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Correlation of neutrophil-to-lymphocyte ratio with the prognosis of non-ST-segment elevation in patients with acute coronary syndrome undergoing selective percutaneous coronary intervention

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Abstract

Objective: We aimed to explore the relationship between neutrophil-to-lymphocyte ratio (NLR) at three timepoints and prognosis of patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) undergoing elective percutaneous coronary intervention (PCI) within 1 year of PCI.

Methods: This retrospective study enrolled 231 patients with NSTE-ACS who received PCI and were followed for 1 year after PCI. The study population was divided into major adverse cardiovascular and cerebrovascular events (MACE) and non-MACE groups.

Results: In total, 214 patients completed the 1-year follow-up; 32 patients (15.0%) had MACE and 182 (85.0%) had no MACE. The MACE and non-MACE groups differed significantly in age, preoperative neutrophil count, preoperative and postoperative NLR, proportion of three-vessel lesion disease, preoperative lymphocyte count, postoperative lymphocyte count within 24 hours, postoperative lymphocyte count over 24 hours, and left ventricular ejection fraction (LVEF). Multivariate logistic regression analysis showed that preoperative NLR, postoperative NLR within 24 hours, age, and LVEF values were independent risk factors for MACE in patients with NSTE-ACS after elective PCI.

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Conclusion: Compared with preoperative NLR, postoperative NLR (within 24 hours) may have a stronger ability to predict the occurrence of MACE in NSTE-ACS patients within 1 year after elective PCI.

Keywords
Neutrophil-to-lymphocyte ratio, major cardiovascular event, major cerebrovascular adverse event, non-ST-elevation acute coronary syndrome, percutaneous coronary intervention, left ventricular ejection fraction, risk factor

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Introduction

Acute coronary syndrome (ACS) has the highest mortality among coronary heart disease, and it is characterized by serious health complications. Almost three-fourths of patients with ACS present with non-ST-segment elevation (NSTE-ACS).[1] NSTE-ACS is triggered by various risk factors that decrease the stability of coronary atherosclerotic plaque, resulting in plaque rupture and thrombus formation and leading to partial or complete obstruction of the coronary artery lumen. As a result, acute ischemia-hypoxia injury and necrosis of myocardial cells develop because of decreased blood supply to the site of the lesions. Inflammatory mechanisms play an important role in the formation of atherosclerosis. Neutrophils and lymphocytes are the main inflammatory cells in the body. Plaque rupture increases the number of neutrophils and induces release of proteolytic enzymes, such as myeloperoxidase, which result in tissue damage.[2] It has been suggested that a high number of neutrophils in patients with suspected acute myocardial infarction increases the risk of death and myocardial infarction.[3] Therefore, a decrease in lymphocyte numbers may reflect the level of neurohormone activation in ACS patients and may be a marker of the physiological stress response induced by high cortisol[4] or catecholamine.[5] High levels of cortisol and catecholamines in patients with coronary heart disease[6,7] can induce lymphocyte apoptosis[8] and downregulate lymphocyte proliferation and differentiation.[5]

Currently, percutaneous coronary intervention (PCI) is the main strategy for revascularization in patients with ACS. Although PCI significantly improves the prognosis of these patients, some patients develop major cardiovascular and cerebrovascular adverse events (MACE) after PCI. However, there is no effective method of predicting the risk of MACE in patients after PCI. The neutrophil-to-lymphocyte ratio (NLR) is a new biomarker that may better reflect the immune status of individuals compared with a single inflammatory cell subtype. In a recent study, NLR was found to be associated with severity and plaque morphology in patients with coronary heart disease.[9] Moreover, the risk of MACE or mortality increased by about 150% in patients with elevated NLR (mean truncation >2.5). Although the exact underlying mechanism of recurrent events in patients with NLR and coronary heart disease is unclear, high NLR may predict short-term and long-term adverse outcomes in patients with ACS.[10]

Dentali et al.[11] reviewed 23 studies covering more than 16,000 patients. They showed that high NLR at admission was associated with higher overall mortality in patients with both ST-segment elevation myocardial infarction (STEMI) and non-ST segment elevation myocardial infarction (NSTEMI) compared with those with low NLR. This indicates that NLR in ACS has a major effect on important clinical outcomes, including hospitalization time, long-term mortality, and MACE. Therefore, NLR could be used as an index to evaluate the inflammation level in patients with NSTE-ACS before and after PCI. Numerous studies have explored the influence of NLR on NSTE-ASC before PCI, but no study has assessed the predictive value of NLR for the occurrence of MACE events in such patients after PCI. In the present study, we retrospectively evaluated NLR at three time points: preoperative, postoperative within 24 hours, and postoperative after 24 hours (24–48 hours), with the aim of determining the prognostic role of NLR in NSTE-ACS patients.

