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ORIGINAL RESEARCH

Machine Learning-Driven Prediction of One-Year Readmission in HFrEF Patients: The Key Role of Inflammation

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Background: Heart failure with reduced ejection fraction (HFrEF) is a global health issue with high morbidity and frequent hospitalizations. Predicting one-year readmission risk is crucial for optimizing treatment and reducing costs.
Methods: We conducted a single-center retrospective study on adult HFrEF patients admitted to the Cardiovascular Department of the First Affiliated Hospital, Zhejiang University School of Medicine on January 2020 and March 2023. Feature selection was performed using LASSO regression, with inflammatory biomarkers (PLR, MLR, NLR, SII, SIRI) prioritized. Seven machine learning (ML) algorithms were trained and validated using a 7:3 dataset split; the metrics of the model included the area under the curve (AUC), accuracy, sensitivity, specificity, F1 score, and Brier score. SHapley Additive exPlanations (SHAP) analysis provided model interpretability. A network-based dynamic nomogram was developed to visualize predictive models.
Results: This study included 733 patients, of whom 231 (31.5%) were readmitted within one year. LASSO regression showed that the key predictors included age, BNP, New York Heart Association (NYHA) class, LVEF, PLR, MLR, AF history, and ACEI/ARB/ARNI usage. The Random Forest (RF) model performed best, with an AUC of 0.89 (95% confidence interval (CI): 0.86–0.93), an accuracy of 0.83, a sensitivity of 0.87, and a specificity of 0.80. SHAP analysis showed that BNP was the most influential feature, followed by NYHA class and LVEF, which were also important predictors. In addition, MLR and PLR also played an important role in prediction, once again confirming the important predictive role of MLR and PLR as inflammatory indicators for readmission within one year in HFrEF patients.
Conclusion: The ML-based RF model effectively predicted one-year readmission in HFrEF patients, with inflammation indicators playing an important role. Integrating such models into clinical practice could improve risk stratification, reduce readmissions, and enhancing patient outcomes.
Keywords: HFrEF, readmission, prediction model, machine learning

Introduction

Heart failure (HF) is a complex clinical syndrome characterized by the heart's inability to pump blood effectively to meet the body's metabolic demands.[1] It remains a significant global health challenge, affecting millions of individuals.[2] Among various types of HF, heart failure with reduced ejection fraction (HFrEF), defined as a left ventricular ejection fraction (LVEF) of less than 40%,[3] accounts for approximately 50% of all cases.[2] HFrEF is associated with persistent symptoms such as fatigue, shortness of breath, and fluid retention, which severely impair patients' quality of life.[4] Moreover, HFrEF patients often experience frequent hospital readmissions and high mortality rates,[5] posing a substantial burden on healthcare systems.

A follow-up study from Sweden shows that among 11,064 patients with HFrEF, 7,061 (63.8%) experienced all-cause readmission within one year, and these patients had the highest risk of cardiovascular (CV) and HF readmission within one year (compared with patients with heart failure with preserved ejection fraction (HFpEF) and heart failure with

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mildly reduced ejection fraction (HFmrEF)).[6] A study initiated by the American Heart Association shows that the all-cause readmission rate for HFrEF patients is 19.7% at 30 days and 59.6% at 1 year.[7] These high readmission rates reflect the unstable condition and often poor prognosis of HFrEF patients.[8,9] Frequent hospitalizations increase medical costs, expose patients to the risk of hospital-acquired infections, and further exacerbate their health problems. Therefore, early identification of patients with high risk of readmission and implementation of targeted interventions are crucial.

In recent years, growing evidence has highlighted the role of inflammation in the progression of HFrEF. Inflammatory biomarkers, such as platelet-to-lymphocyte ratio (PLR) and monocyte-to-lymphocyte ratio (MLR), have emerged as valuable indicators of disease severity and prognosis in HFrEF patients.[10] Elevated levels of these inflammatory markers are associated with worse clinical outcomes, including higher rates of hospitalization and mortality.[11] Additionally, machine learning (ML) has demonstrated efficacy in predicting outcomes for other cardiovascular conditions, including cardiac arrest where inflammatory markers were key predictors.[12] These findings emphasize the importance of incorporating inflammatory biomarkers into readmission risk prediction and intervention measures.

In this study, we aim to incorporate inflammatory biomarkers and develop a ML model to predict the one-year readmission risk of HFrEF patients. ML methods can improve the limitations of traditional prediction methods based on clinical experience and simple statistical models in accurately assessing the complex factors of HFrEF readmission.[13] By analyzing large-scale, high-dimensional datasets and revealing hidden patterns and relationships in the data, they demonstrate higher predictive ability in clinical environments.[14,15] A robust ML model can be used to early identify high-risk patients for HFrEF readmission and provide guidance for implementing personalized preventive measures.

Materials and Methods

Study Participants

This retrospective cohort study data come from the electronic medical record system of the First Affiliated Hospital of Zhejiang University School of Medicine, and included patients over 18 years old who were diagnosed with HFrEF,[3] New York Heart Association (NYHA) functional class II–IV in the cardiology department between January 2020 and March 2023. Exclusion criteria: 1) Patients lost to follow-up; 2) Patients with more than 30% missing important information; 3) Patients with a history of malignant tumors; 4) Patients with severe end-stage diseases of important organs; 5) Patients with mental disorders who were unable to cooperate.

Follow-Up and Outcomes

Readmission events were identified through a comprehensive review of electronic medical records, outpatient visit information, and telephone-based follow-up efforts. The primary outcome measure of this study was defined as readmission to the hospital within one year due to cardiovascular causes. Cardiovascular-related readmissions encompassed a range of conditions such as the deterioration of HF, the occurrence of cardiogenic shock, the presence of arrhythmias, episodes of myocardial ischemia, or other structural or functional heart disorders that necessitated inpatient hospitalization.

