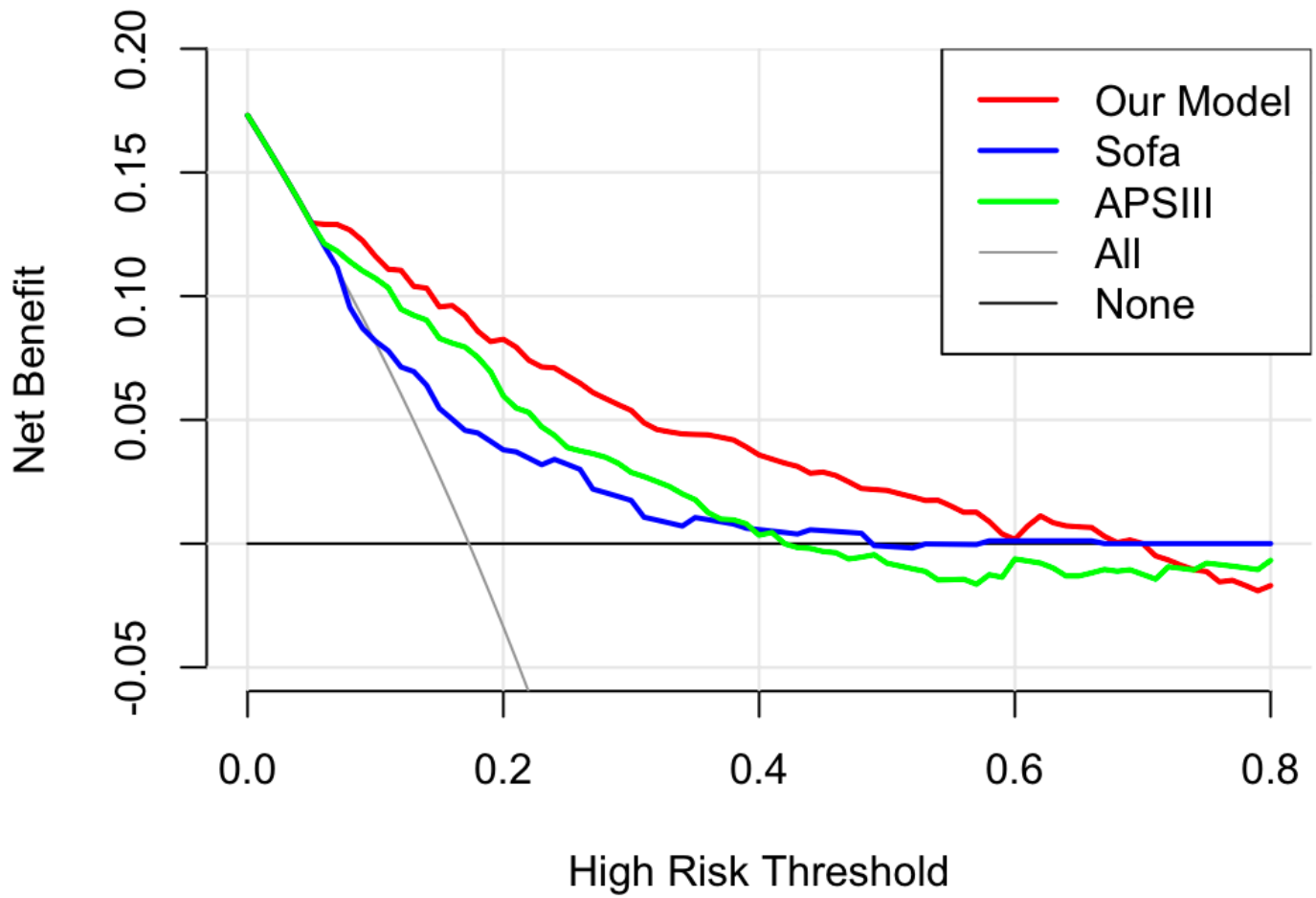


Figure 10

DCA for the Training Set

