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ORIGINAL RESEARCH

Inflammation-Driven Prognosis in Advanced Heart Failure: A Machine Learning-Based Risk Prediction Model for One-Year Mortality

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Background: To develop a machine learning (ML)-based prediction model focused on the one-year mortality risk in patients with advanced heart failure (AdHF), aiming to improve prediction accuracy by integrating inflammatory biomarkers and clinical parameters, assist clinical decision-making, and enhance patient outcomes.

Methods: A retrospective cohort study. Data were obtained from the electronic medical records system of the Affiliated Hospital of Xuzhou Medical University. AdHF patients admitted to the ICU and cardiology department from January 2015 to December 2023 were included with a one-year follow-up. 52 variables potentially affecting prognosis were incorporated. The LASSO algorithm was used for feature selection and dimensionality reduction. Data were split into training and validation sets. Seven ML algorithms were applied to build and evaluate models. The SHAP method was used for model analysis and a dynamic nomogram was created.

Results: The study included 715 AdHF patients. The random forest (RF) model performed best, with an area under the curve (AUC) of 0.83 (95% confidence interval: 0.77–0.88), an accuracy of 0.72, a sensitivity of 0.74, and an F1 score of 0.73. Key predictors of one-year mortality risk included Beta blockers, ACEI/ARB/ARNI, BNP, CRP, NLR, AF, MI, NYHA class, and age. SHAP analysis revealed that elevated CRP, NLR, and age were associated with increased risk, while Beta blockers, ACEI/ARB/ARNI, and lower BNP values were associated with reduced risk. An online dynamic nomogram was developed to provide personalized risk predictions based on patient-specific conditions.

Conclusion: A successful ML-based prediction model was developed to accurately predict the one-year mortality risk in AdHF patients, with inflammation-driven factors being significant. The RF model integrating clinical features and inflammatory markers showed excellent performance and could assist clinical decision-making. Future research should conduct larger, multi-center, and prospective studies to further validate these findings.

Keywords: advanced heart failure, inflammation, machine learning, one - year mortality, risk prediction model

Introduction

Heart failure (HF) is a global public health challenge that affects over 56 million people worldwide.[1] Advanced heart failure (AdHF) refers to a condition in which patients continue to experience progressive and/or sustained severe HF symptoms despite receiving standard or guideline-directed medical therapy, device therapy, or surgical interventions.[2,3] Studies indicate that the community prevalence of AdHF is 0.2%, with a five-year survival rate of only 20% and a one-year mortality rate of 49.9%.[4–6] Chronic inflammation drives HF progression, accelerating cardiac damage.[4] Several studies have shown that inflammatory markers such as C-reactive protein (CRP), the neutrophil-to-lymphocyte ratio (NLR), the systemic immune-inflammation index (SII), and the systemic inflammatory response index (SIRI) are associated with the prognosis of HF patients.[5–7] But their relationship with AdHF prognosis is unclear, and few studies have compared their mortality - predicting abilities.

Machine learning (ML) has made significant progress in the management of cardiovascular diseases globally. Several studies have demonstrated the promising potential of ML algorithms in early warning, dynamic monitoring, and prognosis assessment for HF patients.[8–11] Segar et al created a race - specific HF risk model from four large cohorts,

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with the ML model outperforming traditional ones in identifying HF risk factors.[9] Yao et al developed an ML model integrating clinical knowledge for AdHF patient identification and treatment advice.[10] This model performs comparably to traditional methods while generating clear, concise clinical guidelines that enhance decision-making efficiency. Despite ML's progress in cardiovascular disease management, its application in inflammation - driven AdHF prognosis and mortality risk prediction is still in its infancy.

Therefore, this study aims to develop a ML-based prediction model focused on inflammation-driven prognosis in AdHF, with a particular emphasis on one-year mortality. We utilize advanced ML algorithms, integrating inflammatory biomarkers and other clinical parameters to construct a risk prediction model. The model is designed to enhance the accuracy of predicting one-year mortality risk in AdHF patients, thereby assisting clinical decision-making and improving patient outcomes.

Methods

Study Population and Design

This study is a retrospective cohort study, with data derived from the electronic medical records system of the Affiliated Hospital of Xuzhou Medical University. Data were collected from patients with AdHF admitted to the intensive care unit (ICU) and the department of cardiology between January 2015 and December 2023, with a one-year follow-up period. Strict measures were implemented to protect patient data and privacy throughout the data collection phase. The study was conducted in strict accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (XYFY2024-KL104-01). Given the retrospective nature of the study, the data were sourced from previous clinical diagnoses and treatments, and therefore, the ethics committee waived the requirement for informed consent.

The inclusion criteria for this study were as follows: (1) patients who met the diagnostic criteria for AdHF as outlined in the 2018 position statement on AdHF by the Heart Failure Association (HFA) of the European Society of Cardiology (ESC);[3] (2) age≥18 years. The exclusion criteria were: (1) missing critical data exceeding 30%; (2) loss to follow-up within one year; (3) diagnosis of malignancy with a life expectancy of less than one year; (4) undergoing heart transplantation; (5) presence of severe mental illness that impaired cooperation with clinical management. Patients with concurrent systemic inflammation or infections (such as pneumonia) were included in the cohort to reflect real-world clinical complexity. Inflammatory biomarkers (eg, CRP, NLR) were analyzed as baseline indicators measured at admission, and their prognostic value was retained through LASSO-based feature selection, ensuring robustness across heterogeneous clinical conditions.

Data Collection

Based on previous studies and clinical experience, we included a total of 52 variables that may influence the prognosis of AdHF. These variables encompass demographic characteristics (age, sex, body mass index (BMI), etc), admission vital signs (systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), etc), comorbidities (myocardial infarction (MI), atrial fibrillation (AF), diabetes mellitus (DM), etc), laboratory indicators (blood glucose, lipid profile including triglycerides (TG), total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), brain natriuretic peptide (BNP), etc), echocardiographic data (left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDd)), various inflammatory indices (NLR, SII, SIRI, etc), and medication usage (Beta-blockers, diuretics, Statin, etc).

The computation approaches for diverse indices are detailed below: NLR is the ratio of neutrophils to lymphocytes; PLR is the ratio of platelets to lymphocytes; MLR is the ratio of monocytes to lymphocytes; SII = (platelet*neutrophil)/lymphocyte, SIRI = (neutrophil*monocyte)/lymphocyte, triglyceride-glucose (TYG) index = ln[TG (mg/dL) × fasting blood glucose (FBG) (mg/dL)]/2.