Predictor Variables

Through a comprehensive review of literature and analysis of clinical manifestations and biomarkers in HFrEF patients, we included relevant indicators that reflect the multifaceted characteristics of HFrEF and have potential impacts on patient prognosis.[16–20] Finally, a set of potential prognostic variables were identified, including patient demographics, medical history, echocardiographic parameters, hematological indicators, and the inflammatory and metabolic indicators selected due to the prognostic role of systemic inflammation in HF, including PLR, MLR, Neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII, platelet*neutrophil/lymphocyte), systemic inflammation response index (SIRI, neutrophil*monocyte/lymphocyte), and Triglyceride-glucose index (TYG, ln[total triglycerides (TG) (mg/dL)*fasting blood glucose (FBG) (mg/dL)]/2). The above includes a total of 50 predictive indicators.

Feature Selection and Model Development

Feature selection and dimensionality reduction were conducted using the least absolute shrinkage and selection operator (LASSO) combined with five-fold cross-validation. LASSO is widely used in medical prediction due to its ability to effectively select key features, particularly in high-dimensional data, while mitigating multicollinearity issues.[21,22] By integrating variable selection and regularization, LASSO reduces the risk of overfitting and retains only the most predictive features.[23,24] Features with coefficients reduced to zero were excluded, and the selected variables were visualized for clarity.

The dataset was randomly divided into a 7:3 ratio for the training set and validation set. The training set was used for model training, while the validation set was used for performance evaluation to prevent overfitting. To address class imbalance in the training data, the Synthetic Minority Over-sampling Technique (SMOTE) was applied exclusively to the training set to balance class distribution, while the validation dataset remained unaltered. Based on the features selected by the LASSO algorithm, prediction models were developed using seven ML algorithms: Random Forest (RF), Decision Tree (DT), XGBoost, Support Vector Machine (SVM), Logistic Regression (LR), LightGBM, and Multilayer Perceptron (MLP). Hyperparameters were tuned to optimize model performance. RF used n_estimators=100 and random_state=42. XGBoost parameters: use_label_encoder=False, objective="binary:logistic". LightGBM used random_state=42. SVM and MLP employed probability estimates. LR used "lbfgs" solver (max_iter=3000). DT used default settings with fixed random_state.

Model Interpretation

To improve the interpretability of ML models, SHapley Additive exPlanations (SHAP) analysis was used. SHAP, a game-theoretic approach, quantifies feature contributions to predictions. By calculating SHAP values, we determined each predictor's impact on one-year readmission probability.

Three visualization methods were applied. The SHAP Summary Plot ranks features by average absolute SHAP values to show overall importance, with color for feature value levels. The SHAP Waterfall Plot breaks down feature impacts for a single prediction, starting from the expected output. The SHAP Force Plot shows how features shift predictions relative to the baseline risk. In this study, SHAP plots of all samples were stacked horizontally by output values for a global view of multiple samples' feature contributions.

Development of a Web-Based Dynamic Nomogram

To facilitate clinical application, a web-based dynamic nomogram was developed. This tool integrates the ML model's predictive capabilities, allowing healthcare professionals to input patient-specific information and obtain real-time risk estimates for one-year readmission. The interactive interface enables users to modify input values and instantly observe changes in predicted risk probabilities. This system serves as a clinical decision support tool, helping medical professionals stratify patients based on risk and optimize individualized management strategies.

Statistical Analysis

Statistical analyses were performed using Python 3.9.13, R 3.6.4, and SPSS 26.0. Missing values were addressed using multiple imputation, and all features were standardized for normalization. Continuous variables following a normal distribution were presented as mean ± standard deviation, and between-group differences were assessed using the independent samples t-test. Non-normally distributed continuous variables were expressed as median (M) and interquartile range ($P25$, $P75$), with between-group comparisons conducted using the Mann–Whitney U-test. Categorical variables were reported as frequencies and percentages (%), and between-group differences were analyzed using the chi-square test or Fisher's exact test. A two-sided P-value < 0.05 was considered statistically significant.

Results

Baseline Characteristics

The flow diagram is shown in Figure 1. This study included 733 eligible patients, with a median age of 71 years (range: 18 to 99 years) and an average age of 68.67 years. Men accounted for 65.8% of the participants. Most patients had comorbidities such as hypertension (48.4%), coronary heart disease (36.4%), and AF (32.3%). A total of 231 patients

