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Prognostic Value of the Neutrophil-to-Lymphocyte Ratio in Older Patients with Acute Ischemic Stroke

Shuang Qiu, Jie Liao, Xin Luo and Xiu Chen

Department of Neurology, Affiliated Hospital of Southwest Medical University, Luzhou, China

Background: The prognostic value of the neutrophil-to-lymphocyte ratio (NLR), an inflammatory indicator, for 90-day outcomes has not been determined for patients with acute ischemic stroke aged ≥ 80 years. Therefore, this study examined the predictive significance of the NLR for estimating the 90-day outcomes of older patients with acute ischemic stroke.

Methods: Data from patients aged ≥ 80 years were recorded within 7 days of ischemic stroke onset during the period from January 2019 to June 2021. A Kaplan-Meier curve was drawn based on the incidence of adverse outcomes to compare the survival probability of each group at different time periods. Cox multivariate regression was used to explore adverse events affecting patient prognosis.

Results: A total of 560 patients were initially recruited; of these, 476 were eligible for inclusion. The log-rank test showed that the survival rates of the groups differed. The 90-day survival rate was significantly lower in the group with the highest NLR than in the group with the lowest NLR. Multivariate Cox regression analysis showed that after adjusting for risk factors, a high NLR and a high National Institutes of Health Stroke Scale score were independent risk factors for 90-day mortality. According to the receiver operating characteristic analysis, the area under the curve for predicting mortality at 90 days was 0.74.

Conclusion: This study confirmed that a high NLR is an independent risk factor for acute ischemic stroke and has predictive value for 90-day prognosis in patients aged ≥ 80 years.

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Key words: elderly patients, acute ischemic stroke, neutrophil-to-lymphocyte ratio, prognosis

Introduction

Acute ischemic stroke (AIS) has attracted considerable attention owing to its high incidence and high associated disability and mortality. With population aging, the proportion of older patients with stroke is increasing, and stroke prognosis is attracting increasing attention[1]. Inflammation is involved in the occurrence and development of stroke, and its mechanisms include pathophysiological processes such as coagulation abnormalities, vasculitis or vascular reactivity changes, oxidative stress, activation of pro-inflammatory neutrophils to damage the blood-brain barrier, and hemorrhagic transformation[2–5].

Zhao and Quan et al. showed that the neutrophil-to-lymphocyte ratio (NLR), an inflammatory index, can be used to predict the 90-day prognosis of patients with acute ischemic stroke[6,7]. However, the included patients were 63 (54-70) years old and 47.72 ± 11.94 years old, respectively. In existing studies on the prognostic value of the NLR for AIS outcomes, adult populations aged ≥ 80 years were not systematically included in the analyses. In older patients with bone marrow hematopoietic stem-cell and thymus aging, immune function declines, and the inflammatory response variably decreases[8–10]. Therefore, the value of the NLR as a predictor of prognosis in older patients with acute ischemic stroke has yet to be verified.

This study focused on the prognosis of patients with acute ischemic stroke aged ≥ 80 years. We explored the value of the NLR for predicting the mortality risk in

Correspondence to Xiu Chen, Department of Neurology, Affiliated Hospital of Southwest Medical University, Luzhou 646000, China
E-mail: 1214641848@qq.com
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older patients with stroke and aimed to provide more prognostic indicators for 90-day expected progress.

Materials and Methods

Study Population

Data of patients ≥ 80 years old with acute ischemic stroke from January 2019 to June 2021 were retrospectively collected from the Department of Neurology, Affiliated Hospital of Southwest Medical University. We included patients with (1) acute ischemic stroke within 7 days of onset, (2) age ≥ 80 years, and (3) routine blood examination performed within 24 hours after admission. We excluded patients with (1) recent severe or persistent infection, (2) use of immunosuppressive drugs, (3) malignant tumors, and (4) incomplete basic information and inability to follow-up. The NLR value derived from the routine blood examination at admission was calculated, and the patients were divided into four groups according to the interquartile interval of the NLR: Q1, NLR < 2.97; Q2, 2.97 ≤ NLR < 4.49; Q3, 4.49 ≤ NLR < 7.94; Q4, NLR ≥ 7.94. This study was conducted in accordance with the tenets of the Declaration of Helsinki. The study protocol and data collection were approved by the Ethics Committee of the Affiliated Hospital of Southwest Medical University (IRB Approval No. KY2022043). Informed consent was obtained from all patients or their legal representatives.

