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Predictive value of neutrophil-to-lymphocyte ratio in coronary chronic total occlusion patients

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ABSTRACT

BACKGROUND The neutrophil to lymphocyte ratio (NLR) has been reported as a novel predictor for atherosclerosis and cardiovascular outcomes. This study aimed to determine the effects of NLR on long-term clinical outcomes of chronic total occlusion (CTO) patients.

METHODS A total of 670 patients with CTO who met the inclusion criteria were included at the end of the follow-up period. Patients were divided into tertiles according to their baseline NLR levels at admission: low (n = 223), intermediate (n = 223), and high (n = 224). The incidence of major adverse cardiac events (MACEs) during the follow-up period, including all-cause death, nonfatal myocardial infarction (MI), or ischemia-driven revascularization, were compared among the three groups.

RESULTS Major adverse cardiac events were observed in 27 patients (12.1%) in the low tertile, 40 (17.9%) in the intermediate tertile, and 61 (27.2%) in the high NLR tertile (P < 0.001). Kaplan-Meier analysis demonstrated a significantly higher incidence of MACE, ischemia-driven coronary revascularization, non-fatal MI, and mortality in patients within the high tertile than those in the low and intermediate groups (all P < 0.001). Multivariable COX regression analysis showed that the high tertile of baseline NLR level showed a strong association with the risk of MACE (hazard ratio [HR] = 2.21; 95% confidence interval [CI]: 1.21–4.03; P = 0.009), ischemia-driven coronary revascularization (HR = 3.19; 95% CI: 1.56–6.52; P = 0.001), MI (HR = 2.61; 95% CI: 1.35–5.03; P = 0.043) and mortality (HR = 3.78; 95% CI: 1.65–8.77; P = 0.001).

CONCLUSION Our findings suggest that NLR is an inexpensive and readily available biomarker that can independently predict cardiovascular risk in patients with CTO.

Coronary chronic total occlusion (CTO) is an intricate lesion commonly detected in coronary angiograms (CAG).[1,2] Due to the long-time of CTO occlusion, the intravascular lesion becomes extremely hard, accompanied by vascular tortuosity and calcification. The current success rate of interventional treatment is low, and the complications from the procedure are high. Percutaneous coronary intervention (PCI), also known as percutaneous transluminal coronary angioplasty (PTCA), is a method of dilating a narrowed coronary artery through a catheter to alleviate stenosis and improve the myocardial blood supply. PTCA was first performed by Gruentzig in 1977 with the use of a balloon catheter to dilate a narrowed coronary artery lesion.[3,4] With the development of the technique, coronary stenting, high-frequency rotational atherectomy (HFRA), and directional coronary atherectomy (DCA) have gradually emerged. The safety and success of PCI treatment in CTO patients is now significantly higher than it used to be in the past.[5-7] In addition, successful CTO PCI can reduce the risk of major adverse cardiovascular events (MACE） and improve life quality and long-term prognosis compared with failed PCI.[8-10] However, the long-term clinical survival of CTO patients after successful revascularization remains dissatisfactory.[11,12] Therefore, the early biomarkers in

successful CTO PCI patients are worth exploring.

Inflammation is the initial factor in coronary atherosclerosis, and it plays a key role in its progression.[13,14] Inflammatory mediators secreted by neutrophils can lead to degeneration of the vessel wall. In contrast, lymphocytes regulate the inflammatory response and therefore have an anti-atherosclerotic effect. Thus, the neutrophil-to-lymphocyte ratio (NLR) is considered an inflammatory biomarker and a potential predictor of coronary artery disease (CAD) risk and prognosis. Recently, it has been shown that NLR levels are related to the incidence and severity of CAD and that the elevated NLR predicts the risk of adverse cardiovascular events in patients with acute coronary syndromes.[15-17] In addition, higher baseline NLR level is a risk factor for stent restenosis in post-PCI patients.[18] Until now, the role of assessing preprocedural NLR levels in predicting MACE events in successful CTO-PCI patients at long-term follow-up has not been reported, which motivated the present study.