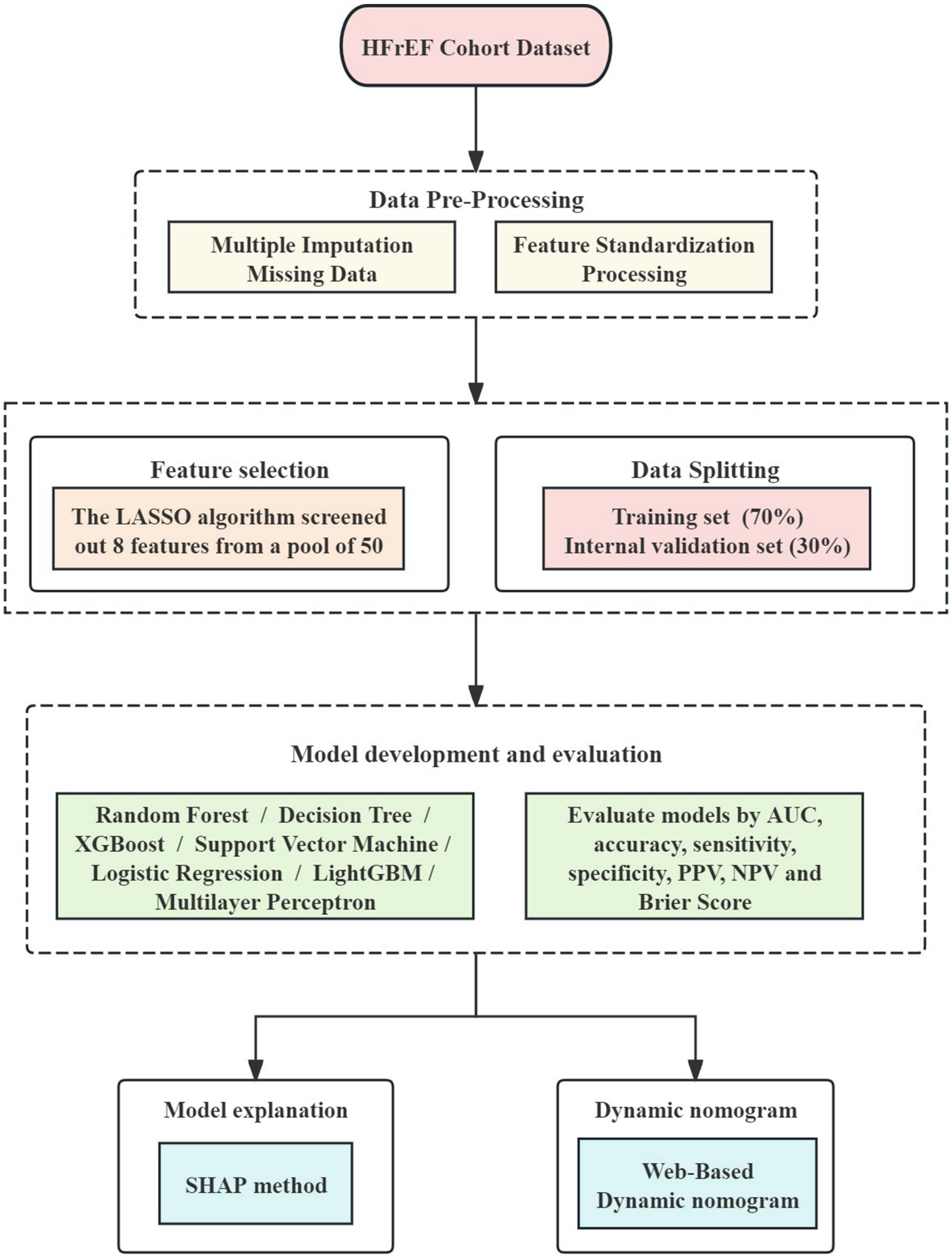

Figure 1 Flow chart of the study design.

(31.5%) were readmitted due to cardiovascular reasons within one year after discharge. According to their readmission status, patients were divided into a non-readmission group (n=502) and a readmission group (n=231).

The readmission cohort was significantly older (mean age 72.6 vs 66.9 years) and had higher NYHA class IV prevalence (41.1% vs 15.3%, both P<0.001; see Table 1). The readmission group also demonstrated a significantly higher prevalence of MI, CHD, AF, and stroke ($P < 0.05$). Furthermore, significant differences were observed in medication history, particularly in the administration of Angiotensin converting enzyme inhibitors (ACEI)/ Angiotensin II Receptor Blockers (ARB)/ Angiotensin Receptor-Neprilysin Inhibitor (ARNI), beta-blockers, and anticoagulants ($P < 0.05$). Additionally, notable differences were identified between the two groups in various clinical and inflammatory markers, including LVEF, NLR, PLR, MLR, SII, SIRI, TYG, CRP, and BNP ($P < 0.05$).

Table 1 Baseline characteristics of Non-readmission and Readmission groups

Variables	Non-Readmission Group (n=502)	Readmission Group (n=231)	*P*-Value
Age	66.9±14.8	72.6±13.3	<0.001
Gender			0.472
Male	331(65.9%)	151(65.4%)	
Female	171(34.1%)	80(34.6%)	
BMI, kg/m^2	23.8(21.1, 26.3)	23.7(20.9, 25.8)	0.277
Smoking (n, %)			0.364
No	347(69.1%)	156(67.5%)	
Yes	155(30.9%)	75(32.5%)	
Drinking (n, %)			0.021
No	436(86.9%)	213(92.2%)	
Yes	66(13.1%)	18(7.8%)	
NYHA class (n, %)			<0.001
II	198(39.4%)	40(17.3%)	
III	227(45.2%)	96(41.6%)	
IV	77(15.3%)	95(41.1%)	
SBP(mmHg)	121.0(107.0, 138.0)	121.0(106.0, 136.0)	0.728
DBP(mmHg)	73.5(65.0, 83.0)	72.0(66.0, 82.0)	0.783
HR	82.0(70.0, 96.0)	82.0(71.0, 96.0)	0.729
Medical history (n, %)			
Hypertension	240(47.8%)	115(49.8%)	0.338
Angina	38(7.6%)	21(9.1%)	0.285
MI	63(12.5%)	41(17.7%)	0.041
CHD	168(33.5%)	99(42.9%)	0.009
AF	139(27.7%)	98(42.4%)	<0.001
PCI	92(18.3%)	54(23.4%)	0.069
Pacemaker	49(9.8%)	29(12.6%)	0.156
Stroke	35(7.0%)	31(13.4%)	0.004
DM	124(24.7%)	66(28.6%)	0.154
COPD	29(5.8%)	20(8.7%)	0.100
Anemia	58(11.6%)	29(12.6%)	0.391
Diuretic	395(78.7%)	193(83.5%)	0.074
Aldosterone-receptor blocker	359(71.5%)	170(73.6%)	0.312
Vasodilator drugs	57(11.4%)	30(13.0%)	0.301
Positive inotropic drugs	67(13.3%)	35(15.2%)	0.292
ACEI/ARB/ARNI	360(71.7%)	118(51.1%)	<0.001
Beta-blockers	307(61.2%)	124(53.7%)	0.034
Antiplatelet Drugs	208(41.4%)	95(41.1%)	0.501
Anticoagulant	170(33.9%)	94(40.7%)	0.044
Lipid-lowering agent	268(53.4%)	137(59.3%)	0.078
CCB	40(8.0%)	17(7.4%)	0.451
Echocardiographic parameters M(*P*25, *P*75)			
LVEF (%)	32.0(27.0,35.0)	29.0(25.0,33.0)	<0.001
LVEDd	68.0(62.0,75.7)	68.0(61.0,76.0)	0.623
Inflammatory and Metabolic Indicators M(*P*25, *P*75)			
NLR	3.0(2.1,4.8)	4.2(2.5,7.4)	<0.001
PLR	128.3(95.3,186.2)	155.7(104.8,229.4)	<0.001
MLR	0.3(0.3,0.5)	0.5(0.3,0.7)	<0.001
SII	554.0(348.1,946.3)	703.8(405.1,1411.5)	<0.001

(*Continued*)

Table 1 (Continued).

