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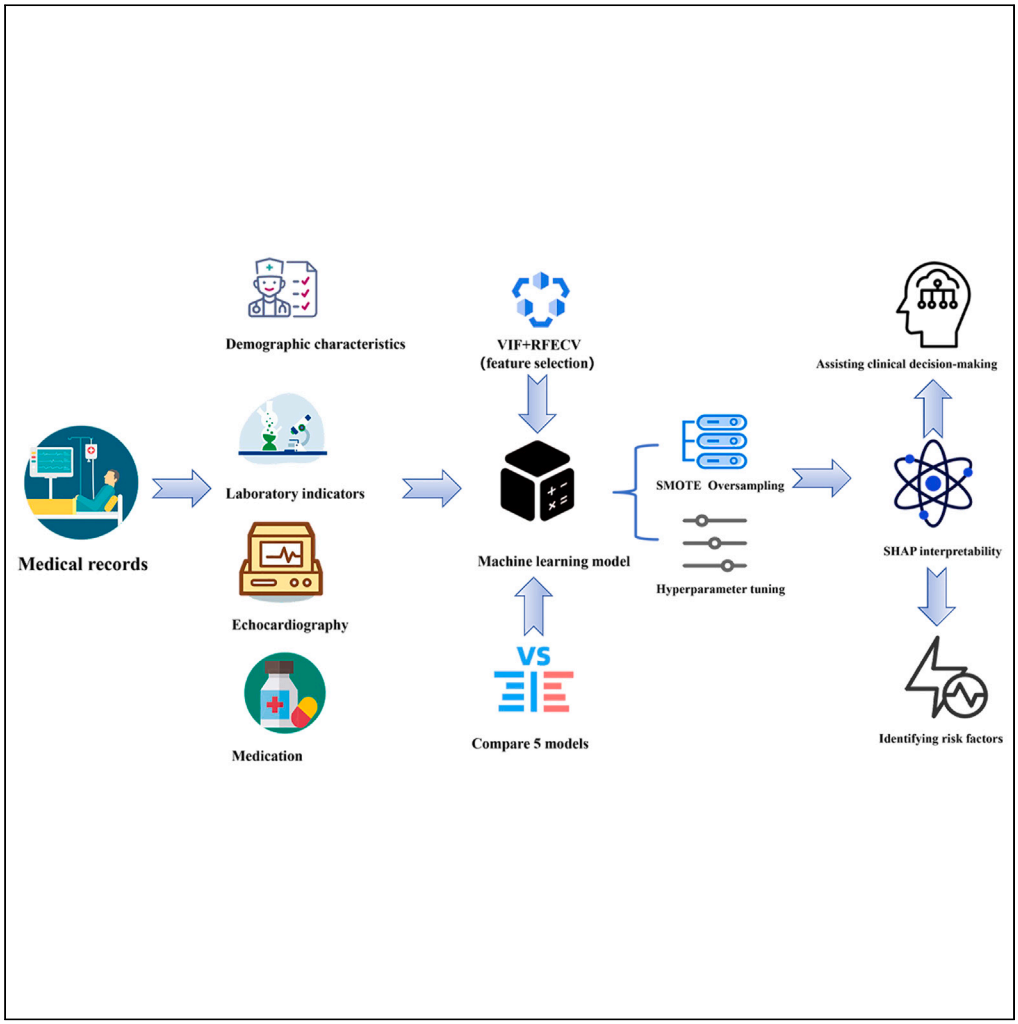

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Highlights

Interpretation of optimal machine learning XGBoost model using SHAP framework

Age, length of hospitalization, and septal thickness are important risk factors

SGLT-2i drugs are used in the treatment of acute heart failure from 2018

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Explainable machine learning for predicting 30-day readmission in acute heart failure patients

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SUMMARY

We aimed to develop a machine-learning based predictive model to identify 30-day readmission risk in Acute heart failure (AHF) patients. In this study 2232 patients hospitalized with AHF were included. The variance inflation factor value and 5-fold cross-validation were used to select vital clinical variables. Five machine learning algorithms with good performance were applied to develop models, and the discrimination ability was comprehensively evaluated by sensitivity, specificity, and area under the ROC curve (AUC). Prediction results were illustrated by SHapley Additive exPlanations (SHAP) values. Finally, the XGBoost model performs optimally: the greatest AUC of 0.763 (0.703–0.824), highest sensitivity of 0.660, and high accuracy of 0.709. This study developed an optimal XGBoost model to predict the risk of 30-day unplanned readmission for AHF patients, which showed more significant performance compared with traditional logistic regression (LR) model.

INTRODUCTION

Acute heart failure (AHF) is characterized by the new onset or acute deterioration of clinical symptoms and signs of heart failure, which are the main reasons for unplanned hospital admission and emergency treatment.[1,2] Previous studies have demonstrated that patients with AHF tend to be readmitted to the hospital within 30–90 days after discharge, accounting for 25–30% of all patients.[3,4] In the United States, 30% of AHF patients are readmitted within three months of admission, and half are readmitted within six months.[5,6] Unplanned short-term readmission of patients with AHF not only brings a huge burden to the national medical finance, but also causes fatal damage or seriously affects the quality of life of the patients.[7,8] According to estimates, over a million of Americans die from AHF each year, and the annual cost of nursing care surpasses 30 billion dollars. Similar trends have also been observed in Asian and European countries.[9–11]