METHODS

Study Population

CTO refers to a chronic occlusive lesion of coronary artery with a duration of more than three months, confirmed by CAG with thrombosis in myocardial infarction (TIMI) flow grade 0.[1,6] Successful revascularization of CTO was defined as the lesion with residual stenosis < 30% and TIMI flow grade 3. We selected 762 patients that received a successful PCI procedure between June 2013 and October 2017; their CTO lesions were confirmed by coronary angiography (CAG) in the Cardiology Department of our hospital. Qualitative and quantitative coronary angiographic analyses were performed by standard methods. Two experienced cardiovascular interventional physicians performed a blinded analysis of the CAG results. The operator determined the treatment strategy and stenting technique. The study exclusion criteria were: (1) signs of acute inflammation; (2) acute myocardial infarction (AMI); (3) history of stroke, renal failure, severe arrhythmias, or coronary artery bypass graft (CABG) surgery; and (4) presence of a malignancy. Out of the 762 patients, 92 were excluded due to AMI (n = 14), missing values (n = 27), and the absence of clinical follow-up data (n = 51); eventually, 670 patients were enrolled in this study; they were divided into tertiles in accordance with their NLR levels. The regular follow-up of cardiovascular adverse events was performed annually by outpatient visits and/or telephone contact between 2014 and 2018. The study was approved by the Research and Ethics Committees of our hospital, and all participants were required to provide written informed consents.

Endpoints and Definitions

The primary endpoint of the work was the composite MACE, including all-cause mortality, nonfatal myocardial infarction, and ischemia-driven coronary revascularization. The secondary endpoints were the various components of MACE. Death was considered due to cardiac etiology unless a definite non-cardiac cause was documented. Myocardial infarction was characterized by the occurrence of pathological and new Q waves on the ECG or an increase in creatine kinase-myocardial band levels to more than three times the normal upper limit. Except for the total occlusion of coronary artery, eligible patients had multivessel CAD, defined as at least one additional coronary lesion that was: (1) in a vessel at least 2.5 mm in diameter, and (2) at least 70% diameter stenosis or 50%–69% diameter stenosis (both by visual estimation) with a fractional flow reserve (FFR) measurement ≤ 0.80.[19]

Demographic Characteristics and Clinical Data

Several demographic, clinical, and analytical data were collected and documented: age, sex, height, weight, and some biochemical variables, such as total white blood cells, neutrophil and lymphocyte count, platelet count, serum uric acid, lipid profile, plasma homocysteine, high-sensitivity C-reactive protein (hs-CRP), and estimated glomerular filtration rate (eGFR). The NLR was calculated by dividing the absolute neutrophil count by the lymphocyte count.[18]

Statistical Analysis

Data are expressed as means ± SD or median and interquartile range for continuous variables and percentages for categorical variables. Continuous variables with normal distribution were analyzed

by one-way analysis of variance (ANOVA) followed by Bonferroni's *post hoc* test, while Kruskal-Wallis test and Bonferroni correction were used for non-normal distribution. Categorical variables and frequencies were compared by the chi-square test. Kaplan-Meier survival curves describing the clinical endpoints of MACE over time were compared by log-rank test. Cox regression analysis was conducted to explore the correlation between the variables and MACE. The strength of the association was determined by estimating hazard ratios (HR) and their 95% confidence intervals. Statistical analysis was performed retrospectively with SPSS 25.0 (SPSS, Inc., Chicago, IL, USA). In all cases, $P < 0.05$ was considered significant.

