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Association between neutrophil to high-density lipoprotein ratio and no-reflow after coronary intervention

A cross-sectional study

Mengyao Hu, MM[a], Zhuoyan Tong, MM[a], Zhiyuan Cai, MM[a], Shiyu Li, MM[a], Dongwei Yang, MD[a,*]

Abstract

Inflammatory responses and lipid metabolism disorders are key components in the development of coronary artery disease and contribute to no-reflow after coronary intervention. This study aimed to investigate the association between the neutrophil to high-density lipoprotein ratio (NHR) and no-reflow phenomenon in ST-segment elevation myocardial infarction (STEMI) patients after primary percutaneous coronary intervention (PPCI). This study enrolled 288 patients with STEMI from September 1st, 2022 to February 29th, 2024, in the Zhengzhou Central Hospital Affiliated to Zhengzhou University. According to postoperative thrombolysis in myocardial infarction flow grades, there were 221 patients in the normal flow group and 67 patients in the no-reflow group. Comparing the clinical data of the 2 groups, the independent risk factors of no-reflow phenomenon in STEMI patients after PPCI were determined by multivariate logistic regression analysis. Additionally, we assessed the diagnostic value of NHR for no-reflow using receiver operating characteristic curve analysis. The no-reflow phenomenon was observed in 67 patients with STEMI following PPCI, representing a prevalence of 23.26%. Compared with the normal group, NHR, as well as the rates of intracoronary thrombolysis and thrombus aspiration, were significantly elevated, while lymphocyte and albumin were lower ($P < .05$). Multivariate logistic regression analysis revealed that NHR was an independent risk factor for no-reflow (OR = 1.241, 95% CI: 1.142–1.349, $P < .001$). In the receiver operating characteristic curve of NHR diagnosis of no-reflow, the area under the curve (AUC) was 0.740 (95% CI: 0.671–0.809, $P < .001$), and the optimal critical value was 7.88, which indicates sensitivity and specificity were 71.6% and 71.50%. NHR may serve as a risk mark for STEMI patients with no-reflow after PPCI, and has diagnosis value for its occurrence.

Abbreviations: NHR = neutrophil to high-density lipoprotein ratio, PPCI = primary percutaneous coronary intervention, ROC = operating characteristic curve, STEMI = ST-segment elevation myocardial infarction.

Keywords: neutrophil to high-density lipoprotein ratio, no-reflow, primary percutaneous coronary intervention, ST-segment elevation myocardial infarction

1. Introduction

Cardiovascular diseases are the most common noncommunicable diseases in the world, accounting for about one-third of all deaths globally, and becoming a main focus of clinical research.[1] It is projected approximately 330 million individuals in China are currently affected by cardiovascular diseases, with 11.39 million specifically diagnosed with coronary heart disease. Notably, the mortality rate associated with coronary heart disease has shown a general upward trend from 2002 to 2021.[2] ST-segment elevation myocardial infarction (STEMI) refers to acute myocardial ischemic necrosis, mostly secondary to thrombosis on the basis of rupture and erosion of unstable plaques in the coronary arteries, leading to sustained and complete occlusion of the coronary arteries. It often causes high mortality and severe clinical complications, making it one of the most aggressive types of coronary heart disease.[3] Primary percutaneous coronary intervention (PPCI) can instantly open the infarct-related arteries and restore the blood supply in the infarcted area, which is the best choice for reperfusion therapy in STEMI patients.[4] However, after the stenosis of the infarcted vessel is removed, the patient may still have impaired myocardial perfusion, a phenomenon known as "no-reflow," the incidence of which fluctuates from 5% to 67%, depending on the method of diagnosis and the timing of the examination.[5] The occurrence of no-reflow is closely related to potential adverse cardiovascular events. In STEMI patients, the frequency of no-reflow is higher in patients who died within 1 year compared to the survivor group.[6]

The inflammatory responses play a crucial part in no-reflow, and those with disorders of lipid metabolism are more likely to

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] *Zhengzhou Central Hospital Affiliated to Zhengzhou University, Henan, China.*

* *Correspondence: Dongwei Yang, Zhengzhou Central Hospital Affiliated to Zhengzhou University, Henan, China (e-mail: yangdongwei@126.com).*

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develop no-reflow.[5] Neutrophils are one of the markers of inflammation and are involved in the formation of unstable plaques and the occurrence and development of non-reflow.[7] High density lipoprotein (HDL), by contrast, is thought to be a protective factor for atherosclerosis.[8] Neutrophil to high-density lipoprotein ratio (NHR), a composite index combining the 2, has been shown to have predictive value in coronary heart disease in several studies.[9,10] However, the correlation between NHR and flow grades after coronary intervention has yet to be noticed or emphasized, and the objective of this article was to evaluate the diagnostic value of NHR for STEMI patients with no-reflow after PPCI.