Methods

Patient enrollment

This retrospective clinical study was performed at the Department of Cardiology of Changshu No. 1 People's Hospital (Changshu, China). A total of 231 consecutive patients with NSTE-ACS who underwent successful elective PCI were enrolled from January 2015 to November 2017. All patients received elective PCI between 24 hours and 3 days after exclusion of high-risk NSTE-ACS. The diagnosis of NSTE-ACS conformed to published diagnostic criteria.[12] The following exclusion criteria were used: (1) definite diagnosis of acute STEMI; (2) severe hepatorenal insufficiency; (3) other serious diseases in addition to unstable angina that affect the short-term survival rate (such as malignant tumors) and hematological diseases, including New York Heart Association (NYHA) grade IV heart failure and severe arrhythmias; (4) MACE occurred within 1 month after elective PCI for NSTE-ACS; (5) allergies to aspirin, clopidogrel/ticagrelor, or statin or discontinuation due to severe adverse reactions; (6) acute and chronic inflammatory diseases; (7) past experience with PCI or coronary artery bypass grafting (CABG); or (8) mental disorder. Selection criteria for PCI based on coronary angiography were residual stenosis $<10\%$ and forward blood flow of TIMI grade 3, absence of significant side branch occlusion, absence of dissection affecting blood flow, and absence of visible thrombosis and peripheral embolism.

This study was approved by the institutional review board of Changshu No. 1 People's Hospital. All sensitive patient information was removed before analysis. Informed consent was not required for this retrospective study according to the institutional review board.

Data collection

The following clinical data were collected from all patients after admission: age, sex, body mass index (BMI), history of hypertension or diabetes mellitus, history of coronary heart disease, smoking history, and drug use after PCI. Physical examination, measurement of height and weight, calculation of BMI, improved electrocardiogram, ambulatory electrocardiogram, transthoracic echocardiography, and routine blood labs were collected before, within 24 hours, and >24 hours after PCI (24–48 hours after the procedure). Coronary angiography and PCI were recorded for the main left artery, three-vessel lesions, bifurcation lesions, number of stents implanted, total length of stents implanted, and average diameter

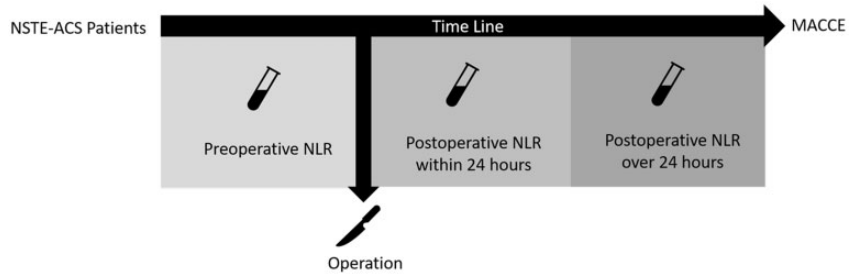

Figure 1. Patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) who underwent elective percutaneous coronary intervention within 1 year were divided into major cardiovascular and cerebrovascular adverse events (MACE) and non-MACE groups. Preoperative and postoperative (within 24 hours and after 24 hours) neutrophil-to-lymphocyte ratios (NLR) were assessed and correlated with presence of MACE.

of stents implanted. The study routine is shown in Figure 1.

Follow-up and major endpoint events

Follow-up was conducted by contact with patients via telephone, at outpatient visits, or upon rehospitalization. All events were classified and processed by a physician not involved in the follow-up process. A total of 231 patients were enrolled, of which 214 were successfully followed up and 17 were lost. The follow-up lasted from January 2015 to November 2017. The amounts of aspirin, clopidogrel, angiotensin-converting enzyme inhibitor (ACEI)/angiotensin II receptor antagonist (ARB), β-blockers, and statins used after discharge were recorded. MACE included (1) all-cause death; (2) non-fatal myocardial infarction; (3) non-fatal stroke (transient ischemic attack, cerebral infarction); and (4) clinical-driven target vessel revascularization (including PCI and CABG).

