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Immune Markers Predict CR Response in CAD: Immunoinflammatory Signatures as Determinants of Cardiac Rehabilitation Efficacy in Patients with Coronary Artery Disease

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ABSTRACT

To explore the association between baseline immune-inflammatory characteristics and the efficacy of standard cardiac rehabilitation (CR) in patients with coronary artery disease (CAD), to identify predictive biomarkers, and to provide evidence for personalized rehabilitation strategies.

This retrospective cohort study included 90 CAD inpatients from the Department of Cardiology (January 2024–January 2025) who completed standard phase II cardiac rehabilitation. Patients were classified into a responder group (n=47) and a non-responder group (n=43) based on clinical outcomes. Baseline clinical data and immune-inflammatory markers (white blood cell count [WBC], neutrophil-to-lymphocyte ratio [NLR], high-sensitivity C-reactive protein [hs-CRP], interleukin-6 [IL-6], tumor necrosis factor-alpha [TNF-α]) were collected. The 6-minute walk distance (6MWD) and SF-36 scores were measured before and after rehabilitation. Multiple logistic regression was used to evaluate the association between baseline markers and CR efficacy.

At baseline, hs-CRP, IL-6, TNF-α, and NLR were significantly higher in the non-responder group than in the responder group. After CR, these markers decreased more substantially in the responder group, which also showed greater improvements in 6MWD, left ventricular ejection fraction (LVEF), and SF-36 scores, as well as a lower incidence of major adverse cardiovascular events (MACE). Multivariable logistic regression analysis identified baseline NLR≥2.6 as independent negative predictors of CR efficacy.

Baseline systemic immune-inflammatory status, particularly elevated NLR and IL-6, is associated with CR efficacy in patients with CAD. Pre-rehabilitation assessment of these markers may aid in identifying patients likely to benefit less from standard CR. External validation in prospective, multicenter cohorts is required.

Keywords: Cardiac rehabilitation; Coronary artery disease; C-reactive protein; Inflammation; Interleukin-6

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INTRODUCTION

With the accelerating aging of the global population and profound changes in lifestyle, cardiovascular

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disease has become a leading cause of morbidity and mortality worldwide. Among cardiovascular diseases, coronary artery disease (CAD) imposes a substantial burden on global healthcare systems because of its high incidence, mortality, and disability rates.[1] According to the World Health Organization (WHO), cardiovascular diseases account for approximately 18 million deaths annually, with coronary artery disease (CAD) contributing substantially to this mortality burden.[2] Cardiac rehabilitation (CR), a key component of secondary prevention for CAD, has been shown to significantly reduce the risk of recurrent cardiovascular events, improve patients' quality of life, and reduce healthcare costs through comprehensive interventions, including exercise training, health education, psychological support, and risk factor management.[3] However, clinical observations have found significant heterogeneity in the response of patients to CR. Some patients can benefit greatly from CR, while others may not achieve satisfactory results. This difference in therapeutic efficacy has become a key bottleneck restricting the optimization and wider adoption of CR.

The immune-inflammatory response plays a pivotal role in the onset, progression, development, and prognosis of CAD.[4] Atherosclerosis is essentially a chronic inflammatory disease. Inflammatory cell infiltration, cytokine release, and the production of acute-phase reactants occur throughout the continuum from the formation of lipid streaks to plaque rupture.[5] As a conventional marker of systemic inflammation, white blood cell count (WBC) has been demonstrated to be closely correlated with unfavorable prognosis in patients with CAD.[6] The neutrophil-to-lymphocyte ratio (NLR) incorporates information derived from both the innate and adaptive branches of the immune system and is more indicative of the body's inflammatory balance than a single biomarker. In recent years, NLR has been demonstrated to serve as an independent predictor of cardiovascular events in patients with CAD.[7] As a classic acute-phase reactant, high-sensitivity C-reactive protein (hs-CRP) serves not only as a biomarker of atherosclerosis but also as a key factor contributing to plaque instability.[8] Interleukin-6 (IL-6) is a key upstream mediator of the inflammatory cascade, it can induce the liver to produce CRP, promote T cell differentiation, and accelerate the process of atherosclerosis.[9] Tumor necrosis factor - α (TNF-α) affects the prognosis of CAD by inducing endothelial cell apoptosis, promoting matrix metalloproteinase expression, and exacerbating myocardial remodeling.[10]

While the role of immune inflammation in the pathophysiological processes of CAD has been extensively acknowledged, its value in predicting CR efficacy has not been fully explored. Existing research has mostly focused on the improvement effect of CR on inflammatory markers, but there is still a lack of systematic evidence on how baseline inflammatory status affects individual differences in CR efficacy.[11] Some small-scale studies suggest that a high inflammatory state may weaken the cardiovascular benefits of exercise training, but the conclusions remain inconsistent.[12,13] In addition, the differences in predictive efficacy of different inflammatory markers for CR efficacy and the optimal predictive combination need to be clarified. In clinical practice, the formulation of rehabilitation regimens is primarily based on in patients' clinical characteristics and the outcomes of exercise tolerance tests, with less emphasis on individualized strategies guided by biomarkers.[14]

In recent years, the concept of precision medicine has rapidly developed in the field of cardiovascular disease, and risk stratification and treatment decision optimization based on biomarkers have become research hotspots.[15] If the association between immunoinflammation characteristics and CR efficacy can be clarified, it will help identify high-risk populations with poor CR response and develop enhanced and targeted rehabilitation strategies for them, such as combined anti-inflammatory treatment, adjusting exercise intensity, increasing monitoring frequency, etc., thereby improving the overall efficacy of CR.[16] Meanwhile, this discovery will also provide new biological explanations for the individual differences in the mechanism of CR action.