Data Collection

We collected basic information on age, sex, medical history, hypertension, diabetes, hyperlipidemia, atrial fibrillation, previous stroke, coronary heart disease, smoking, alcohol use, National Institutes of Health Stroke Scale (NIHSS) scores, and hospital survival or mortality. NIHSS scores 0-5 pertained to minor stroke, 5-15 to mild stroke, and ≥ 15 to severe stroke. Venous blood results assessed within 24 hours after admission including white blood cell, neutrophil, lymphocyte, hemoglobin, and albumin counts; glomerular filtration rate; and total cholesterol, triglyceride, and low-density lipoprotein cholesterol levels were recorded. The first test results were included if the blood test was performed more than once within 24 hours. The NLR, i.e., neutrophil count/lymphocyte count, was calculated with two decimal-place accuracy; anemia was classified as mild (110-119 g/L for women and 110-129 g/L for men), moderate (80-109 g/L), or severe (< 80 g/L). The infarct site was identified via head magnetic resonance imaging, and the culpable vessels were identified with magnetic resonance angiography/computed tomography angiography/digital subtraction angiography to determine the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification.

Follow-Up

The patients were followed-up via telephone 90 days after the occurrence of acute stroke, and the modified Rankin Scale scores and survival status were recorded. If a patient had died, the time of death was recorded, and the patient's death was considered a poor outcome.

Statistical Analysis

SPSS 26.0 (IBM Corp., Armonk, NY) and R 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical data processing, and Graph Pad 9 (GraphPad Software, La Jolla, CA) was used for graph building. The t-test, rank-sum test, and chi-square test were used for between-group comparisons. Kaplan-Meier curves were used to show changes in the survival rate within 90 days between the groups, and the log-rank test was used to evaluate the differences in survival rate and determine whether they reached statistical significance. A Cox regression model was used to explore the factors associated with the risk of death within 90 days, and a receiver operating characteristic (ROC) curve was drawn to evaluate risk factors for 90-day mortality. Statistical significance was set at $p < 0.05$.

Results

Baseline Characteristics

Of the 560 patients screened, 18 with prehospital infection, 10 with immunosuppressive agent use, 18 with malignant tumors, and 38 who were lost to follow-up were excluded. We included in the analyses the data of 476 patients divided into four groups, with 119 patients in each group according to the interquartile interval of the NLR. The median age of the patients was 84 (81-87) years, and 52% (248/476) were men. Hypertension, diabetes, atrial fibrillation, coronary heart disease, and previous history of stroke were present in 83.8% (399/476), 23.1% (110/476), 29.2% (139/476), 54.2% (258/476), and 31.5% (150/476) of patients, respectively. The proportions of mild, moderate, and severe stroke were 45.2% (215/476), 33.2% (158/476), and 21.6% (103/476), respectively. Taking the lowest NLR group as a reference, patients in the highest NLR group had a higher proportion of diabetes mellitus and atrial fibrillation; higher white blood cell, neutrophil, and lymphocyte values; and greater stroke severity. According to the TOAST classification, the atherosclerotic and cardiogenic types were more frequent ($P < 0.05$) (**Table 1**).