Statistical analysis

Data analysis was performed using SPSS version 19.0 software (IBM Corp., Armonk, NY, USA). Continuous variables (with normal distribution) were expressed as means ± standard deviations. Intergroup comparisons were carried out using the independent samples *t*-test, and categorical data were compared using the chi-square test. Logistic regression analysis was carried out to calculate odds ratio and 95% confidence intervals. Receiver operator characteristic (ROC) curves were used to evaluate the predictive value of NLR for the occurrence of MACE before and after PCI. Differences were considered statistically significant at $P < 0.05$.

Results

Comparison of clinical data between MACE and non-MACE groups

A total of 231 patients with NSTE-ACS who underwent elective PCI were followed up. Among them, 214 patients were successfully followed up to the end of the study period and 17 patients were lost—a follow-up rate of 92.6%. Among enrolled patients, 148 were male (69.2%) and 66 were female (30.8%), with an average age of 66.16 (±8.16 years). During follow-up, 32 patients (15.0%) had MACE and 182 cases (85.0%) had no MACE. The patients in the MACE group were older than those in the non-MACE group ($P = 0.001$). In addition, preoperative neutrophil count

($P = 0.036$), preoperative NLR ($P = 0.002$), and postoperative NLR (within 24 hours) ($P = 0.001$), and the ratio of three-vessel lesions disease ($P = 0.001$) were significantly increased in the MACE group compared with the non-MACE group. In contrast, preoperative lymphocyte count ($P < 0.001$), postoperative (within 24 hours) lymphocyte counts ($P < 0.001$), postoperative (more than 24 hours) lymphocyte counts ($P = 0.045$), and left ventricular ejection fraction (LVEF) ($P = 0.003$) were significantly decreased in the MACE group compared with the non-MACE group (Table 1).

Multivariate logistic regression analysis of the incidence of MACE

To validate the relationship between preoperative and postoperative NLR and the occurrence of MACE in patients after elective PCI, multivariate logistic regression analysis was performed. Results revealed that preoperative NLR ($P = 0.025$) and postoperative NLR (within 24 hours) ($P = 0.033$) were correlated with the occurrence of MACE events. Further, we found that older age ($P = 0.021$) and lower LVEF values ($P = 0.015$) were independent predictors of the risk of MACE after elective PCI (Table 2).

Preoperative NLR and total NLR predict MACE

The area under the ROC curve (AUC) of MACE as predicted by preoperative NLR was 0.72 (95% CI: 0.625–0.814). The standard error of the area was 0.048 and confirmed the predictive value of NLR for MACE (Figure 2). This result showed that a higher preoperative NLR indicates a higher risk of MACE ($P < 0.001$). When the preoperative NLR value was 2.918, the sensitivity and specificity of predicting MACE were 68.8% and 77.0%, respectively.

The area under the ROC curve of MACE as predicted by postoperative NLR (within 24 hours) was 0.754 (95% CI: 0.686–0.822) and the standard error was 0.035. This indicates that postoperative NLR may be used to predict MACE ($P < 0.001$) within 24 hours after PCI (Figure 3). When NLR was 4.32 within 24 hours after PCI, the sensitivity and specificity of predicting MACE were 90.6% and 64.8%, respectively. Postoperative NLR (within 24 hours) was positively correlated ($P = 0.001$) with the risk of MACE.

Discussion

In this study, NLR was measured in patients with NSTE-ACS at different time points, and a positive correlation was found between NLR and the risk of MACE. Considering that inflammation plays an important role in the process of atherosclerosis, both NSTE-ACS itself and PCI may lead to acute inflammation. Plaque rupture not only increases the number of neutrophils[2] but also increases the levels of cortisol and catecholamine,[6,7] which trigger lymphocyte apoptosis.[8] The ratio of NLR reflects two subtypes of leukocyte changes. Therefore, NLR is a more accurate indicator of evaluating the inflammatory state of the body. Moreover, the accurate and specific measurement of NLR is superior to measurement of white blood cells, neutrophils, or lymphocyte count in predicting cardiovascular events in patients with coronary heart disease.[13]

Herein, we established that NLR of patients following PCI exhibited dynamic changes over time. These results are consistent with the report by Bressi et al.[14] In their study, NLR values were monitored at 6 and 24 hours after PCI, and they found that NLR significantly increased at 6 and 24 hours after PCI, with mean NLR

Table 1. Comparison of clinical data between MACE and non-MACE groups.