Against this backdrop, this study aims to systematically examine the correlation between baseline immune-inflammatory markers and the effectiveness of standard phase II CR in patients with CAD using a retrospective cohort design. Given its retrospective design, this is an exploratory, hypothesis-generating study due to its retrospective design. We hypothesize that a high baseline inflammatory burden is associated with poor CR efficacy and that specific combinations of inflammatory markers may optimize efficacy prediction. This study aims to identify predictive biomarkers of clinical utility, providing a scientific basis for achieving individualized CR based on inflammatory status, and ultimately improving the long-term prognosis of CAD patients.

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MATERIALS AND METHODS

Study Subjects

This retrospective cohort study included 90 CAD patients who were admitted to the Department of Cardiology at our hospital from January 2024 to January 2025 and successfully completed a standard phase II cardiac rehabilitation program. Based on CR efficacy, patients were classified into a responder group (n=40), defined as an increase in 6-minute walk distance (6MWD) of ≥25 m after CR, and a non-responder group (n=50), defined as an increase of <25 m.[17] All patients underwent detailed baseline assessments before enrollment, including clinical data collection, venous blood sampling, and quality-of-life evaluation. Rehabilitation efficacy, immune-inflammatory markers, quality of life, and other indicators were assessed. The primary objective was to analyze the independent association between baseline immune-inflammatory markers and rehabilitation efficacy and to evaluate the association immune-inflammatory characteristics with rehabilitation outcomes. The research flowchart is shown in Figure 1.

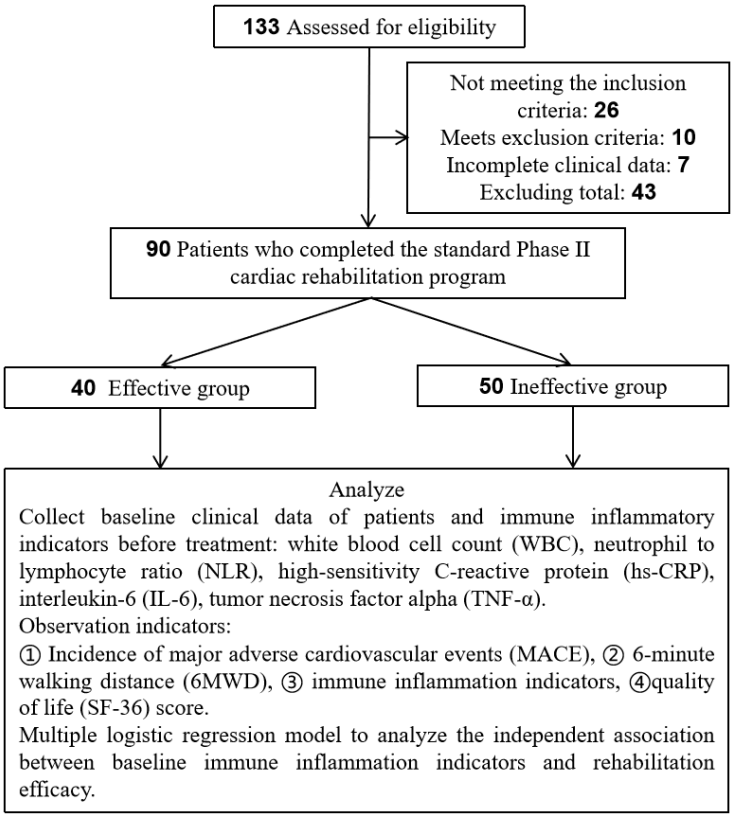

Figure 1 Research Flowchart. A retrospective study of 90 CAD patients undergoing phase II cardiac rehabilitation (CR). Patients were grouped into effective (6MWD increase ≥25 m, n=40) and ineffective (n=50) groups.

Inclusion Criteria

(1) Age 18–80 years.

(2) Diagnosis of stable CAD, including chronic stable angina, the stable phase after acute coronary syndrome, or status post percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).[18]

(3) Completion of at least 12 weeks of a standard phase II cardiac rehabilitation program, including supervised exercise training, health education, psychological support, and risk factor intervention.

(4) Availability of complete baseline immune-inflammatory marker measurements.

(5) Availability of 6-minute walk test, echocardiography, 36-Item Short Form Health Survey (SF-36) quality-of-life scores, and major adverse cardiovascular event (MACE) records before rehabilitation, at the end of rehabilitation, and during

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follow-up.

(6) Alert and able to understand and cooperate with the rehabilitation program.

(7) Complete clinical data, including medical history, laboratory tests, imaging studies, and follow-up records.

Exclusion Criteria

(1) Presence of diseases that may affect inflammatory markers, such as acute infection, autoimmune disease, malignancy, or hematological disorders.

(2) Severe hepatic or renal dysfunction.[19]

(3) New York Heart Association (NYHA) functional class IV or left ventricular ejection fraction (LVEF) <20%[18].

