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ORIGINAL RESEARCH

Red Blood Cell Distribution Width to Albumin Ratio for Predicting Type I Cardiorenal Syndrome in Patients with Acute Myocardial Infarction: A Retrospective Cohort Study

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Purpose: Red blood cell distribution width to albumin ratio (RAR) is a novel inflammatory biomarker that independently predicts adverse cardiovascular events and acute kidney injury. This study aimed to assess the predictive value of RAR for cardio-renal syndrome type I (CRS-I) risk in acute myocardial infarction (AMI) patients.

Patients and methods: This study retrospectively enrolled 551 patients who were definitively diagnosed as AMI between October 2021 and October 2022 at the Affiliated Zhongda Hospital of Southeast University. Participants were divided into two and four groups based on the occurrence of CRS-I and the quartiles of RAR, respectively. Demographic data, laboratory findings, coronary angiography data, and drug utilization were compared among the groups. Logistic regression and receiver operating characteristic curve (ROC) analysis were performed to identify independent risk factors for CRS-I and evaluated the predictive value of RAR for CRS-I.

Results: Among the cohort of 551 patients, 103 (18.7%) developed CRS-I. Patients with CRS-I exhibited significantly elevated RAR levels compared to those without the condition, and the incidence of CRS-I correlated with escalating RAR. Univariate and multivariate logistic regression analyses identified RAR as an independent risk factor for CRS-I. ROC curves analysis demonstrated that RAR alone predicted CRS-I with an area under the curve (AUC) of 0.683 (95% CI=0.642–0.741), which was superior to the traditional inflammatory marker C-reactive protein (CRP). Adding the variable RAR to the model for predicting the risk of CRS-I further improved the predictive value of the model from 0.808 (95% CI=0.781–0.834) to 0.825 (95% CI=0.799–0.850).

Conclusion: RAR is an independent risk factor for CRS-I, and high levels of RAR are associated with an increased incidence of CRS-I in patients with AMI. RAR emerges as a valuable and readily accessible inflammatory biomarker that may play a pivotal role in risk stratification in clinical practice.

Keywords: acute myocardial infarction, cardio-renal syndrome type I, red blood cell distribution width to albumin ratio, inflammatory

Introduction

Cardio-renal syndrome (CRS) is defined as "disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other". The CRS is divided into 5 subcategories according to the organ of origin and whether the initiating insult is acute or chronic.[1] CRS-I is an important subtype of CRS, which refers to an acute kidney injury (AKI) due to acute worsening of cardiac function, with initiating factors including acute coronary syndromes, acute decompensated heart failure, cardiogenic shock and cardiac surgery.[2] Amin observed that the incidence of AKI, using the Kidney Disease: Improving Global Outcomes (KDIGO) definition, was 19.7% among a cohort of 31,532 acute myocardial infarction (AMI) patients.[3] Development of CRS-I in patients with AMI significantly increases the incidence of in-hospital mortality and long-term adverse prognosis.[4] Due to the fact that the exact pathogenesis of CRS-I has not been fully elucidated,

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there is still no effective treatment. Therefore, it is crucial to conduct the screening of patients with risk factors and to promptly adopt preventive strategies aimed at reducing the incidence of CRS-I.

Inflammation is an important non-hemodynamics mechanism of CRS-I, both directly affecting the heart and kidney and mediating interaction between pathophysiological pathways in CRS-I.[5] There are multiple inflammatory states in the organism of AMI patients, including persistent chronic inflammation before AMI, the flaming burst of excess inflammation after AMI, and lingering low-grade excess of inflammation post-AMI.[6] Fu et al discovered that inflammation is related to adverse outcomes in AMI, including higher risk of major adverse cardiac events, cardiovascular death, AKI, and all-cause mortality.[7,8] C-reactive protein (CRP) serves as a classical inflammation biomarker, yet its readings are notably affected by acute inflammation and serious infection.[9] Red blood cell distribution width to albumin ratio (RAR) stands as a novel biomarker exhibiting a stronger correlation with chronic inflammation and has demonstrated associations with various diseases, including AMI, heart failure, aortic aneurysms and AKI.[10–13] Nevertheless, there is a paucity of studies examining the association between RAR and the incidence of CRS-I in patients experiencing AMI. The RAR is emerging as a promising indicator of chronic inflammation due to its validity, simplicity, and cost-effectiveness. This study aimed to assess the predictive value of RAR for CRS-I risk in patients with AMI and provide new perspectives for optimizing models evaluating CRS-I risk.

Methods

Study Population

This study was a retrospective cohort study conducted at a single center, adhering strictly to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. A total of 551 participants diagnosed with AMI at the Department of Cardiology, Zhongda Hospital, Southeast University, between October 2021 and October 2022, were included. The following criteria were used to exclude patients: (1) suffer from severe systemic or local infections; (2) patients with malignant tumors, autoimmune diseases, hematological disorders or coagulation disorders; (3) renal insufficiency with an estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2 or those who had already received renal substitution therapy; (4) incomplete collection of data from patients' medical records (missing data >10%), particularly the absence of admission hematological examination and renal function indicators during the 48–72 hour period following admission (Figure 1).