RESULTS

Study Population and Baseline Characteristics

A total of 670 patients with CTO (mean age: 65.37 ± 10.0 years; 83.6% men) were divided into tertiles according to the baseline NLR levels: low (NLR < 2.1). intermediate (NLR 2.1–3.4). and high (NLR > 3.4). Table 1 and 2 summarize the baseline clinical characteristics and preoperative laboratory results for all subjects. Preoperative age, neutrophil count, white blood cell count, cystatin C, and hs-CRP level were significantly higher in the high tertile group compared with patients in the low and middle tertile groups. However, at admission to the hospital, patients in the high tertile had lower left ventricular ejection fraction, mean eGFR, hemoglobin level, and lymphocyte count than patients in the low and middle tertiles. A history of diabetes was more common in the high tertile group. There were no statistically significant differences between the three groups in terms of oral cardiovascular medications, body mass index (BMI), hypertension, heart rate, and lipid levels (all $P > 0.05$). Table 3 shows the angiographic and procedural characteristics of all CTO patients who underwent PCI and follow-up. No differences were found in the vessels distribution or the number of CTO lesions, length of occlusion, and severity of calcification.

Clinical Outcomes in Total Population

The median follow-up period was 32 months (interquartile range: 20 to 47 months). Table 4 shows the clinical outcomes of all CTO patients. The total ratio of MACE events was 128/670 (17.9%); 27 patients (12.1%) belonged to the low tertile, 40 (17.9%) to the middle tertile, and 61 (27.2%) to the high tertile ($P < 0.001$). The prevalence of ischemia, in-

Table 1 Baseline and clinical characteristics of the study population.

Variables	Low (n = 223)	Intermediate (n = 223)	High (n = 224)	P-value
Mean age, yrs	63.8 ± 10.5	65.1 ± 9.5	67.2 ± 9.8	0.001
Females	47 (21.1%)	35 (15.7%)	28 (12.5%)	0.047
Body mass index, kg/m^2	24.9 ± 3.4	24.6 ± 3.3	24.1 ± 3.4	0.103
Hypertension	125 (56.1%)	112 (50.2%)	135 (60.3%)	0.100
Diabetes	69 (30.9%)	74 (33.2%)	95 (42.4%)	0.027
Smoking	106 (47.5%)	111 (49.8%)	115 (51.3%)	0.721
Prior MI	73 (32.6%)	76 (34.1%)	68 (30.5%)	0.718
Medications at discharge				
DAPT	172 (85.1%)	162 (85.3%)	152 (85.9%)	0.978
Statins	137 (67.8%)	140 (73.7%)	130 (73.9%)	0.322
Beta-blockers	120 (59.4%)	119 (62.6%)	115 (65.3%)	0.491
ACEI/ARB	147 (72.8%)	124 (65.3%)	111 (63.1%)	0.104
Mean Heart Rate	69.7 ± 8.3	70.7 ± 7.7	71.6 ± 9.7	0.064
Mean eGFR	100.5 (83.9-120.0)	100.6 (79.5-117.4)	94.6 (75.8-113.9)	0.007
Ejection fraction	61 (50-68)	60 (45-67)	55 (42-66)	0.002

Data are presented as mean ± SD, median (interquartile range), or n (%) of patients. ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers; DAPT: dual antiplatelet therapy.

Table 2 Results of preoperative laboratory measurements.

Variables	Low (*n* = 223)	Intermediate (*n* = 223)	High (*n* = 224)	*P*-value
Hemoglobin, g/L	137.5 ± 18.4	139.3 ± 18.0	133.3 ± 19.9	0.003
PLT, 10^9/L	190.4 ± 55.5	181.4 ± 54.1	182.0 ± 68.8	0.207
Lymphocyte, 10^9/L	2.1 ± 0.7	1.59 ± 0.4	1.14 ± 0.4	0.000
Neutrophil, 10^9/L	3.3 ± 1.0	4.2 ± 1.1	5.6 ± 2.1	0.000
NLR	1.7 (1.4–1.9)	2.7 (2.3–3.0)	4.7 (3.8–5.9)	0.000
White blood cell, 10^9/L	6.19 ± 1.8	6.4 ± 1.7	7.2 ± 2.8	0.000
Serum uric acid, μmol/L	340 (281.2–396.2)	328 (283–389.4)	340.5 (277.5–406.5)	0.939
Cystatin C, mg/L	0.9 (0.7–1.0)	0.9 (0.8–1.1)	0.9 (0.7–1.2)	0.006
Total cholesterol, mmol/L	3.8 ± 1.0	3.8 ± 1.0	3.7 ± 0.9	0.081
Total triglycerides, mmol/L	1.5 (1.0–2.1)	1.5 (1–2.2)	1.4 (1.0–2.0)	0.284
LDL-C, mmol/L	2.3 ± 0.9	2.2 ± 0.8	2.1 ± 0.8	0.379
HDL-C, mmol/L	0.9 ± 0.2	1.0 ± 0.3	0.9 ± 0.2	0.188
HCY, μmol/L	20.9 (14.5–256.7)	19.8 (13.7–110.0)	23.4 (15.9–223.9)	0.104
hs-CRP, mg/L	1.4 (0.9–1.4)	1.4 (1.0–1.9)	1.4 (1.4–2.2)	0.004