(4) Severe valvular heart disease, cardiomyopathy, or congenital heart disease.

(5) Current use of systemic corticosteroids, immunosuppressants, or other medications with known significant anti-inflammatory effects.

(6) Pregnancy or lactation.

Ethical Statement

This study strictly adhered to the principles of the Helsinki Declaration,[20] and all data related to patient privacy were anonymized. The study protocol was reviewed and approved by the Medical Ethics Committee of our university (Ethics Approval No.: NWYLL2025203). Because of to its retrospective design, this study received an informed consent waiver from the Medical Ethics Committee. Throughout the research process, patient privacy was protected, and all data were only used for scientific research purposes to ensure information security.

Sample Size Estimation

Sample size was estimated using multivariable logistic regression analysis and G*Power software.[21] Based on previous studies,[22] an effect size of Cohen f^2=0.15 was selected, with a 2-tailed significance level (α) of 0.05 and a statistical power (1-β) of 0.95. These parameters required 74 participants; a total of 90 participants were enrolled, exceeding the target and meeting the statistical requirements.

Treatment measures

All patients received standard guideline-directed medical therapy including aspirin (Bayer Aspirin; Bayer AG, Leverkusen, Germany), statins (atorvastatin; Pfizer Inc., New York, NY, USA), β-blockers (metoprolol; Novartis, Basel, Switzerland), and ACE inhibitors (lisinopril; Merck & Co., Rahway, NJ, USA) or ARBs (losartan; Merck & Co., Rahway, NJ, USA). The specific regimen was adjusted according to each patient's individual condition. On this basis, all patients completed the standard Phase II cardiac rehabilitation program at our hospital, which includes: (1) exercise training: mainly moderate-intensity aerobic exercise (target heart rate=(220 age) × 60% -70%), including brisk walking, cycling training, and other activities., for 30-45 minutes each time; combined with resistance training (dumbbells, elastic bands), 15-20 minutes per session, 3 times per week, for a total of 12 weeks; (2) health education: including dietary guidance (low-fat, low-salt, high-fiber diet), smoking cessation and alcohol restriction, and knowledge dissemination on blood pressure/blood sugar/lipid control; (3) Psychological support: Provide psychological counseling for anxiety and depression, with referral to a psychiatry department if necessary.

Baseline Data and Laboratory Testing

Baseline clinical data were collected from all patients, including age, sex, body mass index (BMI), history of hypertension and diabetes, smoking history, number of coronary artery lesions, and history of previous myocardial infarction. Before the initiation of CR treatment, 5 mL of fasting venous blood was collected and centrifuged to obtain serum, which was stored at −80°C until analysis. A fully automated hematology analyzer (DxH 800, Beckman Coulter Inc., Brea, CA) was used to measure white blood cell (WBC), neutrophil, and lymphocyte counts, and the neutrophil-to-lymphocyte ratio (NLR) was calculated accordingly. Serum hs-CRP levels were measured using a human hs-CRP ELISA kit (Quantikine; R&D Systems, Inc., Minneapolis, MN, USA). IL-6 levels were measured using a human IL-6 ELISA kit (Thermo Fisher Scientific Inc., Waltham, MA), and TNF-α levels were measured using a human TNF-α ELISA kit (Abcam plc., Cambridge, UK).

Venous blood samples were collected after an overnight fast (7:00–8:00 AM) within 24 hours before CR initiation. Serum was separated by centrifugation (3000 rpm, 15 min, 4°C) within 1 hour, aliquoted, and stored at −80°C until batch analysis. hs-CRP, IL-6, and TNF-α were measured using commercial ELISA kits (R&D Systems, Inc., Minneapolis, MN; Thermo Fisher

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Scientific Inc., Waltham, MA; and Abcam plc., Cambridge, UK, respectively). Detection limits were as follows: hs-CRP 0.1 mg/L, IL-6 0.3 pg/mL, TNF-α 1.2 pg/mL. Intra-assay CVs: 4.2–5.1%; inter-assay CVs were 6.5–7.3%. Laboratory personnel were blinded to clinical outcomes. WBC and NLR were determined using an automated hematology analyzer (DxH 800).

Observation Indicators

Main Observation Indicators

(1) Exercise capacity: 6MWD measured before and after CR.

(2) Health-related quality of life: SF-36 health survey scores before and after CR.[23]

Secondary Observation Indicators

(1) Immune-inflammatory markers: NLR, WBC, hs-CRP, IL-6, and TNF-α levels before and after CR.

(2) Major adverse cardiovascular events (MACE): incidence of MACE within 6 months after CR.[24] Event information was obtained from electronic medical records and telephone or outpatient follow-up. The follow-up deadline was July 2025.

(3) Cardiac function: Left ventricular ejection fraction (LVEF) measured by echocardiography before and after CR.[25]

Statistical Analysis

The normality of continuous variables was assessed using the Shapiro-Wilk test. Normally distributed data were presented as mean ± SD and were compared using the independent-samples t-test (between groups) or repeated-measures ANOVA (within-group pre-post comparisons). Non-normally distributed data (eg, hs-CRP, IL-6, and all Δ values in Table 5) are presented as median (Q1, Q3) and were compared using the Mann-Whitney U test (between groups) or Wilcoxon signed-rank test (within-group). Homogeneity of variances for parametric tests was checked using Levene's test, and the assumption was met for all such comparisons. A 2-sided $p < 0.05$ was considered statistically significant.