2. Materials and methods

2.1. Subjects

STEMI patients who underwent PPCI from September 1st, 2022 to February 29th, 2024 at Zhengzhou Central Hospital Affiliated to Zhengzhou University were included. Inclusion criteria: 1. All patients diagnosed with STEMI in accordance with the 2023 ESC guidelines[11]; 2. All patients underwent successful PPCI within 12 hours of onset of symptoms; 3. Clinical data were complete for all patients. Exclusion criteria: 1. Patients diagnosed with acute infection or inflammatory diseases; 2. Patients diagnosed with severe hepatic and renal dysfunction, hematologic diseases, malignant tumors, and autoimmune diseases; 3. Patients with a prior history of PPCI or coronary artery bypass grafting; 4. Patients with aortic coarctation. Combining the above inclusion and exclusion criteria, a total of 288 patients were finally included in the study. The subjects were divided into the no-reflow group (67 patients, 23.26%) and the normal flow group (221 patients, 76.74%) according to the postoperative thrombolysis in myocardial infarction (TIMI) flow grading. Individuals involved in data collection are blinded to group assignments. The flow chart of the study is shown in Figure 1 This is a retrospective study approved by the Medical Ethics Committee of Zhengzhou Central Hospital Affiliated to Zhengzhou University (Ethics Approval No. ZXYY2024106).

2.2. Methods

General clinical data, auxiliary examination results, and data related to coronary angiography of patients were collected through the hospital's electronic medical record system. General clinical data included the patient's gender, age, body mass index, history of smoking, alcohol consumption, hypertension, diabetes mellitus, coronary heart diseases, and prehospital medication history. Auxiliary examination results were routine blood, blood biochemistry, coagulation function, glycosylated hemoglobin, N-terminal pro-brain natriuretic peptide, myocardial injury markers, and cardiac ultrasound data. Blood specimens were collected from the anterior elbow vein during the first emergency department visit before PPCI. The same type of blood specimens was analyzed using the same brand of machine. Cardiac ultrasound data was measured within 24 hours of the patient's admission to the hospital. Data related to coronary angiography included infarct-related artery and degree of stenosis, number of vascular lesion branches, number of stents implanted, intraprocedural entrapment, intracoronary thrombolysis, thrombus aspiration, and TIMI flow grades.

2.3. Surgical procedures and related definitions

All STEMI patients were given a loading dose of aspirin 300 mg, ticagrelor 180 mg (or clopidogrel 300 mg), and atorvastatin 20 mg orally before the procedure. Radial artery access was preferred for coronary angiography (femoral artery was the second choice), and 4000 IU of normal heparin was given by static push after puncture, with an additional supplemental amount of 120 IU/kg at the time of intervention in the criminal vessel. Two experienced interventionalists jointly assessed the vascular lesion and TIMI flow grades, and if the results were inconsistent, a third physician was called in.

Definition of TIMI flow grades[12]: grade 0: vessel occlusion with no antegrade flow distal to the vessel; grade 1: the contrast agent partially passes through the occlusion site but fails to fill the distal vessel; grade 2: it takes >3 cardiac cycles for the contrast agent to fill the distal coronary artery; and grade 3: the contrast agent fills the distal coronary artery in <3 cardiac cycles. Definition of no-reflow[12]: coronary angiography forward flows TIMI ≤ grade 2 after exclusion of coronary artery entrapment, spasm, thrombus, obstruction, etc during PPCI. TIMI flow grade 3 is normal flow.