Previous studies have explored the risk factors for readmission in patients with AHF. Studies indicate that risk factors encompass obesity, suboptimal self-care practices, and the manifestation of severe complications such as chronic lung disease and acute renal injury. Additionally, factors including low levels of albumin, elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP), abnormal concentrations of bicarbonate and sodium, along with elevated blood pressure, have been identified as contributors to an augmented susceptibility to readmission.[12–15] In addition, age, length of hospital stays (LOS), and length of discharge were found closely related to the risk of readmission of patients with AHF.[16] Unfortunately, there are some limitations in the risk prediction and stratification of unplanned 30-day readmission for patients with AHF. For example, when using echocardiography to stratify the risk of HFpEF (heart failure with preserved ejection fraction) patients, it is unclear how clinical and echocardiographic data should be included in the monitoring and prognostic evaluation of HFpEF.[17] New Haven Health Services Corporation/Center for Outcomes Research and Evaluation (Yale/CORE) is the most well-known and widely

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implemented risk prediction model for the standardized 30-day readmission risk for patients with HF.[18] However, recent studies have pointed out that this score has only moderate predictive power.[19]

Because of the previous risk factors, some measures have also been proposed to reduce the readmission rate, including ultrasound guided fluid management and the use of mobile health applications to promote self-care, proper exercise training, and the implementation of the Hospital Readmissions Reduction Program.[20,21] These measures have reduced the readmission rate of patients with AHF, but there are also associated problems. Particularly, implementing the Hospital Readmissions Reduction Program has increased 30-day mortality despite the reduction in the readmission rate.[22,23] In prior relevant studies, we investigated the predictors of readmission and event results of AHF patients. Compared with the actual observed event occurrence rate, the risk predicted by the model is generally lower among all risk factors considered.[24] To tackle these challenges, a model with reasonably high accuracy and specificity that can closely combine patients' clinical characteristics is urgently needed to stratify the risk of AHF patients and predict the readmission probability to reduce the readmission rate of AHF patients.

This study aimed to establish a prediction model based on machine learning to assess and predict the risks of unplanned 30-day readmission in AHF patients to intervene in risk factors as early as possible and reduce the readmission rate.

RESULTS

Characteristics of study population

A total of 2232 patients diagnosed with AHF who were discharged from January 1, 2013, to December 31, 2021, were included in this study (Figure 1). The median age was 75.00 years (67.00, 81.00). In total, there were 150 (6.72%) patients with AHF readmitted within 30 days after hospitalization discharge. the median length of stay (LOS) was 8 days. The median age ($p = 0.002$), median LOS ($p < 0.001$), and level of NT.proBNP and D.dimer ($p = 0.072$ and $p = 0.002$) of readmission patients were higher than those of the group without readmission. The baseline clinical characteristics of the patients in the two groups are presented in Table 1.

From 2013 to 2021, diuretics and spironolactone formed the main part of essential in-hospital treatment of AHF, followed by beta-receptor blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. Two new drugs, Angiotensin receptor enkephalin enzyme inhibitor (ARNI) and sodium-glucose cotransporter 2 inhibitors (SGLT2i), were recorded for clinical use for AHF from 2018, with the increasing use of ARNI from 2018 to 2021 (Figure S1).

Establishment and determination of model

Based on the variance inflation factor and CatBoost-based recursive feature elimination 5-fold cross-validation for feature screening, in which there are 7 features with VIF>5, and then the remaining features are subjected to recursive feature elimination, and the best subset of features screened contains 43 features (Figure S2, Table S1).

A grid search on 5-fold cross-validation for parameters was performed to find the optimal model, and parameters producing the best result were chosen (Table S2). Establishing five models under the best parameters, including XGBoost, Catboost, Random Forest, LightGBM, and logistic regression (LR). The results of the five models were exhibited in Table 2. Area under the curve (AUC), accuracy, sensitivity, specificity, and brier score were defined to evaluate the models' performance. Of the five models, the XGBoost had the highest AUC of 0.763 (0.703–0.824), and the highest sensitivity of 0.660. This was followed by the CatBoost model with an AUC of 0.710 (0.635–0.782); and the LR model performed the worst with an AUC of 0.584 (0.498–0.674) (Figure 2). Consequently, the XGBoost model was chosen as the ultimate prediction model attributed to its optimal prediction performance compared to the other four algorithms.

Risk stratification of the patients with acute heart failure

XGBoost model was used to stratify risk levels of readmission of AHF patients within 30 days. Based on the maximal Youden's index as the optimal cut-off value (0.289) with a sensitivity and a specificity of 0.893 and 0.571, respectively, AHF patients were divided into high risk (>0.289) and low risk (<0.289) in Figure 3A. As shown by the Kaplan-Meier curve, the 7 days readmission rate of high-risk group was 2.7% and the low-risk group was 1.8%. The 14 days readmission rate of high-risk group was 4.6% and the low-risk group was 3.4%. The 30-day readmission rate increased progressively in the high-risk group, indicating that patients with higher predictive scores were more likely to have a readmission event (Figure 3B).

Analysis based on gender and length of hospital stay

In the gender sub-analysis, interventricular septum thickness (IVST), age, serum calcium ions, LOS, albumin, systolic blood pressure, left atrial anterior and posterior diameter (LAD), cholinesterase, creatinine, and creatine kinase isoenzyme (CK-MB) were significant predictors for readmission in both male and female patients. Cholinesterase and CK-MB were influential factors unique to male patients and neither was among the top 10 influential factors for female patients. Similarly, creatinine and d-dimer are specifically influences female patients and both are not among the top 10 influences for male patients. (Figures S3A and S3B). A higher risk is attached to males than females in 30-day readmission after discharging (Figure S3C).

