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ORIGINAL RESEARCH

Remnant Cholesterol Inflammatory Index for Predicting Heart Failure Risk in Patients with Coronary Artery Disease and Type 2 Diabetes: A Retrospective Study Using Multiple Machine Learning Approaches

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Background: Patients with coronary artery disease (CAD) and type 2 diabetes mellitus (T2DM) are at markedly increased risk of developing heart failure (HF), yet early identification of high-risk individuals remains challenging. The remnant cholesterol inflammatory index (RCII) has been proposed as a predictor of adverse cardiovascular outcomes, but its role in patients with CAD and T2DM has not been fully elucidated.

Methods: We retrospectively analyzed clinical data from patients treated at our center. Demographic characteristics, comorbidities, medication use, and laboratory parameters were collected. Key features were selected using the Boruta algorithm, and five machine learning models—logistic regression (Logistic), decision tree (DT), elastic net regression (ENet), LASSO regression, and naïve Bayes (NB)—were constructed. Discrimination was assessed by receiver operating characteristic (ROC) curves and area under the curve (AUC), calibration by calibration plots and Brier scores, and interpretability by SHAP analysis.

Results: Among 1181 enrolled patients, 73 developed HF. Median RCII levels were significantly higher in the HF group. Boruta feature selection identified 13 key predictors for model development. Logistic regression demonstrated the best performance, achieving AUCs of 0.88 in the training set and 0.85 in the testing set, with overall accuracy of 0.87 and F1-score of 0.79 in the testing cohort. SHAP analysis revealed that elevated RCII, poor nutritional status, and smoking were major contributors to HF occurrence, with RCII showing a positive association with HF risk.

Conclusion: RCII is a valuable predictor of HF in patients with CAD and T2DM. Higher RCII levels are closely linked to an increased risk of HF.

Keywords: remnant cholesterol inflammatory index, coronary artery disease, type 2 diabetes mellitus, heart failure, machine learning

Background

Coronary artery disease (CAD) and type 2 diabetes mellitus (T2DM) are major global public health concerns, often coexisting and synergistically increasing the risk of adverse cardiovascular events and mortality.[1–4] Epidemiological evidence indicates that individuals with T2DM have a significantly higher risk of developing CAD compared with the general population.[5] Moreover, in patients with established CAD, concomitant diabetes not only accelerates atherosclerotic progression but also markedly raises the incidence of cardiovascular complications.[6] In recent years, heart failure (HF) has emerged as one of the most frequent and severe outcomes in patients with coronary artery disease complicated by type 2 diabetes,[7,8] characterized by poor prognosis, high readmission rates, and elevated mortality. Early identification of high-risk patients and accurate prediction of HF remain pressing clinical challenges.

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Both dyslipidemia and chronic low-grade inflammation are recognized as key drivers of HF development.[9–11] In particular, remnant cholesterol (RC) and low-density lipoprotein cholesterol (LDL-C) contribute to atherosclerosis and myocardial injury by promoting lipid accumulation, endothelial dysfunction, and plaque formation, thereby accelerating the progression from CAD to HF. Remnant cholesterol, a major component of non–high-density lipoprotein cholesterol, reflects the level of triglyceride-rich lipoprotein remnants and has been independently associated with atherosclerosis and cardiovascular events.[12–14] Beyond traditional lipid measures, systemic inflammation has emerged as a novel marker for cardiovascular events, with high-sensitivity C-reactive protein (hsCRP) and other inflammatory indices providing additional prognostic information for HF onset and progression. High-sensitivity C-reactive protein, a classical biomarker of systemic inflammation, has also been linked to both the onset and progression of HF.[15,16] Metabolic abnormalities and inflammatory activation may act synergistically, promoting myocardial injury and adverse remodeling, thereby substantially elevating HF risk.[17,18]

To capture these dual pathophysiological processes, the remnant cholesterol inflammatory index (RCII) has been proposed. This composite marker integrates lipid metabolism abnormalities and systemic inflammation, offering a more comprehensive assessment of cardiovascular risk. Prior studies have demonstrated strong associations between RCII and major cardiovascular or cerebrovascular events;[19–21] however, its prognostic value for HF in patients with CAD and T2DM has not been systematically investigated. Notably, no prior studies have specifically validated RCII as a predictor of HF in CAD patients with T2DM, highlighting a clear knowledge gap that this study aims to address. The present study is the first to explore the predictive role of RCII for HF risk in this population and to evaluate its potential as an early, accessible, and cost-effective biomarker for clinical application.