Parameter	Total (n = 214)	MACE group (n = 32)	Non-MACE group (n = 182)	*P*-value (MACE vs. non-MACE)
Age (year)	66.16 ± 8.16	70.78 ± 8.00	65.48 ± 8.11	0.001
Male (%)	148 (9.2)	26 (81.3)	122 (67.0)	0.108
BMI (kg/m^2)	25.85 ± 6.90	27.05 ± 6.44	25.64 ± 6.97	0.291
Smoking (%)	47 (22.0)	11 (34.4)	36 (19.8)	0.066
Hypertension (%)	160 (74.5)	26 (81.3)	134 (73.6)	0.360
Diabetes (%)	74 (34.6)	8 (25)	66 (36.3)	0.217
LVEF (%)	62.82 ± 7.18	59.06 ± 6.11	63.48 ± 7.17	0.003
LAD (mm)	37.65 ± 5.02	39.44 ± 5.75	37.34 ± 4.84	0.058
Drugs (%)				
Clopidogrel	57 (26.6)	7 (21.9)	50 (27.5)	0.434
Ticagrelor	155 (72.4)	25 (78.1)	130 (72.5)	0.434
ACEI/ARB	93 (43.5)	15 (46.9)	78 (42.9)	0.672
β Blocker	125 (58.4)	19 (59.4)	106 (58.2)	0.905
Blood parameters				
Preoperative neutrophil count ($\times 10^9$)	4.18 ± 1.51	4.83 ± 1.90	4.07 ± 1.41	0.036
Preoperative lymphocyte count ($\times 10^9$)	1.60 ± 0.65	1.28 ± 0.41	1.65 ± 0.66	<0.001
Preoperative NLR	3.01 ± 1.61	4.23 ± 2.36	2.79 ± 1.34	0.002
Postoperative (within 24 h) neutrophil count ($\times 10^9$)	5.31 ± 1.70	5.89 ± 2.40	5.21 ± 1.23	0.001
Postoperative (within 24 h) lymphocyte count ($\times 10^9$)	1.33 ± 0.53	1.03 ± 0.29	1.38 ± 0.54	<0.001
Postoperative (within 24 h) NLR	4.61 ± 2.53	5.97 ± 3.03	4.37 ± 2.36	0.001
Postoperative (after 24 h) neutrophil count ($\times 10^9$)	3.96 ± 1.38	4.17 ± 0.81	3.93 ± 1.46	0.178
Postoperative (after 24 h) lymphocyte count ($\times 10^9$)	1.42 ± 0.49	1.26 ± 0.53	1.44 ± 0.48	0.045
Postoperative (after 24 h) NLR	3.14 ± 1.64	3.72 ± 1.14	3.03 ± 1.70	0.028
LDL-C (mmol/L)	2.30 ± 0.68	2.34 ± 0.70	2.29 ± 0.68	0.683
Preoperative creatinine (μmol/L)	72.64 ± 16.75	71.59 ± 17.86	72.82 ± 16.59	0.703
CK-MB (ng/mL)	8.70 ± 11.2	10.28 ± 10.49	8.42 ± 11.33	0.386
TnI (ng/mL)	1.03 ± 1.84	1.43 ± 2.00	0.96 ± 1.81	0.222
Coronary artery lesions and stents				
Three-vessel lesion ratio (%)	37 (17.3)	12 (37.5)	25 (13.7)	0.001
Bifurcation lesions ratio (%)	109 (50.9)	19 (59.4)	90 (49.5)	0.300
Left main lesion (%)	69 (32.2)	7 (21.9)	62 (34.1)	0.174
Number of stents implanted (individual)	2.25 ± 2.10	1.84 ± 0.92	2.32 ± 2.24	0.239
Average internal diameter of stent (mm)	2.98 ± 0.50	2.92 ± 0.37	2.99 ± 0.52	0.431
Total length of stent (mm)	55.07 ± 33.92	48.81 ± 27.09	56.18 ± 34.93	0.258
Complete revascularization (%)	167 (78.0)	27 (84.4)	140 (76.9)	0.586

MACE, major adverse cardiovascular and cerebrovascular event; BMI, body mass index; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; ACEI, angiotensin-converting-enzyme inhibitors; ARB, angiotensin II receptor blockers; NLR, neutrophil-to-lymphocyte ratio; LDL-C, low-density lipoprotein cholesterol; CK-MB, creatine kinase; MB form; TnI, troponin.