Endpoint Events

The enrolled patients were followed up by professional medical staff for a period of one year, and the date of the final follow-up was December 31, 2024. The follow-up methods included medical record inquiries in the electronic medical

record system, outpatient follow-up, telephone follow-up and other means. The endpoint event in this study was defined as the death of patients with AdHF due to cardiovascular causes within one year.

Data Preprocessing and Model Development

In the data preprocessing stage, multiple imputation was used to iteratively fill in missing values, enhancing the accuracy of imputation. Subsequently, feature scaling was performed using standardization to eliminate differences in measurement scales. In this study, we employed a rigorous approach to feature selection and model evaluation to identify the most predictive variables and the most accurate ML algorithms for our dataset. Initially, we employed the least absolute shrinkage and selection operator (LASSO) algorithm for feature selection and dimensionality reduction of the dataset. The algorithm utilized LASSO regression with cross-validation (CV). Features with coefficient values reduced to 0 were ultimately discarded, and the results were visualized for presentation. Following the feature selection, the data was randomly partitioned into a training set and a validation set in a ratio of 7:3, ensuring that the distribution of target variables was consistent across both subsets.

To address class imbalance in the training set, we applied the Synthetic Minority Over-sampling Technique (SMOTE). SMOTE generates synthetic samples for the minority class (one-year mortality cases) by interpolating between existing minority-class instances, thereby balancing the class distribution. This approach prevents the model from being biased toward the majority class (survivors) and enhances its ability to capture critical risk patterns associated with mortality. The oversampling process was applied exclusively to the training set to avoid data leakage, ensuring that the validation set remained untouched for unbiased performance evaluation.

We then applied seven distinct ML algorithms to the training dataset: Random Forest (RF), Decision Tree (DT), Extreme Gradient Boosting (XGBoost), Support Vector Machine (SVM), Logistic Regression (LR), Light Gradient Boosting Machine (LightGBM), and Multilayer Perceptron (MLP). Each algorithm was carefully tuned to optimize its hyperparameters, and models were trained on the same training dataset to ensure comparability.

The performance of each model was evaluated using a comprehensive set of metrics that included the Area Under the Curve (AUC) of the Receiver Operating Characteristic (ROC) curve, accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and F1 score. In addition to these standard performance indicators, we also considered the computational efficiency of each model by measuring both the training time and the prediction time.

SHAP Interpretability and Dynamic Nomogram Creation

The SHapley Additive exPlanations (SHAP) interpretability method was employed to enhance the transparency of the model's decision-making process. This approach provided a unified measure of feature importance, allowing for the identification of the most influential variables and quantifying their individual contributions to the model's predictions. By analyzing SHAP values, we were able to assess how each feature impacted the model's output and to understand the underlying patterns driving the predictions. Finally, the results were visualized through dynamic nomograms, which offered an intuitive, user-friendly interface to represent the model's predictions and their corresponding performance metrics. These nomograms facilitated real-time risk assessments, enhancing the model's clinical applicability by providing an interactive and visually accessible tool for healthcare decision-making.

Statistical Analysis

Data analysis was conducted using Python 3.6.5, R 3.6.4, and SPSS 23.0. Normally distributed continuous variables were summarized as mean ± standard deviation (X ± SD), while non-normally distributed data were presented as median (M) and interquartile range (P25, P75). Categorical data were expressed as frequency and percentage (%). Statistical comparisons between groups were performed using independent *t*-tests for normally distributed continuous variables, Mann–Whitney *U*-tests for non-normally distributed variables, and chi-square or Fisher's exact tests for categorical variables. A p-value of <0.05 was considered significant.

Results

Baseline Characteristics

This study included 825 patients with AdHF who were admitted to the ICU or the Department of Cardiology at the Affiliated Hospital of Xuzhou Medical University between January 2015 and December 2023. After applying the exclusion criteria, a total of 715 patients were ultimately included in the analysis, as detailed in Figure 1. Among these patients, 318 (44.5%) had heart failure with reduced ejection fraction (HFrEF), 99 (13.8%) had heart failure with mildly reduced ejection fraction (HFmrEF), and 298 (41.7%) had heart failure with preserved ejection fraction (HFpEF).

In the comparison of baseline characteristics between the survivor group (n = 390) and the non-survivor group (n=325), multiple variables were found to have significant differences ($P< 0.05$). Compared with the survivor group, the non-survivor group had an older age, a faster HR, and a higher proportion of NYHA class IV. In terms of past medical history, the non-survivor group had a higher proportion of patients with a history of MI, AF, and stroke. Among the inflammation and blood-related indices, the levels of NLR, PLR, MLR, SII, SIRI, SCr, CRP, and BNP in the non-survivor group were all higher than those in the survivor group. In terms of drug use, the survivor group had a higher proportion of patients using angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blockers (ARB)/angiotensin receptor-neprilysin inhibitor (ARNI) and beta-blockers. See Table 1 for details.

