Research Square

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Application Of Multi-Inflammatory Index To Predict 28-Day Mortality In ICU Patients With Heart Failure: A Retrospective Machine Learning Study Based On The MIMIC-IV Database

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Abstract

Background

Heart Failure(HF) is one of the leading cardiovascular diseases, and its high mortality rate in the Intensive Care Unit (ICU) has drawn increasing attention.HF mortality prediction is critical for developing individualized prevention and treatment plans.The objective of this study is to evaluate how effectively the Multi-Inflammatory Index—I, II, and III (MII-1, MII-2, MII-3)—can forecast mortality rates among ICU patients with heart failure.

Methods

A retrospective analysis was conducted on patients from the MIMIC-IV database, during which clinical data and laboratory findings were gathered. Feature selection was carried out utilizing the Boruta algorithm.We developed four machine learning models: XGBoost, Decision Tree,LightGBM and Naive Bayes.The performance of these models was assessed through five-fold cross-validation.To examine feature importance and model interpretability, SHAP values were employed.

Results

A total of 904 patients with HF were included in the final cohort for this study,with a median age of 71 (61–79)years.The ICU 28-day mortality for patients with HF was 23.23%.The Multi-Inflammatory Index of nonsurvival patients with HF in ICU was significantly higher than that of survival patients.Fourteen variables most associated with death from HF were selected using Boruta algorithm.In comparison,the LightGBM model demonstrated superior predictive performance among the four models, achieving an area under the curve (AUC) of 0.735. On the other hand, the DesicionTree machine exhibited limited generalization ability with an AUC of 0.575, indicating relatively poorer performance in prediction accuracy.The SHAP technique uncovers the 15 most significant predictors of HF based on their ranking in terms of importance, with the duration of shock index, age, and Multi-Inflammatory Index as the foremost predictor variable.

Conclusion

The LightGBM model demonstrated adequate sensitivity and accuracy. Multiple inflammatory Index play an important role in the prediction of death in ICU patients with heart failure.Consequently, this facilitates the development of improved treatment strategies and efficient allocation of resources for optimal patient care.

Introduction

Heart Failure (HF), the terminal phase of many cardiovascular disorders, is a major health care issue with an approximate prevalence of 26 million worldwide and more than 1 million hospital admissions annually in both the United States and Europe[1].Projections show that by 2030 over 8 million Americans will have HF, leading to an increase of 46% from 2012[2].

The increasing attention towards this issue is warranted, as the mortality associated with HF remains alarmingly high, especially in icus, despite advancements in treatment modalities[3]. The ability to predict death in HF patients is essential not only for enhancing clinical decision-making but also for developing tailored prevention and treatment strategies that can improve patient outcomes [4, 5].

Based on laboratory parameters, the Multi-Inflammatory Index—I (MII-1), II (MII-2), and III (MII-3)—serve as metrics to assess inflammation severity. These indices are utilized to forecast the outcomes of numerous conditions, including various cancers and tumors, infectious diseases, ischemic strokes, rheumatic disorders, and pulmonary embolisms[6–9].MII has shown significant potential in cardiovascular disease (CVD) risk assessment[10]. As a simple and accessible metric, MII holds promise for broad clinical application, aiding in risk evaluation and personalized treatment of CVD.

Furthermore, the integration of machine learning algorithms in predicting mortality risk has shown promising results, with models achieving high accuracy rates in identifying patients at risk of death due to HF [11].In conclusion, the prediction of mortality in patients with heart failure is a multifaceted issue that requires a comprehensive approach, incorporating clinical assessments, biomarker evaluations, and advanced predictive modeling[5, 12].

This study aims to investigate the predictive value of Multi-Inflammatory for mortality in patients with HF. We will use machine learning (ML) methods to establish and train predictive models, analyze Multi-inflammatory and other clinical indicators, and assess their ability to predict mortality risk. The ML model will help clinicians accurately identify high-risk patients, not only facilitate informed clinical decision-making but also pave the way for personalized treatment plans that can significantly enhance patient care and outcomes in the ICU setting.

Methods

Data Source

This retrospective investigation utilized the Medical Information Mart for Intensive Care (MIMIC)-IV database (v3.1), an iteration succeeding MIMIC-III. The database, aligned with the Health Insurance Portability and Accountability Act Safe Harbor provision, ensures deidentifcation. MIMIC-IV encompasses robust clinical data from 70,000 adult intensive care unit(ICU) patients at BIDMC between 2008 and 2019.

All patient data within the database is anonymized, obviating the need for informed consent.In adherence to the ethical standards articulated in the 1964 Declaration of Helsinki and its subsequent

amendments, the study was conducted. Access to the database was secured following the completion of the National Institutes of Health Web-based training course and the Protecting Human Research Participants examination (No. 43258214).