Data are presented as mean ± SD, median (interquartile range), or *n* (%) of patients. eGFR: estimated glomerular filtration rate; HCY: homocysteine; HDL-C: high-density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; NLR: neutrophil-lymphocyte ratio; PLT: platelet.

Table 3 Angiographic and procedural characteristics.

Variable	Low (*n* = 223)	Intermediate (*n* = 223)	High (*n* = 224)	*P*
Diseased vessels				
Single-vessel disease	39 (17.5%)	28 (12.6%)	29 (12.9%)	0.255
Double-vessel disease	30 (13.5%)	24 (10.8%)	22 (9.8%)	0.454
Triple-vessel disease	132 (59.2%)	145 (65%)	144 (64.3%)	0.382
LM disease	22(9.9%)	26(11.7%)	39(12.9%)	0.591
Target-vessel CTO				
RCA CTO	84 (37.7%)	66 (29.6%)	76 (33.9%)	0.196
LAD CTO	59 (26.5%)	72 (32.3%)	65 (29.0%)	0.399
LCX CTO	40 (17.9%)	38 (17.0%)	36 (16.1%)	0.871
Double-vessel CTO	37 (16.6%)	42 (18.8%)	40 (17.9%)	0.825
Triple-vessel CTO	3 (1.3%)	5 (2.2%)	7 (3.1%)	0.445
Occluded length, mm	18.4 ± 8.2	17.5 ± 5.9	20.4 ± 5.5	0.395
Moderate or severe calcifications	73 (33.0%)	71 (31.7%)	67 (29.8%)	0.806
J-CTO score	1.89 ± 1.15	1.95 ± 1.23	1.91± 1.20	0.341
Successful PCIs	106 (53.8%)	107 (52.1%)	90 (47.4%)	0.411
Retrograde approach	47 (21.3%)	51 (23.1%)	58 (26.0%)	0.476
Number of stents implanted	2 (2, 3)	2 (2, 3)	2 (2, 3)	0.941
Total stent length, mm	38.4 ± 8.2	38.1 ± 6.9	40.8 ± 7.5	0.670

Data are presented as mean ± SD, median (interquartile range), or *n* (%) of patients. CTO: chronic total occlusion; J-CTO: Japanese-CTO; LAD: left anterior descending coronary artery; LCX: left circumflex coronary artery; LM: left main coronary artery; RCA: right coronary artery.

duced by coronary revascularization, and mortality were significantly higher in the high tertile ($P < 0.001$). There were no differences in non-fatal MI observed in these groups ($P > 0.05$). Kaplan-Meier analysis showed that the incidence of MACE, coronary revascularization-driven ischemia, nonfatal

Table 4 Clinical outcomes on follow-up of all patients included in the study.