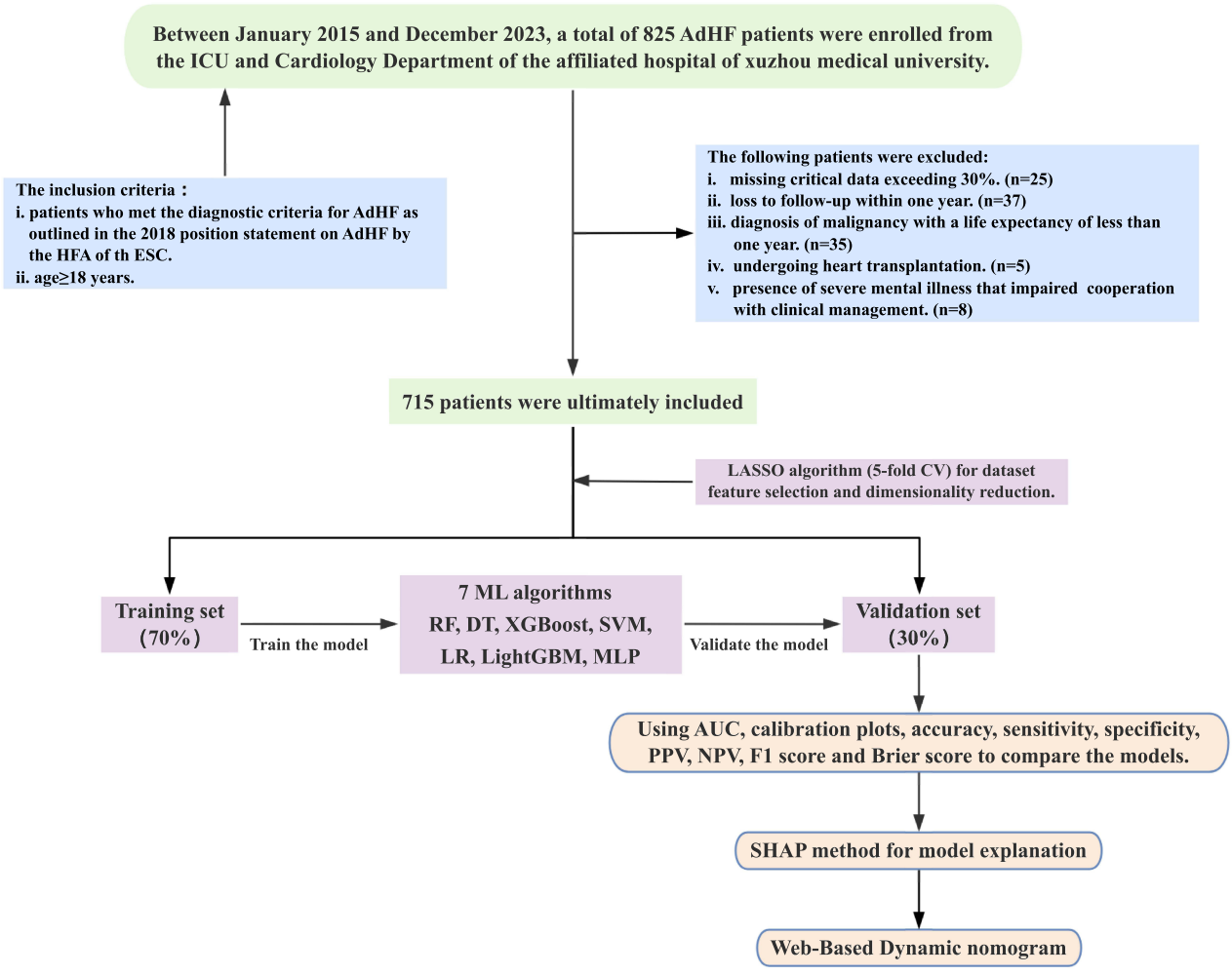

Figure 1 Flow chart of the study design.

Abbreviations: AdHF, advanced heart failure; ICU, intensive care unit; HFA, Heart Failure Association; ESC, European Society of Cardiology; LASSO, least absolute shrinkage and selection operator; 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; SHAP, SHapley Additive exPlanations.

Table 1 Baseline Characteristics of Survivors and Non-Survivors Groups

Variables	Survivors Group (n=390)	Non-Survivors Group (n=325)	*P*-value
Age	69.36±11.47	73.10±12.06	<0.001
Gender (n, %)			
Male	204 (52.3%)	182 (56.0%)	0.324
Female	186 (47.7%)	143 (44.0%)	
HF Classification			0.767
HFrEF (LVEF≤40)	173 (44.4%)	145 (44.6%)	
HFmrEF (LVEF=41-49)	51 (13.1%)	48 (14.8%)	
HFpEF (LVEF≥50)	166 (42.6%)	132 (40.6%)	
BMI, kg/m2	23.54 (20.95,25.91)	23.46 (20.76,25.99)	0.834
SBP (mmHg)	123.00 (107.00,139.25)	122.00 (107.00,150.40)	0.790
DBP (mmHg)	74.00 (65.00,84.00)	74.00 (65.50,83.00)	0.960
HR	81.00 (70.00,94.00)	85.00 (73.00,98.00)	0.031
Smoking (n, %)	112 (28.7%)	95 (29.2%)	0.880
Drinking (n, %)	39 (10.0%)	27 (8.3%)	
NYHA class (n, %)			<0.001
III	249 (63.8%)	151 (46.5%)	
IV	141 (36.2%)	174 (53.5%)	
Past medical history (n, %)			
Hypertension	183 (46.9%)	142 (43.7%)	0.388
MI	47 (12.1%)	75 (23.1%)	<0.001
CHD	135 (34.6%)	124 (38.2%)	0.327
AF	97 (24.9%)	113 (34.8%)	0.004
PCI	86 (22.1%)	66 (20.3%)	0.570
Pacemaker	33 (8.5%)	32 (9.8%)	0.521
Stroke	27 (6.9%)	37 (11.4%)	0.037
DM	104 (26.7%)	93 (28.6%)	0.561
COPD	28 (7.2%)	23 (7.1%)	0.958
CKD	41 (10.5%)	42 (12.9%)	0.316
Thyroid dysfunctions	34 (8.7%)	34 (10.5%)	0.429
Anemia	41 (10.5%)	40 (12.3%)	0.451
LVEF (%)	45.50 (27.00,55.00)	44.00 (27.00,54.00)	0.760
LVEDd	62.00 (53.00,70.00)	63.00 (55.00,70.25)	0.345
Hb	126.00 (115.00,138.00)	124.00 (111.00,137.00)	0.280
Indices			
NLR	3.02 (2.10,4.29)	4.27 (2.53,6.48)	<0.001
PLR	129.32 (96.83,176.87)	151.18 (101.21,230.00)	<0.001
MLR	0.34 (0.26,0.45)	0.44 (0.27,0.68)	<0.001
SII	554.48 (355.77,786.50)	676.73 (431.88,1321.55)	<0.001
SIRI	1.47 (0.96,2.18)	2.06 (1.13,4.05)	<0.001
TYG	8.65 (8.26,9.07)	8.56 (8.15,9.06)	0.272
SCr (umol/L)	88.00 (70.00,113.00)	95.00 (78.00,125.00)	0.001
UA (umo/L)	395.00 (310.00,467.25)	380.00 (307.50,483.50)	0.464
TG (mmol/L)	1.30 (0.92,1.77)	1.16 (0.84,1.62)	0.029
TC (mmol/L)	3.76 (3.11,4.52)	3.69 (3.00,4.47)	0.105
LDL-C (mmol/L)	2.00 (1.46,2.77)	1.97 (1.35,2.61)	0.369
FBG (mmol/L)	5.23 (4.64,6.54)	5.39 (4.64,7.09)	0.181
K (mmol/L)	4.06 (3.76,4.39)	4.08 (3.72,4.50)	0.450
Na (mmol/L)	142.00 (140.00,144.00)	141.00 (139.00,143.00)	0.008
Cl (mmol/L)	104.00 (101.00,107.00)	104.00 (101.00,107.00)	0.391
CRP (mmol/L)	4.08 (1.30,12.51)	17.48 (7.65,35.85)	<0.001
BNP (pg/mL)	1088 (512,1953)	1366 (771,3654)	<0.001

(*Continued*)

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Table 1 (Continued).