Participant selection

Patients fulfilling specific criteria were screened through the MIMIC-IV database (version 3.1) for this study.We identifed individuals in the database meeting the following criteria:

(1) patients were diagnosed with Heart Failure according to the International Classification of Diseases, as indicated by ICD-9 codes, or ICD-10 codes;

(2)excluded the values of CPR,Neutrophils,Lymphocytes and Platelet count is Null;

(3)the ICU stay was more than 1 day;

(4)patients were aged 18 years or older.

(5)patients who had more than 20% missing values were excluded.

Ultimately,904 adult patients diagnosed with Heart Failure were included out of a total of 16469 patients in the MIMIC-IV database.The depiction of the patient screening process can be observed in Fig. 1.

Data Collection

The predicted outcome of this study is defined as the probability of 28-day ICU mortality rate.The collected clinical data comprised various parameters, including demographic information such as gender, age, and comorbidities, as well as severity scoring. Additionally, laboratory indicators encompassed measurements of white blood cells, neutrophils,lymphocytes,hemoglobin, platelets,red cell distribution width, bilirubin,platelet count (PLT),creatinine,coagulation function and blood gas indexes. Examination indicators included heart rate, systolic and diastolic blood pressure, and respiratory rate.

MII-1 is calculated as the neutrophil/lymphocyte ratio (NLR) multiplied by CRP, MII-2 is calculated as platelet/lymphocyte ratio (PLR) multiplied by CRP, and MII-3 is calculated as SII multiplied by CRP.SII is calculated by multiplying the neutrophil/lymphocyte ratio (NLR) by the platelet count.

Feature Selection

The Boruta algorithm was used to construct the corresponding shadow features for each variable, and the random forest technique was used to calculate the importance score of the original and shadow

features. Compared with the traditional variable selection method, Boruta algorithm shows more comprehensive, accurate and efficient characteristics in the process of variable selection.

Machine learning Model

We developed four common ML models: XGBoost, Decision Tree,Light Gradient Boosting Machine (LightGBM) and Naive Bayes models. Five-fold cross-validation(CV) was used to evaluate model generalization.

Feature Importance and Model Interpretability

We selected the best-performing ML model for feature importance analysis to determine the impact of features on prediction. Feature importance was calculated based on the model's internal mechanisms.

Statistical Analysis

The categorical variables are manifested as total quantities and percentages, and the $\chi 2$ test or Fisher exact test is adopted to contrast the differences among groups. The continuous variables are represented by their median and interquartile range (IQR), with the Wilcoxon rank sum test applied for comparisons between the two groups.Statistical analysis was conducted using Python 3.9 and R 4.3.2.

Table 1
Descriptive Characteristics of Overall Participants

VariableNames	Overall	Survivors	Nonsurvivors	P value
n	904	694	210	
age	71 (61–79)	70 (60–78)	73 (66–80)	< 0.001
Sofa	5 (3–8)	5 (3–7)	6 (4–9)	< 0.001
Apsiii	50 (38–63)	47 (37–60)	58 (46–70)	< 0.001
Shock_index	1.226 (0.969–1.527)	1.171 (0.939–1.451)	1.453 (1.145–1.886)	< 0.001
Heart_Rate	89 (76–105)	89 (76–105)	90 (78-106.75)	0.368
Nbps	117 (102–134)	117 (102–134)	116 (102-134.75)	0.790
Nbpd	68 (57–80)	67.5 (57–80)	68 (56–81)	0.789
Respiratory_rate	21 (17–25)	21 (17–25)	20.5 (18–26)	0.424
SpO2	97 (94–99)	97 (95–100)	97 (94–99)	0.089
Temperature	98.2 (97.6–98.8)	98.2 (97.625–98.8)	98.2 (97.6–98.7)	0.839
CReactive_Protein	89.1 (36.25-165.75)	80.6 (32.75–159.4)	113.1 (57.05-177.325)	0.004
Lymphocytes	8.7 (5-13.5)	9.4 (5.6–14)	6.55 (3.5-10.975)	< 0.001
MII_2	2011.528 (662.948-5097.579)	1762.427 (585.326-4563.635)	3337.312 (1066.753-8214.456)	< 0.001
Neutrophils	81 (74-86.6)	80 (73.4-85.875)	83.3 (77.075–89.25)	0.001
MII_3	159563.252 (49789.884-422251.826)	134181.831 (43226.192-368985.906)	277498.958 (85407.24-664095.564)	< 0.001
MII_1	835.488 (270.034-1940.72)	695.158 (230.871-1652.085)	1427.917 (509.706-2896.069)	< 0.001
Hematocrit	31.15 (26.7–36.5)	31.3 (26.7–36.5)	30.95 (26.7-36.725)	0.578
Hemoglobin	9.9 (8.475–11.7)	10 (8.5–11.8)	9.8 (8.4-11.475)	0.345