Variables	Non-Readmission Group (n=502)	Readmission Group (n=231)	*P*-Value
SIRI	1.5(0.9,2.5)	2.0(1.3,4.0)	<0.001
TYG	8.6(8.2,9.1)	8.6(8.2,8.9)	0.010
Hematological Indicators M(*P*25, *P*75)			
Scr (umol/L)	93.0(76.0,118.0)	99.0(82.0,134.0)	0.621
UA (umol/L)	402.0(320.8,491.0)	386.0(325.0,489.0)	0.247
TC (mmol/L)	2.8(1.3,4.0)	2.3(1.1,3.7)	0.288
TG (mmol/L)	2.3(1.3,3.7)	2.3(1.1,3.5)	0.261
LDL-C (mmol/L)	2.0(1.5,2.7)	1.9(1.3,2.5)	0.431
FBG (mmol/L)	5.2(4.6,6.7)	5.5(4.7,7.0)	0.640
K (mmol/L)	4.1(3.8,4.4)	4.1(3.8,4.4)	0.451
Na (mmol/L)	142.0(139.0,143.0)	141.0(139.0,143.0)	0.118
Cl (mmol/L)	104.0(101.0,106.0)	104.0(101.0,106.0)	0.104
CRP (mmol/L)	3.4(1.1,8.9)	6.5(1.8,16.8)	0.001
BNP (pg/mL)	189.9(127.9,648.2)	1009.0(399.0,2925.9)	<0.001

Abbreviations: BMI, body mass index; NYHA, New York Heart Association; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; MI, myocardial infarction; CHD, coronary heart disease; AF, atrial fibrillation; PCI, percutaneous coronary intervention; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; CCB, calcium channel blocker; LVEF, left ventricular ejection fraction; LVEDd, left ventricular end-diastolic dimension; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocytes-to-lymphocytes ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; TYG, triglyceride-glucose; Scr: serum creatinine; UA, uric acid; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; FBG, fast blood glucose; K, Kalium; Na, Natrium; Cl, Chlorine; CRP, C-reactive protein; BNP, brain natriuretic peptide.

Feature Selection with Model Development and Comparison

The LASSO regression algorithm was used for feature selection, which identified 8 key predictive factors with non-zero coefficients (Figure 2). The selected features include age, NYHA class, LVEF, PLR, MLR, BNP, ACEI/ARB/ARNI usage, and AF history.

Seven ML models were developed and compared: RF, DT, XGBoost, SVM, LR, LightGBM, and MLP. Evaluate model performance using AUC, accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and F1 scores (Table 2). Figure 3 shows the ROC curves of seven models, demonstrating the discriminative ability of each model.

Compared with other models, the RF and LightGBM models demonstrated superior performance in predicting the readmission risk of HFrEF patients. Specifically, the RF model achieved the highest AUC value of 0.89 (95% CI: 0.86–0.93), indicating excellent discriminative ability to distinguish between patients with and without readmission risk. The RF model also outperformed other models in terms of accuracy (0.83), sensitivity (0.87), and specificity (0.80). The high sensitivity indicates that the RF model is effective in correctly identifying patients at risk of readmission, while the high specificity reflects its ability to accurately rule out patients who are not at risk. Additionally, the RF model achieved the lowest Brier Score (0.132), indicating the highest overall predictive accuracy and reliability. Furthermore, it demonstrated the highest positive predictive value (PPV, 0.79) and negative predictive value (NPV, 0.87), suggesting strong clinical utility in both confirming and excluding readmission risk. Overall, the RF model performs the best in predicting the readmission risk of HFrEF patients.

Model Interpretability

Figure 4A and B provide a global explanation of the size of the features that affect the model output. Figure 4A shows the average impact of each feature on the model output (average SHAP value). SHAP analysis revealed BNP as the most

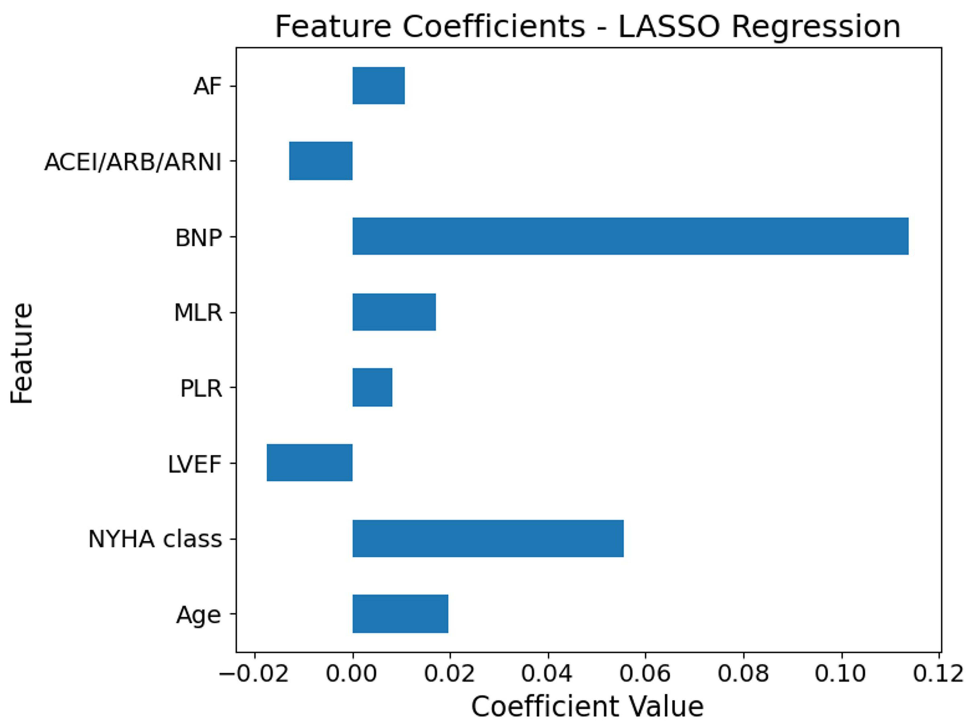

Figure 2 Predictor selection and coefficient magnitudes from LASSO regression modeling.
Abbreviations: AF, atrial fibrillation; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; BNP, brain natriuretic peptide; MLR, monocytes-to-lymphocytes ratio; PLR, platelet-to-lymphocyte ratio; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