LOS was highly correlated with readmission risk in AHF patients based on the risk levels analysis. Thus, we divided patients into long and short groups according to the LOS. Firstly, we based on SHAP to find the optimal cut-off value of 8 days (Figure S4C). After that, we divided the patients into long (>8 days) and short groups (≤8 days). The 7 days readmission rate of the long LOS group was 2.8%, and the short LOS

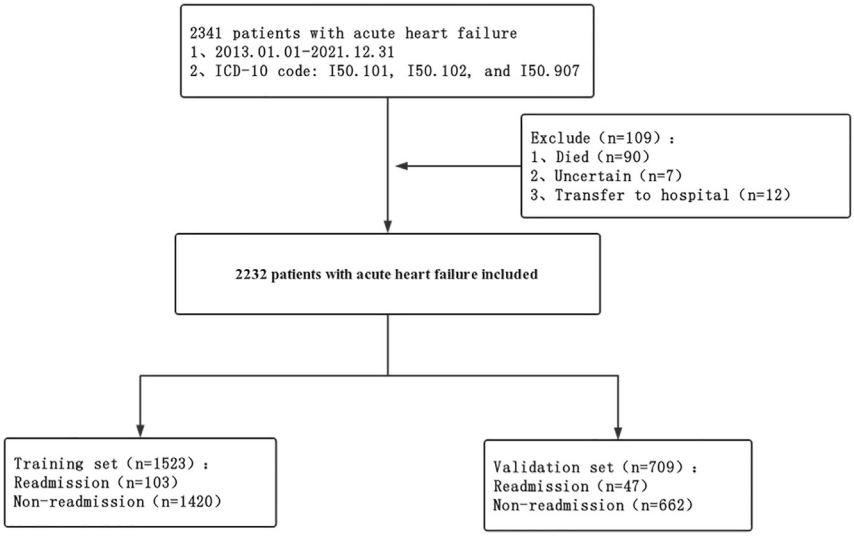

Figure 1. Patient inclusion flow chart

group was 1.8%. The 14 days readmission rate of the long LOS group was 5%, and the short LOS group was 3.1%. The long LOS group's patients have a higher risk of readmission within 30 days than the short LOS group, and the trend become more obvious along with the increase in the days' discharge (Figure S5C). The feature importance rankings are presented in Figures S5A and S5B. The top five risk factors affecting readmission of AHF patients in two groups are basically similar.

Model interpretation

In our study, we adopted the XGBoost model as the predictive model. According to the SHAP summary plots to unplanned 30-day readmission in AHF patients, the related features ranked by feature importance score (in descending order) were IVST, age, LOS, Ca, albumin, SBP, LAD, creatinine, cholinesterase (Figure 4A). Different colors represented different feature values. e.g., red means the high-risk value and blue means the low-risk value. As we can see from the chart, larger inter-ventricular septal thickness, older age, longer hospital stay, lower blood calcium concentration, and higher albumin concentration are associated with a higher 30 days readmission rate in patients with AHF (Figure 4B). The thickness of the inter-ventricular septum in most patients is mainly concentrated between 10 and 11mm, and the 30 days readmission risk of elderly heart failure patients increases significantly with age, with a similar normal distribution of hospital stays (Figures S4B and S4C).

This study displayed two individual samples with prediction and explanation computed by the force plot method of the SHAP package. The probability of readmission in 81-year-old AHF patients with mildly reduced ejection fraction, 29 days of hospitalization, a septal thickness of 10.15 mm, and activated partial thromboplastin time of 40.4 s being 84.94%, and SHAP value being 1.73 (Figure 4C). The probability of readmission in 69-year-old AHF patients with 3 days of hospitalization, the septal thickness of 10.08 mm, and normal left ventricular short-axis contractility (FS = 39.74%) being 11.30%, and SHAP value being −2.06 (Figure 4D).

DISCUSSION

AHF is the most common cause of hospitalization in patients aged 65 and above, associated with high rates of subsequent mortality and readmission.[25–27] A high readmission rate will not only significantly increase the medical financial burden, but also bring negative influence to AHF patients. This hard truth suggests that we need to further assist clinicians to intervene in the risk population as early as possible and minimize the risk of readmission. Therefore, we constructed a machine learning-based prediction model for predicting 30-day unplanned readmission risk in patients with AHF. Among the five machine learning risk prediction models constructed, the XGBoost model had the best prediction performance, with an AUC of 0.763 (95% CI:0.703–0.824), much higher than the other four prediction models. XGBoost has received widespread attention in clinical prediction model research due to its fast computational speed, strong generalization ability, and high prediction performance.[28] Meanwhile, this study used SHAP values to quantify risk factors, allowing clinicians to intuitively understand the impact of key features in the XGBoost model on outcomes. In terms of drug therapy, although diuretics and spironolactone are still the main drugs used in the treatment of patients with AHF, two new drugs, angiotensin receptor enkephalinase inhibitor (ARNI) and sodium-glucose cotransporter 2 inhibitor (SGLT2i), were found to be gradually used in the clinical treatment of AHF through the trend of patients' medication use in the recent years.

Overall, this study has the following contributions: first, this study successfully constructed a 30-day readmission risk prediction model for AHF patients by the XGBoost algorithm, and combined it with other state-of-the-art machine learning methods, such as the KNN (K-nearest neighbors) nearest-neighbor algorithm for missing-value filling, the hyperparameter tuning based on lattice searching, and the Yoden index-based risk stratification. The results show that these methods can effectively improve the model's performance in predicting readmission risk within 30 days in patients with AHF.