Table 1 Baseline level characteristics of the different NLR groups

Characteristics	Overall (n=476)	Q1 (NLR<2.967) (n=119)	Q2 (2.967≤NLR<4.491) (n=119)	Q3 (4.491≤NLR<7.935) (n=119)	Q4 (NLR≥7.935) (n=119)	*P*
Age, median (IQR), years	84 (81–87)	84 (81–87)	83 (81–87)	84 (81–87)	84 (81.87)	0.989
Female, n (%)	228	57 (25.00%)	48 (21.05%)	58 (25.44%)	65 (28.51%)	0.178
Hypertension	399	95 (23.81%)	95 (23.81%)	101 (25.31%)	108 (27.07%)	0.068
Diabetes	110	21 (19.09%)	38 (34.55%)	20 (18.18%)	31 (28.18%)	0.015
Atrial fibrillation	139	26 (18.71%)	28 (20.14%)	42 (30.22%)	43 (30.94%)	0.020
Coronary heart disease	258	58 (22.48%)	61 (23.64%)	63 (24.42%)	76 (29.46%)	0.094
Previous stroke	150	39 (26.00%)	38 (25.33%)	35 (23.33%)	38 (25.33%)	0.950
WBC	7.78 (5.96–9.87)	6.16 (4.85–7.42)	7.1 (5.73–8.34)	8.3 (6.34–9.97)	10.89 (8.84–14.11)	<0.001
Hemoglobin	129 (118–140)	129 (118–141)	132 (120–141)	128 (119–138)	128 (115–139)	0.358
GFR	74.1 (55.7–83.2)	74.7 (58.5–82.1)	77.1 (58.2–83.7)	74.5 (54.8–83.9)	70.6 (53.75–81.3)	0.514
L-LDL	2.57 (2.00–3.25)	2.42 (2.01–3.17)	2.65 (2.06–3.25)	2.6 (1.95–3.37)	2.57 (1.99–3.25)	0.719
Anterior circulation	398	97 (24.37%)	102 (25.63%)	102 (25.63%)	97 (24.37%)	0.675
Smoking, n (%)	90	24 (26.67%)	28 (31.11%)	21 (23.33%)	17 (18.89%)	0.313
NIHSS score, median (IQR)	6 (3, 13)	4 (2, 7)	5 (3, 10)	7 (3, 13)	13 (7, 20)	<0.001

NLR: neutrophil-to-lymphocyte ratio, IQR: interquartile range, WBC: white blood cell, GFR: glomerular filtration rate, LDL: low-density lipoprotein

Association of NLR with Adverse Clinical Outcomes

Univariate Cox regression analysis indicated that female sex (hazard ratio (HR) 1.845, 95% confidence interval (CI) 1.274-2.671), atrial fibrillation (HR 3.317, 95% CI 2.309-4.766), coronary heart disease (HR 1.816, 95% CI 1.240-2.659), NIHSS score (HR 1.130, 95% CI 1.111-1.148), hemoglobin level (HR 0.986, 95% CI 0.977-0.994), glomerular filtration rate (HR 0.991, 95% CI 0.983-1.000), and NLR (HR 1.044, 95% CI 1.032-1.056) were influencing factors for poor prognosis. The above factors and those clinically associated with the risk of death in patients with AIS were further included in the multivariate Cox regression analysis, and the results showed that the NLR was an independent influencing factor. The ROC analysis (**Table 2**) showed that the area under the curve for the NLR's ability to predict 90-day mortality was 0.740. When the optimal truncation value of the NLR was 6.5, the sensitivity and specificity were 61.9% and 78.5%, respectively (**Fig. 1**). There were 119 deaths (25.0%) during the 90 days of follow-up. The survival rate in group order was Q1 > Q2 > Q3 > Q4, $\chi^2 = 79.69$, $P < 0.001$ (**Table 3**; **Fig. 2**).

Discussion

This study examined the predictive significance of the NLR for estimating the 90-day outcomes of older patients with acute ischemic stroke. The value of NLR can be an independent factor for 90-day prognosis in patients ≥ 80 years old with cerebral apoplexy. As the NLR value increases, the incidence of adverse outcomes also increases. We obtained an AUC of 0.74, indicating that the NLR plays a certain role in predicting the adverse prognosis of older patients with ischemic stroke. Concurrently, we also found that female sex, NIHSS score, atrial fibrillation, coronary heart disease, anemia, and low glomerular filtration rate also affect survival in this patient population.