Variables	Survivors Group (n=390)	Non-Survivors Group (n=325)	*P*-value
Inotropic drugs (n, %)			
Diuretic	320 (82.1%)	260 (80.0%)	0.485
Aldosterone-receptor blocker	278 (71.3%)	237 (72.9%)	0.626
Nitrate esters	62 (15.9%)	53 (16.3%)	0.882
Digitonin	100 (25.6%)	72 (22.2%)	0.277
ACEI/ARB/ARNI	302 (77.4%)	179 (55.1%)	<0.001
Beta-blockers	269 (69.0%)	168 (51.7%)	<0.001
Antiplatelet Drugs	174 (44.6%)	151 (46.5%)	0.622
Anticoagulant	115 (29.5%)	113 (34.8%)	0.131
Statin	225 (57.7%)	192 (59.1%)	0.708
CCB	31 (7.9%)	23 (7.1%)	0.660

Abbreviations: HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFmrEF, had heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; NYHA, New York Heart Association; MI, myocardial infarction; CHD, coronary heart disease; AF, atrial fibrillation; PCI, percutaneous coronary intervention; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; LVEF, left ventricular ejection fraction; LVEDd, left ventricular end-diastolic dimension; Hb, hemoglobin; 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; 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; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; CCB, calcium channel blocker;

Feature Selection and Predictive Performance of ML Model

To develop and validate the risk prediction model in this study, we employed LASSO regression with 5-fold CV to identify variables with significant predictive value. The analysis revealed that, when the optimal alpha value was set to 0.029, Beta blockers, ACEI/ARB/ARNI, BNP, CRP, NLR, AF, MI, NYHA class, and age were identified as key predictors of one-year mortality risk in patients with AdHF (Figure 2). The importance of these features is reflected in their respective coefficients within the model, providing crucial insights for the accurate prognosis assessment of AdHF patients.

In this study, seven ML algorithms were used to predict one-year mortality risk in AdHF patients. The RF model had the highest AUC (0.83), outperforming other models (Figure 3). To further evaluate the reliability of the predicted probabilities, we assessed the calibration of the ML models using calibration plots and Brier score. As shown in the calibration plots (Figure 4), the RF model demonstrated the best calibration, with its predicted probabilities closely matching the observed outcomes across all probability levels. This is further supported by its lowest Brier score of 0.176 (Table 2), indicating superior accuracy in probability prediction.

Although XGBoost and LightGBM had a slightly higher sensitivity than RF (0.76 vs 0.74) and XGBoost showed a slightly higher accuracy (0.73 vs 0.72), the RF model balanced sensitivity (0.74) and specificity (0.70) well (see Table 2 for details). This balance is crucial for reducing false positives without sacrificing true positives in clinical decision - making. Importantly, the narrow and high-value AUC confidence interval (CI) of the RF model (0.77–0.88) indicated better robustness and generalizability compared to boosting models, which are more sensitive to hyperparameters and data variability. Overall, considering its excellent discrimination (AUC), well-balanced performance, stability, as well as its superior calibration demonstrated by the calibration curve (Figure 4) and the lowest Brier score of 0.176, the RF model emerged as the optimal model. These factors make it a highly suitable choice for guiding clinical interventions in AdHF.

Model's Explainability

To further elucidate the RF model, SHAP (SHapley Additive exPlanations) analysis was conducted, providing both global and local interpretations. Figure 5 illustrates the overall impact of features on the model's output using SHAP values. In Figure 5A, elevated levels of CRP, NLR, and Age are associated with positive SHAP values, indicating an increased risk of one-year mortality in patients. Notably, high CRP levels significantly drive the increase in mortality risk. In contrast, Beta blockers, ACEI/ARB/ARNI generally show negative SHAP values, suggesting that their use is

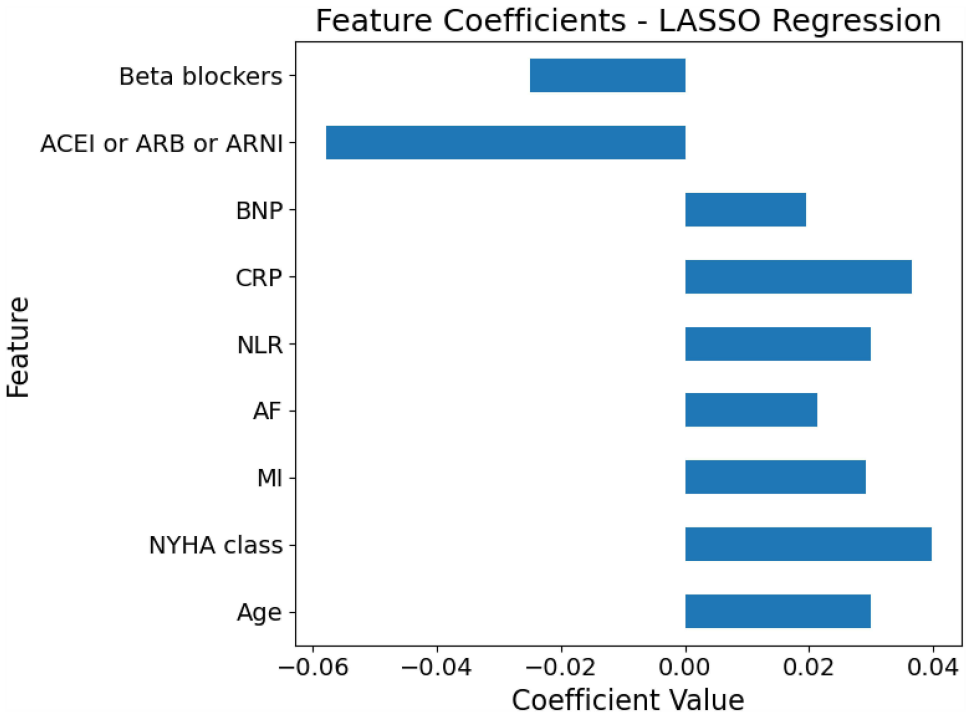

Figure 2 LASSO for feature selection and dimensionality reduction.
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; BNP, brain natriuretic peptide; CRP, C-reactive protein. NLR, the neutrophil-to-lymphocyte ratio; AF, atrial fibrillation; MI, myocardial infarction; NYHA, New York Heart Association.