impactful predictor of HFrEF outcomes (mean |SHAP value| approximately equal to 0.16), followed by NYHA class, LVEF, and inflammatory markers (MLR, PLR). Figure 4B demonstrates the directional effects of these features, where red/blue data points indicate higher/lower values of each variable, respectively. For example, elevated BNP (red) consistently increased predicted risk, while higher ACEI/ARB/ARNI (blue) showed protective effects.

Figure 5A and B provide local explanations of how specific features affect the risk prediction of readmission for each patient. Figure 5A shows how the model output of a specific sample is accumulated from the contributions of various features. For this sample, the contribution of NYHA class is 0.22 and the contribution of BNP is 0.1. The final model output (f (x)) is 0.8, and the baseline value (E (f (X)) is 0.486. Figure 5B is a graph obtained by sorting all samples according to their output values, rotating and stacking them together. Each position on the x-axis represents a sample of the data. Red represents a positive contribution to the prediction results, while blue represents a negative contribution to the prediction results.

Table 2 Comparative Analysis of Performance Results for Different Machine Learning Models

Models	AUC	Accuracy	Sensitivity	Specificity	PPV	NPV	F1 Score	Brier Score
RF	0.89	0.83	0.87	0.80	0.79	0.87	0.82	0.132
DT	0.73	0.73	0.68	0.78	0.73	0.74	0.70	0.278
XGBoost	0.86	0.79	0.83	0.76	0.75	0.84	0.79	0.156
SVM	0.83	0.75	0.77	0.73	0.72	0.79	0.74	0.170
LR	0.82	0.72	0.76	0.69	0.72	0.77	0.72	0.177
LightGBM	0.87	0.82	0.84	0.80	0.78	0.85	0.81	0.148
MLP	0.83	0.76	0.81	0.73	0.72	0.81	0.86	0.172

Abbreviations: RF, Random Forest; DT, Decision Tree; XGBoost, extreme gradient Boosting; SVM, Support Vector Machine; LR, Logistic Regression; LightGBM, light gradient boosting machine; MLP, Multilayer Perceptron; AUC, the area under the receiver-operating characteristic; PPV, positive predictive value; NPV, negative predictive value.

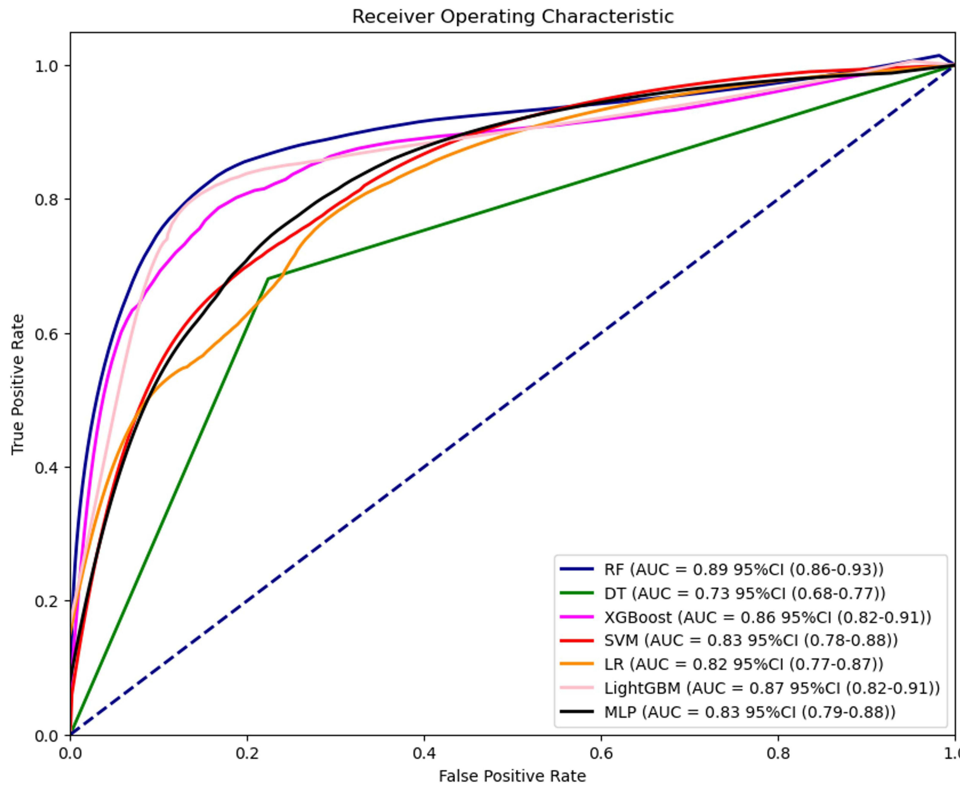

Figure 3 ROC curves of seven machine learning algorithms for 1-year HFrEF readmission prediction.
Abbreviations: RF, Random Forest; DT, Decision Tree; XGBoost, extreme gradient Boosting; SVM, Support Vector Machine; LR, Logistic Regression; LightGBM, light gradient boosting machine; MLP, Multilayer Perceptron; AUC, the area under the receiver operating characteristic; CI, confidence interval.