In a study involving 13,018 patients with a median age of 63 (54-70) years, Quan et al.[6] showed that the NLR was positively correlated with age, atrial fibrillation, and stroke severity, and the proportion of large atherosclerotic and cardiogenic lesions was higher in patients with a high NLR than in those with a low NLR value. Moreover, the NLR was associated with poor prognosis, which is consistent with the results of our study. Therefore, we speculate that the NLR could be universally applied to evaluate the possibility of poor prognosis in middle-aged and older patients with acute stroke. In a previous study, the median NIHSS score was 3 (2-6) and the 90-day mortality rate was 1.50% (195/13,018)[6]. The median NIHSS score was 3 (2-6) and the 90-day mortality rate was 1.96% (13/663) in another study who included patients aged 66.81±12.58 years. In this study, the median NIHSS score was 6 (3-13), and 90-day mortality was 25.0% (119/476), which may indicate that the severity of stroke in older patients is grave, and the risk of death is high.

Table 2 Cox regression analysis model of adverse prognosis in patients with AIS

Characteristics	HR	95%CI	*P*	HR	95% CI	*P*
Age	1.006	0.962–1.051	0.807			
Sex	1.845	1.274–2.671	0.001	1.432	0.964–2.126	0.075
Hypertension	1.023	0.626–1.671	0.928			
Diabetes	1.445	0.970–2.153	0.070			
Atrial fibrillation	3.317	2.309–4.766	<0.001	1.219	0.719–2.068	0.463
Coronary heart disease	1.816	1.240–2.659	0.002	0.690	0.431–1.104	0.122
Previous stroke	0.983	0.666–1.451	0.932			
Smoking	0.583	0.339–1.002	0.051			
NIHSS score	1.130	1.111–1.148	<0.001	1.111	1.087–1.135	<0.001
Hemoglobin	0.986	0.977–0.994	0.001	0.996	0.986–1.006	0.437
Albumin	0.961	0.918–1.005	0.084			
GFR	0.991	0.983–1.000	0.044			
TC	0.999	0.844–1.184	0.995			
TG	1.022	0.866–1.206	0.797			
L-LDL	0.971	0.814–1.159	0.745			
NLR	1.044	1.032–1.056	<0.001	1.023	1.002–1.044	0.034

HR: hazard ratio, CI: confidence interval, NIHSS: National Institutes of Health Stroke Scale, GFR: glomerular filtration rate, TC: total cholesterol, TG: triglyceride, LDL: low-density lipoprotein, NLR: neutrophil-to-lymphocyte ratio

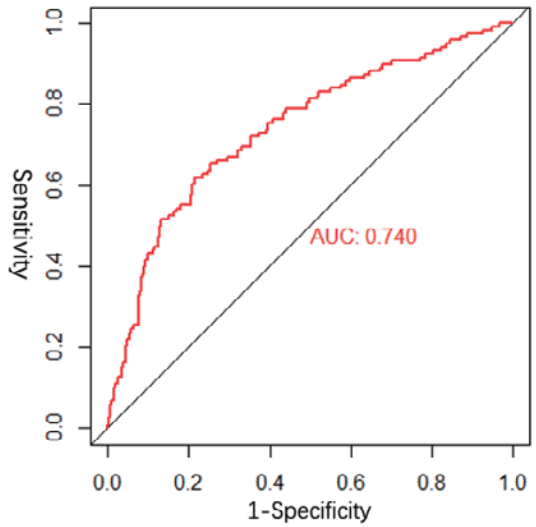

Fig. 1 Receiver operating characteristic curve of the neutrophil-to-lymphocyte ratio evaluating its prognostic value for 90-day mortality

Table 3 Log-rank test survival gap across the groups

Characteristics	X^2	*P*
NLR	79.691	<0.001

As shown in the Kaplan-Meier curve, the cumulative survival rate of patients decreased significantly within 14 days from onset, and the decreasing trend was significantly higher in the high NLR group (69.7%) than in the low NLR group (95.0%). Further review of the data