To account for the risk of Type I error due to multiple comparisons, the Benjamini-Hochberg false discovery rate (FDR) method was applied with a Q value of 0.05 for all between-group comparisons of inflammatory and clinical variables. All comparisons reported as statistically significant ($p<0.05$) remained significant after FDR correction.

To evaluate the discriminative ability and clinical practicality of identified immune inflammatory markers in predicting CR efficacy, receiver operating characteristic (ROC) curves were plotted based on the predicted probabilities from the final multivariable logistic regression model. The area under the ROC curve (AUC) was calculated. To control for overfitting and evaluate internal validity, we performed bootstrap internal validation with 1000 resamples.

RESULTS

Baseline Characteristics

Table 1 shows a comparison of baseline characteristics between 2 groups of patients with coronary artery disease. The 2 groups were comparable with respect to these baseline characteristics ($p>0.05$).

Baseline Immune Inflammatory Markers

Table 2 shows the between-group comparison of baseline immune inflammatory indicators between the responder group and the non-responder group. The ineffective group exhibited significantly higher WBC counts than the effective group ($P=0.047$). For the remaining immune inflammatory markers, levels of NLR, hs-CRP, IL-6, and TNF-α were significantly higher in the CR-nonresponsive group than in the CR-responsive group (all $P<0.001$). These results suggest that baseline high inflammatory status may be associated with poor CR efficacy.

Improvement of Exercise Tolerance and Cardiac Function

Table 3 shows the changes in 6MWD and LVEF of two groups of patients before and after rehabilitation. Baseline 6MWD was comparable between the two groups ($p=0.701$). After rehabilitation, the 6MWD of the responder group increased by 30.8±4.2 m compared to baseline, while the non-responder group increased by only 15.4±4.4 m from baseline, and the between groups difference was highly statistically significant ($p<0.001$). In terms of LVEF, the groups were well-matched at baseline ($p=0.835$). After rehabilitation, the LVEF of the responder group increased by 10.1±6.1%, while that of the non-responder group increased by 6.3±3.3%. The between group difference in rehabilitation improvement achieved statistical significance ($p<0.05$). Repeated-measures analysis of ANOVA revealed significant group× time interaction effects ($p<0.05$ for all).

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Table 1 Baseline characteristics [mean±SD, n (%), M (Q1, Q3)]

Variables	Effective group (*n*=40)	Ineffective group (*n*=50)	χ^2/t	*p*
Gender				
Male	24 (60.0)	26 (52.0)	0.576	0.448
Female	16 (40.0)	24 (480.)		
Age (years)	60.4±3.3	60.3±3.9	0.182	0.856
BMI (kg/m^2)	24.6±3.7	24.5±3.8	0.226	0.822
Smoking History	13 (32.5)	18 (36.0)	0.121	0.728
Alcohol history	13 (32.5)	18 (36.0)	0.121	0.728
Hypertension	21 (52.5)	27 (54.0)	0.020	0.887
Hyperlipidemia	10 (25.0)	15 (30.0)	0.277	0.599
Diabetes mellitus	15 (37.5)	23 (46.0)	0.658	0.417
Previous MI	3 (7.5)	8 (16.0)	0.809	0.368
NYHA				
I	11 (27.5)	17 (34.0)		
II	25 (62.5)	26 (52.0)	2.014	0.365
III	3 (7.5)	8 (16.0)		
LVEF	48.7±6.5	47.9±6.8	0.477	0.634
Socioeconomic status				
Education (≥ high school)	25 (62.5)	24 (48.0)	1.884	0.170
Monthly household income (≥¥5000)	20 (50.0)	21 (42.0)	0.573	0.449
Medication use				
Antiplatelet therapy	39 (97.5)	49 (98.0)	0.026	0.873
Statins	40 (100)	50 (100)	–	–
Beta-blockers	33 (82.5)	41 (82.0)	0.004	0.951
ACEI/ARB	30 (75.0)	35 (70.0)	0.277	0.599
Number of core drug classes	4 (3, 4)	4 (3, 4)	0.329	0.742
PHQ-9 score	5 (4, 7)	5 (5, 7)	1.238	0.216

BMI: Body Mass Index; MI: myocardial infarction; NYHA: New York Heart Association; LVEF: Left Ventricle Ejection Fraction; PHQ-9: Patient Health Questionnaire-9; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker. The same below. All comparisons were corrected by Benjamini Hochberg FDR (Q=0.05), and variables labeled with P<0.05 remained significant after correction.

Table 2 Baseline immune inflammatory markers (mean±SD)

	Effective group (*n*=40)	Ineffective group (*n*=50)	*t*	*P*
WBC (×10^9/L)	6.4±1.5	7.0±1.5	2.016	0.047
NLR	2.1±0.6	3.3±0.9	7.279	<0.001
hs-CRP (mg/L)	3.2±1.1	6.3±1.9	9.147	<0.001
IL-6 (pg/mL)	5.2±1.3	10.0±2.7	10.467	<0.001
TNF-α (pg/mL)	12.8±3.1	20.1±5.7	7.352	<0.001

WBC: white blood cells; NLR: neutrophils and lymphocytes; hs-CRP: high-sensitivity C-reactive protein; IL-6: interleukin-6; TNF-α: tumor necrosis factor-α.

