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ORIGINAL RESEARCH

Prognostic Value of the Neutrophil-to-Lymphocyte Ratio in Patients with Chronic Internal Carotid Artery Occlusion Complicated by Cerebral Infarction

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Purpose: This study aims to investigate the prognostic value of the peripheral neutrophil-to-lymphocyte ratio (NLR) in patients with chronic internal carotid artery occlusion (CICAO) complicated by cerebral infarction.

Patients and Methods: The clinical data of 99 CICAO patients complicated by cerebral infarction were retrospectively analyzed. The modified Rankin Scale (mRS) was used to assess their 3-month prognosis, and a multivariate logistic regression model was established to explore risk factors for poor prognosis.

Results: Multivariate logistic regression analysis demonstrated that NLR (OR=2.114; 95% CI: 1.129–3.959) and baseline National Institute of Health Stroke Scale (NIHSS; OR=1.288, 95% CI: 1.053–1.574) score were risk factors of poor prognosis. The area under the receiver operator characteristic (ROC) curve of NLR in predicting the 3-month outcome after onset was 0.717 (95% CI: 0.606–0.828, $P<0.000$). The optimal cut-off value was 3.22, with a sensitivity of 0.743 and a specificity of 0.791.

Conclusion: NLR is an independent risk factor for the poor prognosis of CICAO patients complicated by cerebral infarction and can serve as an indicator for clinical prognosis.

Keywords: chronic internal carotid artery occlusion, cerebral infarction, neutrophil-to-lymphocyte ratio, prognosis, predictive factors

Introduction

Cerebral infarction has a high incidence rate, disability, recurrence, and mortality.[1] Chronic internal carotid artery occlusion (CICAO), with an onset beyond four weeks, is an uncommon but important cause of cerebral infarction. Statistically, the annual cerebral infarction recurrence rate is 5%–6% among CICAO patients with transient ischemic attacks or mild cerebral infarction and up to 20% in patients with insufficient compensatory CICAO.[2] Around 70% of CICAO cases are due to atherosclerosis, and the embolism caused by the thrombi from the occlusion stump or the atherosclerotic plaques is one of the common mechanisms for subsequent ischemic stroke.[3] Elevated inflammatory markers correlate with poor prognosis in this population with large-vessel atherothrombotic cerebral infarction.[4]

The neutrophil-to-lymphocyte ratio (NLR) as a systemic inflammatory marker is clinically practicable as it is easy to perform and low cost. Furthermore, NLR predicts the disease condition and outcome in patients with vascular diseases[5] and is associated with the infarct size, illness severity, and prognosis of patients with acute cerebral infarction.[6] Few studies have evaluated the prognostic value of NLR for CICAO patients with cerebral infarction; therefore, this study investigated the predictive value of NLR for the 3-month outcome of CICAO patients with comorbid cerebral infarction.

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Subjects and Methods

Subjects

Patients with acute cerebral infarction who were admitted to Suzhou Ninth People's Hospital from September 2015 to September 2021 were included in this study if they 1) were aged > 18 years old, 2) had an onset-to-treatment time ≤ 1 week, 3) had unilateral ICAO confirmed by head and neck computed tomographic angiography (CTA), magnetic resonance angiography (MRA), or digital subtraction angiography (DSA), 4) manifested symptoms of neurological deficit and imaging findings were associated with CICAO, 5) had complete clinical data, including 3-month follow-up data. Patients were excluded if they 1) were not classified as large-vessel atherothrombotic cerebral infarction according to TOAST (The Trial of Org 10,172 in Acute Stroke Treatment) criteria, 2) had concurrent intracranial tumors or epilepsy, 3) had severe cardiac, lung, liver, and kidney diseases or malignancies, 4) or had infectious or immune diseases. In total, 99 patients were included in the present study, including 78 males and 21 females with an average age of 62.8 ± 11.7 years old. All study participants or their legally authorized representatives provided written informed consent during hospitalization.

Clinical Data

The patient's demographic and clinical data were acquired, including age, gender, individual life history, risk factors for cerebrovascular disease, white blood cell (WBC) count, neutrophil count, blood lipid, C-reactive protein (CRP) level, the US National Institute of Health Stroke Scale (NIHSS) score, and head and neck imaging findings (occlusion site and contralateral artery stenosis).

Follow-Up

The patients were followed up via a clinic visit or telephone 3 months after onset and were assigned a modified Rankin Scale (mRS) score: 0, no symptoms; 1, mild symptoms without significant dysfunction; 2, mild disability; 3, moderate disability, help needed in some cases; 4, moderate-to-severe disability, help needed for walking and to meet their own needs; 5, severe disability, bedridden, incontinent, ongoing care and attention needed; 6, death. Patients were then assigned to the good prognosis group (mRS score ≤ 2) and the poor prognosis group (mRS score > 2) based on the mRS score.