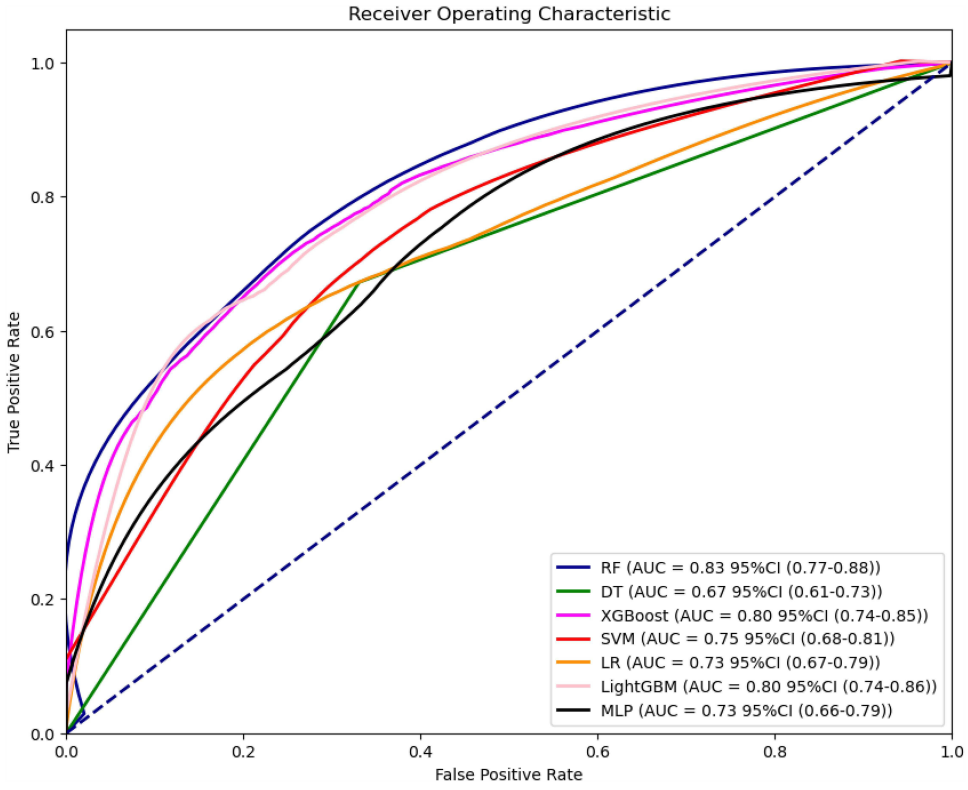

Figure 3 ROC curve comparison of seven machine learning models.
Abbreviations: AUC, the area under the receiver-operating characteristic; CI, confidence interval; RF, Random Forest; DT, Decision Tree; XGBoost, Extreme Gradient Boosting, SVM, Support Vector Machine; LR, Logistic Regression; LightGBM, Light Gradient Boosting Machine; MLP, Multilayer Perceptron.

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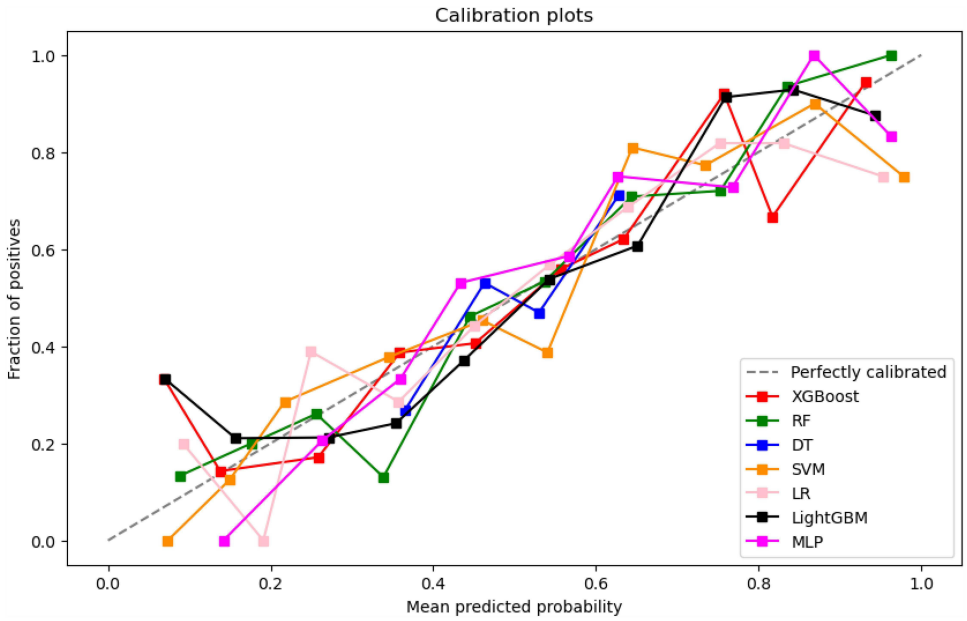

Figure 4 Calibration plots for the machine learning models.
Abbreviations: XGBoost, extreme gradient Boosting; RF, Random Forest; DT, Decision Tree; SVM, Support Vector Machine; LR, Logistic Regression; LightGBM, light gradient boosting machine; MLP, Multilayer Perceptron.

associated with a reduced risk. Lower BNP values are negatively correlated with mortality risk, indicating a protective effect. Higher NYHA class levels, as well as the presence of AF and MI, increase the risk, although to a lesser extent. Figure 5B compares the SHAP value distributions for high and low feature values. For instance, when CRP is elevated, it has a significant positive impact, while a decrease in CRP weakens its effect. The use of Beta blockers shows a clear reduction in risk when their values are high, with this effect diminishing as the values decrease, further enhancing the understanding of feature impact on the model.

Figure 6 focuses on the model's prediction for individual samples. In Figure 6A, the prediction function and feature coefficients reflect the model's comprehensive, feature-based prediction approach. For example, the coefficient for CRP indicates the direction of its influence on the prediction result for each unit change. Samples are ordered by predicted output values, with the average risk value indicated; samples on the right represent high-risk individuals, while those on the left correspond to low-risk individuals. In high-risk samples, positive feature values are typically high, while negative feature values may be low or absent. Figure 6B visually represents the sample distribution, which corresponds with the risk ranking results shown in Figure 6A. High-risk samples cluster in regions associated with high-risk patterns, whereas low-risk samples are found in regions indicative of lower risk, aiding the understanding of the model's local prediction mechanism and enhancing its interpretability.

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

Models	AUC	Accuracy	Sensitivity	Specificity	PPV	NPV	F1 Score	Brier Score
RF	0.83	0.72	0.74	0.70	0.72	0.72	0.73	0.176
DT	0.67	0.67	0.67	0.67	0.68	0.66	0.68	0.346
XGBoost	0.80	0.73	0.76	0.70	0.72	0.73	0.74	0.211
SVM	0.75	0.68	0.75	0.62	0.67	0.70	0.71	0.205
LR	0.73	0.66	0.68	0.63	0.67	0.66	0.67	0.209
LightGBM	0.80	0.72	0.76	0.68	0.71	0.73	0.73	0.194
MLP	0.73	0.66	0.71	0.61	0.65	0.67	0.68	0.208

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.