Table 1. Baseline clinical characteristics of patients with acute heart failure

Characteristic	Overall (*N* = 2232)	Non-readmission (*N* = 2082)	Readmission (*N* = 150)	P
Gender(%)				0.989
female	1151 (51.57)	1074 (51.59)	77 (51.33)	
male	1081 (48.43)	1008 (48.41)	73 (48.67)	
Age	75.00 [67.00,81.00]	75.00 [67.00,81.0]	76.50 [71.00, 83.00]	0.002
Smoking (%)				0.664
No	1701 (76.21)	1584 (76.08)	117 (78.00)	
Yes	531 (23.79)	498 (23.92)	33 (22.00)	
Drinking (%)				0.992
No	1863 (83.47)	1738 (83.48)	125 (83.33)	
Yes	369 (16.53)	344 (16.52)	25 (16.67)	
SBP	135.00 [118.00,145.01]	135.00 [118.00,145.79]	132.00 [116.00,140.12]	0.027
DBP	80.00 [70.00,88.05]	80.00 [70.00,88.88]	76.00 [67.24, 85.86]	0.005
Temperature	36.50 [36.40, 36.70]	36.50 [36.40, 36.70]	36.50 [36.30, 36.65]	0.222
RR	20.00 [20.00, 22.32]	20.00 [20.00, 22.39]	20.00 [20.00, 22.03]	0.946
LOS	8.00 [5.00, 12.00]	8.00 [5.00, 11.75]	10.00 [7.00, 14.00]	<0.001
Insurance (%)				0.196
medical insurance for residents	1513 (67.79)	1423 (68.35)	90 (60.00)	
medical insurance for employees	485 (21.73)	444 (21.33)	41 (27.33)	
other social insurance	150 (6.72)	137 (6.58)	13 (8.67)	
own expense	84 (3.76)	78 (3.75)	6 (4.00)	
Diabetes (%)				0.526
No	1921 (86.07)	1795 (86.22)	126 (84.00)	
Yes	311 (13.93)	287 (13.78)	24 (16.00)	
NYHA (%)				0.093
unknown	1963 (87.95)	1835 (88.14)	128 (85.33)	
II	15 (0.67)	15 (0.72)	0 (0.00)	
III	75 (3.36)	72 (3.46)	3 (2.00)	
IV	179 (8.02)	160 (7.68)	19 (12.67)	
NT.proBNP	4891.51 [1994.54, 8506.79]	4869.02 [1983.00,8412.86]	5385.95 [2698.81, 10000.79]	0.072
CRP	59.33 [14.04, 92.31]	60.33 [14.52, 93.22]	51.36 [9.69, 84.38]	0.052
D.dimer	0.35 [0.15, 1.00]	0.36 [0.15, 1.00]	0.20 [0.13, 0.80]	0.002
GGT	48.00 [25.70, 86.90]	48.00 [25.60, 86.75]	49.00 [27.12, 87.07]	0.658
ALT	24.00 [14.30, 40.62]	24.10 [14.50, 40.31]	22.00 [12.77, 41.22]	0.354
LDH	233.00 [198.00, 287.00]	233.00 [198.33, 286.42]	230.91 [194.25, 303.75]	0.719
TT	16.60 [15.49, 17.70]	16.60 [15.45, 17.70]	16.46 [15.62, 17.60]	0.61
APTT	31.10 [27.40, 37.30]	31.10 [27.40, 37.15]	31.15 [27.80, 38.72]	0.413
AST	29.00 [21.00, 41.00]	29.00 [21.00, 41.95]	27.35 [19.22, 37.08]	0.044
MCA	53.30 [20.83, 83.85]	53.30 [19.64, 84.39]	53.02 [28.82, 77.99]	0.791
Urea	7.40 [5.60, 10.51]	7.40 [5.60, 10.45]	8.23 [6.00, 11.17]	0.168
Uric.acid	395.45 [314.16, 510.63]	392.97 [314.01,508.98]	429.20 [325.98,554.8]	0.068
Cl	102.80 [99.14, 106.00]	102.90 [99.20, 106.10]	102.23 [98.90,105.72]	0.229
Triglyceride	1.09 [0.89, 1.35]	1.08 [0.88, 1.35]	1.13 [0.99, 1.35]	0.02
LEU	7.09 [5.38, 9.67]	7.10 [5.40, 9.78]	6.97 [5.09, 8.97]	0.226
Albumin	38.10 [34.60, 41.40]	38.00 [34.60, 41.40]	38.65 [35.06, 41.38]	0.311
P	1.07 [0.96, 1.26]	1.07 [0.95, 1.25]	1.09 [0.99, 1.36]	0.039

(*Continued on next page*)

Table 1. *Continued*

Characteristic	Overall (*N* = 2232)	Non-readmission (*N* = 2082)	Readmission (*N* = 150)	P
RBC	4.04 [3.60, 4.47]	4.04 [3.60, 4.48]	3.98 [3.59, 4.39]	0.415
Fibrinogen	3.00 [2.38, 4.06]	2.99 [2.38, 4.02]	3.14 [2.46, 4.27]	0.157
Creatinine	86.35 [68.00, 118.50]	86.00 [67.73, 116.52]	100.10 [71.65,141.50]	0.001
CK	98.85 [74.18, 144.00]	99.00 [74.39, 144.97]	96.85 [71.13, 126.17]	0.346
CK.MB	9.47 [2.50, 13.11]	9.30 [2.50, 13.10]	11.55 [2.87, 13.38]	0.063
TNT	0.05 [0.03, 0.16]	0.05 [0.03, 0.16]	0.05 [0.03, 0.10]	0.707
Cholinesterase	5.51 [5.02, 5.98]	5.51 [5.01, 5.98]	5.56 [5.05, 6.00]	0.429
GLU	6.80 [5.70, 7.80]	6.80 [5.69, 7.81]	6.81 [5.88, 7.77]	0.883
PLT	168.00 [131.54, 216.00]	167.00 [131.00,216.00]	176.00 [136.00,215.0]	0.328
Hemoglobin	114.00 [107.45, 130.00]	114.00 [107.68,130.00]	112.29 [106.00,128.0]	0.367
Ca	2.14 [2.11, 2.19]	2.14 [2.11, 2.19]	2.14 [2.09, 2.16]	0.032
EF	51.94 [45.33, 59.25]	52.00 [45.14, 59.48]	51.67 [46.49, 58.42]	0.862
FS	36.00 [28.00, 39.08]	35.78 [27.74, 39.00]	37.80 [32.00, 39.83]	0.001
LAD	36.97 [36.18, 40.00]	36.94 [36.15, 40.00]	37.21 [36.58, 38.21]	0.074
IVST	10.44 [10.10, 11.00]	10.43 [10.08, 11.00]	10.53 [10.36, 11.00]	0.006
Diuretics (%)				
No	130 (5.82)	118 (5.67)	12 (8.00)	0.319
Yes	2102 (94.18)	1964 (94.33)	138 (92.00)	
Cardiotonic (%)				0.131
No	696 (31.18)	658 (31.60)	38 (25.33)	
Yes	1536 (68.82)	1424 (68.40)	112 (74.67)	
CCB (%)				0.137
No	1793 (80.33)	1680 (80.69)	113 (75.33)	
Yes	439 (19.67)	402 (19.31)	37 (24.67)	
CPD (%)				0.088
No	914 (40.95)	863 (41.45)	51 (34.00)	
Yes	1318 (59.05)	1219 (58.55)	99 (66.00)	

Continuous variables were calculated as median (IQR).