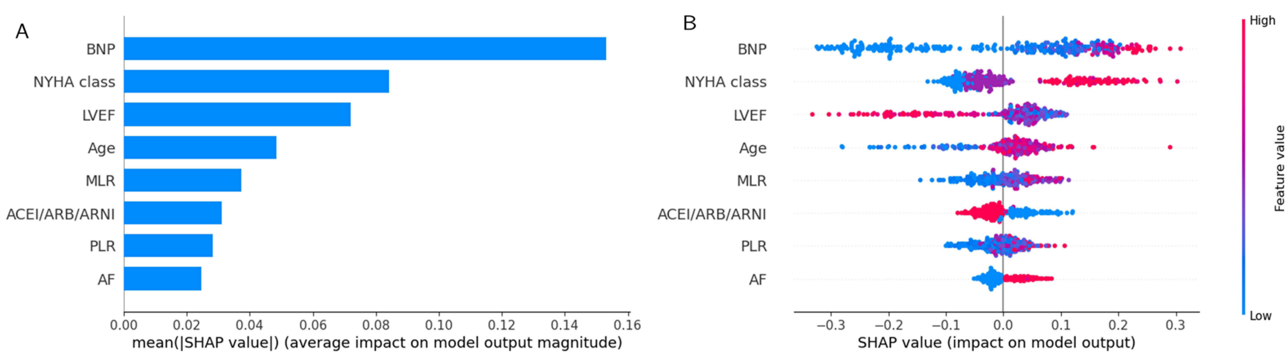

Figure 4 Global model explanation by the SHAP method. (**A**) SHAP summary bar plot. (**B**) SHAP summary dot plot.
Abbreviations: BNP, brain natriuretic peptide; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; MLR, monocytes-to-lymphocytes ratio; PLR, platelet-to-lymphocyte ratio; AF, atrial fibrillation; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor.

Generation Example of Dynamic Nomogram

In order to more intuitively represent the predictive impact of various features in the RF model on readmission risk, we constructed a dynamic bar chart. Users can input their personal characteristics (such as age, NYHA class, LVEF, PLR, MLR, BNP level, ACEI/ARB/ARNI and AF) on the website, (https://hfref.shinyapps.io/DynNomapp/) to generate real-time predictions and provide corresponding prediction probabilities (Figure 6).

Figure 6A presents an interactive nomogram where users can adjust clinical variables (Age, NYHA class, LVEF, PLR, MLR, BNP, ACEI/ARB/ARNI usage, and AF history) by sliders to simulate patient profiles. Figure 6B depicts the 95% Confidence Interval for the predicted readmission probability, with a black line for the point estimate and horizontal

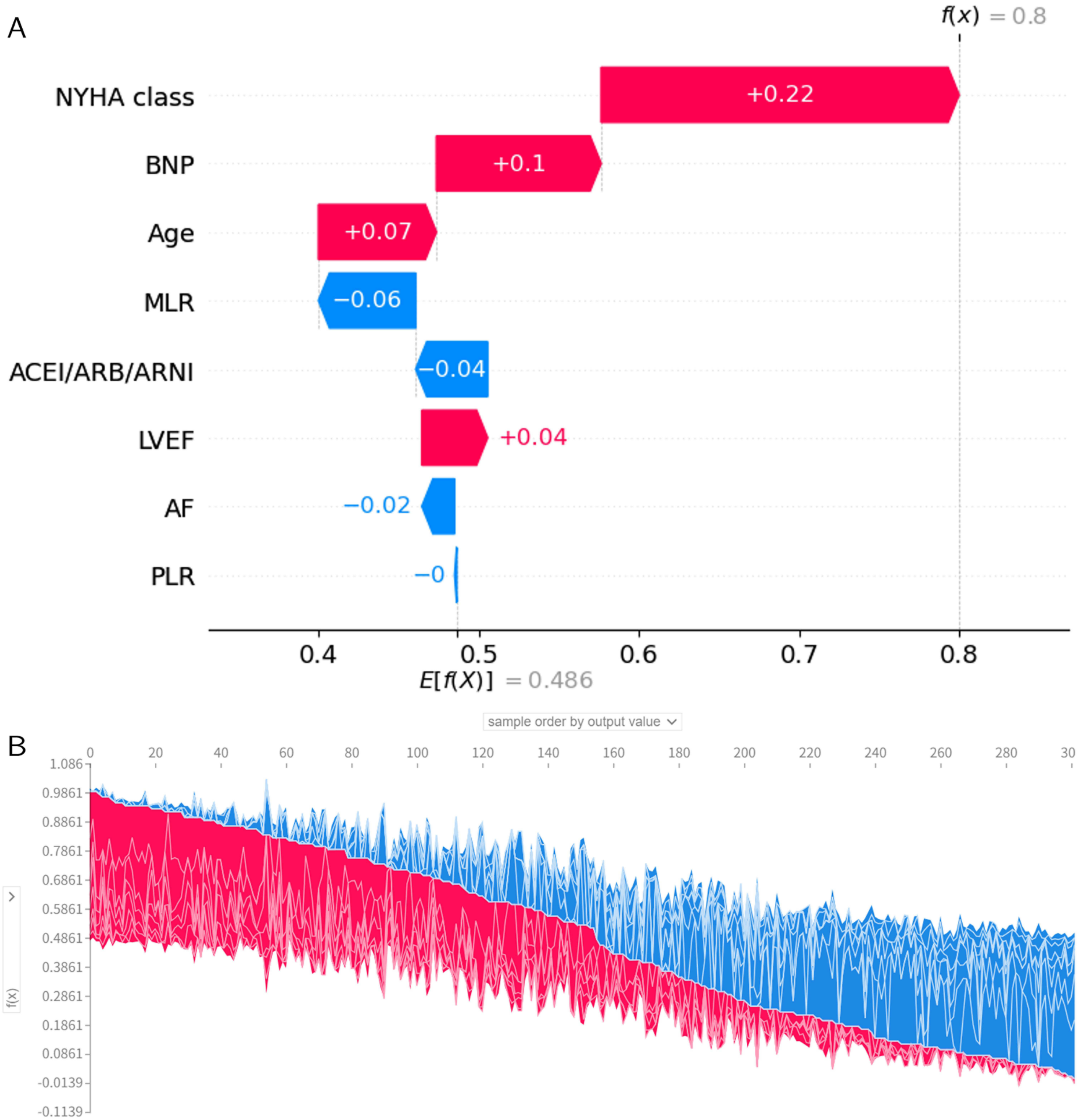

Figure 5 Local model explanation by the SHAP method. (**A**) waterfall plot. (**B**) Force plot.
Abbreviations: BNP, brain natriuretic peptide; MLR, monocytes-to-lymphocytes ratio; PLR, platelet-to-lymphocyte ratio; NYHA, New York Heart Association; AF, atrial fibrillation; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; LVEF, left ventricular ejection fraction.