Methods

Study Population

We retrospectively collected clinical data from patients who underwent first-time coronary angiography (CAG) at Minda Hospital of Hubei Minzu University between January 2021 and June 2025. CAD was defined as ≥70% stenosis in a non–left main coronary artery or ≥50% stenosis in the left main artery. As shown in Figure 1, patients without CAD, without T2DM, lacking high-sensitivity hsCRP measurements, or missing follow-up information were excluded. A total of 1181 patients met the eligibility criteria and were included in the analysis. All data were anonymized. The study was approved by the Ethics Committee of Minda Hospital of Hubei Minzu University. The requirement for informed consent was waived due to the use of de-identified retrospective data and the absence of any interventions. This study was conducted in accordance with the Declaration of Helsinki.

Data Collection

Clinical variables included demographic characteristics (sex, age), comorbidities (hypertension, hyperlipidemia, stroke, hyperuricemia, atrial fibrillation, smoking history), medication use (β-blockers, angiotensin receptor–neprilysin inhibitors, anticoagulants), and laboratory indices. Laboratory data covered hematologic parameters (white blood cell count [WBC], neutrophils [NEUT], lymphocytes [LYM], monocytes [MONO], hemoglobin [Hb], mean corpuscular volume [MCV], platelets), Lipid profile (total cholesterol[TC], triglycerides [TG], high-density lipoprotein cholesterol [HDL-C], and low-density lipoprotein cholesterol[LDL-C]), biochemical and renal markers (alanine aminotransferase [ALT], direct bilirubin [DBIL], albumin [ALB], creatinine [Cr], uric acid [UA], urea), thyroid function (thyroid-stimulating hormone [TSH]), and coagulation parameters (fibrinogen [FIB], D-dimer). RCII was calculated as remnant cholesterol multiplied by hsCRP, divided by 10.

Feature Selection

To identify the most relevant predictors, the Boruta algorithm was applied to all candidate variables. Boruta, based on the random forest framework, iteratively compares the importance of true features against randomized shadow features, thereby selecting stable and statistically significant predictors. The top-ranked features were retained, and an importance ranking plot was generated to illustrate their relative contributions to model construction.