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Table 3 Comparison of exercise capacity and cardiac function (mean±SD)

	Effective group (*n*=40)	Ineffective group (*n*=50)	*t*	*p*
6MWD (m)				
Baseline	387.5±48.5	378.1±44.0	0.966	0.337
After CR	414.5±45.7	393.5±43.8	2.213	0.030
Δ6MWD	30.8±4.2	15.4±4.4	16.842	<0.001
	P-Group<0.001	P-Time<0.001	P-Group*Time=0.010	
LVEF (%)				
Baseline	48.4±6.1	48.1±7.0	0.209	0.835
After CR	58.6±6.4	54.4±6.7	3.329	0.001
ΔLVEF	10.1±6.1	6.3±3.3	3.782	<0.001
	P-Group<0.001	P-Time<0.001	P-Group*Time=0.027	

* indicates there is a significant difference in the comparison within the group compared to the level of baseline, $p<0.05$. Δ represents the value after CR treatment minus the value before CR treatment within the group. The same below.

Improvement of Exercise Tolerance and Cardiac Function

Table 3 shows the changes in 6MWD and LVEF of two groups of patients before and after rehabilitation. Baseline 6MWD was comparable between the two groups (p=0.701). After rehabilitation, the 6MWD of the responder group increased by 30.8±4.2 m compared to baseline, while the non-responder group increased by only 15.4±4.4 m from baseline, and the between groups difference was highly statistically significant (p<0.001). In terms of LVEF, the groups were well-matched at baseline (p=0.835). After rehabilitation, the LVEF of the responder group increased by 10.1±6.1%, while that of the non-responder group increased by 6.3±3.3%. The between group difference in rehabilitation improvement achieved statistical significance (p<0.05). Repeated-measures analysis of ANOVA revealed significant group× time interaction effects (p<0.05 for all).

Improvement in Quality of Life

Table 4 shows the changes in SF-36 scores between the 2groups of patients. The 2 groups showed no statistically significant differences in the SF-36 total score or any of its dimension scores at baseline (p>0.05). After CR treatment, the total SF-36 score of the effective group increased by 21.5±11.3 in the responder group and by 13.0 ±9.7 in the non-responder group 13.0±9.7, with a significant between-group difference in improvement (p<0.001). Repeated-measures analysis of ANOVA revealed significant group × time interaction effects (p<0.05 for all). These findings suggest that patients with a lower baseline immune-inflammatory status experience greater improvement in quality of life after CR.

Changes in Immune Inflammatory Indicators before and after CR Treatment

Table 5 shows the comparison of changes in immune inflammatory indicators between 2 groups of patients after rehabilitation treatment relative to baseline. The decrease in WBC, NLR, hs-CRP, IL-6, and TNF-α in the responder group were markedly higher than those in the non-responder group (p<0.001). This suggests that the improvement effect of CR on inflammation is more pronounced in the responder group.

MACE Occurrence Situation

Table 6 shows that during the 6-month follow-up period, a total of 26 patients (28.9%) of MACE, including 6 (15.0%) in the responder group and 20 (40.0%) in the non-responder group. This discrepancy reached statistical significance (χ^2=6.761, p=0.009). The incidence of MACE in the responder group was significantly lower than that in the non-responder group. Among the MACE events that occurred, unplanned revascularization was the most common (15 cases), followed by readmission due to heart failure (7 cases) and non fatal myocardial infarction (6 cases), with no patients experiencing cardiac death.

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Table 4 Comparison of SF-36 scores (mean±SD)

	Effective group (*n*=40)	Ineffective group (*n*=50)	*t*	*p*
Baseline	51.6±8.2	52.5±9.2	0.499	0.619
After CR	73.1±6.6	65.6±7.3	5.124	<0.001
ΔSF-36	21.5±11.3	13.0±9.7	3.838	<0.001
	P-Group<0.001	P-Time<0.001	P-Group*Time=0.027	

*The meaning of * and Δ are the same as Note 3.

Table 5 Changes in immunoinflammatory markers after rehabilitation [M (Q1, Q3)]

	Effective group (*n*=40)	Ineffective group (*n*=50)	*Z*	*p*
ΔWBC (×10^9/L)	0.8 (0.6, 1.1)	0.4 (0.3, 0.6)	4.815	<0.001
ΔNLR	0.6 (0.5, 0.9)	0.4 (0.3, 0.5)	4.624	<0.001
Δhs-CRP (mg/L)	1.2 (0.8, 1.8)	0.5 (0.3, 0.7)	5.323	<0.001
ΔIL-6 (pg/mL)	2.2 (1.7, 3.1)	0.9 (0.4, 1.4)	6.147	<0.001
ΔTNF-α (pg/mL)	2.9 (2.6, 4.0)	1.3 (0.5, 1.8)	6.317	<0.001

The meaning of WBC, NLR, hs-CRP, IL-6 and TNF-α are the same as Note 2.