VariableNames	Overall	Survivors	Nonsurvivors	P value
Platelet_Count	205.5 (144.75-289.25)	209 (151–289)	194.5 (128-289.75)	0.272
Rdw	15.6 (14.2–17.4)	15.4 (14.1–17.2)	15.9 (14.6–18.2)	< 0.001
Red_blood_cells	3.43 (2.92–4.12)	3.465 (2.94–4.16)	3.38 (2.9-3.957)	0.171
White_blood_cells	12.05 (8.4-16.825)	11.8 (8.4–16.4)	12.5 (8.8-17.275)	0.039
Albumin	2.9 (2.6–3.3)	3 (2.6–3.3)	2.8 (2.5-3.175)	< 0.001
Anion_Gap	15 (12–18)	14 (12–17)	15 (13–18)	0.113
Calcium_Total	8.4 (7.9–8.8)	8.4 (7.9–8.9)	8.3 (7.9–8.8)	0.084
Chloride	102 (97–106)	102 (98–106)	101 (97–105)	0.034
Glucose	135 (108-179.25)	134 (107.25–178)	138.5 (110.25–184)	0.991
Potassium	4.3 (3.9–4.8)	4.2 (3.9–4.8)	4.35 (3.9–4.8)	0.332
Sodium	138 (134–141)	138 (134–141)	137 (134–141)	0.348
Lactate	1.6 (1.1–2.5)	1.6 (1.1–2.4)	1.8 (1.2–2.8)	0.003
PCO2	41 (36–48)	41 (36–47)	42 (37–50)	0.126
PH	7.38 (7.31–7.43)	7.38 (7.32–7.43)	7.355 (7.29–7.417)	< 0.001
PO2	70 (43–139)	73 (44–142)	60 (40–118)	0.039
INR	1.4 (1.2–1.7)	1.4 (1.2–1.7)	1.4 (1.2-1.775)	0.662
PT	15 (13.2–18.7)	14.85 (13.125–18.5)	15.4 (13.325–19.225)	0.683
APTT	32.3 (28.4-39.925)	32.1 (28.3–39.3)	33.5 (28.825–41.55)	0.741
ALT	23 (14-48.25)	23 (14–46)	25 (14-55.5)	0.511
AST	35 (21-74.25)	34 (21-67.75)	41 (24-93.25)	0.768
Bilirubin_Total	0.6 (0.4-1)	0.6 (0.4-1)	0.6 (0.4-1.275)	0.002
Creatinine	1.4 (0.9-2.425)	1.3 (0.9–2.3)	1.6 (1-2.8)	0.595
Urea_Nitrogen	30 (19–49)	28.5 (18-46.75)	34.5 (22.25–57.75)	0.002

VariableNames	Overall	Survivors	Nonsurvivors	P value
Lactate_Dehydrogenase	301.5 (223-432.5)	293 (220–403)	344.5 (236.75-522.25)	0.262
gender (%)	382 (42.26)	299 (43.08)	83 (39.52)	0.404
	522 (57.74)	395 (56.92)	127 (60.48)	
Hypertension (%)	786 (86.95)	594 (85.59)	192 (91.43)	0.037
	118 (13.05)	100 (14.41)	18 (8.57)	
Acute_Kidney_Injury (%)	336 (37.17)	278 (40.06)	58 (27.62)	0.001
	568 (62.83)	416 (59.94)	152 (72.38)	
Liver_cirrhosis (%)	842 (93.14)	655 (94.38)	187 (89.05)	0.012
	62 (6.86)	39 (5.62)	23 (10.95)	
Pneumonia (%)	520 (57.52)	426 (61.38)	94 (44.76)	< 0.001
	384 (42.48)	268 (38.62)	116 (55.24)	

Results

Baseline Characteristics

Table 1 presents the baseline characteristics of study participants.In this study, 904 adult patients were analyzed, with 694 classified as survivors and 210 as nonsurvivors.The 28-day ICU mortality rate was 23.23% in our cohort.The overall median age of the cohort was 71 years (range 61–79), revealing significant differences between the survivor group (median age 70 years) and the nonsurvivor group (median age 73 years, $P < 0.001$).The SOFA scores were significantly higher in the nonsurvivor group, and the APS III scores,shock index also indicated a significant disparity.While vital signs showed no significant differences in heart rate or blood pressure measurements, significant differences were noted in laboratory parameters, including C-reactive protein levels and lymphocyte counts.Additionally, the nonsurvivor group exhibited significantly higher neutrophil counts ,MII_1,MII_2,MII_3 levels.Hemoglobin levels did not show significant differences, while hematocrit levels were comparable between groups.Notably, the nonsurvivor group had a higher prevalence of acute kidney injury and pneumonia, with liver cirrhosis also significantly different.