Statistical Analysis

Data analysis was performed with SPSS 22.0. Measurement data were presented as mean ± standard deviation (SD) or as the median. Data that followed a normal distribution were analyzed with the *t*-test, and data that did not follow a normal distribution were analyzed using a non-parametric test. Enumeration data were expressed as the number of cases (n) with percentage (%) and compared using the chi-squared test. Bivariate correlations were conducted using the Spearman test. Multivariate Logistic regression was performed to identify risk factors. Accuracy of the regression model was verified with the Hosmer-Lemeshow goodness-of-fit test. The prognostic value of NLR was evaluated using the receiver operator characteristic (ROC) curve. $P<0.05$ referred to a statistically significant difference.

Results

Comparison of the General Data Between Groups

Patients in the poor prognosis group were older than those in the good prognosis group. The proportion of patients with comorbid diabetes, NLR levels, and NIHSS scores in the poor prognosis group was also significantly higher than those in the good prognosis group ($P<0.05$) (Table 1).

Logistic Regression Analysis of Prognostic Risk Factors

Multivariate logistic regression was conducted using patients' prognosis as a dependent variable (1 for poor prognosis and 0 for good prognosis) and age, comorbid diabetes, NLR, and baseline NIHSS score as independent variables, revealing that NLR and baseline NIHSS score were independent risk factors for poor prognosis (Table 2). The multivariate regression had a good fit, as indicated by the Hosmer-Lemeshow goodness-of-fit ($P=0.202>0.05$).

Table 1 Comparisons of General Data Between Two Groups

	Good Prognosis Group (n=64)	Poor Prognosis Group (n=35)	*P* value
Male [n(%)]	50 (78.1)	28 (80.0)	0.827
Age (years)	61.5±9.5	65.8±8.7	0.029
Hypertension [n(%)]	45 (70.3)	26 (74.3)	0.675
Diabetes [n(%)]	9 (14.1)	12 (34.3)	0.019
Smoking [n(%)]	27 (42.2)	17 (48.6)	0.541
Drinking [n(%)]	10 (15.6)	6 (21.4)	0.499
Extracranial arterial occlusion [n(%)]	18 (28.1)	15 (42.9)	0.137
Contralateral stenosis [n(%)]	22 (34.4)	12 (34.3)	0.993
HDL (mmol/L)	1.03±0.20	0.99±0.27	0.404
LDL (mmol/L)	2.24±0.84	2.34±1.11	0.945
TC (mmol/L)	4.07±0.94	4.03±1.31	0.875
TG (mmol/L)	1.55±0.96	1.53±1.01	0.955
CRP (mg/dl)	6 [5,7]	6 [5,7]	0.913
NLR	3.10±0.73	3.59±0.67	0.002
Baseline NIHSS score	5 [3,7]	6 [5,8]	0.015

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglycerides; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio.

Table 2 Multivariate Logistic Regression Analysis of the Poor Outcome of Patients

	Regression Coefficient	SD	*WALD*	*P*	*OR*	95% *CI*	
						Lower Limit	Upper Limit
Age	0.022	0.023	0.867	0.352	1.022	0.976	1.069
Diabetes	0.914	0.571	2.561	0.110	2.494	0.814	7.637
NLR	0.749	0.320	5.473	0.019	2.114	1.129	3.959
Baseline NIHSS score	0.253	0.102	6.087	0.014	1.288	1.053	1.574

Abbreviation: NLR, neutrophil-to-lymphocyte ratio.

Prognostic Value of NLR for 3-Month Prognosis

A ROC curve was plotted to assess the prognostic value of NLR for a 3-month prognosis after onset, and the area under the curve (AUC) was 0.717 (95% CI: 0.606–0.828, $P<0.000$) (Figure 1). The best cut-off value was 3.22 with a sensitivity of 0.743 and specificity of 0.791.

Comparisons of General Data in Patients with Different NLR Levels

Patients were classified into two groups using the best cut-off value of 3.22. Patients with NLR>3.22 had a higher incidence of diabetes and contralateral internal carotid artery stenosis, as well as a higher NIHSS score than patients with NLR≤3.22 ($P<0.05$; Table 3).

Correlation Analysis of NLR and NIHSS

There was a positive correlation between NLR level and baseline NIHSS score in patients with CICAO and cerebral infarction ($r=0.305$, $P=0.002$).