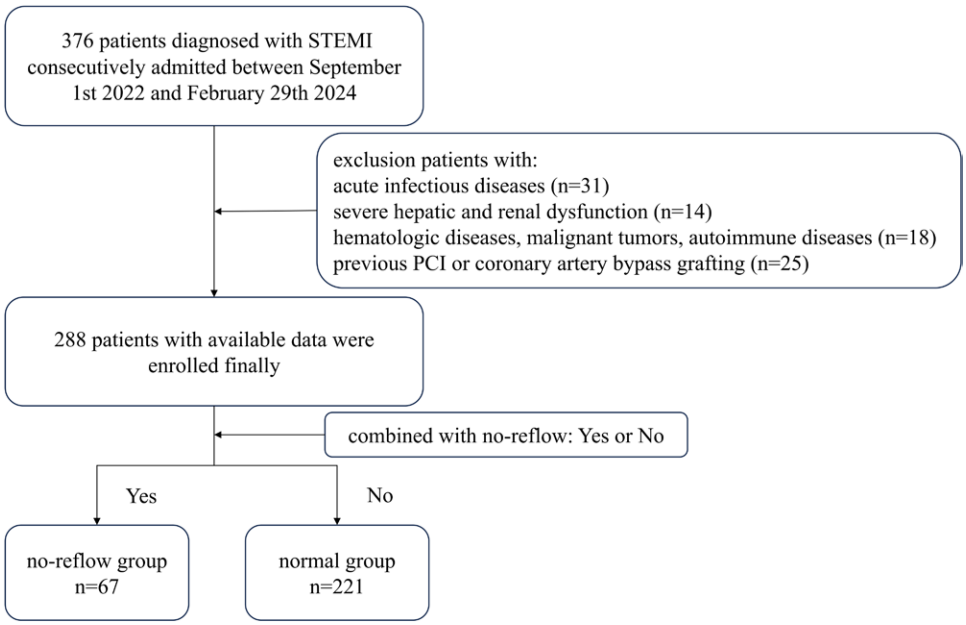

Figure 1. Study flow chart.

2.4. Statistical analysis

A comprehensive power analysis was undertaken based on alfa = 0.05, power = 0.90, and estimated effect size = 0.79,[13] which ascertained the sample size required for valid statistics of 35 participants each for the no-reflow group and the normal blood flow group. Hence the sample size in our study was sufficient.

Data analysis was conducted using SPSS26.0 statistical software, with a threshold of $P < .05$ set to determine statistical significance. 1. Count data were expressed as component ratios, and the chi-square test was used to analyze differences between groups; 2. Measurements that followed a normal distribution were reported as mean ± standard deviation. Intergroup comparisons were conducted using 2 independent samples of *t* test. 3. Measurements that were not normally distributed were expressed as median (interquartile range) and were compared with the Mann–Whitney *U* test; 4. The risk factors affecting the occurrence of no-reflow after PPCI were analyzed by multivariate logistic regression; 5. The receiver operating characteristic (ROC) curve was used to analyze the predictive capability of relevant indexes for the occurrence of no-reflow, and the curve was plotted.

3. Results

3.1. General clinical characteristics

No statistical differences were observed between the 2 groups regarding gender, age, BMI, smoking history, alcohol consumption, hypertension, diabetes mellitus, coronary artery diseases, and prehospital medication history ($P > .05$), as presented in Table 1.

3.2. Hematologic and cardiac function data

Compared with the normal flow group, patients in the no-reflow group exhibited elevated leukocytes, neutrophils, and NHR, while lymphocytes and albumin were lower ($P < .05$). Furthermore, statistical analysis revealed no significant differences between the 2 groups regarding platelets, mean platelet volume, C-reactive protein, total cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, serum creatinine, serum uric acid, fibrinogen, D-dimer, glycated hemoglobin, N-terminal pro-brain natriuretic peptide, cardiac troponin T, creatine kinase isoenzyme, and left ventricular ejection fraction ($P > .05$), as shown in Table 2. The level of NHR in the no-reflow group was significantly higher than those observed in the normal flow group [9.70 (6.77, 12.65) vs 6.34 (4.53, 8.60), $P < .001$], as illustrated in Figure 2.

Table 1

General clinical data of the 2 groups.