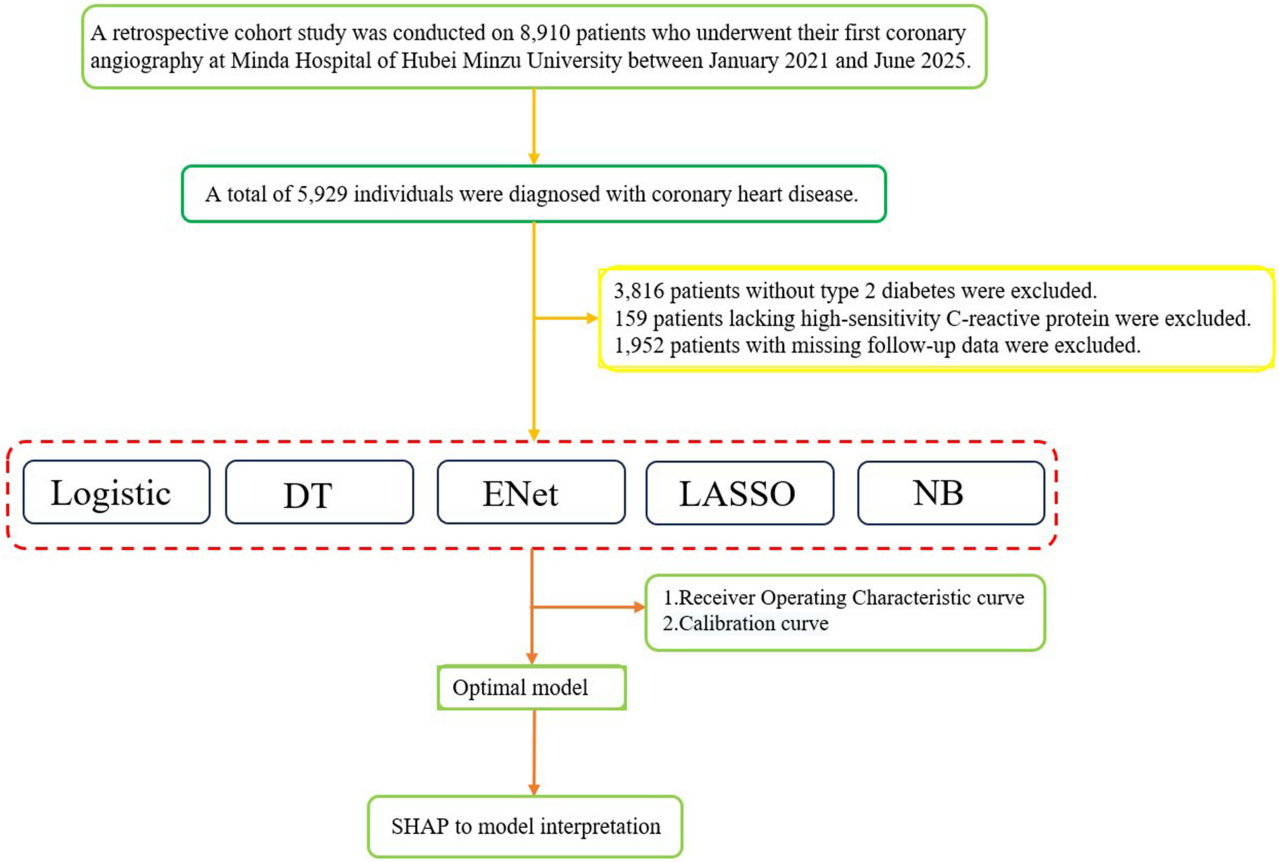

Figure 1 Flowchart of the Study Design.

Model Development and Evaluation

Five predictive models were established and compared: logistic regression (Logistic), decision tree (DT), elastic net regression (ENet), LASSO regression, and naïve Bayes (NB). The dataset was randomly split into a training set (70%) and a testing set (30%). Models were trained on the training set, with five-fold cross-validation performed to assess generalizability, and validated on the testing set. Discrimination was evaluated using receiver operating characteristic (ROC) curves and area under the curve (AUC). Calibration was assessed by calibration plots and Brier scores. In addition, accuracy, sensitivity, F1-score, positive predictive value (PPV), and negative predictive value (NPV) were calculated in both training and testing cohorts to compare overall performance.

Feature Importance and Interpretability

The best-performing model was further interpreted using SHapley Additive exPlanations (SHAP). Based on Shapley values from cooperative game theory, SHAP quantifies the marginal contribution of each feature across different combinations, thereby assessing its influence on model predictions. Both global and individual interpretability were evaluated, with mean absolute SHAP values used to identify the top five predictors. SHAP summary and dependence plots were generated to visualize feature importance, contribution direction, and consistency.

Statistical Analysis

Continuous variables with normal distribution were expressed as mean ± standard deviation (SD) and compared using independent-samples t tests. Non-normally distributed variables were presented as median (interquartile range, IQR) and compared using the Mann–Whitney *U*-test. Categorical variables were summarized as counts and percentages (n, %) and

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compared with χ^2 or Fisher's exact tests. All analyses were two-tailed, and a P value <0.05 was considered statistically significant. Data processing and analysis were conducted using Python 3.9 and R 4.3.2.

Results

Baseline Characteristics

As summarized in Table 1, among the 1181 patients included, 73 developed HF during follow-up. No significant differences were observed between the HF and non-HF groups in sex, age, use of β-blockers, angiotensin receptor–neprilysin inhibitors (ARNI), cerebrovascular disease, or anticoagulant therapy. In contrast, atrial fibrillation, smoking history, hypertension, hyperlipidemia, and hyperuricemia were all significantly more prevalent in the HF group. Patients who developed HF also demonstrated more pronounced inflammatory and hematologic abnormalities, with higher white blood cell and neutrophil counts, lower lymphocyte counts, and reductions in hemoglobin and albumin, suggesting anemia and poorer nutritional status. Renal function parameters, including creatinine and uric acid, differed significantly between groups. Notably, the median RCII was markedly elevated in the HF group compared with the non-HF group (7.14 vs 1.29, P < 0.001), indicating a heightened inflammatory burden. Coagulation indices also differed, with higher fibrinogen and D-dimer levels observed in HF patients.