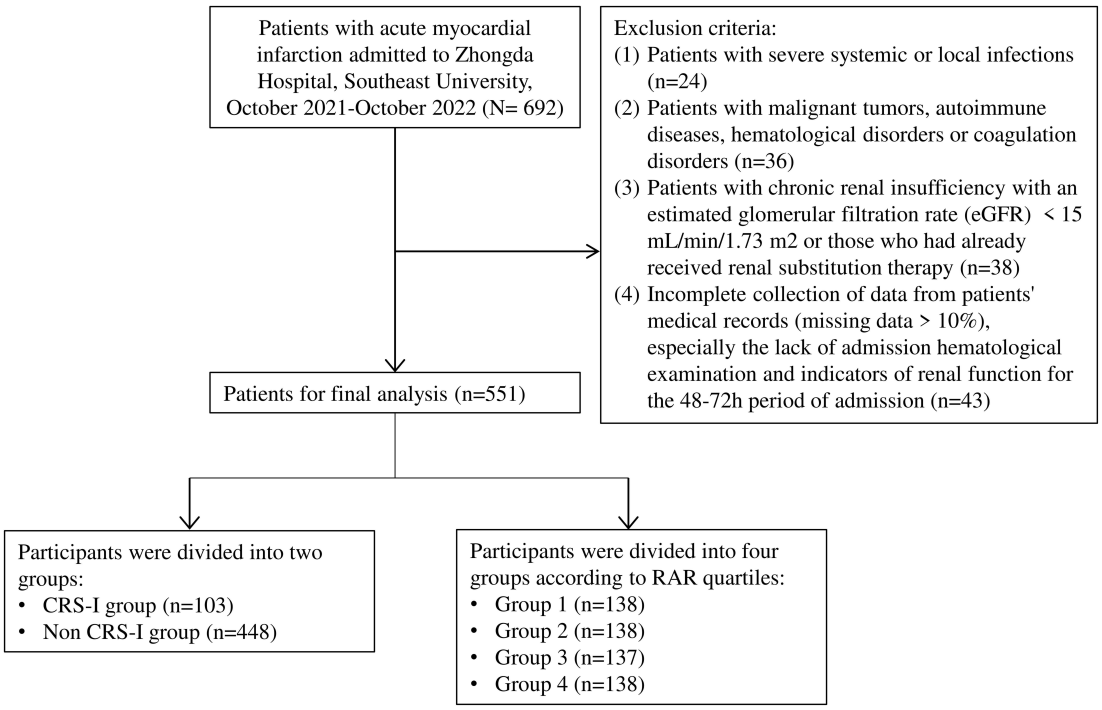

Figure 1 Flow diagram of participants selection.

Groups

Participants were categorized into two groups based on occurrence of CRS-I: non-CRS-I group (n=103) and CRS-I group (n=448). Furthermore, participants were categorized into four quartiles as follows: Group 1 (n=138, RAR ≤3.06), Group 2 (n=138, 3.06< RAR ≤ 3.35), Group 3 (n=137, 3.35< RAR≤ 3.73), and Group 4 (n=138, 3.73<RAR).

Data Collection

Baseline characteristics of the study population, encompassing demographic details and medical history, were collected from the electronic medical records of the Zhongda Hospital, Southeast University, alongside the vital sign data and Killip class. Additionally, the data regarding the history of antiplatelet therapy, beta-blocker usage, lipid-modulating therapy, as well as the administration of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers during hospitalization. We also gathered information on coronary angiography (CAG) and deaths during hospitalization.

Laboratory analysis encompassed findings from routine blood tests, serum creatinine (Scr), serum lipid, albumin (ALB), cardiac troponin I, N-terminal pro-brain natriuretic peptide (NT-proBNP) and eGFR. Echocardiographic assessments encompassed parameters such as left ventricular ejection fraction (LVEF), and all measurements were acquired during the initial hospital examination.

Definitions

AMI diagnosis followed the criteria set forth in the Fourth Universal Definition of Myocardial Infarction.[14] The diagnosis of AKI following AMI adhered to the Kidney Disease: Improving Global Outcomes (KDIGO) guideline, wherein three criteria were outlined: (1) Serum creatinine (Scr) level increases by 0.3 mg/dl (26.5 μmol/l) within 48 hours; (2) Scr level increases by 50% from the basal value within 7 days; (3) Urine output is less than 0.5 mL/kg/hour for 6 consecutive hours; the diagnosis can be made if one of the above three conditions is met.[15] Our center implemented the prophylactic hydration protocol based on the strategy outlined in the AMACING trial.[16]

Sample Size Calculation

The sample size calculation in this study was performed from two perspectives. Firstly, for the retrospective cohort study, the sample size was determined using the PASS software version 2021 (www.ncss.com). The calculation was based on the pre-experimental results with P1=0.26 and P2=0.10, while setting α=0.05 and β=0.10. The resulting sample sizes for the exposed and non-exposed groups were determined to be 116 each.[17] Secondly, a prediction model was constructed for this study, and the sample size calculation was conducted using the formula n = (1.96/δ) ^2 $\phi(1-\phi)$ to estimate the sample size for the training set.[18] Here, ϕ represents the expected incidence rate of the outcome, which was determined as ϕ = 0.20 based on previous studies.[3] δ represents the desired margin of error, set at δ = 0.05. The minimum sample size required for the training set was determined to be 246. The sample size included in this study meets the requirements for both the retrospective cohort study and the prediction model.

Statistical Analysis

Statistical analysis was conducted using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA), R version 4.3.2 (www.rproject.org). Multiple imputation was utilized to address missing values, which were less than 10% of the data. Normally distributed continuous variables were presented as means ± standard deviation and analyzed using independent sample t-tests. For continuous variables displaying poor normality, interquartile ranges were used, and rank-sum tests were employed for analysis. The Chi-square test or Fisher's exact test was applied to compare the frequency and percentages of categorical variables. Pearson's or Spearman's rank correlation coefficient analysis was performed to investigate correlations between RAR and other baseline clinical data. Collinearity analysis was conducted to identify variables significantly associated with RAR.

To assess risk factors for incident CRS-I, univariate and multivariate logistic regression analyses were performed. The predictive value of RAR for CRS-I was evaluated using the ROC curve. Prior to constructing the predictive model, the synthetic minority oversampling technique (SMOTE) was employed to address data distribution imbalance. The clinical predictive model was constructed using the Forward Selection method. The DeLong method was utilized to compare the

area under the curve (AUC) of the model before and after the inclusion of RAR. A nomogram was created to visualize the model. Internal validation was performed using the bootstrap method, and the consistency index (C-index) was used to assess the predictive ability of the model.

For validation purposes, 30% of the overall patients were randomly selected as the test set, while the remaining sample was used as the training set for 10-fold cross-validation. Validation of the model included calibration and discrimination, with calibration plots assessing prediction accuracy. The clinical utility of the model was estimated using decision curve analysis (DCA). Sensitivity analyses were conducted, including subgroup and interaction analyses. A significance level of $P < 0.05$ was considered statistically significant in all analyses.

Results

Baseline Characteristics

Five hundred fifty-one patients with AMI were consecutively enrolled. The study population included 419 males and 132 females, with a mean age of 66.97±13.48 years. Among the enrolled patients, 103 (18.7%) developed CRS-I. Table 1 summarizes the baseline characteristics of the enrolled population. Compared to participants in the non-CRS-I group, those in the CRS-I group had had significantly higher RAR (3.64 vs 3.28, P<0.001). Patients who developed CRS-I were older and exhibited a higher prevalence of hypertension, diabetes mellitus (DM), previous stroke, anemia, a higher cardiac function class, elevated levels of leukocyte count, red blood cell distribution width (RDW), D-dimer, CRP, Scr, uric acid, and LVEF, eGFR, and ALB compared to those without CRS-I. Moreover, the CRS-I group had lower rates of aspirin usage and hydration, and they were more likely to undergo coronary angiography (CAG) and receive diuretic treatment compared to the non-CRS-I group. Finally, patients in the CRS-I group had a higher risk of in-hospital mortality (17.6% vs 2.2%, $P < 0.001$).