Variable	Low (n = 223)	Intermediate (n = 223)	High (n = 224)	P
MACE	27 (12.1%)	40 (17.9%)	61 (27.2%)	0.000
Mortality (all)	7 (3.1%)	21 (9.4%)	36 (16.1%)	0.000
Cardiac deaths	2 (0.9%)	6 (2.7%)	13 (5.8%)	
Non-cardiac deaths	5 (2.2%)	15 (6.7%)	23 (10.3%)	
Myocardial infarction	4 (1.8%)	10 (4.5%)	14 (6.3%)	0.060
STEMI	1 (0.4%)	4 (1.8%)	6 (2.7%)	
NSTEMI	3 (1.3%)	6 (2.7%)	8 (3.6%)	
Revascularization	13 (5.8%)	27 (12.1%)	52 (23.2%)	0.000

Data are percentages as n (%). MACE: major adverse cardiovascular event; MI: myocardial infarction; NSTEMI: non-ST segment elevation myocardial infarction; STEMI: ST segment elevation myocardial infarction.

MI, and mortality were significantly higher in the high NLR tertile (all $P < 0.001$) (Figure 1).

We performed Cox regression hazard models using NLR level tertile as a categorical variable, as previously described. Figure 2 shows the risk of each adverse cardiovascular outcome assessed by comparing the low tertile (reference group) with the middle and high tertile groups. The high tertile of NLR levels was correlated with composite MACE (hazard ratio [HR] = 2.21; 95% CI: 1.21–4.03; P = 0.009), coronary revascularization-induced ischemia (HR = 3.19; 95% CI: 1.56–6.52; P = 0.001), nonfatal MI (HR = 2.61; 95% CI: 1.35–5.03; P = 0.043) and mortality (HR = 3.78; 95% CI: 1.65–8.77; P = 0.001).