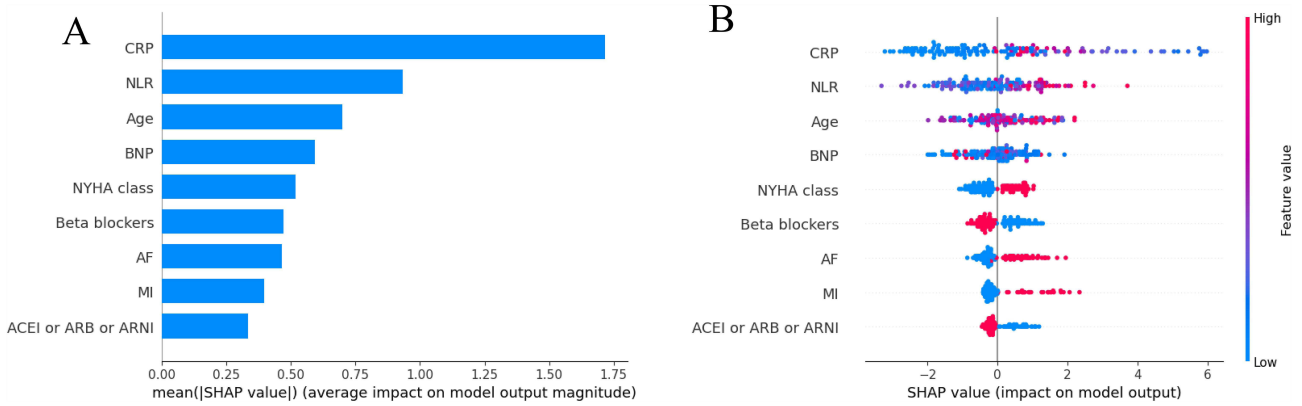

Figure 5 Global model explanation by the SHAP method. (**A**) SHAP summary bar plot. (**B**) SHAP summary dot plot.
Abbreviations: CRP, C-reactive protein; NLR, the neutrophil-to-lymphocyte ratio; BNP, brain natriuretic peptide; NYHA, New York Heart Association; AF, atrial fibrillation; MI, myocardial infarction; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor.

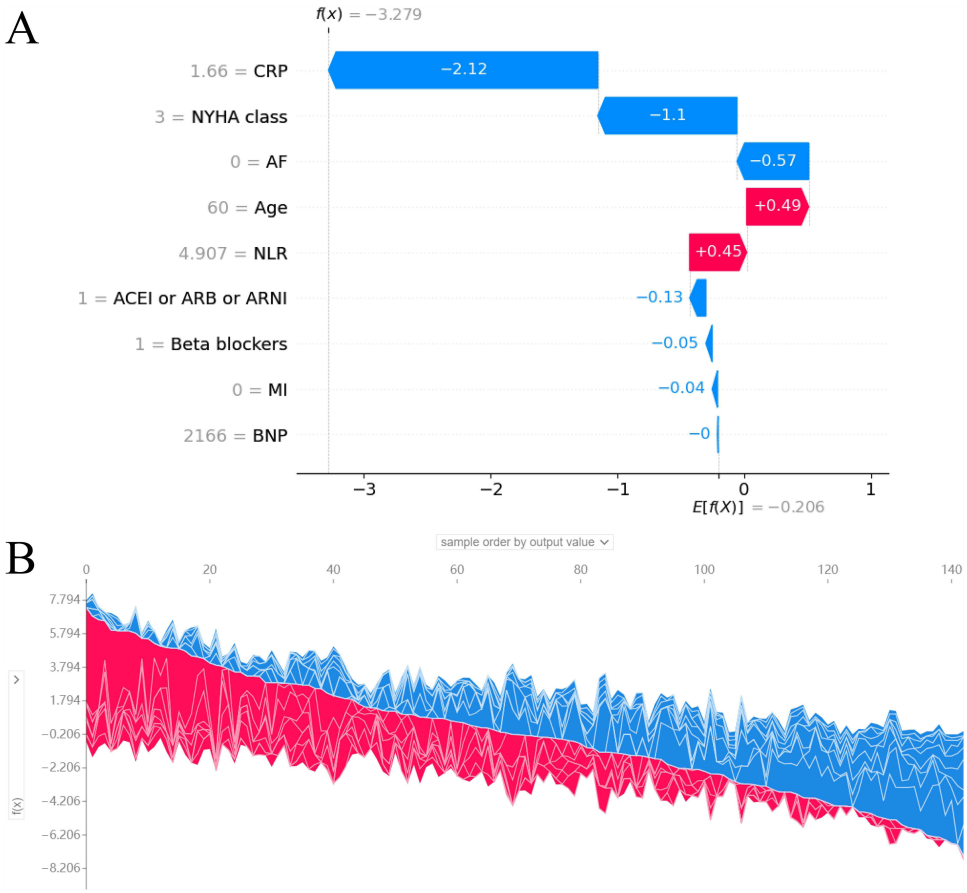

Figure 6 Local model explanation by the SHAP method. (**A**) waterfall plot. (**B**) Force plot.
Abbreviations: CRP, C-reactive protein; NYHA, New York Heart Association; AF, atrial fibrillation; NLR, the neutrophil-to-lymphocyte ratio; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; MI, myocardial infarction; BNP, brain natriuretic peptide.

Generation of Dynamic Nomogram

Finally, we developed an online dynamic nomogram (https://scinomogram.shinyapps.io/CNABNBAMA/) based on the RF model, which incorporates features such as Age, NYHA class, MI, AF, NLR, CRP, BNP, ACEI/ARB/ARNI, and Beta blockers, as shown in Figure 7. The significance of this tool lies in its ability to visually present the combined impact of