Table 1 Baseline Characteristics of the CRS-I and Non-CRS-I Groups

Variables	Total Participants (n = 551)	Non-CRS-I Group (n = 448)	CRS-I Group (n = 103)	P-value
RAR	3.35 (3.06, 3.73)	3.28 (3.04, 3.64)	3.64 (3.24, 4.41)	<0.001
Age, years	66.97±13.48	65.80±13.15	72.03±13.78	<0.001
Male, %	419 (76.0%)	353 (78.8%)	66 (64.1%)	0.002
BMI, kg/m^2	24.91±3.36	24.96±3.20	24.68±3.96	0.511
SBP, mmHg	133.02±55.98	133.16±60.70	132.41±27.42	0.903
DBP, mmHg	77.14±14.87	77.38±13.99	76.07±18.24	0.493
NSTEMI, %	296 (53.7%)	243 (54.2%)	53 (51.5%)	0.609
Hypertension, %	373 (67.7%)	290 (64.7%)	83 (80.6%)	0.002
DM, %	200 (36.3%)	147 (32.8%)	53 (51.5%)	<0.001
CKD, %	28 (5.1%)	15 (3.3%)	13 (12.6%)	<0.001
Previous stroke, %	155 (28.2%)	110 (24.5%)	45 (43.7%)	<0.001
Anemia, %	100 (18.1%)	63 (14.1)	37 (35.9%)	<0.001
Atrial fibrillation, %	32 (5.8%)	24 (5.4%)	8 (7.8%)	0.346
Killip III+IV	85 (15.4%)	46 (10.3%)	39 (37.9%)	<0.001
LVEF, %	56.56±12.61	57.87±12.23	50.87±12.69	<0.001
Leukocyte count, $10^9/L$	8.90 (7.00, 11.20)	8.74 (6.9, 1073)	9.76 (8.26,12.85)	<0.001
Red blood cell, $10^9/L$	4.47±0.80	4.57±0.75	4.14±0.90	0.001
Hemoglobin, g/L	136.61±23.03	138.95±20.95	126.44±28.45	<0.001
RDW, %	13.20 (12.70, 13.70)	13.1 0 (12.7, 13.50)	13.60 (13.00, 14.50)	<0.001
TnI, ng/mL	0.51 (0.08, 2.40)	0.46 (0.06, 2.98)	0.61 (0.16, 1.80)	0.483
D-dimer, mg/L	0.48 (0.28, 0.97)	0.44 (0.26, 0.82)	0.83 (0.42, 1.61)	<0.001
CRP, mg/L	3.42 (1.35,14.83)	2.99 (1.26, 11.95)	7.66 (2.55, 47.15)	<0.001
Scr, μmo/l/L	81 (67, 103)	78 (66, 97)	107 (82, 169)	<0.001

(*Continued*)

Table 1 (Continued).

Variables	Total Participants (n = 551)	Non-CRS-I Group (n = 448)	CRS-I Group (n = 103)	P-value
eGFR, mL/min/1.73m^2	87.15 (54.96, 102.56)	91.78 (67.92, 104.20)	49.74 (26.35, 85.00)	<0.001
Uric acid, μmol/L	380.20±129.03	366.62±110.92	439.24±177.56	<0.001
TG, mmol/L	1.37 (0.99, 1.99)	1.37 (0.98, 1.98)	1.38 (1.07, 2.24)	0.364
TC, mmol/L	4.16±1.25	4.18±1.18	4.08±1.49	0.504
LDL-C, mmol/L	2.42±0.92	2.45±0.90	2.29±0.98	0.128
HDL-C, mmol/L	0.98±0.25	0.98±0.25	0.97±0.28	0.644
Albumin, g/dL	3.91±0.50	3.96±0.47	3.69±0.58	<0.001
CAG, %	481 (87.3%)	406 (90.4%)	75 (73.5%)	<0.001
Number of stents	1.37±1.20	1.33±1.16	1.57±1.36	0.062
Gensini score	68.00 (38.00, 98.00)	68.00 (38.00, 94.00)	69.00 (8.00, 108.00)	0.784
Syntax score	22.25 (17.00, 28.00)	22.50 (16.50, 28.00)	22.00 (19.00, 27.00)	0.606
Contrast agent, mL	100.00 (100.00, 200.00)	100.00 (0.00, 200.00)	100.00 (100, 200)	0.004
Aspirin, %	531 (96.4%)	437 (97.5%)	94 (91.3%)	0.002
Clopidogrel/ticagrelor, %	527 (95.6%)	431 (96.2%)	96 (93.2%)	0.178
ACEI/ARB, %	211 (38.3%)	167 (37.3%)	44 (42.7%)	0.306
Beta blockers, %	393 (71.3%)	318 (71.0%)	75 (72.8%)	0.711
Statin, %	538 (97.6%)	439 (98.0%)	99 (96.1%)	0.441
Hydration, %	443 (80.4%)	373 (83.3%)	70 (68.0%)	<0.001
Diuretic, %	316 (57.4%)	232 (51.8%)	84 (81.6%)	<0.001
Deaths in hospital, %	28 (5.1%)	10 (2.2%)	18 (17.6%)	<0.001

Abbreviations: CRS-I, cardio-renal syndrome type I; RAR, red blood cell distribution width to albumin ratio; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; NSTEMI, non-ST elevation myocardial infarction; DM, diabetes mellitus; CKD, chronic kidney disease; LVEF, left ventricular ejection fraction; RDW, red blood cell distribution width; TnI, troponin I; CRP, C-reactive protein; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CAG, coronary angiography; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers.

Participants were further categorized into four groups based on the quartile of RAR. Illustrated in Figure 2, the incidence of CRS-I exhibited a gradual increase with each ascending RAR quartile, and patients in the highest RAR quartile faced a significantly elevated risk of developing CRS-I compared to those in the lowest quartile (P<0.001). Moreover, there were

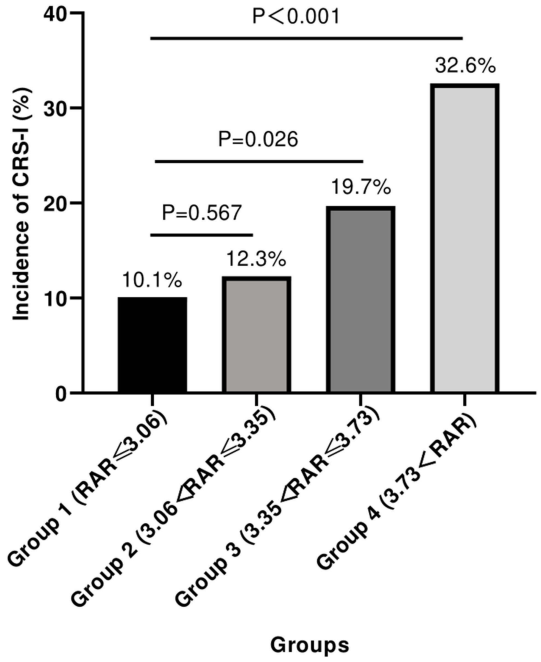

Figure 2 The incidence of CRS-I in different RAR groups.