Table 1 Baseline Characteristics

Variable	Non HF (n=1108)	HF (n=73)	P-value
Gender=man (%)	747 (67.4)	46 (63.0)	0.438
Beta-blockers=1 (%)	840 (75.8)	55 (75.3)	0.928
ARNI=1 (%)	241 (21.8)	15 (20.5)	0.809
CVA=1 (%)	119 (10.7)	10 (13.7)	0.432
Anticoagulation=1 (%)	74 (6.7)	7 (9.6)	0.341
Atrial Fibrillation=1 (%)	29 (2.6)	7 (9.6)	0.001*
History of smoking=1 (%)	148 (13.4)	48 (65.8)	<0.001*
Hypertension=1 (%)	784 (70.8)	65 (89.0)	0.001*
Hyperlipidemia=1 (%)	373 (33.7)	39 (53.4)	0.001*
Hyperuricemia=1 (%)	157 (14.2)	25 (34.2)	<0.001*
Age (median [IQR])	62.00 [55.00, 71.00]	66.00 [53.00, 71.00]	0.659
WBC (median [IQR])	6.49 [5.06, 8.29]	7.17 [5.02, 10.74]	0.05*
Neutrophil (median [IQR])	4.12 [3.24, 5.23]	4.94 [3.68, 10.00]	<0.001*
Lymphocyte (median [IQR])	1.39 [1.05, 1.80]	1.07 [0.85, 1.48]	<0.001*
Monocyte (median [IQR])	0.41 [0.33, 0.52]	0.40 [0.35, 0.53]	0.395
Hemoglobin (median [IQR])	137.00 [123.00, 150.00]	118.00 [104.00, 132.00]	<0.001*
MCV (median [IQR])	90.20 [87.20, 92.60]	90.00 [85.10, 93.50]	0.818
Platelet (median [IQR])	187.00 [151.00, 225.00]	193.00 [147.00, 243.00]	0.474
Triglycerides (median [IQR])	2.06 [1.36, 3.35]	1.65 [1.32, 3.16]	0.097
RCII (median [IQR])	1.29 [0.49, 3.50]	7.14 [1.55, 38.92]	<0.001*
ALT (median [IQR])	20.80 [14.00, 31.00]	19.00 [14.50, 39.00]	0.422
DBIL (median [IQR])	3.70 [2.70, 5.00]	3.80 [2.80, 4.80]	0.901
Albumin (median [IQR])	41.30 [38.60, 44.20]	35.90 [32.40, 40.00]	<0.001*
Creatinine (median [IQR])	73.95 [61.00, 90.00]	89.00 [65.00, 114.00]	<0.001*
Uric Acid (median [IQR])	318.50 [258.00, 383.00]	300.00 [252.00, 363.00]	0.046*
Urea (median [IQR])	5.89 [4.67, 7.16]	6.06 [4.22, 10.34]	0.271
TSH (median [IQR])	1.98 [1.19, 3.30]	1.71 [1.16, 2.89]	0.25
Fibrinogen (median [IQR])	3.13 [2.68, 3.77]	3.87 [3.29, 4.88]	<0.001*
D-dimer (median [IQR])	0.50 [0.40, 1.00]	0.70 [0.43, 1.90]	0.005*

Note: * P<0.05.

Abbreviations: RCII, Remnant cholesterol inflammatory index; CVA, Cerebrovascular Accident; ARNI, Angiotensin Receptor-Neprilysin Inhibitor; WBC, White Blood Cell count; MCV, Mean Corpuscular Volume; ALT, Alanine Aminotransferase; DBIL, Direct Bilirubin; TSH, Thyroid Stimulating Hormone.

Feature Selection by Boruta Algorithm

Figure 2 ranks the predictive importance of candidate variables. The box plot on the left highlights the 13 variables most strongly associated with HF risk in CAD patients with T2DM, while the line plot on the right illustrates the stability of variable importance across 100 classifier iterations. The relatively small fluctuations suggest that the feature selection process was robust. These 13 predictors were retained for model construction.

Model Comparison

We evaluated the performance of five machine learning models in both training and testing cohorts. As shown in Figure 3, all models achieved relatively high discrimination in the training set (AUC range 0.82–0.87). In the testing set, logistic regression yielded the highest AUC, demonstrating the strongest generalizability. Calibration curves (Figure 4) further indicated that logistic regression achieved the best calibration, with Brier scores of 0.0433 in the training set and