Table 6 Comparison of MACE incidence rates [n (%)]

	Effective group (*n*=40)	Ineffective group (*n*=50)	χ^2	*p*
Unplanned Revascularization	3 (7.5)	10 (20.0)		
Heart Failure Readmission	2 (5.0)	5 (10.0)		
Non-Fatal Myocardial Infarction	1 (2.5)	5 (10.0)		
Overall	6 (15.0)	20 (40.0)	6.761	0.009

MACE: Major Adverse Cardiovascular Events.

Multivariate Logistic Regression Analysis

Multivariate Logistic Regression Analysis Model

As shown in Table 7, with the effectiveness of CR treatment as the dependent variable, NLR, which reflects the balance between innate and adaptive immune responses, and IL-6, an upstream mediator of the inflammatory cascade, were included as independent variables in the multiple logistic regression model based on their biological relevance. WBC was excluded because of its low specificity, while hs-CRP and TNF-α were excluded because of their downstream nature and measurement limitations, respectively, to minimize potential collinearity and improve model robustness. Key clinical factors, including medication use and depression, were also included in the model. After adjustment for potential confounders, baseline NLR≥2.6 (OR=0.221, 95% CI: 0.059–0.833, *p*=0.026) and IL-6≥7.7 (OR=0.031, 95% CI: 0.007–0.135, *p*<0.001) were independently associated with lower odds of CR treatment effectiveness. Specifically, patients with a baseline NLR≥2.6 had 77.9% lower odds of treatment success, whereas those with a baseline IL-6≥7.7 had 96.9% lower odds of treatment success. The number of core drug types used did not show independent predictive value after adjusting for other variables (*p*>0.05).

Model Performance and ROC Analysis

ROC curve analysis (Figure 2, Table 8) shows that NLR≥ .6 (AUC=0.793, 95% CI 0.694-0.871, *p*<0.001) and IL-6≥7.7 (AUC=0.909, 95% CI 0.829-0.959, *p*<0.001) had good predictive power for the effectiveness of CR. The predictive performance of the combined model incorporating both markers was further improved, with an AUC of 0.941 (95% CI 0.871-0.980, *p*<0.001), and its sensitivity (98.83%) and specificity (84.31%) were higher than those of either marker alone.

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Table 7 Multivariate Logistic regression analysis

Variables	B	SE	Wald	*p*	OR	95% CI for OR	
						Lower limits	Upper limits
NLR≥2.6	-1.509	0.677	4.973	0.026	0.221	0.059	0.833
IL-6≥7.7	-3.479	0.752	21.408	<0.001	0.031	0.007	0.135
PHQ-9	0.119	0.151	0.619	0.431	1.126	0.837	1.515
Number of core drug classes	0.35	0.606	0.333	0.564	1.419	0.432	4.658
Constant	-0.127	2.158	0.003	0.953	0.881		

χ^2=4.257, P=0.833, Nagelkerke R^2=0.578.

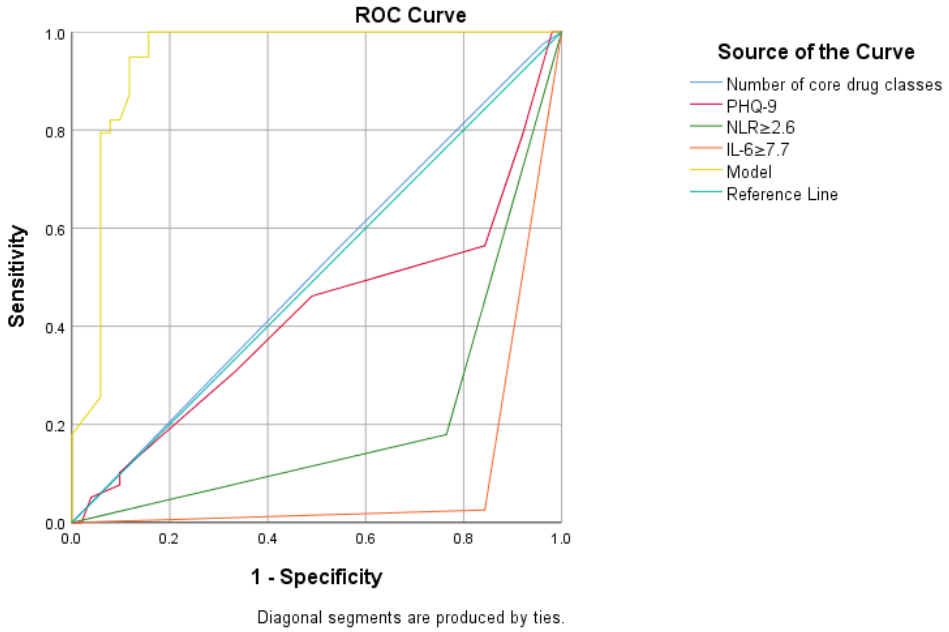

Figure 2 ROC curve. ROC curve of the multivariate logistic regression model for predicting cardiac rehabilitation efficacy. The diagonal dashed line represents the reference line (AUC = 0.5).

Table 8 ROC Curve Parameters

Variables	AUC	95% CI	Sensitivity (%)	Specificity (%)	*p*
NLR ≥ 2.6	0.793	0.694, 0.871	82.05	76.47	<0.001
IL-6 ≥ 7.7	0.909	0.829, 0.959	97.44	84.31	<0.001
Joint model	0.941	0.871, 0.980	98.83	84.31	<0.001

AUC: Area under the curve.