statistically significant differences among the four groups in age, body mass index (BMI), diastolic blood pressure (DBP), non-ST-elevation myocardial infarction (NSTEMI), chronic kidney disease (CKD), previous stroke, anemia, cardiac function class, LVEF, CAG, syntax score, leukocyte count, red blood cell, hemoglobin, RDW, D-dimer, CRP, Scr, eGFR, uric acid, triglyceride (TG), total cholesterol (TC), ALB, contrast agent, hydration, and diuretic. Furthermore, the in-hospital mortality rate of AMI patients increased with higher RAR values. (Supplementary Table 1).

Correlation Between RAR and Clinical Baseline Data

To investigate the relationship between the RAR and baseline characteristics, Pearson's or Spearman's rank correlation analysis was performed. The RAR showed a positive correlation with age, D-dimer, CRP, Scr and uric acid, and a negative correlation with BMI, LVEF, hemoglobin, eGFR, TG, TC, LDL-C and contrast agent ($p < 0.05$) (Table 2).

Independent Risk Factors for CRS-I in Patients with AMI

Univariate logistic regression analysis showed that RAR, age, sex, hypertension, diabetes mellitus, previous stroke, anemia, cardiac function class, LVEF, leukocyte count, red blood cell, hemoglobin, RDW, D-dimer, CRP, Scr, eGFR, uric acid, ALB, CAG, contrast agent, aspirin, hydration, and diuretic were the risk factors for CRS-I (Supplementary Table 2). Collinearity analysis was used to clarify whether there is a strong correlation among variables. RAR had a high degree of collinearity with red blood cell (Tolerance:0.104, VIF:9.599), hemoglobin (Tolerance:0.076, VIF:13.098), Scr (Tolerance:0.148, VIF:6.749), and eGFR (Tolerance:0.120, VIF:8.357) (Supplementary Table 3). Multivariate logistic regression analysis excluded these four variables and indicted that RAR (adjusted OR: 1.693, 95% CI: 1.114-2.575), DM, Killip III+IV, leukocyte count, uric acid were independent risk factors for CRS-I after adjusting for potential confounding risk factors.

Predictive Value of RAR for CRS-I

ROC curve analysis was utilized for evaluating the predictive value of RAR in CRS-I. Figure 3 shows RAR alone predicted the development of CRS-I in acute myocardial infarction patients with an AUC of 0.683 (95% CI=0.624–0.741), which was superior to the traditional inflammatory marker C-reactive protein AUC of 0.635 (95% CI=0.577–0.693). Compared with

Table 2 Correlation Between RAR and Potential Risk Factors

Variables	Correlation Coefficient (r)	P-value
Age	0.434	<0.001
BMI	−0.180	<0.001
LVEF, %	−0.252	<0.001
Leukocyte count, 10^9/L	−0.053	0.218
Hemoglobin, g/L	−0.533	<0.001
D-dimer, μg/L	0.464	<0.001
CRP, mg/L	0.372	<0.001
Scr, μmol/L	0.362	<0.001
eGFR, mL/min/1.73m2	−0.538	<0.001
Uric acid, μmol/L	0.133	0.002
TG, mmol/L	−0.231	<0.001
TC, mmol/L	−0.220	<0.001
LDL-C, mmol/L	−0.192	<0.001
HDL-C, mmol/L	−0.040	0.345
Contrast agent, mL	−0.263	<0.001

Abbreviations: BMI, body mass index; LVEF, left ventricular ejection fraction; CRP, C-reactive protein; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