Parameters	No-reflow flow (n = 67)	Normal flow (n = 221)	*P*
Male	52 (77.61%)	176 (79.64%)	.721
Age/years	59.33 ± 13.04	58.19 ± 12.26	.514
Body mass index (kg/m^2)	24.82 (23.03, 27.13)	24.61 (22.86, 27.05)	.870
History of smoking	37 (55.22%)	134 (60.63%)	.430
History of drinking	24 (35.82%)	83 (37.56%)	.797
History of hypertension	28 (41.79%)	104 (47.06%)	.448
History of diabetes mellitus	22 (32.84%)	88 (39.82%)	.303
History of coronary heart diseases	11 (16.42%)	27 (12.22%)	.373
History of prehospital medication			
Antiplatelet drugs	10 (14.93%)	26 (11.76%)	.493
Statins	16 (23.88%)	39 (17.65%)	.255
β-Blocker	13 (19.40%)	43 (19.46%)	.992
ACEI/ARB	14 (25.37%)	53 (23.98%)	.600

ACEI = angiotensin-converting enzyme inhibitors, ARB = angiotensin receptor blockers.

3.3. Intraoperative clinical data

A statistically significant difference was observed between the 2 groups regarding intracoronary thrombolysis and thrombus aspiration ($P < .05$). Conversely, no significant differences were found in terms of time from symptom onset to balloon dilatation, infarct-related artery, the number of coronary lesions, the number of stents implanted, and occurrences of coronary artery dissection ($P > .05$), as detailed in Table 3.

3.4. Multivariate logistic regression analysis

Leucocytes and neutrophils were excluded from the regression analysis due to their covariance with NHR. In a multifactorial regression model, inclusion of lymphocyte, NHR, albumin, intracoronary thrombolysis, and thrombus aspiration, higher NHR (OR = 1.241, $P < .001$) and lower albumin (OR = 0.893, $P = .023$) were independent risk factors for no-reflow in patients with STEMI after PPCI, as presented in Table 4 and Figure 3.

3.5. Analysis of ROC curve

The ROC curve was used to calculate the value of NHR and albumin for diagnosing no-reflow after PPCI in patients with STEMI. A larger AUC indicates a greater diagnostic capability. The value corresponding to the maximum Youden index represents the diagnostic cutoff value for no-reflow. A significant increase in the risk of no-reflow was observed when the level of NHR exceeded 7.88, with an AUC of 0.740 and a 95%CI ranging from 0.671 to 0.809 ($P < .001$). At this threshold, sensitivity was recorded at 71.6%, while specificity was 71.5%. The diagnostic threshold for albumin was 38.05, in which the AUC was 0.614, and 95%CI fluctuated between 0.538 and 0.690 ($P < .05$). And the sensitivity and the specificity were 54.8% and 65.7%. As depicted in Figure 4, the AUC of NHR is greater than that of albumin, indicating that NHR offers superior diagnostic value.

4. Discussion

PPCI is an absolute indication for patients with STEMI. If timely PPCI is not possible, thrombolysis therapy is the next best option, which is rapid and easy to perform. No-reflow is a common complication after PPCI in STEMI patients and is significantly linked to adverse cardiovascular events such as cardiogenic shock, malignant arrhythmia, recurrent infarction, heart failure, and cardiac death.[14] Early identification of high-risk patients and the use of appropriate intervention techniques can reduce the incidence of no-reflow. The main mechanisms of no-reflow include myocardial ischemia-reperfusion damage, distal embolization, as well as individual susceptibility to microvascular dysfunction.[5] The longer the duration of ischemia, the more pronounced the ischemia-related adverse effects. Anaerobic metabolism leads to the failure of ion pumps, acidosis, dysfunctional mitochondria, and the formation of reactive oxygen species.[15] Accumulation of various catabolic metabolites has direct toxic effects on cells, leading to cell swelling and interstitial edema.[15] Inflammatory response, including neutrophils, macrophages, and lymphocytes, is the central mechanism of myocardial ischemia–reperfusion injury, with excessive inflammatory activation leading to necrosis of cardiomyocytes and vascular endothelial cells.[16] Distal embolization is caused by microemboli composed of platelet aggregates, fibrin, hyaluronan, and cholesterol-rich

atherosclerotic plaque material, which result in microinfarcts that are also accompanied by an inflammatory response.[17] Further obstruction of the microcirculation is due to the aggregation of neutrophils and platelets, which produces large amounts of vasoconstrictors and inflammatory mediators, amplifying the body's inflammatory response.[18]