DISCUSSION

This study systematically examined the predictive value of baseline immune-inflammatory characteristics for the efficacy of standard stage II CR in CAD patients using a retrospective cohort design.

The main findings were as follows: (1) patients with poor CR efficacy (the non-responder group) exhibited a significantly greater systemic inflammatory burden at baseline, as reflected by elevated WBC, NLR, hs-CRP, IL-6, and TNF-α levels; (2) following CR, the reductions in inflammatory markers were significantly greater in the responder group than in the non-responder group; (3) baseline NLR and IL-6 were potential predictors of poor CR efficacy; and (4) baseline NLR≥2.6 and IL-6≥7.7 pg/mL may help identify patients at high risk of an unfavorable response to CR. These findings provide a new perspective for understanding the biological mechanisms underlying individual differences in CR efficacy and suggest that assessment of inflammatory status may optimize risk stratification and the development of personalized strategies for CR patients.

Chronic systemic inflammation represents a core pathophysiological mechanism driving the onset and progression of CAD. Inflammatory cells infiltrate the vascular wall, secrete substantial quantities of cytokines and chemokines, and promote the formation, progression and rupture of atherosclerotic plaques.[26] This study found that patients with higher baseline levels of inflammatory markers had poorer responsiveness to CR, which may be related to the following aspects. First, a high inflammatory state may weaken the cardiovascular benefits of exercise training. Preclinical evidence shows that inflammatory mediators, including TNF-α, impair nitric oxide synthesis by suppressing both the expression and the activity of endothelial nitric oxide synthase, thereby impairing the improvement of exercise-induced vasodilation function. In addition, sustained elevation of IL-6 can activate the signal transduction and transcription activator 3 (STAT3) pathway, promote cardiomyocyte apoptosis and myocardial fibrosis, and limit the reversal effect of exercise training on ventricular remodeling. Second, the inflammatory state may affect the patient's exercise tolerance and rehabilitation compliance. An elevated inflammatory burden is strongly associated with manifestations including muscle atrophy, fatigue, and depression.[27] In this study, the enhancement of health-related quality of life, especially in the energy dimension score, was greater in the responder group, indirectly supporting this hypothesis. IL-6 and TNF-α may accelerate muscle protein catabolism while suppressing muscle protein anabolism, thereby contributing to the development of sarcopenia,[28] which is an important predictor of poor CR efficacy.[29] Therefore, patients with high baseline inflammation may have limited exercise ability and poor subjective perception, which may affect the intensity and quality of rehabilitation training, forming a vicious cycle. Furthermore, an inflammatory state may reflect the potential severity and instability of the disease. Hs-CRP functions not merely as an inflammatory marker but also, as an active molecule that directly participates in atherosclerotic plaque destabilization.[30] Patients with high baseline hs-CRP levels may have more extensive coronary atherosclerosis burden or more vulnerable plaques, and these pathological bases may limit the benefits of CR. Although this study did not directly evaluate plaque characteristics, the significantly increased incidence of MACE in the non-responder group supports this hypothesis. In addition, inflammation and oxidative stress promote each other, and oxidative stress accompanying by high inflammation can damage mitochondrial function and affect energy metabolism of myocardial cells,[31] thereby weakening the effect of CR on improving on cardiac function.

Among the numerous inflammatory markers, this study identified NLR and IL-6 as independent factors influencing CR efficacy through multivariable analysis, which has important clinical significance. NLR integrates innate immune signals mediated by neutrophils and adaptive immune signals associated with lymphocytes and can better reflect the immune-inflammatory balance in the body than a single indicator.[32] Neutrophils secrete pro-inflammatory mediators including myeloperoxidase and elastase, whereas lymphocytes exert anti-inflammatory and immunomodulatory activities. An increase in NLR reflects a proinflammatory/anti-inflammatory imbalance, a state that is closely correlated with atherosclerotic plaque instability and adverse cardiovascular events.[33] IL-6 not only induces the production of CRP in the liver but also, promotes T cell differentiation and B cell activation, playing a key role in adaptive immunity.[34] Exercise training can usually cause an acute elevation of IL-6 levels, but this elevation

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mainly comes from muscle fibers and has anti-inflammatory and metabolic regulatory effects.[35] However, chronic systemic elevation of IL-6 reflects pathological inflammatory status. This study found that patients with baseline IL-6 ≥ 7.7 pg/mL showed a 96.9% reduction in total response to CR therapy, indicating that distinguishing the source of IL-6 is crucial for prognostic assessment. In clinical practice, continuously elevated IL-6 levels may indicate uncontrolled inflammatory processes and warrant further elevation for infections, autoimmune diseases, or residual cardiovascular risks.

If confirmed in future prospective studies, the thresholds of NLR ≥2.6 or IL-6 ≥7.7 pg/mL might help identify patients who are less likely to respond to standard CR. For such patients, future research could explore whether certain strategies—such as optimizing guideline-directed medical therapy (statins, ACEIs/ARBs), stricter risk factor control, or closer monitoring—could improve rehabilitation outcomes. However, any suggestion of adding anti-inflammatory therapies (eg, colchicine) or intensifying rehabilitation protocols remains speculative at this stage and requires testing in dedicated interventional trials.[36] Given the retrospective, single-center design of the present study, these proposals should be viewed as hypothesis-generating only.