Feature Selection Using Boruta

Boruta confirmed the importance of 14 variables most associated with mortality in ICU patients with HF(Fig. 2). The results of the Boruta feature selection analysis demonstrate the importance of each

variable through boxplots. The results showed that Shock_index had the highest variable importance, followed by MII_3 and MII_1.

Model Comparison

Figure 3 visually presents the performance comparison of XGBoost, Decision Tree, LightGBM and Naive Bayes models.In this study, we evaluated the classification performance of four machine learning models, including Decision Tree, LightGBM, Naive Bayes (NB), and XGBoost (XGB), by ROC curves. The results showed that the LGBM model performed best with an area under the curve (AUC) of 0.735, indicating its high sensitivity and specificity in distinguishing positive and negative samples. The AUC of the XGBoost model was 0.734, which followed closely, showing good classification ability. In contrast, the AUC of the naive Bayes model was 0.604, which showed poor performance, while the AUC of the decision tree model was only 0.575, showing that its classification performance on this dataset was limited.

Explaining LightGBM Models Using SHAP

The SHAP method is employed to assess the contribution of each predictor variable to the predictions made by the LightGBM model. Figure 4 displays the variable importance plot, where variables are sorted in descending order of importance. Among all predictors, the mean value of shock index and age exhibits the highest predictive value, followed closely by Multi-Inflammatory Index. To further examine the positive or negative correlations between predictors and the target outcome, we utilize SHAP values to identify risk factors associated with mortality. As illustrated in Fig. 5, the color indicates whether the variable is high (purple) or low (yellow) for that observation. We observe that increases in shock index, age and Multi-Inflammatory Index contribute to the prediction of the 28-Day mortality in ICU patients with HF.

Discussion

In our study, we found that Multi-Inflammatory Index is a risk factor for 28-day mortality in ICU patients with HF and can significantly affect the prognosis and progression of the disease. Using the Boruta algorithm for feature selection, we identified the significance of 14 variables most associated with mortality in ICU patients with HF. Among the models compared, the LightGBM demonstrated superior performance, showcasing the highest accuracy, indicating its strong predictive capability for 28-day mortality in ICU patients with heart failure. Furthermore, we employed SHAP to interpret the predictions made by the LightGBM model. Shock Index, Age and higher MII levels were positively associated with the 28-day mortality in ICU patients. The SHAP Importance plot illustrated the impact of each feature on the model's output, elucidating the direction of influence of different feature values on 28-day mortality risk in ICU.

Inflammation plays an important role in the pathogenesis of heart failure, and many studies have shown that elevated inflammatory markers are closely related to the severity and prognosis of heart failure. For example, C-reactive protein (CRP) levels in serum have been found to be significantly associated with

outcomes in patients with heart failure, with higher CRP levels generally associated with poor clinical outcomes[13–15]. In addition, changes in the number of inflammatory cells such as neutrophils and lymphocytes are also considered to be important indicators of prognosis in patients with heart failure[16, 17].Our research is based on the mimic database, using machine learning models, showed that calculation of MII-1, MII-2, and MII-3 in patients diagnosed with HF in the ICU predicted mortality.

In recent years, a number of studies have investigated the role of different inflammatory markers in the prognosis of heart failure. The promotion of myocardial fibrosis and remodeling is significantly influenced by inflammatory responses, especially through cytokines, leading to myocardial fibrosis and structural changes in the heart[18]. The neutrophil-to-lymphocyte ratio (NLR) has been identified as an inflammatory marker, and its elevation is associated with worsening myocardial fibrosis, subsequently affecting systolic and diastolic cardiac function [19].

In addition, the inflammatory response is a key factor in promoting thrombosis. Inflammation can lead to endothelial dysfunction, which increases the risk of thrombosis. Elevated inflammatory markers, such as platelet-to-lymphocyte ratio (PLR), are associated with enhanced platelet activation and aggregation, thereby promoting thrombosis[20]. This thrombotic activity increases the burden on the heart, leading to worsening heart failure and increasing the risk of death.

Despite the strengths of our study, there are limitations that should be acknowledged. Our study has limitations, including its retrospective nature and a single-center sample,limiting generalizability. The retrospective design may introduce bias, and future prospective studies with larger, multicenter populations are warranted to validate our findings. Additionally, the complex mechanisms between inflammation and mortality in ICU patients with heart failure warrant further exploration.External validation of the LightGBM model is needed, which will further confirm the model’s robustness and generalizability across different populations and settings.