A few simple and easily accessible indicators are used to predict the occurrence of no-reflow. Serum uric acid/albumin ratio is an independent predictor of no-reflow in STEMI patients with a sensitivity of 82%.[19] Electrocardiographic parameters, such as precordial total Q wave duration to precordial total R wave duration ratio, is a powerful predictor of no-reflow in patients with acute anterior myocardial infarction.[20] A prospective study confirmed that fibrinogen/albumin ratio can be used to assess microvascular perfusion in patients after coronary intervention.[21] A high C-reactive protein–albumin ratio implies a high thrombotic load after PPCI in STEMI patients.[22] A study of 1834 patients confirmed the predictive value of HbA1c/C-peptide ratio for no-reflow, which contributes to the risk stratification of patients with STEMI.[23] CHA2DS2-VASc score can be used to estimate thromboembolic events in patients with atrial fibrillation and also to predict the occurrence of no-reflow in patients with STEMI after PPCI.[24] Furthermore, no-reflow is a possible stage of disease progression after intervention in STEMI patients. More precise scores are needed to predict endpoints regarding these patients. For example, the Naples score, which combines inflammation and nutritional status, is an independent predictor of long-term mortality after PPCI in patients with STEMI and allows risk stratification.[25]

NHR, as a novel composite indicator, can provide a more comprehensive reflection of an individual's inflammatory status and lipid metabolism compared to traditional single biological markers. And it is easy to obtain and less expensive. Neutrophils reach the peak of infiltration within 24 hours of ischemia–reperfusion, and at the same time release a large number of reactive oxygen species and pro-inflammatory chemokines to further recruit more inflammatory cells to the site of damage,[26] and their secretion of S100A8/A9 proteins, which are important initiators of inflammatory storms, can produce an amplified response to the inflammatory cascade,[27] and enhance thrombosis through different mechanisms, including the production of neutrophil extracellular trap production, protease release, and neutrophil–platelet interactions.[28] HDL can retrogradely transport cholesterol to the liver for metabolism, thereby reducing intravascular lipid deposition.[29] In addition, it plays an important role in anti-inflammatory, antioxidant, antithrombotic, and maintenance of vascular endothelial function.[8,30] High HDL level in plasma is a robust marker of reduced risk of cardiovascular disease.[31] In addition, HDL can inhibit neutrophil activation and migration.[32]

NHR is strongly associated with coronary artery stenosis and can be used as an independent predictor of it.[33] A prospective

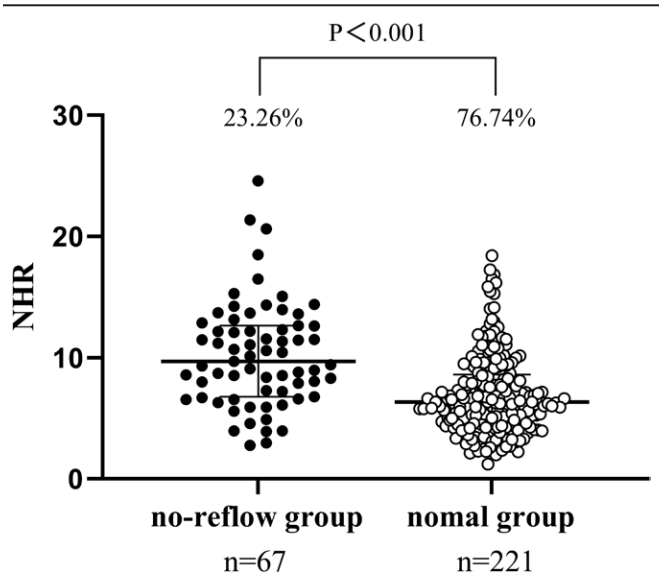

Figure 2. Comparison of NHR between the no-reflow group and the normal group. Individual symbols represent data points and bars represent median and interquartile range. NHR = neutrophil to high-density lipoprotein ratio.

Table 2

Hematologic and cardiac function data of the 2 groups.