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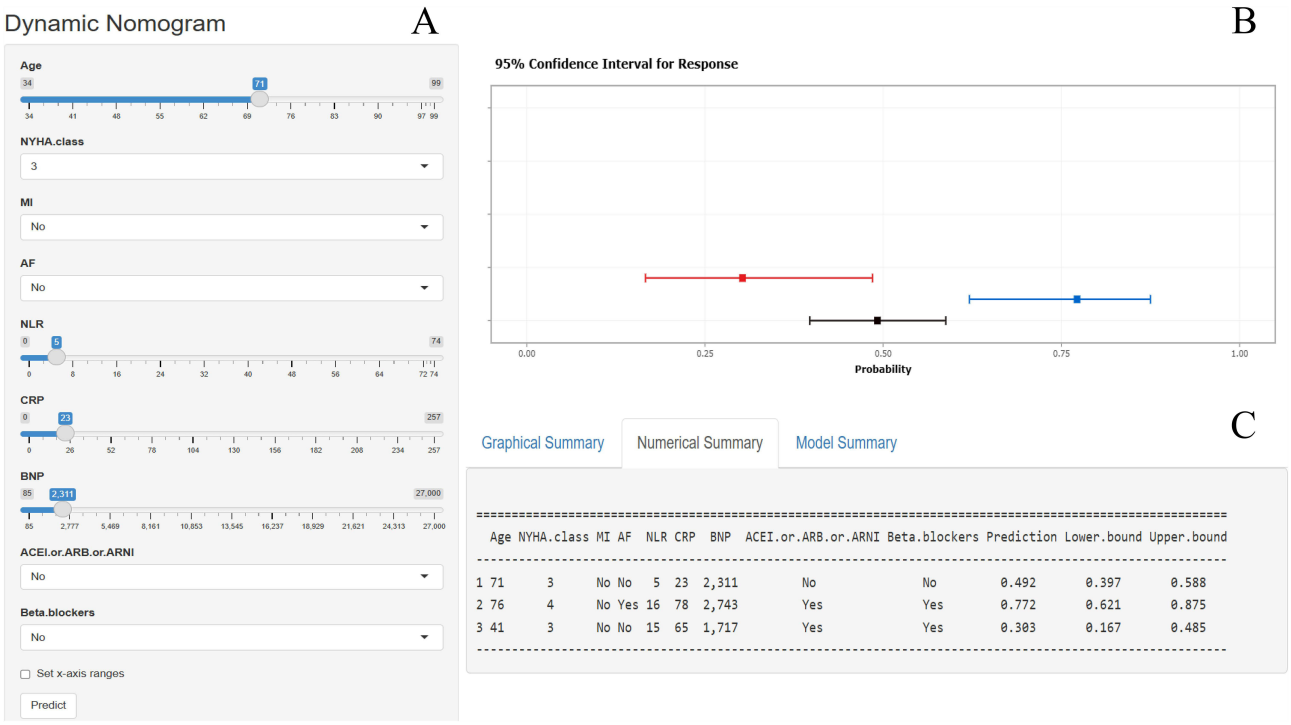

Figure 7 Dynamic Nomogram for Predicting One-Year Mortality Risk in AdHF Patients. (**A**) Input page: Enter the patient's information according to the relevant variables on this page. (**B**) Graphical summary: This page shows the probability of a patient being readmitted to hospital with heart failure 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; MI, myocardial infarction; AF, atrial fibrillation; NLR, the neutrophil-to-lymphocyte ratio; CRP, C-reactive protein; BNP, brain natriuretic peptide; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor.

these features on the one-year mortality risk in patients with AdHF. Users can adjust the feature parameter values based on the patient's specific condition on the webpage to obtain personalized risk predictions, thereby assisting clinical decision-making. This has important value in the risk assessment and management of the disease.

Model Performance Example

The RF model demonstrated excellent performance in predicting one-year mortality risk and holds potential for guiding clinical decisions. For instance, a 75-year-old patient with NYHA class IV, a history of AF but no history of MI, an NLR of 26, CRP of 66 mmol/L, and BNP of 5655 pg/mL, who is receiving ACEI/ARB/ARNI and beta-blockers, was accurately predicted by the model to have an 87.0% (95% CI: 68.5–95.4%) probability of mortality within one year. The analysis suggests that key variables, such as advanced age, severe cardiac dysfunction (NYHA IV), elevated inflammatory markers (NLR, CRP), and high BNP levels, align with the risk factors identified by the model for predicting mortality. This example illustrates how the tool can stratify high-risk patients, prompting clinicians to intensify monitoring or consider advanced therapies. Early identification of such patients allows for timely interventions, including optimization of guideline-directed medical therapy, closer follow-up, and consideration of AdHF treatments such as mechanical circulatory support or heart transplantation. By integrating this prediction model into clinical workflows, healthcare providers can proactively manage high-risk patients, potentially improving long-term outcomes and reducing mortality.

Discussion

In this study, we successfully developed a ML-based prediction model to assess the one-year mortality risk in patients with AdHF, with particular emphasis on inflammation-driven prognostic factors. RF model performed exceptionally well in this study, with an AUC of 0.83 and demonstrating balanced, excellent performance across metrics such as accuracy and sensitivity. The RF model is capable of handling high-dimensional data, automatically selecting important features,

and addressing complex interactions between features, making it highly suitable for prognosis prediction in AdHF. Angraal et al focused on all-cause mortality and HF hospitalizations within three years in HF patients as their study endpoints and found that a prediction model based on the RF algorithm demonstrated superior predictive performance, significantly outperforming traditional statistical modeling methods.[12] This aligns with our study's observations that the RF algorithm excelled in predicting one-year mortality rates in patients with AdHF, further confirming the practicality and effectiveness of ML algorithms in the management of HF. The model integrates multi-dimensional information, including clinical features, inflammatory markers, and medication use, specifically CRP, NLR, age, BNP, NYHA class, Beta blockers, AF, MI, and ACEI/ARB/ARNI, with the aim of enhancing prediction accuracy and supporting clinical decision-making. We included 715 patients and conducted a one-year follow-up, during which 325 AdHF patients died, accounting for 45.5%. This mortality rate is consistent with the 49.9% reported in previous studies conducted in US populations, underscoring the severity of the prognosis in AdHF patients and highlighting the urgent need for precise prediction and effective intervention.[13]