bars indicating the confidence range. Figure 6C includes a Numerical Summary listing input variables with their SHAP values and a Model Summary showing the predicted probability with its 95% confidence interval.

There was a 70-year-old male patient with NYHA class III, a BNP level of 1008 pg/mL, an MLR of 1, a PLR of 299, an LVEF of 30%, no ACEI/ARB/ARNI usage and AF history. The model accurately predicted that this patient had a 57.7% probability of being readmitted within one year. Analyzing the reasons, key variables such as the patient's older age, lower LVEF, higher BNP level, NYHA class, higher PLR, MLR and histories of AF were consistent with the risk

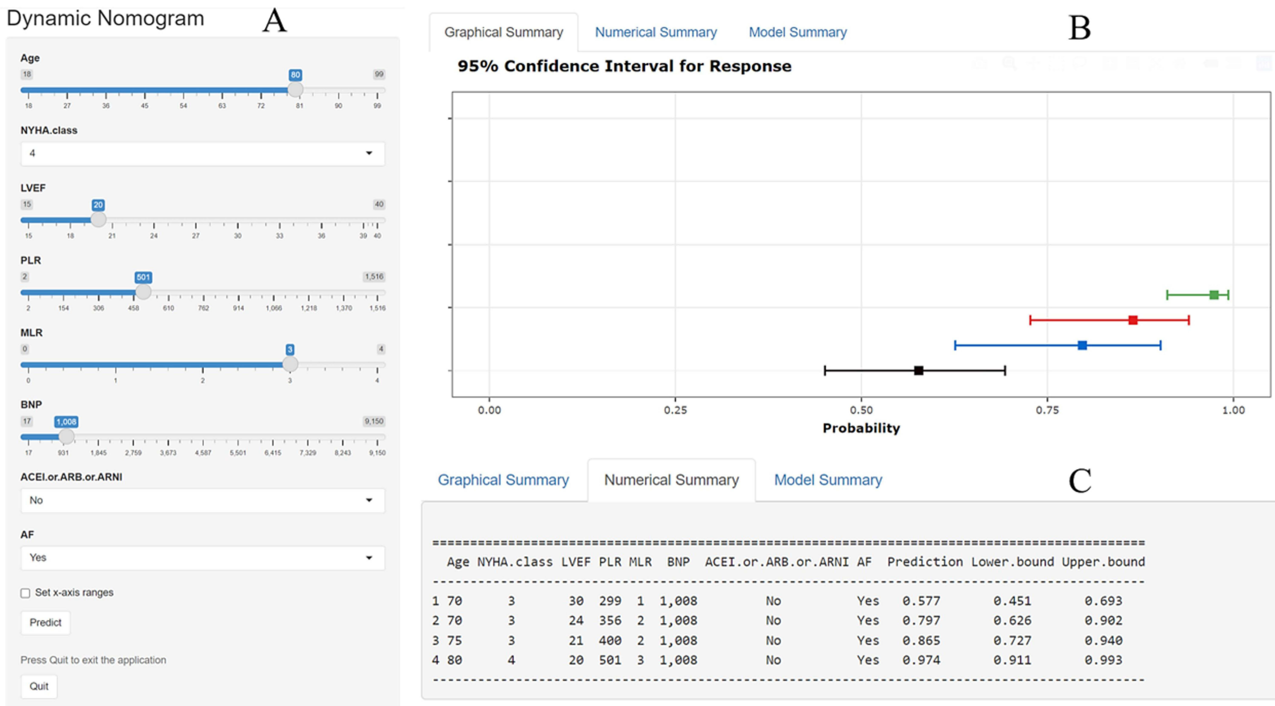

Figure 6 Web-based dynamic nomogram used for predicting 1-year readmission in patients with HFrEF. (**A**) Input page: Enter the patient's information according to the relevant variables on this page. (**B**) Graphical summary: This page shows the probability of a patient being readmitted for heart failure and the 95% confidence interval. (**C**) Numerical summary: Display the specific values of the patient's indicators and predicted outcomes.
Abbreviations: NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; PLR, platelet-to-lymphocyte ratio; MLR, monocytes-to-lymphocytes ratio; BNP, brain natriuretic peptide; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; AF, atrial fibrillation.

factors for readmission predicted by the model. These factors combined enabled the model to accurately predict the patient's readmission situation.

Discussion

This study developed a ML model for predicting the risk of readmission within one year in patients with HFrEF. By integrating Patient Demographics, Medical History, Echocardiographic Parameters, Hematological Indicators, and Inflammatory Indicators, our model demonstrated strong predictive performance, with the RF algorithm achieving the highest AUC (0.89) and accuracy (0.83). The findings highlight the potential of ML techniques in risk stratification and early intervention planning for HFrEF patients. At the same time, the study identified several significant predictors of one-year readmission risk, including BNP, NYHA class, LVEF, MLR, age, PLR, AF history, and ACEI/ARB/ARNI usage.