Parameters	No-reflow flow (n = 67)	Normal flow (n = 221)	*P*
Leukocytes (×10⁹/L)	11.79 (9.06, 14.13)	8.98 (7.41, 11.36)	<.001
Neutrophils (×10⁹/L)	8.89 (6.81, 11.13)	5.89 (4.44, 7.86)	<.001
Lymphocytes (×10⁹/L)	1.80 (1.24, 2.58)	2.26 (1.42, 3.30)	.023
Platelets (×10⁹/L)	252.85 ± 67.02	235.79 ± 64.17	.060
Mean platelet volume (fL)	9.90 (9.10, 10.90)	10.10 (9.55, 10.85)	.481
C-reactive protein (mg/L)	1.60 (0.50, 5.82)	1.23 (0.50, 2.89)	.168
Total cholesterol (mmol/L)	4.73 ± 1.08	4.62 ± 1.07	.460
Triglyceride (mmol/L)	1.57 (1.08, 2.20)	1.53 (1.14, 2.19)	.757
High-density lipoprotein (mmol/L)	0.87 (0.77, 1.07)	0.94 (0.80, 1.10)	.179
Low-density lipoprotein (mmol/L)	2.68 ± 0.92	2.56 ± 0.86	.325
NHR	9.70 (6.77, 12.65)	6.34 (4.53, 8.60)	<.001
Serum creatinine (μmmol/L)	73.7 (63.6, 83.9)	69.5 (60.4, 80.2)	.102
Uric acid (μmmol/L)	361.92 ± 129.46	342.01 ± 103.69	.196
Albumin (g/L)	37.38 ± 3.23	38.59 ± 3.24	.008
Fibrinogen (g/L)	2.83 (2.43, 3.26)	2.87 (2.47, 3.22)	.684
D-dimer (mg/L FEU)	0.36 (0.25, 0.85)	0.33 (0.24, 0.47)	.066
Glycated hemoglobin (%)	6.0 (5.5, 6.8)	5.9 (5.6, 7.0)	.885
NT-pro-BNP (pg/mL)	277 (106, 980)	177 (87, 492.5)	.055
cTnT (ng/mL)	0.036 (0.01, 0.21)	0.015 (0.01, 0.11)	.131
CK-Mb (ng/mL)	7.4 (2.6, 46.0)	5.4 (2.0, 16.0)	.070
LVEF (%)	57 (48, 60)	58 (53, 62)	.127

CK-Mb = creatine kinase-MB, cTnT = cardiac troponin T, FEU = fibrinogen equivalent unit, LVEF = left ventricular ejection fraction, NT-pro-BNP = N-terminal pro-B-type natriuretic peptide.

Table 3

Intraoperative clinical data of the 2 groups.

Parameters	No-reflow flow (n = 67)	Normal flow (n = 221)	*P*
Time from onset to balloon dilatation/h	4 (2, 5)	4 (3, 5)	.555
IRA			.095
LAD	37 (55.22%)	130 (58.82%)	
LCX	4 (5.97%)	30 (13.57%)	
RCA	26 (38.81%)	61 (27.60%)	
Number of coronary lesions			.418
Single vessel	11 (16.42%)	44 (19.91%)	
Double vessel	18 (26.87%)	72 (32.58%)	
Triple vessel	38 (56.72%)	105 (47.51%)	
Intracoronary thrombolysis	33 (49.25%)	70 (31.67%)	.009
Thrombus aspiration	11 (16.42%)	15 (6.79%)	.016
Number of stents implanted	1 (1, 2)	1 (1, 1)	.300
Coronary artery dissection	6 (8.96%)	21 (9.50%)	.893

IRA = infarct-related artery, LAD = left anterior descending artery, LCX = left circumflex artery; RCA = right coronary artery.

Table 4

Multivariate logistic regression analysis of no-reflow.

Parameters	B	SE	Wald	*P*	OR	95% CI	
						Lower	Upper
Lymphocytes	–0.145	0.109	1.771	.183	0.865	0.699	1.071
NHR	0.216	0.042	26.034	<.001	1.241	1.142	1.349
Albumin	–0.113	0.049	5.199	.023	0.893	0.811	0.984
Intracoronary thrombolysis	0.553	0.341	2.636	.104	1.739	0.892	3.391
Thrombus aspiration	0.504	0.524	0.925	.336	1.655	0.593	4.623

NHR = neutrophil to high-density lipoprotein ratio.