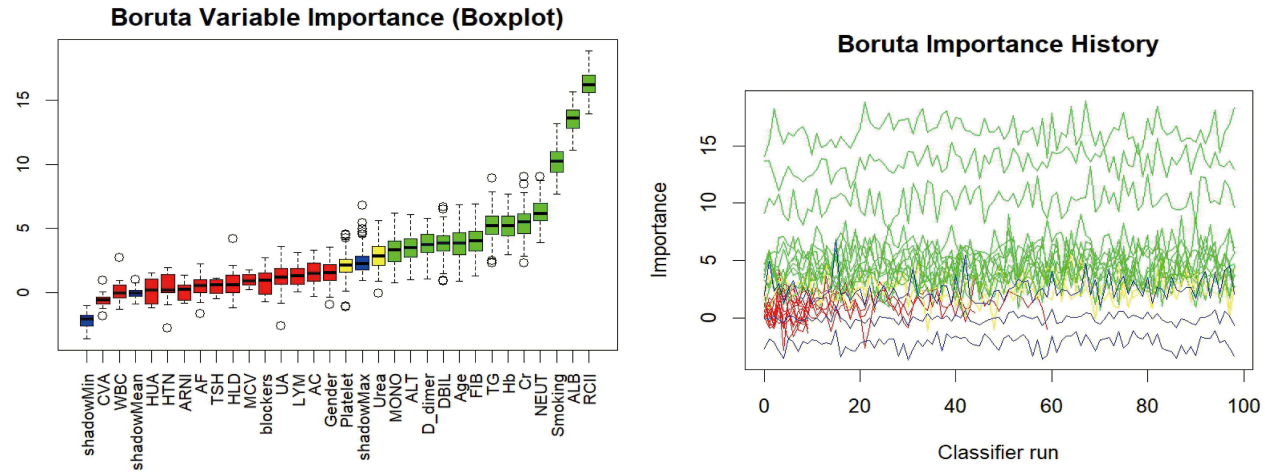

Figure 2 Boruta Analysis Identifying Key Predictor Variables.

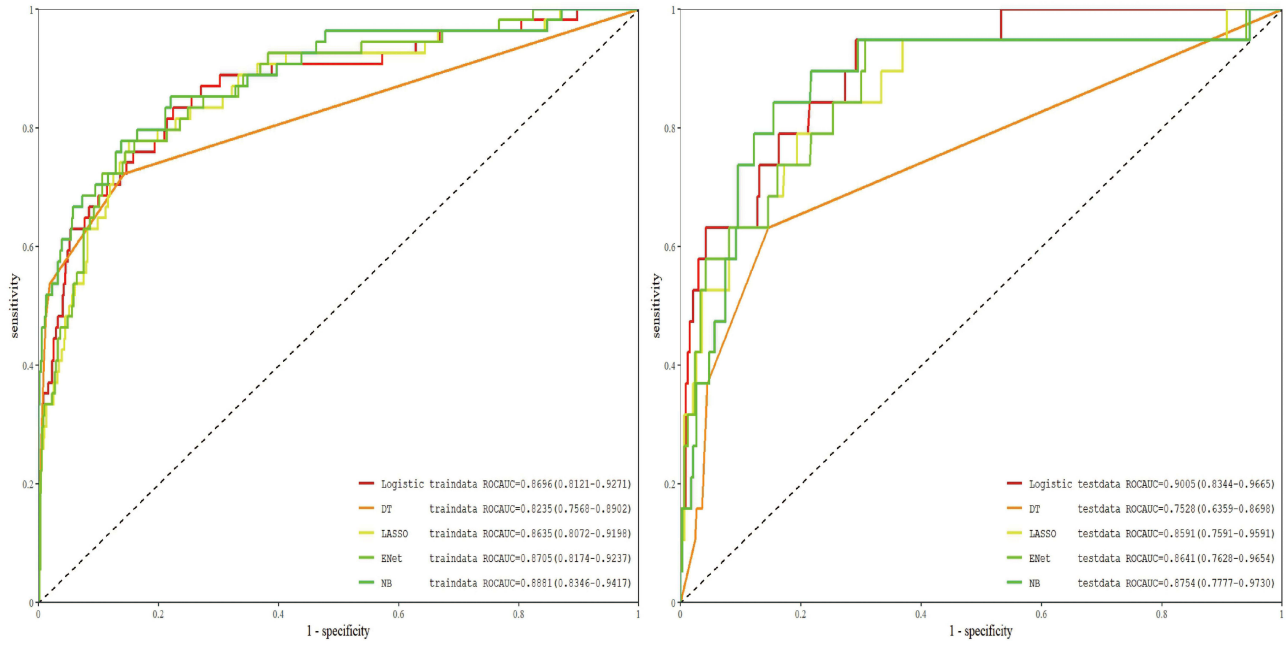

Figure 3 Receiver Operating Characteristic (ROC) Curves for Test and Validation Sets.