Inflammatory markers were identified as key predictive factors in this study, holding significant relevance for the prognosis assessment of patients with AdHF. Numerous studies have demonstrated that inflammation plays a critical role in the onset and progression of HF, with chronic inflammation accelerating the deterioration of cardiac structure and function.[14,15] In this study, the levels of NLR and CRP in the non-survivor group were significantly higher than those in the survivor group, consistent with previous findings.[5,6,16] Long-term elevated high-sensitivity CRP is closely associated with mortality in patients with acute heart failure.[5] Elevated CRP levels may reflect an exacerbation of the inflammatory state within the body, leading to sustained cardiac tissue damage and further decline in cardiac function. A study has shown that in patients with acute HF, high-sensitivity C-reactive protein (hsCRP) levels are independently associated with the risk of death and the total risk of HF readmission after discharge.[17] As an indicator that comprehensively reflects the inflammatory state, an increased NLR suggests enhanced neutrophil-mediated inflammatory response, while lymphocyte function may be suppressed. This imbalance in immune function is detrimental to cardiac repair and the maintenance of heart function.[6] Moreover, the inflammatory response may affect the prognosis of AdHF patients through various pathways. For instance, inflammation itself causes myocardial damage, which accelerates the progression of HF. Conversely, HF perpetuates the inflammatory environment within the heart, leading to a vicious cycle.[18] Additionally, inflammatory factors can promote cardiomyocyte apoptosis and induce myocardial fibrosis, leading to myocardial remodeling, which further increases the cardiac burden and mortality risk.[19] Curran et al discovered that the neutrophil-to-lymphocyte ratio (NLR) appears to offer superior predictive value compared to the absolute counts of neutrophils or lymphocytes alone.[20] An elevated NLR is associated with adverse outcomes in HF patients, regardless of whether they have HFrEF or HFpEF.[20] Furthermore, previous studies have indicated that an increased NLR serves as an independent predictor of in-hospital mortality, HF readmission, and long-term adverse outcomes in both acute and chronic HF patients.[21,22] These findings suggest that NLR could serve as a crucial indicator for risk stratification and prognostic assessment in HF patients. Studies have shown that anti-inflammatory therapy can reduce the risk of cardiovascular events in patients with acute HF, with a significant decrease in CRP levels observed at the end of treatment.[23] Several clinical trials have demonstrated the outstanding efficacy of SGLT2 inhibitors in reducing HF hospitalizations and cardiovascular mortality, with their anti-inflammatory effects potentially serving as one of the key cardiovascular protective mechanisms.[24,25] While our study underscores the prognostic significance of inflammation in AdHF, the clinical translation of anti-inflammatory interventions remains an area of active investigation.

Age is a significant prognostic factor in patients with AdHF. As individuals age, the heart undergoes a series of physiological changes, including myocardial hypertrophy, increased apoptosis, alterations in the extracellular matrix, and decreased cardiac compliance.[26,27] Additionally, vascular wall thickening and sclerosis occur, leading to a reduced ability to supply coronary blood flow.[28] These changes result in diminished cardiac reserve in elderly patients, making it more difficult for the heart to withstand the burdens imposed by HF, thus significantly increasing the risk of poor prognosis. The NYHA class is an important indicator for assessing the severity of symptoms and exercise tolerance in HF patients. A higher NYHA classification is often associated with more severe myocardial remodeling, activation of the neuroendocrine system, and enhanced inflammatory responses.[29–31] These factors interact and collectively accelerate disease

progression and increase the risk of mortality. Several studies have indicated that age and NYHA class are significant predictors of mortality in HF patients.[32,33]

MI is one of the key contributors to the onset and progression of AdHF. Following MI, a significant number of myocardial cells in the infarcted region undergo necrosis, and myocardial tissue is replaced by fibrous scar tissue, leading to impaired cardiac structure and function. AF is a common arrhythmia in AdHF patients. During AF episodes, there is an increased risk of thrombus formation and embolism. Additionally, the rapid and irregular ventricular rate increases myocardial oxygen demand, which may lead to myocardial ischemia and further deterioration of heart function. Studies have shown that a history of MI or AF are independent risk factors for poor prognosis in HF patients.[34,35] BNP is primarily synthesized and secreted by ventricular myocytes and serves as a sensitive indicator of cardiac function. Study has shown that BNP and its precursor, NT-proBNP, can reliably predict one-year mortality in HF patients.[36] ACEI/ARB/ARNI and beta-blockers play a central role in the treatment of HF. Research has indicated that the use of ACEIs/ARBs/ARNI or beta-blockers has a positive impact on the prognosis of HF patients, including reductions in mortality and readmission rates.[37,38]

Limitations

First, this study, a single - center retrospective analysis using data from the Affiliated Hospital of Xuzhou Medical University, has limitations. The single - center setup may cause selection bias, reducing the generalizability of results, thus future multi-center studies are needed. The retrospective approach brings a risk of missing medical record data. Although 52 variables were included, crucial prognostic factors like iron deficiency, estimated glomerular filtration rate (eGFR), and use of Sodium-Glucose Cotransporter 2 Inhibitors were absent due to data unavailability. This can affect analysis accuracy and control of confounding factors.

Second, variations in treatment protocols are an important factor to consider. Given the long time span of the study (2015–2023), the treatment guidelines and pharmacological therapies for heart failure may have undergone multiple adjustments. For example, the use of ACEI, ARBs, ARNIs, and Beta-blockers varied over different periods, and changes in treatment protocols could potentially impact patient prognosis. Furthermore, the treatment regimen received by patients during hospitalization, particularly adjustments in medication such as the use of Beta-blockers or adherence to ACEI/ARB/ARNI therapies, may also affect their disease course and prognosis. Although this study attempted to control for these treatment variables, the implementation and adjustments of different treatment protocols may still influence the results to some extent. Therefore, future studies should consider stricter control of these factors or use a prospective design to further validate the impact of these treatment changes on mortality risk prediction in AdHF patients.

Third, due to the retrospective nature of this study and the limited sample size, we divided the data into a training set (70%) and a validation set (30%), without setting aside a separate test set. While this approach was adopted to meet the requirements of model development under the given circumstances, it indeed restricts the independent evaluation of the model's generalizability. Future research with larger sample sizes should incorporate a test set to enable a more rigorous and comprehensive assessment of the model's performance.

Fourth, our study did not account for hemodynamic phenotypes of HF, which have been identified as significant prognostic indicators. Four phenotypic groups are generally recognized: warm and dry, warm and wet, cold and wet, and cold and dry.[39] Specifically, the "cold and dry" phenotype, often observed in elderly patients with AdHF, has been associated with poor outcomes.[40,41] Future studies should incorporate these phenotypes to further refine risk stratification models.

Finally, this study only collected inflammatory markers at the time of admission and did not include dynamic monitoring. While the significance of inflammatory markers in predicting one-year mortality has been established, inflammation in AdHF progresses dynamically. Enhanced dynamic monitoring would allow for more accurate prognosis assessment, provide a basis for treatment strategy adjustments, and ultimately improve clinical outcomes.

Conclusion

In conclusion, our study successfully developed a ML-based prediction model that accurately predicts the one-year mortality risk in patients with AdHF. The model, which integrates clinical features and inflammation-driven factors such

as CRP and NLR, demonstrated significant predictive power, aligning with previous research that highlights the effectiveness of ML in cardiovascular prognosis. The RF model, in particular, showed excellent performance and has the potential to assist in clinical decision-making. Future research should aim to expand the sample size, conduct multi-center studies, and adopt a prospective design to enhance the robustness and generalizability of the model.

Data Sharing Statement

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

Ethics Approval and Consent to Participate

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 Affiliated Hospital of Xuzhou Medical 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.

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.

Disclosure

The authors declare that they have no competing interests in this work.

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