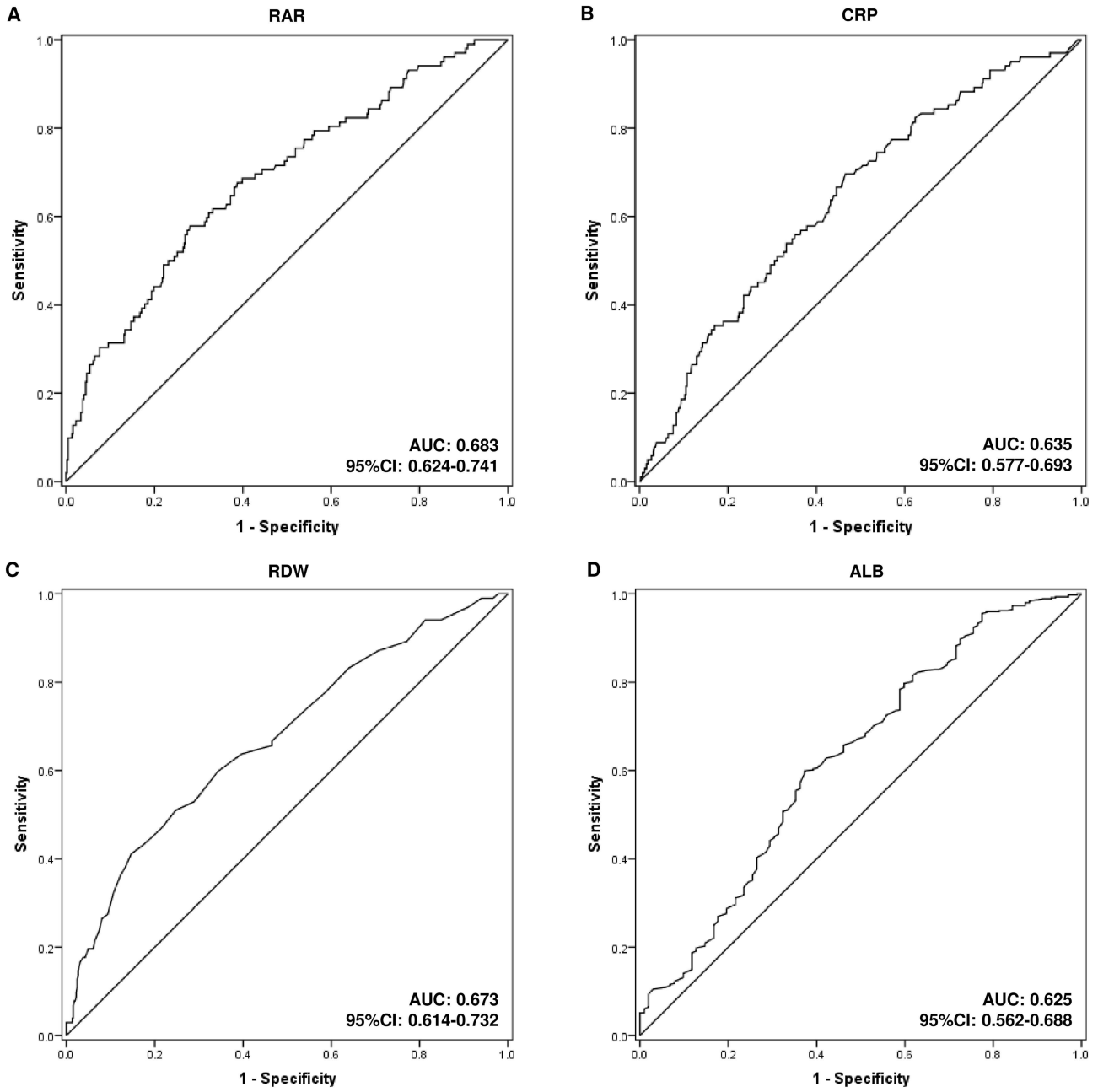

Figure 3 The ROC curve of RAR, CRP, RDW and ALB for predicting CRS-I. (**A**) The ROC curve of RAR for predicting CRS-I. (**B**) The ROC curve of CRP for predicting CRS-I. (**C**) The ROC curve of RDW for predicting CRS-I. (**D**) The ROC curve of ALB for predicting CRS-I.

RDW and ALB, RAR had a better predictive effect, the AUC intuitively showed this (Figure 3). The optimal cut-off value of RAR was 3.58, with a sensitivity and specificity of 57.3% and 71.9%, respectively.

Nomogram of CRS-I in Patients with AMI

Variables were selected using the Forward Selection method to develop a risk assessment model for CRS-I. The selected variables included RAR, sex, hypertension, DM, cardiac function class, uric acid, leukocyte count, and diuretic usage. Model 1, which did not include RAR, yielded an area under the curve (AUC) of 0.808 (95% CI: 0.781–0.834) in the ROC curve analysis. After adding RAR to the model, the AUC increased to 0.825 (95% CI: 0.799–0.850), indicating that the inclusion of RAR improved the predictive value of the risk model. This improvement is demonstrated in Figure 4,

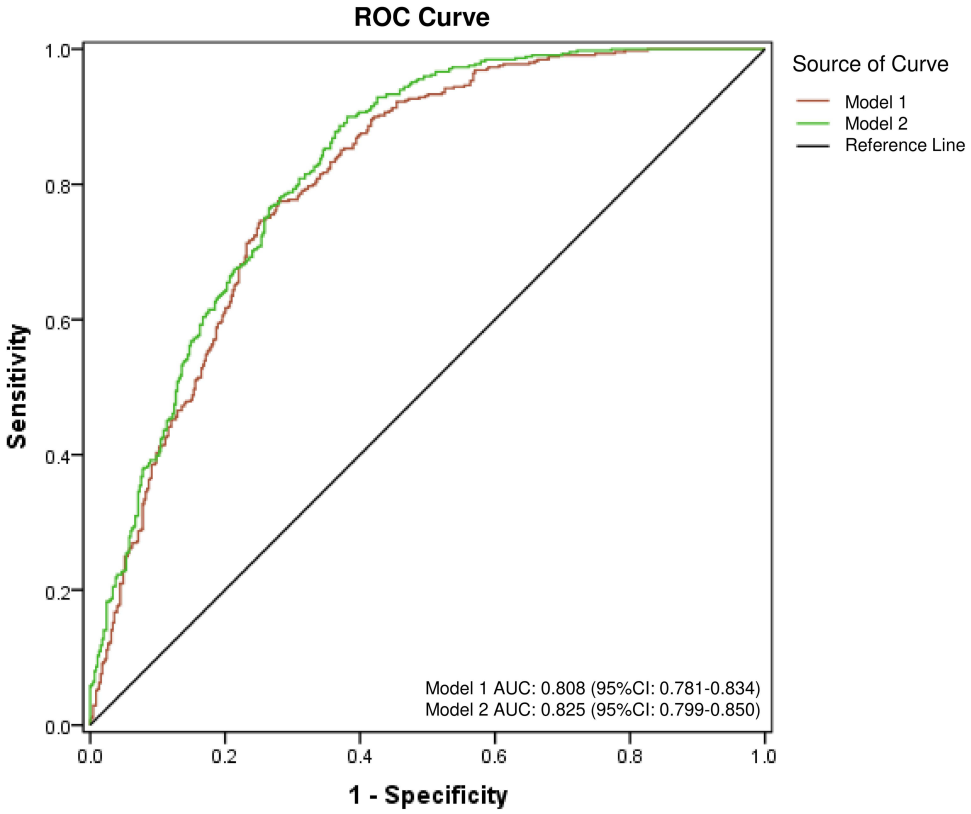

Figure 4 The ROC curve of model 1 and model 2 for predicting CRS-I.

which shows the ROC curve. To further assess the significance of adding RAR to the model, the DeLong's test was used to compare the AUC of Model 1 (without RAR) and Model 2 (with RAR). The results revealed a statistically significant difference between the two models (Z=2.934, p=0.003), confirming that the inclusion of RAR enhanced the predictive performance of the model. Norman diagrams were constructed for Model 2 to visualize the predictive model. This diagram provides a visual representation of the model's performance and aid in understanding the contribution of each variable to the prediction of CRS-I (Supplementary Figure 1).

Evaluation and Validation of the Nomogram

To assess the performance and clinical utility of Model 2, an internal validation was conducted using the bootstrap method. The C-index of Model 2 was calculated to be 0.827 (95% CI: 0.825–0.829), indicating good discrimination ability of the model. Furthermore, to evaluate the generalizability of the model, 165 patients (30% of the total sample) were randomly selected as the test set, while the remaining patients were used as the training set for 10-fold cross-validation. The AUC was 0.830 (95% CI: 0.799–0.862) in the validation set and 0.811 (95% CI: 0.760–0.862) in the test set, as depicted in Supplementary Figure 2. These results suggest that Model 2 has good predictive performance and can effectively discriminate between patients with and without CRS-I. The calibration curve, shown in Figure 5, demonstrates that the predicted incidence of CRS-I in AMI patients closely aligns with the ideal diagonal line. This indicates strong consistency between the predicted and observed values, indicating good calibration of the model. Additionally, decision curve analysis (DCA) was performed to evaluate the clinical utility of Model 2. The results, presented in Figure 6, demonstrate the favorable clinical applicability of Model 2 in predicting the incidence of CRS-I among AMI patients.