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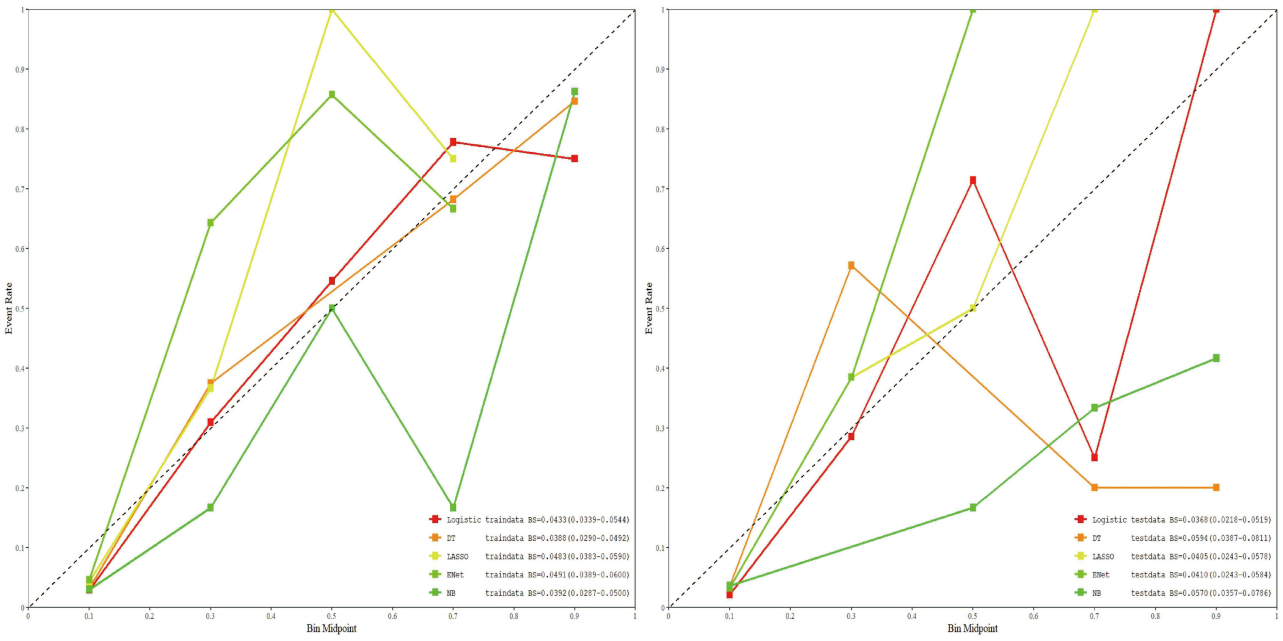

Figure 4 Calibration Curves for Test and Validation Sets.

0.0368 in the testing set, reflecting close agreement between predicted probabilities and observed outcomes. LASSO and ENet showed moderate calibration, while DT and NB performed less favorably. Table 2 further confirmed the robust overall performance of logistic regression in the testing cohort. Cross-validation results are displayed in Figure 5, showing that, except for DT, all models achieved their best performance in Fold 5. Logistic regression reached ROC_AUC values approaching 0.98, highlighting their stability and generalizability. Taken together, logistic regression demonstrated superior discrimination and calibration across analyses.

Interpretability of the Logistic Regression Model Using SHAP

As illustrated in Figure 6, SHAP analysis was applied to interpret the logistic regression model. The SHAP summary plot (Figure 6A) indicated that poor nutritional status (both low hemoglobin and low serum albumin), elevated RCII, and smoking were among the most influential factors driving HF occurrence. The mean absolute SHAP values (Figure 6B) ranked the relative importance of predictors, with RCII consistently the second-highest contributor. Dependence analysis (Figure 6C) showed a positive relationship between RCII and SHAP values, demonstrating that higher RCII levels were consistently associated with an increased predicted risk of HF.