Discussion

CICAO is an important cause of cerebrovascular ischemic events, and there are significant differences in the clinical manifestations and prognosis across CICAO patients complicated by cerebral infarction. Furthermore, collateral circulation is closely interrelated with the prognosis of patients with cerebral infarction. Asymptomatic CICAO patients have

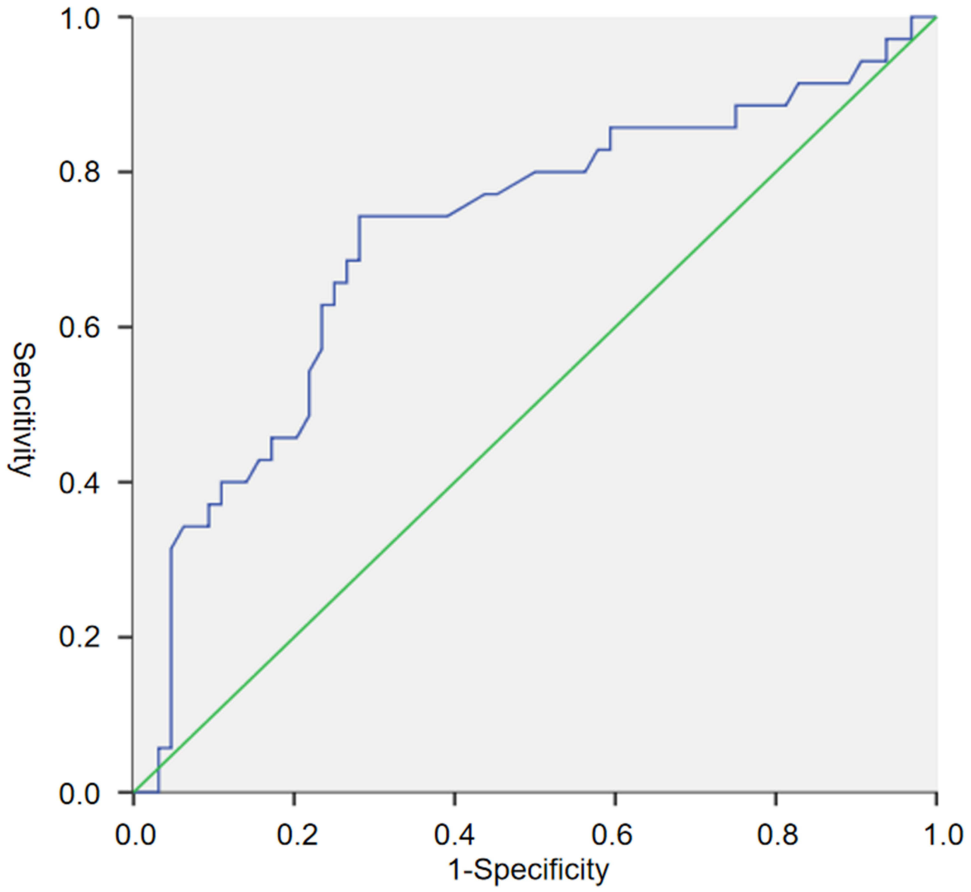

Figure 1 ROC curve for NLR. NLR levels with respect to predictive capability for 3-month prognosis after onset, the area under the curve (AUC) reached a value of 0.717 (95% CI: 0.606-0.828, *P*<0.000).
Abbreviations: NLR, neutrophil-to-lymphocyte ratio.

a high opening rate of collateral circulation, and those with collateral circulation opening tend to have mild clinical symptoms and a good prognosis when they are complicated by cerebral infarction.[7] The main etiology of occlusion is atherosclerosis, and inflammation contributes to atherogenesis,[8] as well as the formation of collateral circulation through

Table 3 Comparisons of General Data in Patients with Different Levels of NLR

Item	NLR≤3.22 (n=55)	NLR>3.22 (n=44)	*P* value
Male [n(%)]	41 (74.5)	37 (84.1)	0.248
Age (years)	62.7±12.7	62.9±10.4	0.947
Hypertension [n(%)]	41 (74.5)	30 (68.2)	0.485
Diabetes [n(%)]	7 (12.7)	14 (31.8)	0.021
Smoking [n(%)]	25 (45.5)	19 (43.2)	0.821
Drinking [n(%)]	18 (14.5)	8 (18.2)	0.629
Extracranial arterial occlusion [n(%)]	16 (29.1)	17 (38.6)	0.317
Contralateral stenosis [n(%)]	14 (25.5)	20 (45.5)	0.037
HDL (mmol/L)	1.02±0.22	1.00±0.24	0.533
LDL (mmol/L)	2.25±0.94	2.45 ± 0.93	0.281
TC (mmol/L)	3.99±0.52	4.13±1.21	0.504
TG (mmol/L)	1.54±1.07	1.54±0.85	0.991
Baseline NIHSS score	4 [3,6]	6 [4.25,7.25]	0.003
Poor prognosis [n(%)]	14 (25.5)	21 (47.7)	0.021

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglycerides.

multiple mechanisms.[9] An elevated lymphocyte count correlates with excellent collateral circulation, while a high WBC count and NLR level are associated with poor collateral circulation.[10] The present study indicated that a high NLR level was closely associated with a poor 3-month outcome of CICAO patients with cerebral infarction, illustrating that NLR can serve as a prognostic factor.