Sensitivity Analysis

Subgroup analyses were performed to delve deeper into the association between the RAR and CRS-I, as illustrated in Figure 7. The results of subgroup analyses based on age, sex, hypertension, DM, cardiac function class, LVEF, leukocyte count, hydration, or diuretic were in line with the findings of the overall group.

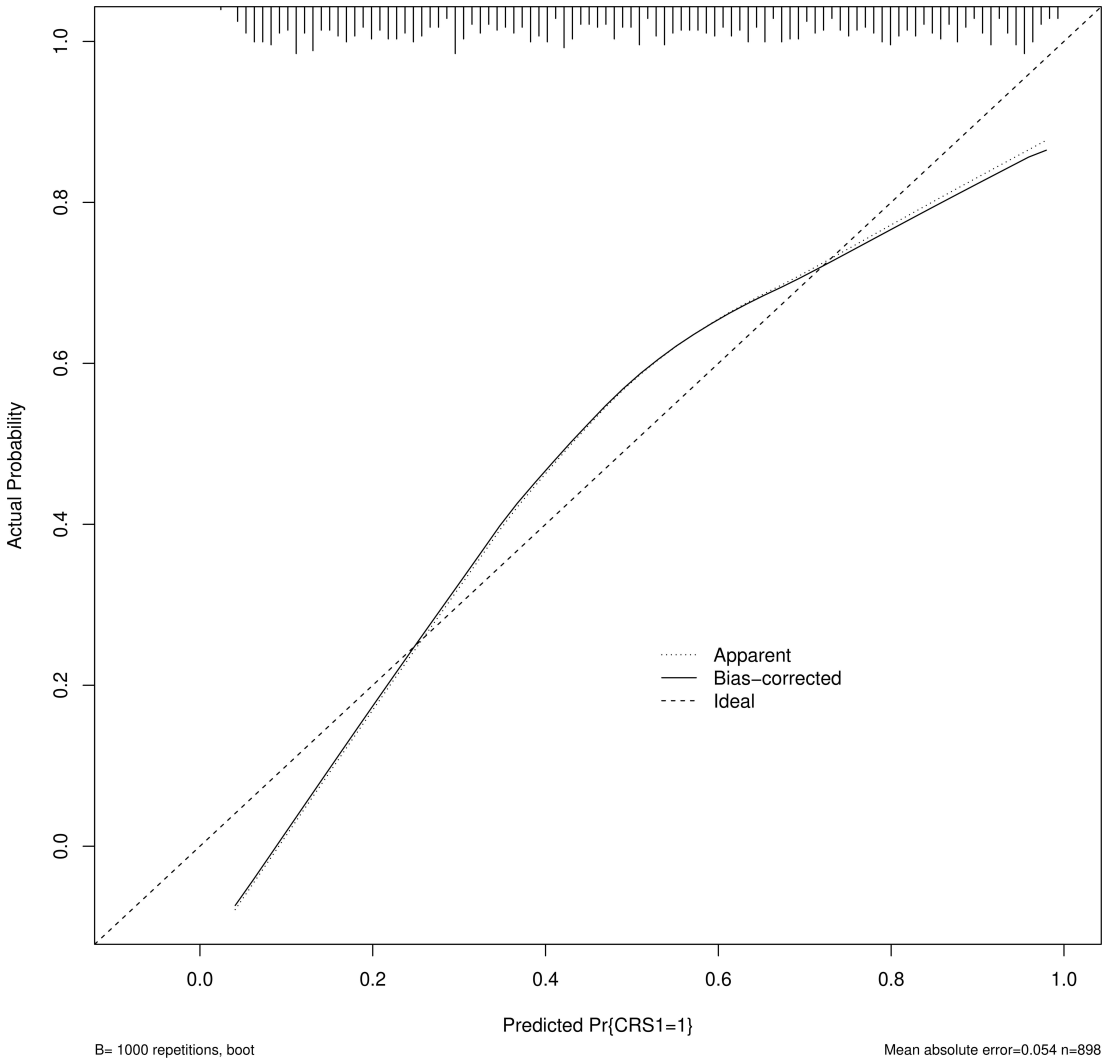

Figure 5 The calibration plots for model 2.

Discussion

This study is the first to investigate the use of the inflammatory marker RAR as a predictor of CRS-I in patients with AMI. The results demonstrated that patients with CRS-I had significantly higher RAR values compared to those without CRS-I. Furthermore, RAR emerged as an independent risk factor for CRS-I after adjusting for confounding factors. The inclusion of RAR in the established risk model resulted in a significant improvement in risk stratification for CRS-I. This finding suggests that RAR has an incremental effect in enhancing the predictive value of the model. The clinical predictive model, which incorporated RAR, demonstrated good clinical utility in predicting the incidence of CRS-I among AMI patients.

In our study, we examined the median and interquartile range of contrast agents used in both the CRS and non-CRS groups, which were found to be 100.00 (100, 200) and 100.00 (100, 200), respectively. The corresponding mean ranks were 238.39 and 284.54, with a p-value of 0.004. These results indicate that a higher amount of contrast agents was utilized in the non-CRS group, which initially seems counterintuitive. We hypothesized that this discrepancy might be attributed to critically ill patients who did not undergo coronary angiography, as they exhibited a higher incidence of CRS-I (38.6% in this study). To address this, we conducted a stratified analysis excluding patients who did not undergo coronary angiography. After excluding these patients, we found that the median and interquartile range of contrast agents in both the CRS and non-CRS groups were 100.00 (100, 200). The mean ranks were 241.43 and 240.92, respectively,