SBP,systolic blood pressure; DBP,diastolic blood pressure; RR,respiratory rate; LOS,length of hospital s-tay; NYHA,New York Heart Association; CRP,C-reactive protein; GGT,gamma-glutamyltransferase; ALT,Alanineaminotransferase; LDH,lactate dehydrogenase; TT,Thrombin time; APTT, Activated partial thromboplastin time; AST,Aspartate aminotransferase; MCA,Microalbumin; LEU,White blood cell count; RBC,R-ed blood cell count; CK,creatine kinase; CK-MB,creatine kinase isoenzyme; TNT,Troponin T; GLU,gluc-ose; PLT,Total platelet count; EF,Ejection fraction; FS,shortening fraction; LAD,left atrial anterior and *p*-osterior diameter; IVST, ventricular septal thickness; CCB,Calcium channel blocker; CPD,Chinese *p*-atent drug; P,phosphorus.

Secondly, our research showed that the older the patients with AHF are, the higher the risk of readmission within 30 days. As for age, many studies have also shown that older age is associated with the risk of hospital readmission for various diseases,[29–31] which may be related to the basic complications of elderly patients, post-discharge syndrome, and other factors.[32] For the index of the LOS, our research found that the longer the LOS is, the higher the risk of readmission is within 30 days. In other studies, LOS and readmission rates have the same trend. A high readmission rate often has a previously high LOS, and a lower LOS is followed by a lower readmission rate,[33–35] which may be related to overall improved medical care and physical condition.

Finally, interpreting ML-based constructed predictive models and visualizing the prediction results to clinicians is always a challenge. Therefore, we applied the SHAP framework to the XGBoost prediction model for optimal prediction and interpretability to help clinicians better understand the decision-making process of the prediction model instead of blindly trusting the algorithm's results. In this study, we used SHAP values to rank the importance of features. The SHAP summary plot shows the importance of these features to the risk of readmission. A higher SHAP value means a higher contribution to readmission. This means that when using the model to predict the risk of readmission within 30 days for patients with AHF, it is more beneficial for clinicians to understand the outcome of the treatment and to individualize the patient's measures. In the study of readmission risk factors, we found that risk factors such as septal thickness, age, EF, length of hospitalization, LAD, albumin, and triglycerides were important in the prediction of readmission in patients with AHF, which is in line with the results of previous studies in the literature.[36] However, the risk factors such as systolic blood pressure, diastolic blood pressure, creatinine, blood phosphorus, prothrombin time, and AST included in this study have been rarely reported

Table 2. Performance of different models

Models	AUC (95% CI)	Accuracy	Sensitivity	Specificity	Brier
XGBoost	0.763(0.703–0.824)	0.709	0.66	0.713	0.197
LightGBM	0.729(0.662–0.800)	0.704	0.596	0.711	0.229
Random Forest	0.726(0.649–0.799)	0.783	0.489	0.804	0.187
CatBoost	0.710(0.635–0.782)	0.707	0.553	0.718	0.191
Logistic Regression	0.584(0.498–0.674)	0.616	0.553	0.621	0.232

AUC, area under the curve; XGBoost:eXtreme Gradient Boosting;CatBoost:Gradient Boosting+ Categorical Features; LightGBM: Light Gradient Boosting Machine.

in previous heart failure literature. Our findings suggest that these risk factors can improve the model's performance in predicting 30-day readmission risk in patients with AHF, stratify patients between high and low risk, and assist clinicians in targeting and individualizing treatment for patients.

In conclusion, this study developed an XGBoost model in predicting the risk of 30-day unplanned readmission for AHF patients, which showed more significant performance compared to traditional predictive tools. Age, LOS, and IVST are the most essential factors for 30-day readmission in AHF patients.