Recently, neuroinflammation has received increasing attention in ischemic stroke. An extensive body of research has verified that inflammatory mechanisms play a vital role in the pathogenesis and progression of ischemic stroke.[11–13] NLR is widely applied in evaluating the severity and prognosis of multiple diseases as a simple, convenient inflammatory marker. A review of NLR as a bio-markers of morbidity and mortality rates for cardiovascular surgery suggested that it could help identify patients at high risk of periprocedural adverse events.[14] A meta-analysis showed that an elevated NLR level was associated with mortality, poor outcomes, and hemorrhagic transformation of cerebral infarction patients; thus, NLR could be utilized to instruct clinical decisions as a potential prognostic biomarker.[6] In the study of Gong et al[15] of 1060 ischemic stroke patients receiving intravenous thrombolysis, NLR elevated was an independent risk factor for early-stage neurological deterioration, and patients with low NLR levels benefited more from thrombolysis. Compared to high-sensitivity C-reactive protein, NLR is strongly associated with the occurrence of stroke-associated pneumonia.[16] Hu et al[17] reported that NLR is associated with 90-day poor outcomes in stroke patients, however, the AUC of high NLR was insufficiently high to predict the poor outcome. In contrast, the AUC of NLR (0.717) in the present study had a good predictive value. Overall, inflammation occurs throughout the occurrence, development, stroke-related complications, and prognosis of cerebral infarction. Indeed, whether NLR is a good predictor for stroke in different etiologies requires further exploration.

The underlying mechanism between NLR increase and poor prognosis is involved in the overactivation of inflammatory responses and immunosuppression. Neutrophils are short-lived, innate immune cells and play a limited immunological role. After cerebral infarction, neutrophils migrate toward the ischemic area through the disrupted blood-brain barrier under the mediation of cytokines and chemokines.[18] Meanwhile, neutrophils release oxygen radicals and matrix metalloproteinases to further disrupt the blood-brain barrier and recruit more immune cells, worsening tissue edema and inducing cell death.[19] A study revealed that inhibiting neutrophil aggregation in the ischemic penumbra could alleviate neurological deficits in mouse models.[20] Lymphocytes also play a vital role in the immune response after cerebral infarction. They are detected in the cerebral tissues within 24 h of ischemic stroke and continue to increase to exert neuroprotective effects.[21] Patients with large-vessel occlusive stroke have significantly increased levels of WBC and lymphocytes, and the elevation is closely associated with patient prognosis. This study indicated that vessel occlusion could induce an inflammatory response in cerebral tissues.[22] Another study revealed that after cerebral infarction, increased lymphocytes mediate the autoimmune response and release oxygen radicals and inflammatory factors to aggravate brain injury.[23] This discrepancy between the two studies might be due to different lymphocyte subgroups. CD4+ regulatory T lymphocytes are a subgroup of CD4+ T cells that are immunosuppressive and decrease the production of inflammatory factors, playing a protective role against multiple ischemic diseases including ischemic stroke.[24] It was demonstrated that a decrease in regulatory T lymphocytes was interrelated with a poor prognosis in cerebral infarction patients.[25] Regulatory T lymphocytes may exert neuroprotective effects by maintaining the integrity of the blood-brain barrier, inhibiting the activation of microglial cells, and regulating the microglial phenotype transformation.[24]

The limitations of this study reside in three aspects. First, the study has a selection bias since it is a single-center retrospective study with a small sample size. Second, the NLR level was not dynamically monitored. Last, occluded internal carotid artery was not further assessed via high-resolution MR. In the future, a multi-center study with larger sample size is required.

Conclusion

Taken together, neutrophils and lymphocytes are crucial in cerebral infarction given their regulatory role in neuroinflammation and neuroprotective effects. NLR is an inflammatory index that is easy to acquire and low cost, and a high NLR level is correlated with a poor prognosis; thus, an increased NLR level can be used as an indicator of poor 3-month prognosis in CICAO patients with cerebral infarction.

Ethical Approval

The study was approved by the Ethical Committee of Suzhou Ninth People's Hospital (No. KY2022-008-01) and conducted in accordance with the Declaration of Helsinki.

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Disclosure

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

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