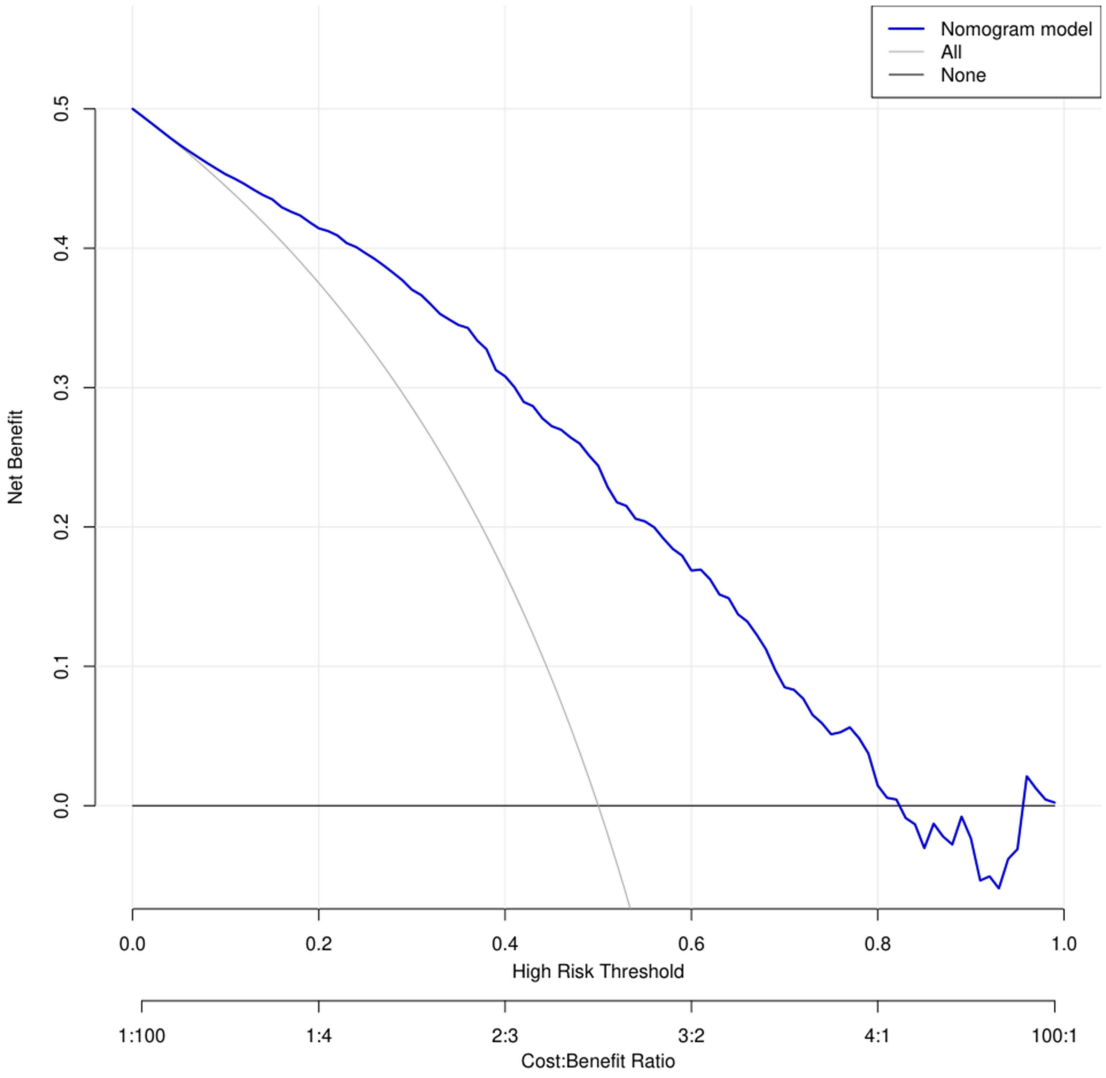

Figure 6 Decision curve analysis of model 2.

resulting in a p-value of 0.974. This indicates that there is no statistically significant difference in the distribution of contrast agents between the two groups. In previous studies, contrast agents have been regarded as an independent risk factor for medically induced AKI.[19] However, this perspective has been challenged by a joint statement issued by the American College of Radiology and the National Kidney Foundation, which reveals a significantly lower incidence of contrast-induced AKI than previously reported. The statement emphasizes that the majority of AKI induced by intravenous contrast are not primarily caused by the contrast agent itself, but rather by other nephrotoxic exposures.[20] Our study aligns with and supports this revised understanding.

The development of CRS-I in AMI patients was strongly associated with a worse prognosis. Previous studies have reported that patient with CRS-I exhibits elevated in-hospital morbidity and mortality rates, coupled with a prolonged hospital stay, along with a higher risk of progression to end-stage renal disease and subsequent hospitalization for cardiovascular and renal events.[21,22] Although there is still a lack of high-quality evidence or guidelines to guide the treatment of CRS-I, caution in the use of diuretics and nephrotoxic drugs, discretion in the type of contrast agent and its dosage, and employ hydration can be effective in preventing the occurrence of CRS-I.[19] It is imperative to find biomarkers with good predictive utility for early identification of patients at high risk of CRS-I and promptly implement preventive strategies. Inflammation plays a crucial role as a non-hemodynamic mechanism in CRS-I, and we aim to identify effective biomarkers accordingly. In a prospective study involving 2063 patients with AMI, the incidence and

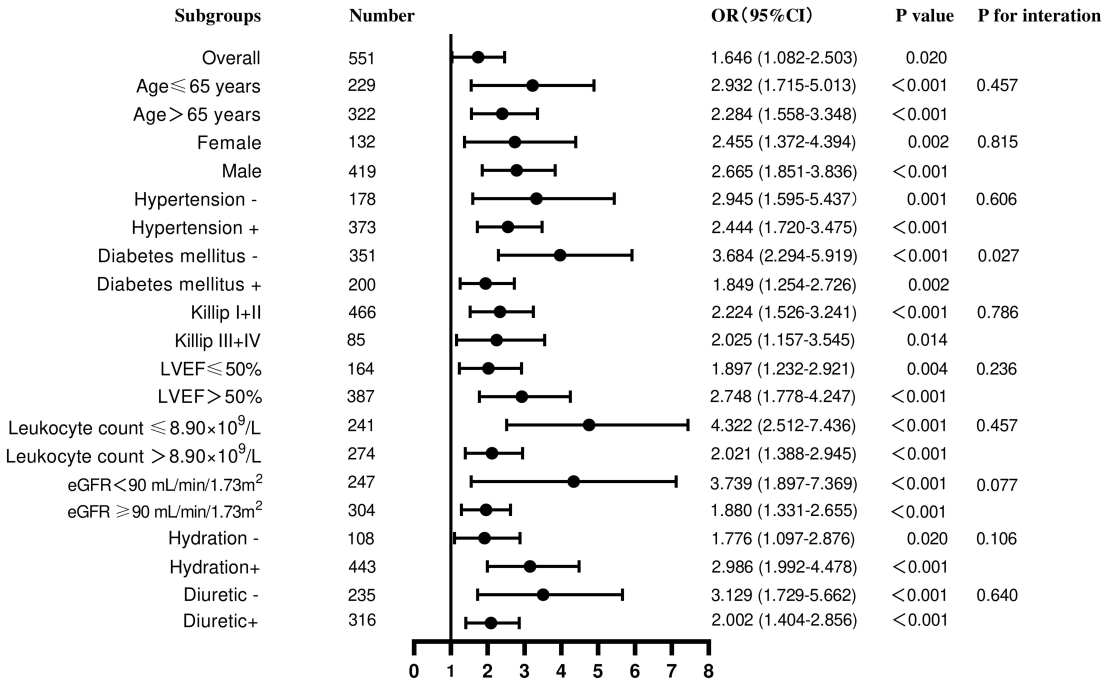

Figure 7 Subgroup analyses for the association between the RAR and CRS-I.