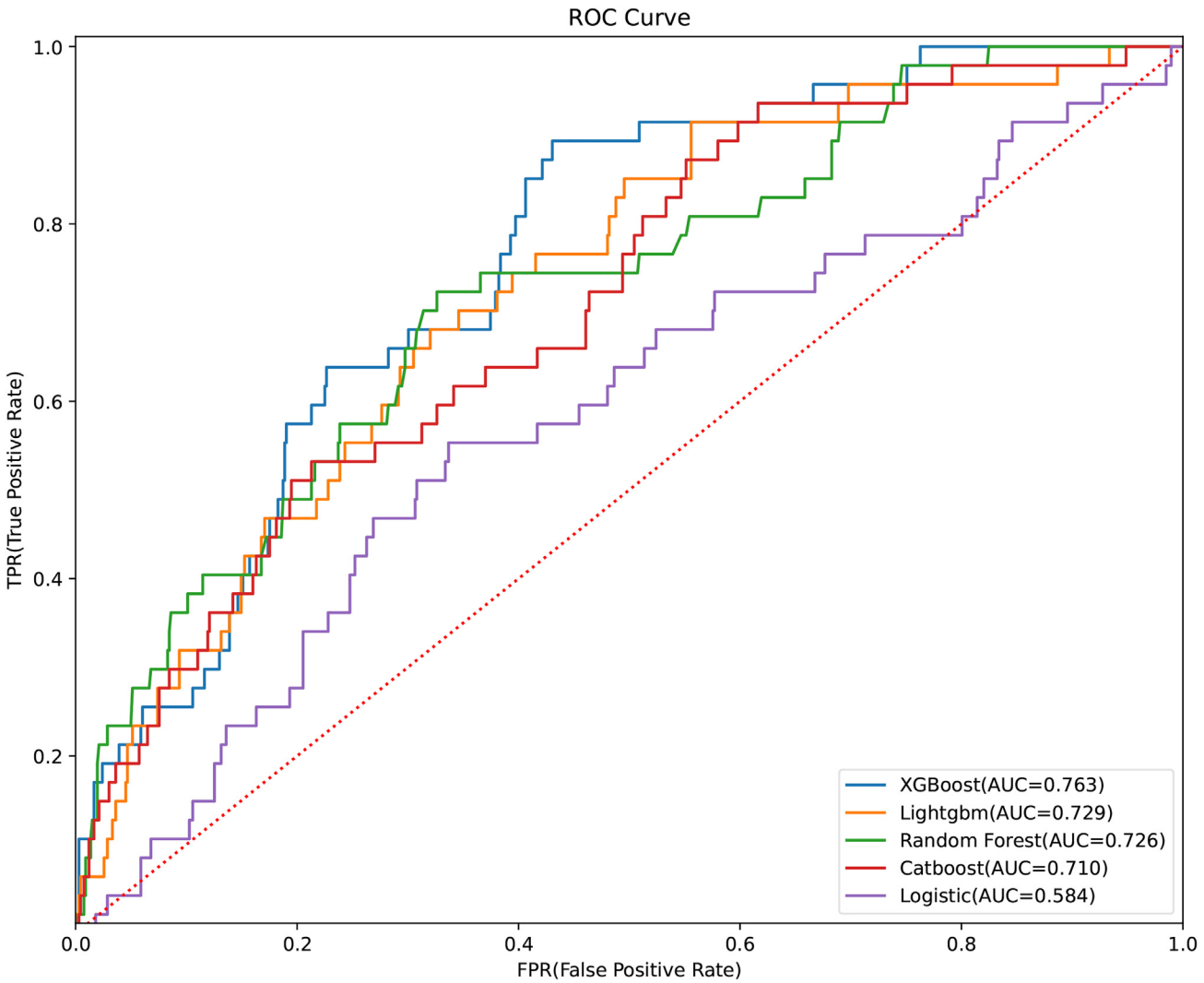

Figure 2. Receiver operating characteristic curve for five machine learning-based prediction models

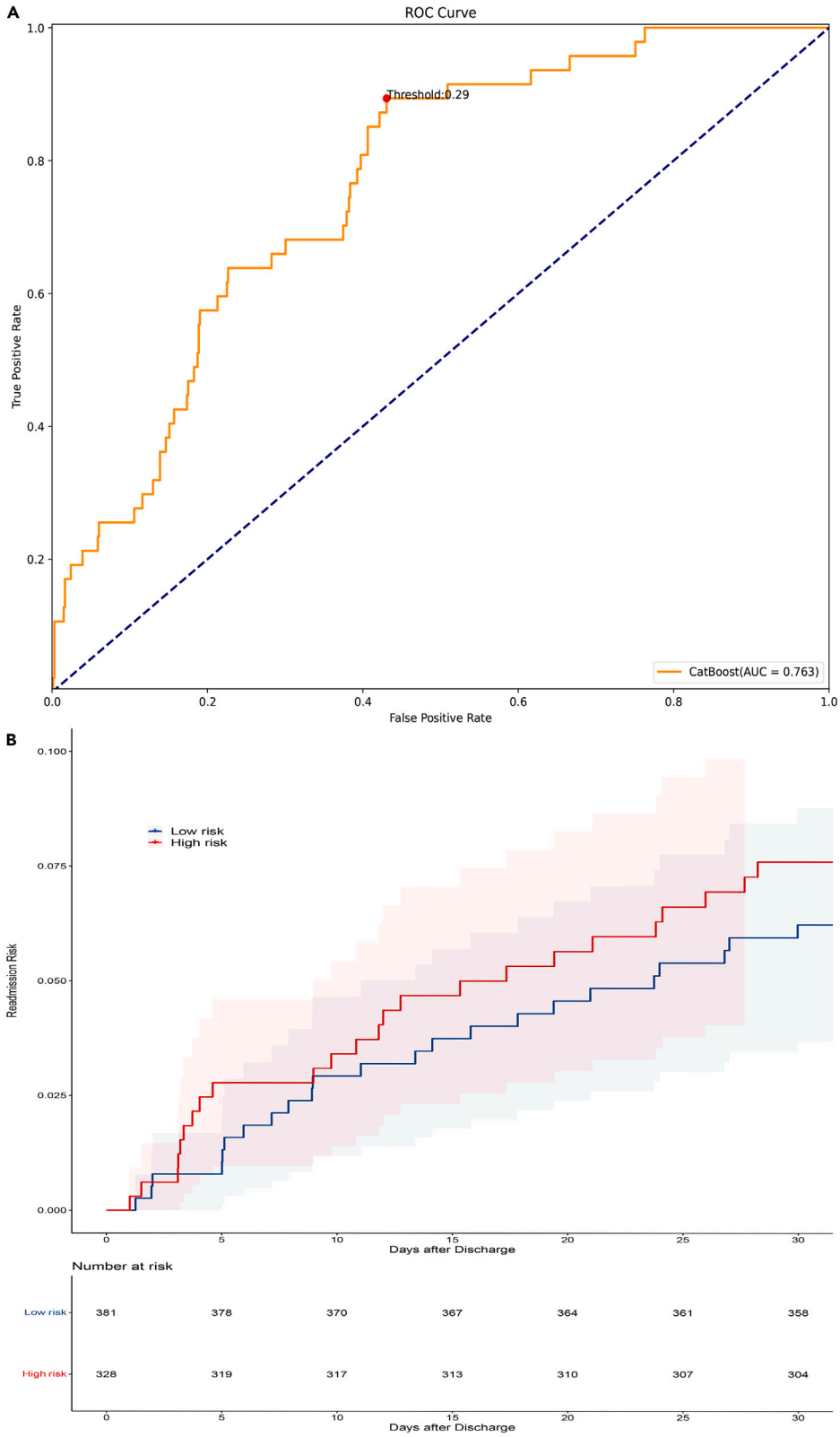

Figure 3. Risk stratification based on XGBoost

(A) The ROC of XGBoost.