Table 2. Multivariate logistic regression analysis of major adverse cardiovascular and cerebrovascular events after percutaneous coronary intervention in patients with non-ST-segment elevation acute coronary syndrome.

Parameter	Odds ratio	95% CI	*P*-value
Preoperative NLR	1.307	1.034–1.651	0.025
NLR within 24 hours after operation	1.189	1.014–1.394	0.033
NLR 24 hours after operation	1.062	0.806–1.400	0.667
Age	1.069	1.010–1.131	0.021
LVEF	0.934	0.884–0.987	0.015
Three-vessel lesions	2.508	0.884–0.987	0.060

NLR, neutrophil-to-lymphocyte ratio; LVEF, left ventricular ejection fraction.

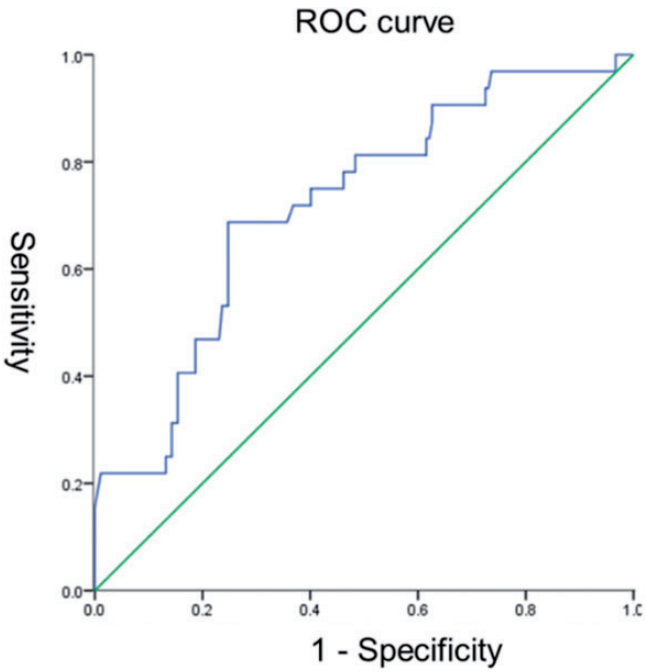

Figure 2. Receiver-operator characteristic (ROC) curve of major cardiovascular and cerebrovascular adverse events predicted by preoperative neutrophil-to-lymphocyte ratio (NLR).

values of 4.430 (3.390 to 6.020, 6 hours post-operation), 4.720 (3.940 to 5.750, 24 hours post-operation), and 3.255 (2.763 to 3.995, pre-operation). The NLR was significantly correlated with preoperative myocardial injury at 6 and 24 hours after PCI. We also found that postoperative NLR (within 24 hours) was significantly higher than preoperative NLR. Postoperative NLR (within 24 hours) in the MACE and non-MACE groups were 5.97 ($\pm$3.03) and 4.37 ($\pm$2.36), respectively. The postoperative (after 24 hours) NLR was 3.72 ± 1.14 in the MACE group and 3.03 ± 1.70 in non-MACE group. These results indicate that patients in the MACE group had stronger inflammatory responses than those in the non-MACE group.

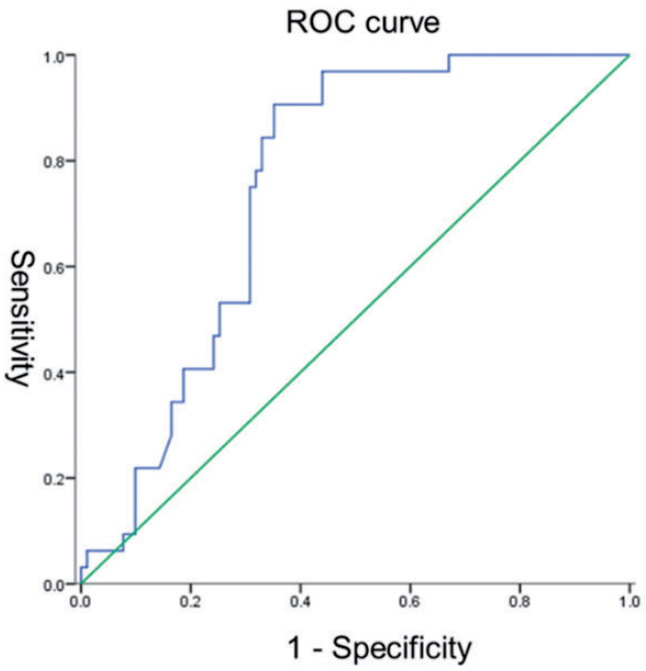

Figure 3. Receiver-operator characteristic (ROC) curve of major cardiovascular and cerebrovascular adverse events predicted by neutrophil-to-lymphocyte ratio (NLR) within 24 hours after surgery.