Conclusion

The LightGBM model demonstrated adequate sensitivity and accuracy. Multiple inflammatory Index play an important role in the prediction of death in ICU patients with heart failure.Consequently, this facilitates the development of improved treatment strategies and efficient allocation of resources for optimal patient care.

Declarations

Ethical approval

All patient data within the database is anonymized, obviating the need for informed consent.In adherence to the ethical standards articulated in the 1964 Declaration of Helsinki and its subsequent amendments, the study was conducted.

Conflicts of Interest

None.

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Author Contribution

LC Liu, ZJ Dai, and XS Yu conceived the study; LC Liu,XS Yu performed the analysis, LC Liu, Z Chen, YQ Lin interpreted the results, and drafted the manuscript. All authors revised the manuscript. All authors read and approved the final manuscript.

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Figures

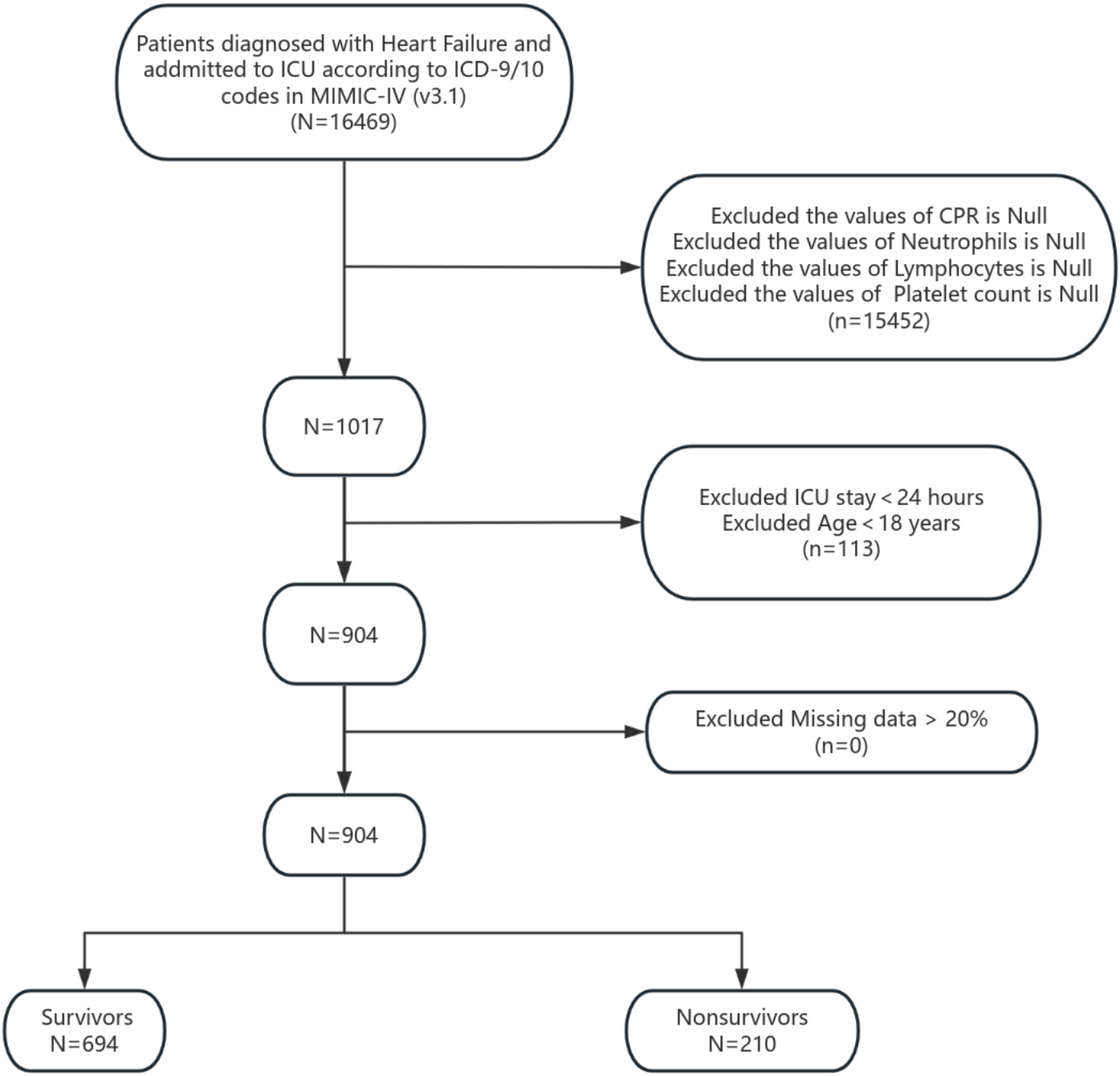


Figure 1

Flowchart for Patient Selection. ICD: International Classification of Diseases

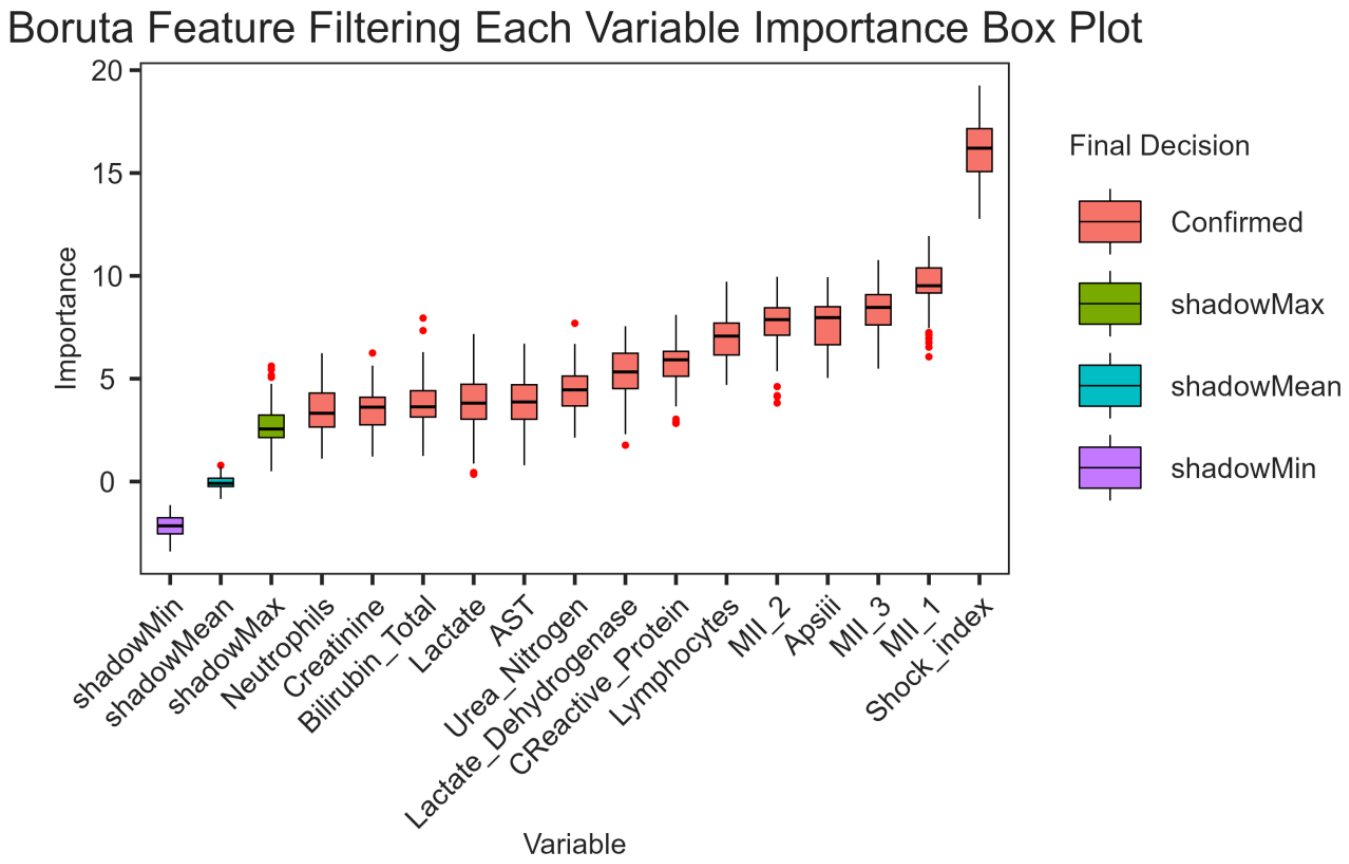