(B) The Kaplan-Meier curve.

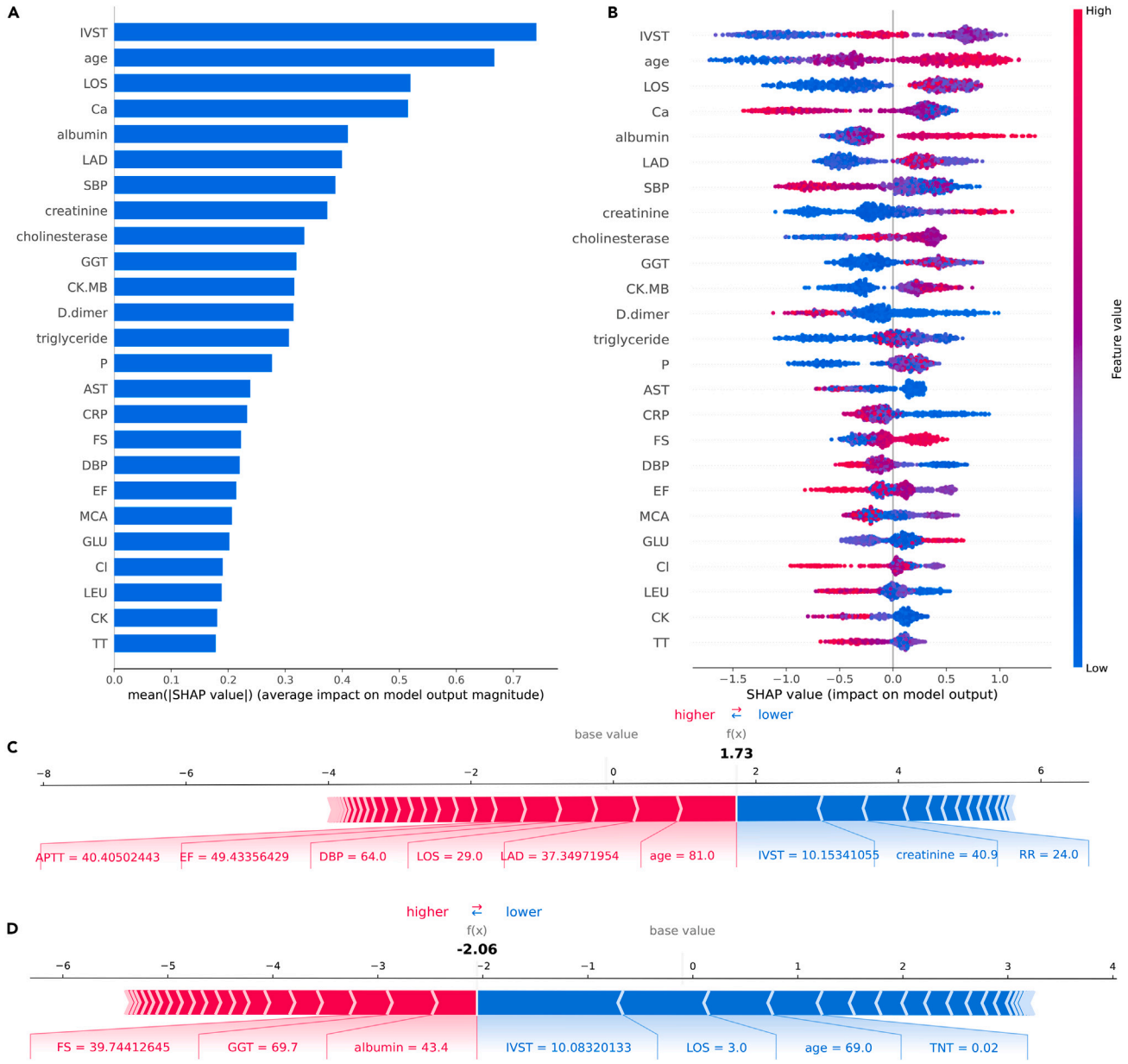

Figure 4. SHAP explanations for XGBoost model

(A) The most impactful features on prediction (ranked from most to least important).

(B) The distribution of the impacts of each feature on the model output. Within each row, each dot represents a patient. The colors of the dots represent the feature values: red for larger values and blue for lower.

(C and D) show the individualized predictions for two patients. The bars in red and blue represent risk factors and protective factors, respectively; longer bars represent greater feature importance.

Limitations of the study

There are some limitations to our study. Firstly, the data included in this study are static features, and laboratory test data and cardiac ultrasound data at different time points during hospitalization were not collected, which could not accurately show the changes in patients' conditions during hospitalization, and had a certain impact on the effect of predicting patients' readmission. Secondly, there is a situation of missing data of some indicators, and the algorithm is utilized to fill in the missing values, which may have some deviation from the actual clinical data. Finally, the generalization ability of the model has to be further verified.

STAR★METHODS

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2024.110281.

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AUTHOR CONTRIBUTIONS

Y.Z., T.X., and Y.W. was responsible for the drafting, reviewing of the manuscript and the statistical analysis; T.S., C.Y., H.L., M.D., B.Z., K.K., M.S., and Q.X. participated in the discussion part; T.L., F.K., and X.L. provided the study concept and design. All authors have read and approved the final version of the manuscript.