Accordingly, postoperative and preoperative NLR were positively correlated with the occurrence of MACE.

NLR is correlated with the short- and long-term prognosis of patients with coronary heart disease after PCI. In a previous study, 664 patients were treated with ST-segment elevation for emergency PCI, and the high NLR group (≥9.45) was associated with MACE during hospitalization.[15] Preoperative NLR is related to the occurrence of MACE in patients with acute myocardial infarction within 1 year after PCI.[16,17] Moreover, a predictive value for MACE was found 5 years after elective PCI in patients with stable coronary heart disease.[18] A study with longer follow-up confirmed that preoperative NLR may predict the prognosis of patients with stable PCI coronary heart disease after elective PCI.[19] That study focused on the predictive value of NLR at different time points for patients with NSTE-ACS within 1 year after elective PCI. It was found that preoperative NLR and NLR within 24 hours after PCI were independent risk factors.

Most previous studies have focused on the effect of preoperative NLR on MACE after elective PCI in NSTE-ACS patients[19–21] and rarely report the predictive value of postoperative NLR for postoperative adverse events. Bath et al.[22] studied the relationship between postoperative NLR and adverse events after elective aneurysm repair. They found that an increase of NLR within 1 week after surgery was closely related to postoperative complications. It is thought that NLR after surgery is related to the occurrence of MACE in patients with NSTE-ACS after elective PCI. In the present study, we confirmed that the NLR within 24 hours after PCI was an independent risk factor for MACE in NSTE-ACS patients within 1 year. Moreover, we found

that advanced age and decreased LVEF value were independent risk factors for MACE in patients with NSTE-ACS after elective PCI.

A previous study showed that the ROC AUC for predicting the mortality of patients with ACS before surgery was 0.843.[23] Another study reported that the ROC AUC of NLR before surgery was 0.792.[21] In our study, the NLR AUC before surgery and within 24 hours after surgery were calculated. The NLR AUC before surgery was 0.72, and the AUC for predicting MACE by NLR within 24 hours after surgery was 0.754. Interestingly, there is no report on the efficacy of NLR in predicting the occurrence of MACE before and within 24 hours after elective PCI for patients with NSTE-ACS. Combined with the ROC analysis, we confirmed that NLR may be superior in predicting the occurrence of MACE within 24 hours after elective PCI on NSTE-ACS patients.

This study was based on a modest sample size and it confirms that NLR, which is a parameter of the acute systemic inflammatory response, increases the risk of MACE in patients with NSTEMI. Moreover, unlike previous investigations, the results of this study demonstrate that postoperative NLR within 24 hours is a superior predictive factor for MACE in NSTE-ACS patients.

This study has several limitations. First, the modest sample size may introduce selection bias. This was a single-center study and thus lacks external validation. Therefore, our findings need to be validated in a multi-institutional study with a larger sample size. Second, we did not consider hepatic function, C-reactive protein, or other traditional markers of inflammation that may affect white blood cells and platelet counts. Finally, patient follow-up was short and thus does not reflect the predictive value of NLR for a longer period after PCI. However, in this study, NLR was evaluated upon admission to the hospital, and dynamic changes were assessed during the follow-up period. The post-PCI values of NLR (within 24 hours) were confirmed to be predictive of the clinical outcomes, which may help to predict adverse events following PCI.

Conclusions

In this study, elevated preprocedural NLR, elevated postoperative NLR within 24 hours, increased age, and declining LVEF values were associated with a high risk of clinical adverse events within 1 year. Postoperative NLR (within 24 hours) was superior to preoperative NLR in predicting the occurrence of MACE in patients with NSTE-ACS within 1 year after elective PCI.

Data availability

The data used to support the findings of this study are available from the corresponding author (Leng Han) on reasonable request.

Declaration of conflicting interest

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

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