Table 2 The Comprehensive Evaluation of the Performance of Predictive Models

Model	Set	AUC	Accuracy	Sensitivity	F1 Score	PPV	NPV
Logistic	Training	0.8696268	0.78	0.833	0.331	0.206	0.985
	Test	0.9004543	0.766	0.842	0.278	0.167	0.988
DT	Training	0.8235224	0.849	0.722	0.384	0.262	0.978
	Test	0.7528195	0.842	0.632	0.3	0.197	0.976
ENet	Training	0.8705143	0.837	0.778	0.384	0.255	0.982
	Test	0.8641134	0.845	0.684	0.321	0.21	0.98
Lasso	Training	0.8635339	0.845	0.778	0.396	0.266	0.982
	Test	0.8591009	0.842	0.632	0.3	0.197	0.976
NB	Training	0.8881453	0.857	0.778	0.416	0.284	0.982
	Test	0.8753916	0.845	0.789	0.353	0.227	0.986

Abbreviations: PPV, positive predictive value; NPV, negative predictive value.

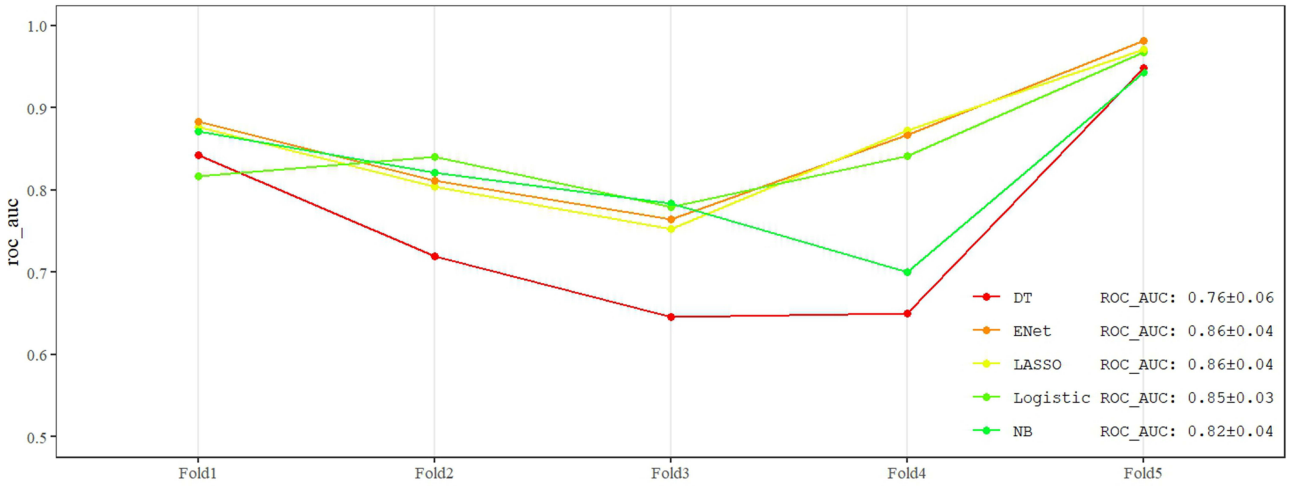

Figure 5 Comparison of ROC AUC for Five Machine Learning Models Across 5-Fold Cross-Validation.

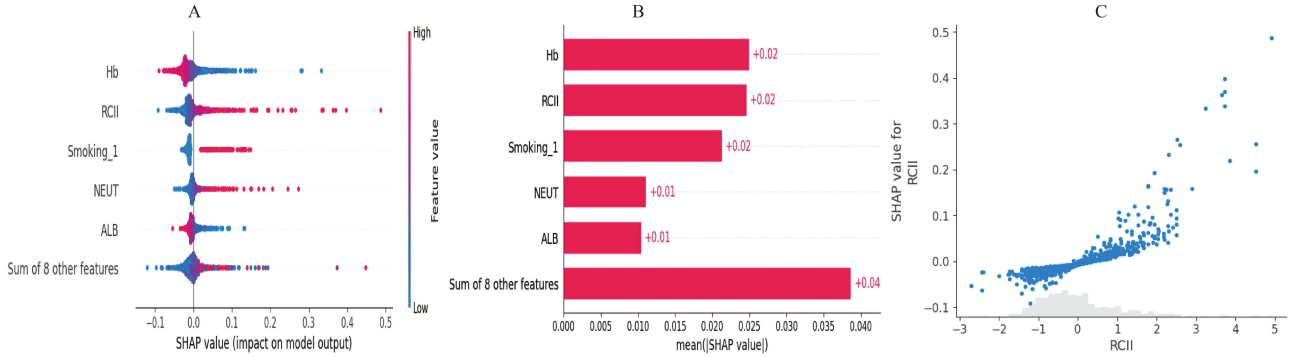

Figure 6 SHAP Analysis of Feature Importance. (**A**) Feature Attributes; (**B**) SHAP-Based Feature Importance Ranking; (**C**) SHAP Dependence Plot.