Figure 2

The process of feature selection based on Boruta's algorithm

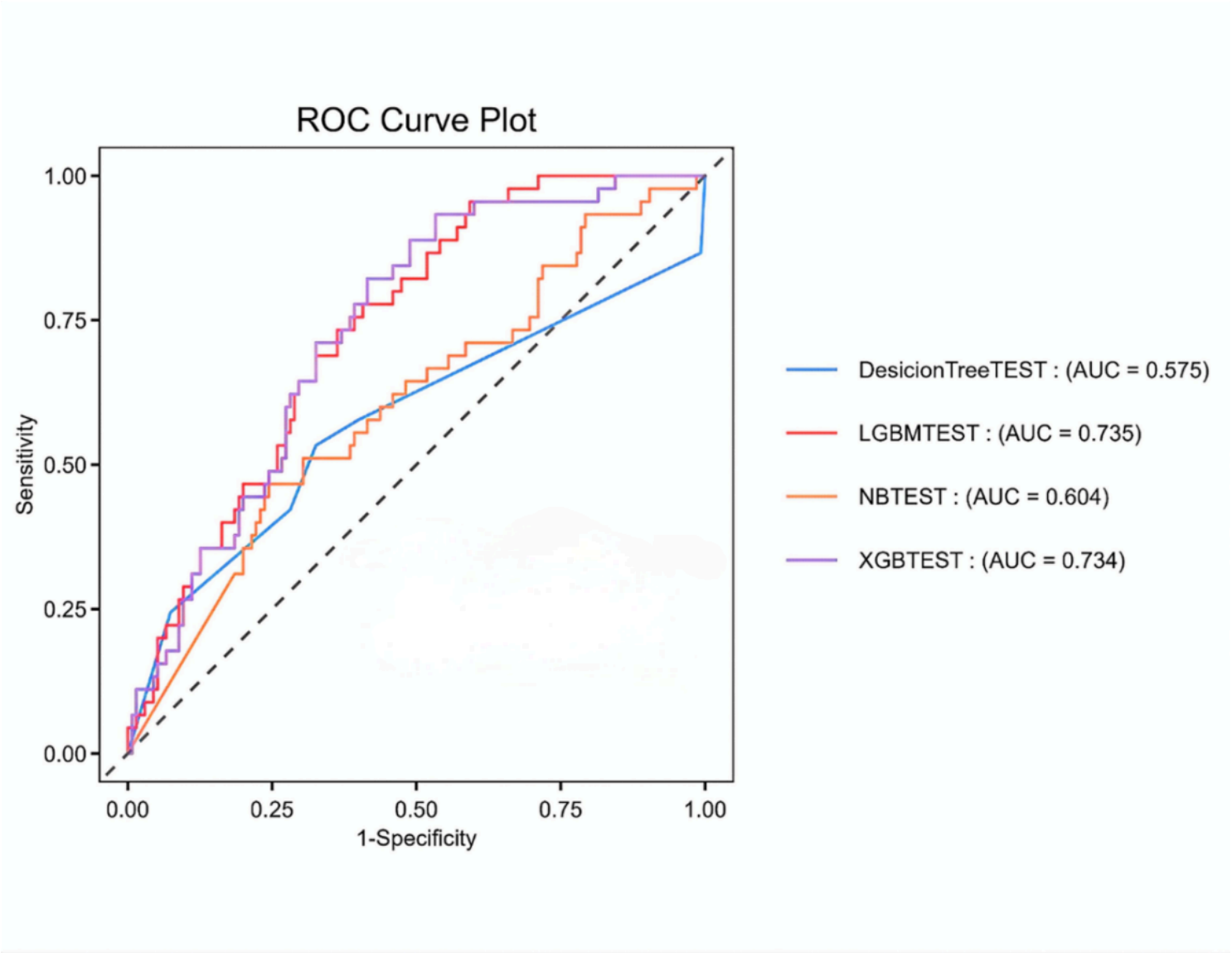


Figure 3

The ROC curve comparing the performance of the four models

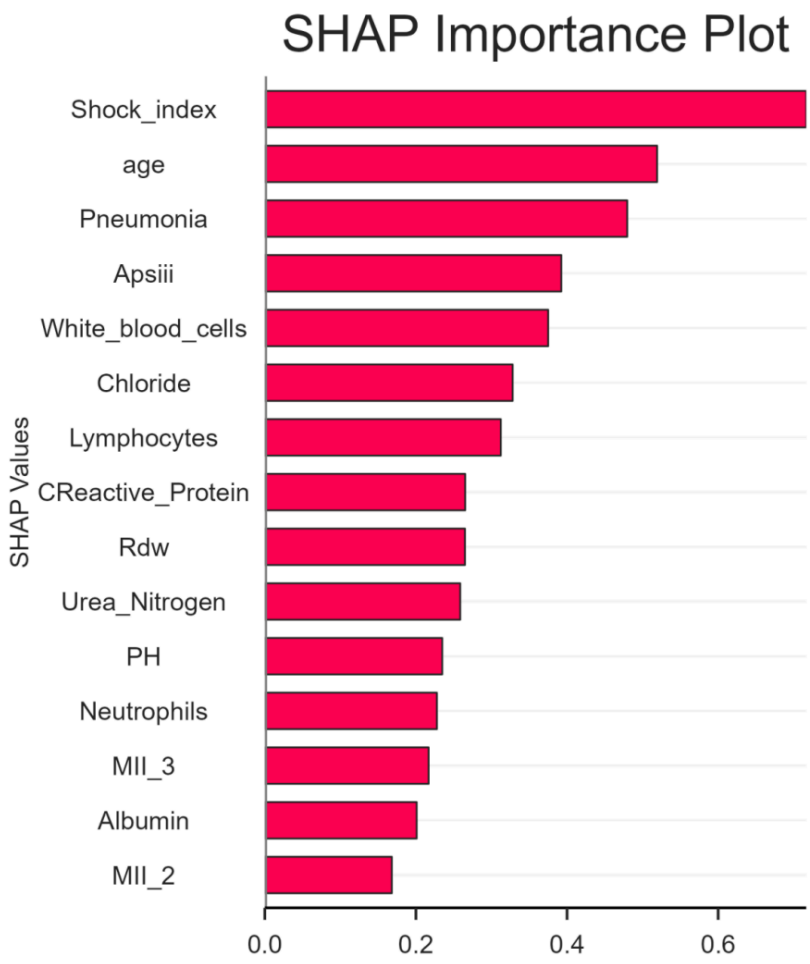


Figure 4

The weights of variables importance

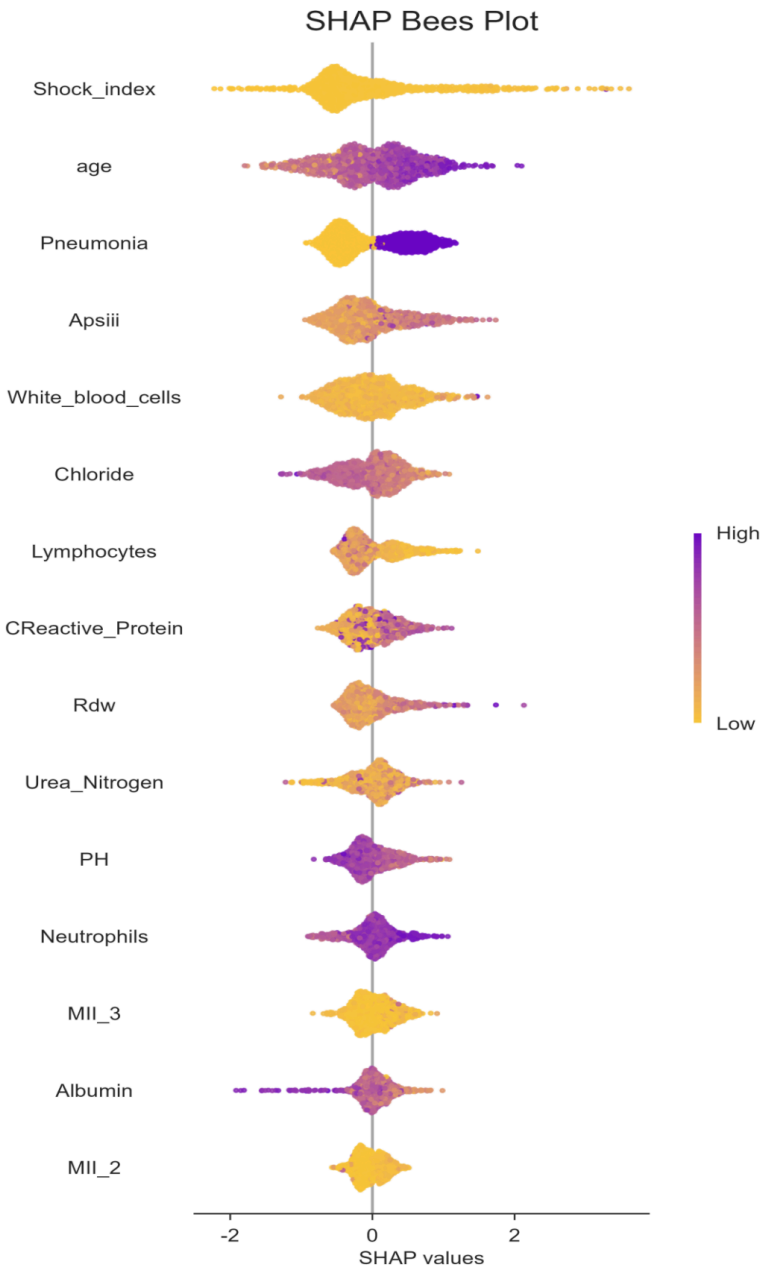


Figure 5

The SHapley Additive exPlanation (SHAP) values