This study observed that the responder group showed a significant decrease in all inflammatory indicators after rehabilitation treatment, while the non-responder group had a smaller decrease or even no significant change in some indicators. This suggests that CR itself has a clear anti-inflammatory effect and that this effect is closely related to clinical efficacy. The anti-inflammatory mechanisms of exercise training are multifaceted. First, by reducing visceral adipose tissue, which secretes inflammatory factors like IL-6 and TNF-α, regular exercise exerts anti-inflammatory effects.[37] Second, by stimulating the release of anti-inflammatory factors (e.g., IL-10, IL-1ra), exercise promotes an anti-inflammatory environment.[38] In addition to classical cytokines, other mediators such as IL-17A may also contribute to persistent inflammation in certain patient subsets,[39] although this was not directly examined in our study. Furthermore, exercise can inhibit nuclear factor kappa B (NF-κB) activity and reduce pro-inflammatory gene transcription by activating the AMPK pathway.[40] NF-κB activates B cells to upregulate the expression of pro-inflammatory cytokines including TNF-α, IL-1, IL-6 and IL-8.[41] In addition, exercise improves endothelial function, lowers blood pressure and blood sugar, and indirectly reduces vascular inflammation. However, this study also found that the non-responder group had limited education in inflammatory markers despite completing the CR procedure. This may be related to the phenomenon of "inflammation resistance". With chronic inflammation stimulation, some patients experience decreased immune responsiveness to anti-inflammatory interventions such as exercise, manifested by sustained elevation of inflammatory markers. This resistance state may be related to factors such as genetic polymorphisms, epigenetic modifications, and dysbiosis of the gut microbiota.[42] Future research needs to delve into the molecular mechanisms underlying individual differences in CR anti-inflammatory effects, identify phenotypic features of inflammation resistance, and develop targeted intervention strategies.

The findings of the present study are partially consistent with prior investigations while incorporating certain novel extensions. Early studies by Rauramaa et al.[43] observed that high baseline CRP levels were associated with attenuated efficacy of exercise training on carotid intima-media thickness improvement, but the sample size was small and multi biomarker combinations were not evaluated. Milani et al.[44] found that CR can reduce CRP levels in patients with myocardial infarction, but only reported intra group changes without comparing responders and non responders. This study provides stronger evidence through a more systematic combination of biomarkers and clear efficacy grouping. It is worth noting that this study did not find independent predictive value for WBC and TNF-α. This discrepancy may be attributable to variations in sample size, patient selection, and CR regimen. WBC, as a non-specific indicator, is susceptible to interference from various factors; The half-life of TNF-α is relatively short, and a single test may not accurately reflect its long-term level. Compared with research in cancer rehabilitation, research on inflammation-based prediction in CR lags behind. In oncology, it has been established that baseline inflammatory status (such as Glasgow Outcome Scale) can predict chemotherapy response and survival.[45] This study draws on this approach and systematically explores the predictive value of immune inflammatory features on CR efficacy, filling a gap in this field. Future research can further explore the value of dynamically monitoring changes in inflammatory indicators for

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efficacy evaluation, as well as whether early intensified anti-inflammatory intervention can improve the prognosis of high-risk patients.

This study has several limitations. First, the retrospective design inevitably introduces potential selection and information bias. Although data were collected independently, some clinical information may have been missing or inaccurate. Second, the sample size was relatively small and was drawn from a single center, limiting the generalizability of our findings. Differences in baseline inflammatory levels and CR responses across regions, races, or health care systems warrant validation in multicenter studies. Third, we did not capture quantitative exercise data (e.g., intensity, adherence, heart rate monitoring) or longitudinal lifestyle changes (diet, smoking), which may confound the relationship between inflammatory markers and CR efficacy. Fourth, several additional confounders could not be fully controlled due to the retrospective design, including differential statin intensity, concurrent anti-inflammatory therapies (eg, colchicine), and granular exercise adherence beyond program completion. These unmeasured variables may have influenced the observed associations. Fifth, serial longitudinal monitoring of inflammatory biomarkers during rehabilitation was not available. Sixth, this study excluded patients who did not complete 12 weeks of rehabilitation, which may introduce a “healthy adherer bias” and may potentially overestimate the association between low inflammatory status and favorable outcomes.

In summary, this exploratory, hypothesis-generating study suggests that baseline systemic immune-inflammatory status, particularly elevated NLR and IL-6, may be associated with CR efficacy in patients with coronary artery disease. Specifically, baseline NLR≥2.6 and IL-6≥7.7 pg/mL were identified as potential negative predictors of response to standard phase II CR. However, due to the retrospective, single-center design and potential selection bias (exclusion of non-completers), these findings require external validation in prospective, multicenter cohorts before any clinical application. The proposed thresholds should be considered hypothesis-generating only. Future prospective studies are needed to validate the predictive value of these immune-inflammatory markers and to develop individualized rehabilitation strategies for patients with a high inflammatory burden.

STATEMENT OF ETHICS

This study was approved by the Ethics Committee of the Fifth People Hospital of Ningxia Hui Autonomous Region (Approval No.:NWYLL2025203).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Not applicable.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

AI ASSISTANCE DISCLOSURE

The authors declare that no artificial intelligence (AI) tools were used in the preparation, analysis, or writing of this manuscript.

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