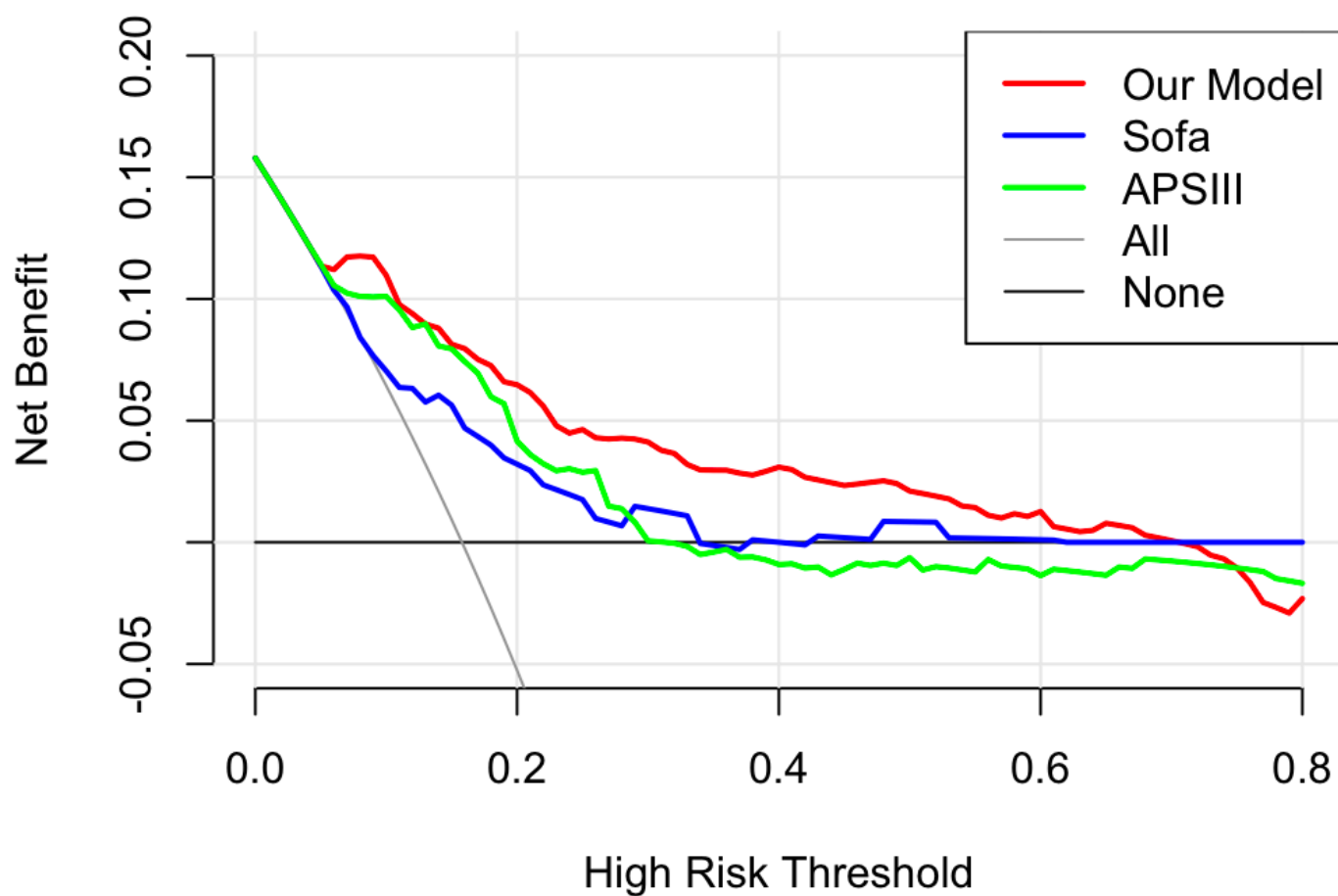


Figure 11

DCA for the Validation Set