Discussion

In the present study, RCII levels were markedly elevated in CAD patients with T2DM who developed HF compared with those who did not (7.14 vs 1.29). The presence of atrial fibrillation also increased the likelihood of HF onset. Using the Boruta algorithm, we identified 13 variables most strongly associated with HF risk in this population. Among the predictive models evaluated, logistic regression achieved the best overall performance in both training and testing cohorts, with superior accuracy and calibration, suggesting strong predictive capability for HF development. Model interpretability analysis with SHAP further revealed that poor nutritional status, elevated RCII, and smoking were major contributors to HF risk. The SHAP dependence plots highlighted a consistent positive relationship between RCII and model output, reinforcing its importance as a predictor.

Mechanistically, hs-CRP can activate endothelial cells, facilitate inflammatory cell infiltration into myocardial tissue, and promote myocardial fibrosis through NF-κB and TGF-β signaling.[22,23] Additionally, hs-CRP induces oxidative stress and cardiomyocyte apoptosis, impairing contractile function.[24] RC, a triglyceride-rich lipoprotein particle, can penetrate the vascular endothelium and deposit in the arterial wall, triggering localized inflammation and atherosclerosis. Beyond endothelial injury and ischemia,[25] RC activates inflammatory mediators further contributing to myocardial remodeling and fibrosis.[26] The combined effect of RC and hs-CRP may be particularly detrimental, with stronger predictive value for cardiovascular events than either marker alone.[27,28] Elevated RC together with low-grade inflammation may act synergistically to substantially increase the risk of adverse outcomes.[29]

Malnutrition is common among HF patients and strongly linked to poor prognosis.[30,31] Elevated hs-CRP levels have been consistently associated with HF onset and progression, even in patients with well-controlled LDL-C,[32] highlighting

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inflammation as an independent driver of cardiovascular risk. Notably, most prior studies linking hsCRP to HF focus on HFpEF, emphasizing the broader relevance of inflammatory biomarkers across HF phenotypes. Smoking remains a major modifiable risk factor, with long-term smokers exhibiting nearly double the risk of HF compared with non-smokers;[33] this excess risk may persist even years after cessation. Other inflammatory indices, such as the CRP/albumin ratio and systemic immune-inflammation index, have also been associated with HF risk, although RCII may provide a more integrated measure of lipid-driven inflammation. Additionally, dyslipidemia plays a critical role not only in coronary disease but also in carotid plaque instability and related cerebrovascular events,[34] suggesting that RCII could have broader vascular implications beyond the coronary circulation. These findings align with our results, reinforcing the reliability of our conclusions. Notably, the prediction model developed in this study achieved AUCs ranging from 0.75 to 0.90 across both training and testing sets, outperforming previously reported models. The improved discrimination suggests that integrating RCII into risk calculators or follow-up protocols could help identify high-risk CAD/T2DM patients earlier and guide individualized preventive strategies. It is important to note that RCII should currently be considered a correlative biomarker rather than a confirmed causal factor, reflecting the combined effect of lipid abnormalities and inflammation on HF risk.

Nevertheless, several limitations warrant consideration. First, this was a single-center retrospective study with a relatively limited sample size, restricting the generalizability of our findings. Second, certain potential predictors, such as cardiac imaging parameters and natriuretic peptides (eg, BNP), were not included, which may limit the comprehensiveness of the model. Future research should validate our findings in larger, multicenter cohorts with longer follow-up and integrate additional HF-specific biomarkers to further refine model accuracy and enhance clinical utility.

Looking forward, translating this predictive model into clinical practice will require prospective multicenter validation and integration with electronic health records. Developing a user-friendly decision support interface and establishing clear clinical pathways for high-risk patients are essential steps. Such efforts could move this work beyond retrospective analysis toward practical risk stratification and evidence-based interventions, ultimately enhancing patient care and informing policy or risk management decisions.

Conclusions

Elevated RCII is closely associated with increased HF risk in CAD patients with T2DM. Logistic regression models incorporating RCII demonstrated strong predictive performance, with poor nutritional status, RCII, and smoking identified as key contributors. RCII may serve as a practical biomarker for early risk stratification, supporting targeted prevention and follow-up in high-risk patients.

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Disclosure

The authors report no conflicts of interest in this work.

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