Both biochemical and clinical indicators demonstrated strong predictive value in our cohort. BNP has long been established as a critical biomarker in the diagnosis and prognosis of HF.[25] Elevated BNP levels indicate increased ventricular wall stress and correlate with higher mortality and readmission rates. Our research confirms that BNP is a strong predictor of readmission, indicating a high correlation between BNP and the prognosis of HFrEF patients, which is consistent with multiple current studies.[26,27] BNP guided therapy has been proposed as a strategy for optimizing treatment, indicating that enhanced monitoring of BNP levels after discharge can help reduce hospitalization rates and identify high-risk patients.[28,29] NYHA functional class is a widely used clinical indicator of HF severity and a well-documented predictor of readmission.[30] In our study, patients with NYHA class III or IV had a significantly higher risk of readmission, which is consistent with previous reports demonstrating that worsening functional status is associated with poor prognosis.[4] The association between NYHA class and readmission underscores the importance of aggressive symptom management and close follow-up in these patients. These findings support: (1) BNP monitoring for risk stratification, and (2) intensified follow-up for NYHA III–IV patients.

LVEF remains a cornerstone parameter in HF classification and risk stratification.[3] Our study demonstrated that lower LVEF was significantly associated with higher readmission risk, reinforcing prior evidence that reduced systolic function is linked to adverse outcomes.[31,32] Recent advancements in guideline-directed medical therapy (GDMT) have shown benefits in improving LVEF and reducing readmissions, emphasizing the need for optimized pharmacological interventions.[33]

Inflammatory markers, including NLR, PLR, MLR, SII, and SIRI, have gained increasing attention in cardiovascular disease research.[34] Our study highlights the key predictive value of MLR and PLR in identifying one-year readmission risk among HFrEF patients, underscoring the critical role of inflammation in HF progression. Specifically, elevated MLR and PLR levels were strongly associated with increased readmission risk, suggesting that monocyte- and platelet-driven inflammatory pathways may significantly contribute to adverse outcomes in HFrEF. The association between elevated PLR levels and adverse cardiovascular outcomes is consistent with evidence suggesting that high PLR is linked to severe atherosclerosis in patients with asymptomatic systolic HF.[35] Additionally, the predictive value of MLR aligns with findings demonstrating that MLR is an independent predictor of in-hospital mortality of HF patients, with a threshold of MLR > 0.48 identified as the strongest indicator of both mortality risk and prolonged hospitalization.[36] These studies underscore the critical role of inflammation, as reflected by PLR and MLR, in driving myocardial remodeling and exacerbating HF outcomes.

ACEI/ARB/ARNI usage and AF history were also retained as key variables. The protective effect of ACEI/ARB/ARNI aligns with established evidence indicating their benefits in reducing hospitalization and mortality in HFrEF patients.[37] Meanwhile, the presence of AF has been linked to an increased risk of hemodynamic instability and recurrent cardiovascular events, necessitating close monitoring.[38]

Traditional risk prediction models, such as Cox proportional hazards models, have been widely used in clinical practice but are limited by their assumptions of linearity and independence among predictors.[39] However, our ML-based methods can effectively capture the complex nonlinear interactions between multiple risk factors, which has been confirmed by previous studies.[40,41] In addition, this study used LASSO regression for feature selection, minimizing overfitting by retaining only the most relevant predictive factors and improving the interpretability of the model.

Prior studies have proposed readmission risk models for HFrEF patients, often incorporating demographic and clinical variables.[42,43] However, these models often lack biomarkers and advanced echocardiographic parameters. By integrating a comprehensive panel of predictors, our model provides a more comprehensive assessment of readmission risk.

The ML model developed in this study can assist clinical doctors in real-time risk assessment, improve decision-making efficiency, and optimize resource allocation; It can also accurately identify high-risk patients for targeted interventions. In addition, by integrating key clinical and biochemical predictive factors, personalized management strategies can be provided for patients, and early identification of patients at risk of readmission provides an opportunity for implementing preventive measures. Notably, elderly patients showed attenuated clinical improvement despite similar therapeutic intensity, possibly reflecting accumulated comorbidities and physiological aging processes.[44] This warrants specialized management approaches.

This study has several limitations. Firstly, retrospective study design may introduce biases such as incomplete data or selection bias, but retrospective analysis is crucial for result based model validation. We also ensure the reliability of data and models by incorporating comprehensive data as much as possible and rigorously cleaning and organizing the data. Secondly, the single-center design represents a key limitation that may restrict generalizability, necessitating external validation in multi-center cohorts to confirm the predictive performance of PLR/MLR and algorithm stability across diverse populations before clinical translation can be considered. The robust performance of the RF model validated by ML techniques can provide a solid foundation for future multi center research. Finally, the limited inclusion of certain biomarkers, such as the inability to obtain NT proBNP data, may hinder more comprehensive analysis of cardiac biomarkers. However, we have also attempted to obtain more comprehensive indicators to ensure reliability, and future research may expand the inclusion of biomarkers to improve predictive accuracy. In addition, our research ensures its scientific and practical validity through comprehensive feature selection, advanced ML, model interpretability through SHAP analysis, and practical network-based nomogram.

While the current model focuses on HFrEF readmission prediction, the methodology could potentially be adapted to predict HFpEF-to-HFrEF transition in non-responding patients. This would require: 1) Prospective collection of serial echocardiographic and biomarker data from HFpEF cohorts; 2) Additional features capturing diastolic dysfunction progression (e.g., E/e' ratio, LA volume index); 3) Validation in dedicated HFpEF trials (such as PARAGON-HF or DELIVER).

Conclusion

Based on the RF algorithm, the one-year readmission risk of HFrEF patients can be predicted. The most critical predictive factors include age, NYHA class, LVEF, PLR, MLR, BNP level, ACEI/ARB/ARNI usage, and AF history. This model provides valuable tools for clinical doctors to identify high-risk patients and implement timely interventions.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Ethical Approval

The study was performed according to the guidelines of the Declaration of Helsinki. The use of medical data was approved by the Ethics Committee of the first Affiliated Hospital of, College of Medicine, Zhejiang University. The requirement for informed consent was waived by the Ethics Committee due to the retrospective nature of the study and the anonymization of patient data. All patient data were strictly kept confidential and used solely for this research. The study adhered to relevant ethical standards, ensuring the privacy and security of patient information.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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