DECLARATION OF INTERESTS

All authors declare that they have no conflict of interest.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
Python	Version3.7.0	https://www.python.org/downloads/release/python-370/#/
Scikit-learn	Version1.2.2	https://scikit-learn.org/stable/whats_new/v1.2.html
Matplotlib	Version3.3.1	https://matplotlib.org/3.3.1/
Shap	Version0.41.0	https://github.com/shap/shap
R	Version4.2.0	https://mirrors.tuna.tsinghua.edu.cn/CRAN/#/
Tableone	Version 0.13.2	https://mirrors.tuna.tsinghua.edu.cn/CRAN/web/packages/tableone/index.html
Glmnet	Version4.1.7	https://mirrors.tuna.tsinghua.edu.cn/CRAN/web/packages/glmnet/index.html
Car	Version3.1.2	https://mirrors.tuna.tsinghua.edu.cn/CRAN/web/packages/car/index.html
Re-admission model	This study	Please request from lead contact (xiaozhuliu2021@163.com) for non-commercial, research purposes

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Xiaozhu Liu (e-mail: xiaozhuliu2021@163.com).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- All data reported in this paper will be shared by the lead contact upon request.
- This paper does not report original code.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Patient information

We collected a total of 2,232 patients hospitalized with acute heart failure from the Chongqing Medical University Medical Data Platform in Chongqing, China.(https://demo.yiducloud.com.cn/pub/#/register). There were 1,151 male patients (51.57%) and 1,081 female patients (48.43%), 98.86% of the patients were Han ethnic group, and the average length of stay was 8 days(Table S3).Inclusion criteria:(a)data between 1 January 2013 and 31 December 2021;(b)ICD-10 code:I50.101, I50.102, and I50.907; Exclusion criteria: (a) death during hospitalization,(b) transfer to another hospital during hospitalization, and(c) uncertain discharge status.Clinical characteristics information, including demographics(gender,age,etc), medical history(diabetes,NHYH,etc),current medication treatments(diuretics,calcium channel blocker,etc), echocardiographic results(LVEF,IVST,etc), and laboratory examination results(NT.proBNP,D.dimer,etc).

Ethical statement

This study was approved by the Ethics Committee of Chongqing Medical University (Ethics number: 2022194). Informed consent was waived by the Ethics Committee because of the retrospective nature of the study. This study was conducted in accordance with the principles of the Declaration of Helsinki.

METHOD DETAILS

Data preprocessing and feature selection

The structured database initially contained 117 clinical variables. During the data analysis, we used categorical features in the binary (0 or 1) format. For example, in the feature gender, 0 represents female, and 1 represents male. Characteristics related to the patient's personal history, such as smoking, drinking, and marriage, were encoded as 0 and 1 (yes = 1, no = 0). However, a patient who was widowed or divorced was encoded as 2. The insurance types were defined as 1 to 4 (resident medical insurance = 1, employee medical insurance = 2, other social insurance = 3, and all at their own expense = 4). Features with less than 30% missing values were retained and filled with the KNN algorithm (K = 5). The KNN proximity algorithm determines the nearest K samples with missing data based on Euclidean distance or correlation analysis and estimates the missing data for that sample by weighing the average of these K values.[37]

For feature screening,the covariance between individual features is first solved by calculating the Variance Inflation Factor (VIF) of each feature to exclude features with VIF>5. If the features have VIF>5, it indicates that there is a high degree of correlation between the individual variables, which may lead to the multicollinearity problem.[38] The remaining features are then subjected to further feature screening by CatBoost-based recursive feature elimination method to reduce the data dimensional and find the optimal feature combination. The main idea of recursive feature elimination is to repeatedly construct the model and score the features according to the feature coefficients at the end of each round of model training, eliminate the features with the lowest scores, and then repeat the process on the remaining features until all the features have been traversed.

Model development and performance evaluation

We developed five machine learning models to predict the 30-day specific readmission rate of AHF after feature screening, including eXtreme Gradient Boosting (XGBoost), Random Forest, Categorical Boosting (CatBoost), Light Gradient Boosting Machine (LightGBM), and logistic regression (LR). Using a random sampling method, all the included patients were divided into a training and a validation group at a ratio of 7:3. In the model training, Synthetic Minority Oversampling Technique (SMOTE) are used to mitigate the effect of imbalanced categories. We used grid-search combined with five-fold cross-validation to optimize the hyper-parameters of the machine learning model. Finally, the performance of each model was evaluated in the validation group.

The discrimination ability of the machine learning model was comprehensively evaluated by sensitivity, specificity, Area Under the Curve (AUC), and other evaluation indicators. Brier Score and calibration curves were obtained for each test set to evaluate prediction and calibration loss. The highest Youden index was used to define the optimal threshold and to distinguish patients with low and high machine-learning (ML) predicted risk. Kaplan-Meier curves and log-rank tests were used to evaluate statistical significance. At last, an interpretable method based on ML and SHapley Additive exPlanations (SHAP) method is deployed to calculate the 30-day readmission risk and generate a separate interpretation of model decisions.

QUANTIFICATION AND STATISTICAL ANALYSIS

In this study, we compared the baseline features of the patients with AHF between the readmission group and the non-readmission group. All continuous variables were calculated as median values (i.e., IQR). The difference was analyzed by Mann-Whitney U test. The categorical variables were expressed in quantities and percentages, and analyzed by the Chi-square test. For all tests, $P < 0.05$ was selected to indicate a statistically significant difference. We employ AUC (Area Under the Curve), Accuracy, Recall, and Specificity as the evaluation metrics to assess the performance of diverse algorithms.Statistical analyses were performed by R software(version 4.2.0) and Python software(version 3.7).