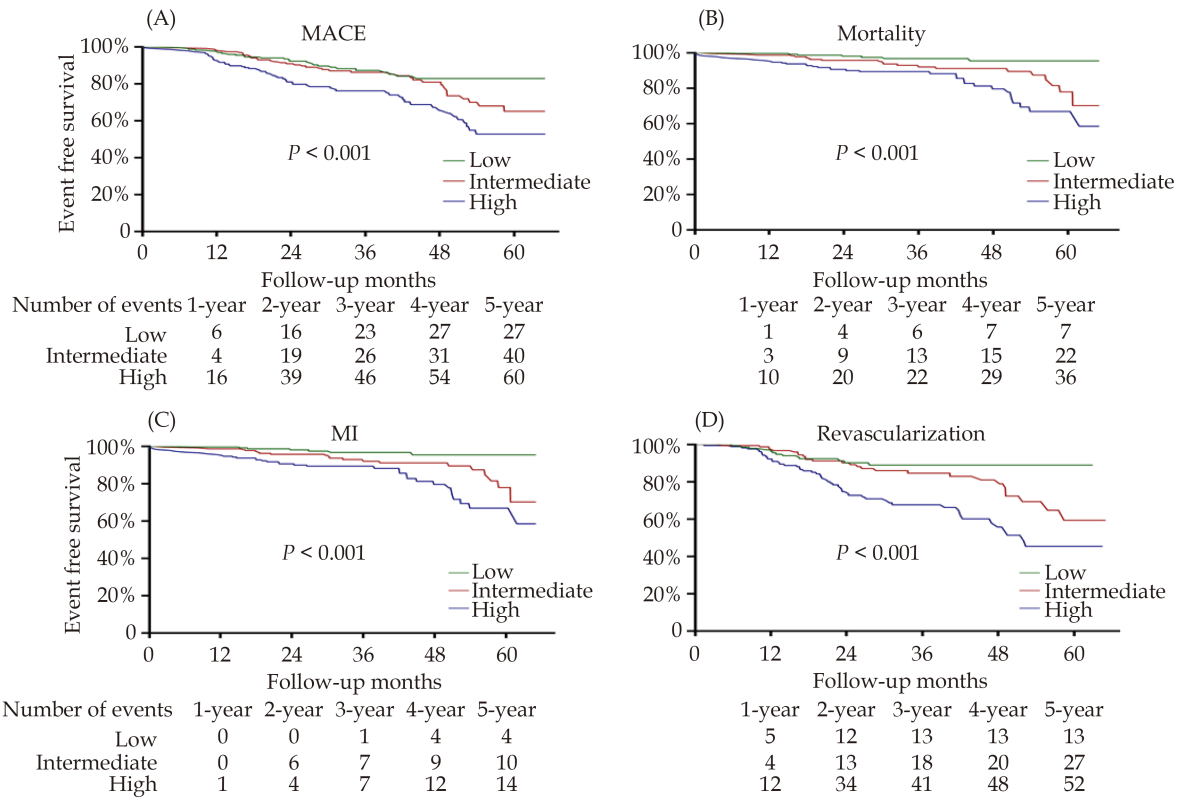

Figure 1 Survival curves by tertiles of baseline NLR level. (A): Freedom from MACE by tertiles of baseline NLR level (low versus intermediate versus high); (B): freedom from mortality by tertiles of baseline NLR level (low versus intermediate versus high); (C): freedom from MI by tertiles of baseline NLR level (low versus intermediate versus high); (D): freedom from ischemia-driven coronary revascularization by (low versus intermediate versus high). Cumulative survival rates were calculated by the Kaplan-Meier method and compared with the log-rank test. MACE: major adverse cardiac events; MI: myocardial infarction; NLR: neutrophil to lymphocyte ratio.

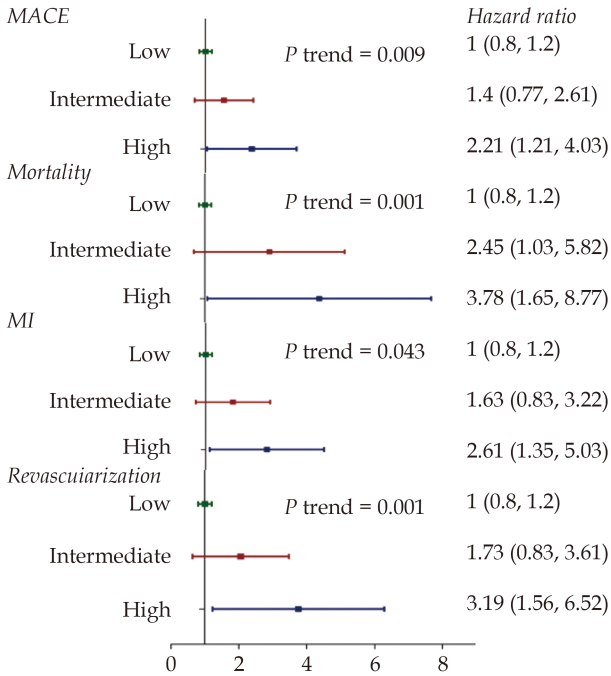

Figure 2 Forest plot showing the adjusted hazard ratios for outcomes. The model was adjusted for baseline variables significantly and factors closely related to the outcome of patients with cardiovascular disease, such as age, sex, BMI, diabetes mellitus, hypertension, and LDL-C, LVEF, eGFR, CRP, and procedural success. BMI: body mass index; CRP: C-reactive protein; LDL-C: low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; MACE: major adverse cardiovascular events; MI: myocardial infarction.

DISCUSSION

The aim of this study was to assess the predictive value of NLR levels on MACE in CTO-PCI patients. The results were as follows: (1) at long-term follow up, the rate of MACE was higher in the high tertile (NLR > 3.4) than in the low and intermediate tertiles; (2) elevated preoperative NLR level was an independent predictor of the MACE event in CTO patients. With the advancement of CTO revascularization techniques and devices, such as retrograde method, Cross-Boss catheter, dissection method, and retrograde method, the success rate of CTO PCI has significantly improved.[5,7,20] In addition, new anti-ischemic drugs, drug-eluting stents, and potent antiplatelet agents have helped to reduce the progression of CVD. However, worsening of clinical conditions, such as CTO and in-stent restenosis, are common.[11,12,21] Revascularization of CTO is a strong predictor of subsequent adverse events, such as cardiac death, coronary revascularization-induced ischemia, and other symptoms, whereas CTO-PCI is not associated with a reduction in long-term MACEs.[12,21] The pathophysiological mechanism of the recurrent events in CTO-PCI patients is largely unknown. Therefore, in consideration of the various adverse cardiovascular outcomes associated with CTO-PCI, researchers' focus has shifted to the etiology of atherosclerosis and the need to identify new markers to accurately predict the prognosis of patients with CTO and achieve better risk stratification.