severity of AKI, as well as the rate of the composite endpoint, increased in parallel with hs-CRP quartiles.[23] Wang reported that the high and very high neutrophil-lymphocyte ratio groups had a higher risk of AKI incidence (RR = 1.44, 95% CI= 1.06–1.95, P = 0.018 and RR = 1.34, 95% CI= 0.87–2.07, P = 0.180) compared with low-NLR group.[24] Based on these studies, it is reasonable to infer that those inflammatory markers have the potential to predict CRS-I.

The RAR, a combination of two independent parameters, has been established as a new index to reflect the severity of inflammation. In contrast to hs-CRP and NLR, which are closely associated with acute inflammation, RAR is more affected by chronic inflammation.[25] RDW reflects the distribution of erythrocyte sizes and serves as a reliable index of anisocytosis. Traditionally, it is commonly used in laboratory hematology for differential diagnosis of anemias. Studies have shown that a strong, positive and independent association exists between RDW and conventional inflammatory biomarker.[26] Inflammation influences the RDW through various pathways, encompassing direct myelosuppression of erythroid precursors, promotion of red cell apoptosis, reduction of erythropoietin production, diminished iron bioavailability, and the development of erythropoietin resistance in erythroid precursor cell lines.[27] In a study that included 1596 consecutive patients with AMI, RDW was found to be higher in patients with 12-month major adverse cardiac events (MACEs; 13.8% versus 13.3%).[28] Moreover, other studies have found that elevated RDW is linked to an unfavorable prognosis in AMI, and that the underlying mechanism may be related to chronic inflammation.[29–31]

ALB is an essential protein in human plasma that helps maintain nutrition and osmotic pressure. In recent years, several studies have investigated the relationship between CRP and albumin levels, and they found that in inflammatory conditions, the CRP levels increase, while albumin levels decrease.[32] In addition to the fact that inflammation suppresses the rate of albumin synthesis, inflammation itself is associated with a higher rate of catabolism in the body. Moreover, inflammation induces anorexia, diminishing the effective utilization of dietary protein and energy intake. These factors together contribute to a decrease in albumin concentration.[33]

The RAR may be a better predictor of CRS-I than one of the markers alone, as intuitively shown by the AUC of our study. Although mechanisms underlying the association between RAR and CRS-I risk remain uncertain, we speculate that it may be associated with chronic inflammation. Atherosclerosis serves as an antecedent process to AMI, and in patients with atherosclerosis, there is usually a long-term chronic hyperinflammatory state.[34] Chronic inflammation significantly influences the prognosis of patients with AMI. Meanwhile, inflammation is intricately associated with the

initiation of AKI and plays a crucial role in the progression from AKI to CKD.[35,36] Prospective studies and basic studies are needed to further explore the relationship between RAR, inflammation and CRS-I. RDW and ALB can be directly obtained from admission blood test data, thereby facilitate immediate utilization. Therefore, RAR emerges as a relatively simple yet potentially reliable parameter for high-risk CRS-I patients. Utilizing the optimal cut-off value of RAR ≥3.58, proactive preventive measures can be enacted. However, the AUC of RAR was 0.683, indicating average predictive accuracy for CRS-I. Consequently, we advocate evaluating RAR in conjunction with other risk factors.

Limitations

Our study has several limitations that should be acknowledged. Firstly, it was a retrospective study conducted in a single center, resulting in a relatively small number of cases. Consequently, it was challenging to fully establish a causal association between RAR and the incidence of CRS-I. Secondly, a subset of patients with AMI who had a rapid deterioration and insufficient laboratory data were excluded from the analysis. This led to a loss of data on patients with severe AMI, who are known to have a higher incidence of CRS-I. Thirdly, despite employing multivariable modeling to identify independent risk factors, the presence of unmeasured confounders may have influenced the study's findings. Fourthly, RAR was calculated only once upon admission, and we did not monitor changes in RAR during the study period, potentially missing important temporal variations. Fifthly, due to the challenges associated with collecting and analyzing diuretic data, the role of diuretic type and dosage in the incidence of CRS-I was not further investigated in this study. Finally, although we constructed a nomogram model, the lack of external validation limits the certainty of its utility. Future research should aim to prospectively validate the performance of the nomogram model by collecting additional data.

Conclusion

Our study indicates that elevated RAR levels independently contribute to the risk of developing CRS-I in patients with AMI. Furthermore, incorporating RAR into the established models enhanced the predictive value for CRS-I. RAR emerges as a valuable and readily accessible inflammatory biomarker that may play a pivotal role in risk stratification in clinical practice.

Abbreviations

RAR, red blood cell distribution width to albumin ratio; CRS-I, cardio-renal syndrome type I; AMI, acute myocardial infarction; ROC, receiver operating characteristic curve; AUC, area under the curve; CRP, C-reactive protein; CRS, Cardio-renal syndrome; KDIGO, Kidney Disease: Improving Global Outcomes; eGFR, renal insufficiency with an estimated glomerular filtration rate; Scr, serum creatinine; ALB, albumin; CAG, coronary angiography; NT-proBNP, N-terminal pro-brain natriuretic peptide; LVEF, left ventricular ejection fraction; C-index, consistency index; BMI, body mass index; DBP, diastolic blood pressure; NSTEMI, non-ST-elevation myocardial infarction; RDW, red blood cell distribution width; CKD, chronic kidney disease; TG, triglyceride; TC, total cholesterol; DM, diabetes mellitus; DCA, decision curve analysis; MACEs, major adverse cardiac events; CAG, coronary angiography.

Data Sharing Statement

The data used to support the findings of this study, as described in the research article, are available from the corresponding author upon request.

Ethics Approval and Informed Consent

This study was conducted in accordance with the Declaration of Helsinki and has been approved by the Clinical Research Ethics Committee of Affiliated Zhongda Hospital of Southeast University. Due to the study being a retrospective analysis, the review committee waived the requirement for written informed consent. The data presented in this study do not allow for the identification of individuals. We affirm our commitment to maintaining the confidentiality of patient data (No: 2023ZDSYLL265-P01).

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Disclosure

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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