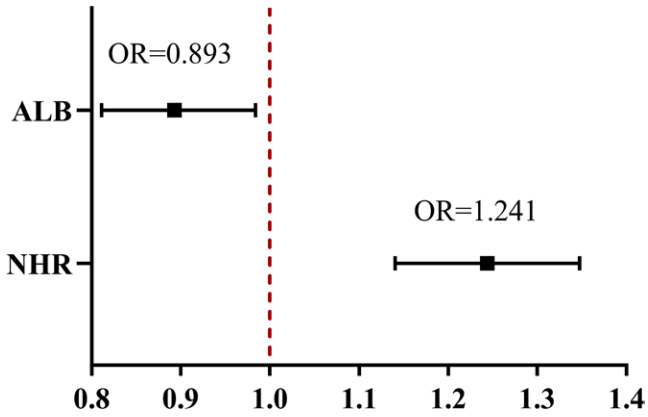

Figure 3. Comparison of OR for NHR and albumin. ALB = albumin, NHR = neutrophil to high-density lipoprotein ratio.

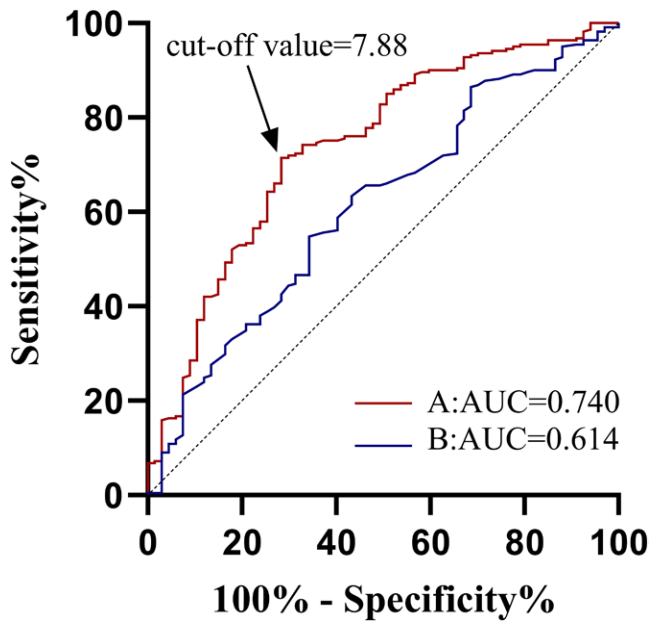

Figure 4. ROC curve of NHR and albumin diagnosis of no-reflow. The A curve represents NHR and the B curve represents albumin. The arrow points to the diagnostic cutoff for NHR. NHR = neutrophil to high-density lipoprotein ratio, ROC = receiver operating characteristic curve.

study that included 528 elderly patients with acute myocardial infarction confirmed that a high level of NHR was associated with higher long-term mortality and risk of recurrent myocardial infarction.[34] In addition, NHR has the predictive value for in-hospital adverse cardiovascular events and after PPCI in STEMI patients and is superior to monocyte-to-HDL-cholesterol ratio.[35] NHR has also been used in other areas of research outside of coronary heart diseases. A prospective study that included 1639 patients showed that NHR is an independent risk factor for death in patients with hepatocellular carcinoma and can be used to assess prognosis.[36] Yu et al pointed out that NHR level positively correlates with the severity of acute ischemic stroke.[37]

In this study, the rate of no-reflow was 23.26%, aligning closely with the findings reported in prior research.[5] NHR was higher in the no-reflow group compared to the normal group. It is an independent risk factor for the occurrence of no-reflow after PPCI in STEMI patients, which has good sensitivity and specificity in predicting no-reflow events.

However, we have to acknowledge that this study still has several limitations. First, this study is a single-center, cross-sectional study. Data are collected at a point in time and dynamic changes in data are not tracked, which may limit the generalizability of the results. More prospective studies with multiple centers are needed. Secondly, this study was limited to a specific region with a relatively small sample size, which may influence the statistical power of the results. More researches with diverse populations and bigger sample sizes are needed in the future. Thirdly, this study used TIMI flow grades in coronary angiography to determine whether no-reflow occurred, which underestimated the incidence of no-reflow compared with cardiac magnetic resonance.

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Author contributions

Conceptualization: Mengyao Hu.
Data curation: Mengyao Hu, Zhuoyan Tong, Zhiyuan Cai, Shiyu Li.
Formal analysis: Mengyao Hu, Zhuoyan Tong.
Methodology: Mengyao Hu.
Writing – original draft: Mengyao Hu.
Writing – review & editing: Dongwei Yang.

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