Inflammation plays an essential role in the pathogenesis of atherosclerosis, and elevated inflammatory biomarkers indicate the activation of coronary artery injury.[15,22] Numerous inflammatory biomarkers have been identified, such as white blood cell count, hs-CRP, mean platelet volume (MPV), platelet distribution width (PDW), red blood cell distribution width (RDW), platelet-to-lymphocyte ratio (PLR), NLR, and interleukin-1; these biomarkers can be used to study the relationship between CAD and inflammatory response.[14,15,18,23] The NLR is much simpler to obtain compared with many other inflammatory markers. Moreover, it represents inherent and acquired immune responses, which makes it a better predictor than independent parameters, and it is more stable when subjected to changes such as dehydration, exercise, and blood specimen handling.

The relationship between elevated NLR and risk of cardiovascular events in CTO patients can be explained by various possible mechanisms. Neutrophils can localize in the vicinity of atherosclerotic plaques, especially those plaques with easy rupture characteristics, and further enhance the adhesion and migration of monocytes to atherosclerotic plaques.[24] Additionally, neutrophils may contribute to endothelial cell dysfunction and oxidative stress by releasing myeloperoxidase, NADPH oxidase, lipoxygenase, and neutrophil extracellular traps, thus making plaques more vulnerable.[25,26] On the contrary, lymphocytes can both protect against and contribute to atherosclerosis. However, most of the literature reported that absolute lymphocyte count is negatively associated with cardiovascular events. Most T lymphocytes in the atherosclerotic plaques are CD4+T helper (Th) cells, which belong to the type 1 pro-inflammatory Th1 subgroup and secrete pro-atherogenic cytokines such as IFN-γ and TNF.[27,28] Nevertheless, regulatory T (Treg) cells

and TH2 cells, which produce the anti-inflammatory mediators IL-10 and transforming growth factor-b, have a protective effect on CVD. B cells can also alter the balance in either direction: B1 cells produce IgM, which labels lipids for Fc receptor-mediated clearance, whereas B2 cells secrete atherogenic inflammatory cytokines.[25]

The C-reactive protein (CRP), one of the inflammatory biomarkers, has been found to be strongly associated with CVD risk and prognosis and has a positive correlation with neutrophils, monocytes and NLR.[29-31] Previous studies have shown that NLR can be a potential alternative marker of systemic inflammation because of its ability to predict hs-CRP and CRP levels; CRP can influence the significant association between NLR and CVD.[32,33] In our study, the pattern of clinical outcomes did not change when adjusting for event risk using a Cox proportional hazards model including hs-CRP, which suggests that NLR may be independently associated with MACE in patients with CTO-PCI.

Our study had several limitations. First, although most potential confounders in the three groups of patients did not show statistically significant differences, we were unable to correct for unmeasured potential variables. Second, routine angiographic follow-up was not scheduled, so information about in-stent restenosis in the clinical setting was completely missing, and we were unable to assess the true impact of baseline NLR on in-stent restenosis. Finally, our results may not be applicable to other studies because of the limited sample size.

Conclusion

In conclusion, elevated baseline NLR levels are an independent predictor for MACEs in CTO-PCI patients in follow-up. This study shows that NLR values appear to be additive compared to traditional cardiovascular risk factors and commonly used biomarkers in predicting MACEs in patients with CTO.

DISCLOSURE

Funds

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Ethics Approval and Consent

All authors take responsibility for every aspect of the work to ensure that questions associated with the accuracy or completeness of any section of the work are properly surveyed and addressed. The trial was conducted following the Declaration of Helsinki (revised 2013). The study was approved by the Research Committee and Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University (XJTU1AF2012LSK-313), and all participants voluntarily joined this study with informed consents.

Conflicts of Interest

None.

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