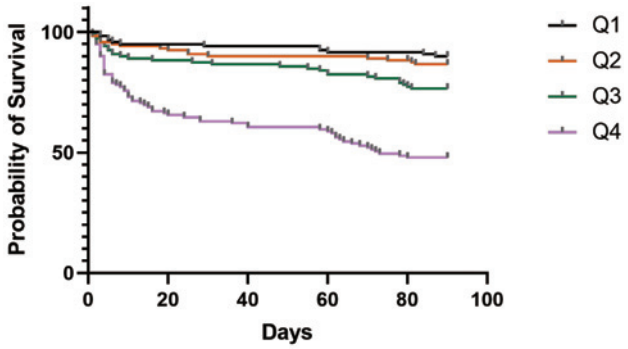

Fig. 2 Kaplan-Meier survival curves showing changes in the survival rate among the neutrophil-to-lymphocyte ratio groups

showed that in the first week of onset, most patients died of respiratory and cardiac arrest due to extensive neurological impairment caused by severe cerebral infarction and cerebral hernia formation. One week later, most patients died of respiratory and cardiac arrest due to serious infections, deep vein thrombosis, nutrition, and other causes. Infection is a common complication of stroke with pulmonary infection being the most common with an incidence of approximately 14.3%[11]. The baseline data in this study showed that the incidence of SAP was 26.9% (128/476), which was higher than that in the general population given the deterioration of immune function and increase in pulmonary diseases in older patients.

After ischemic stroke, the white blood cells in the pe-

ripheral circulation participate in the inflammatory response of the brain tissue through recruitment of the microglia[12]. Neutrophils are the first blood-derived immune cells to reach the ischemic brain tissue[13]. They infiltrate the central nervous system by binding to adhesion molecules on activated endothelial cells[12], resulting in sterile inflammation and a significant short-term increase in the neutrophil count. Due to immunosuppression after stroke, there is a relative decrease in lymphocyte production and neuroprotective T cell subtypes[14]. Furthermore, the effect of lymphocytes requires cytokine transduction; therefore, there are fewer early lymphocytes[11]. This is consistent with our findings. However, the median NLR in this study was 4.49, while that in previous studies was 2.54, indicating that the NLR value after ischemic stroke of those aged 80 and above is higher than that of the population aged less than 80 years. Therefore, it is speculated that the symptoms of ischemic stroke in the elderly are more serious and that the inflammatory reaction is more severe.

The univariate Cox regression analysis in this study showed that atrial fibrillation (HR 3.317, 95% CI 2.309-4.766), coronary heart disease (HR 1.816, 95% CI 1.240-2.659), anemia (HR 0.986, 95% CI 0.977-0.994), and low glomerular filtration rate (HR 0.991, 95% CI 0.983-1.000) were also associated with poor outcomes in older patients with acute stroke. Patients with atrial fibrillation are more likely to experience cardiogenic embolism, which leads to rapid blockage of major blood vessels, poor collateral compensation, large infarct area, more serious neurological defects, and often severe paralysis, which increases the probability of bedsores and deep venous thrombosis, resulting in poor prognosis[15–17]. Anemia is a common comorbidity in older patients with ischemic stroke and is mostly seen in older patients with cardiovascular or gastric diseases[18,19]; the prevalence of anemia in older adults is higher than that in the general population. Previous studies have shown an increased length of hospital stay and mortality in older patients with acute ischemic stroke and anemia[20].

In patients with hypertension, high blood pressure leads to damage of vascular endothelial cells. Low-density lipoprotein depositions can activate endothelial and tunica intima cells to express adhesion molecules and inflammatory genes, resulting in local inflammation and an increased NLR[20–22]. The same is true for patients with coronary heart disease. Increased NLR values lead to weakened stability of atherosclerotic plaques and activation of cellular targets, such as monocytes and endothelial cells, resulting in imbalance between procoagulant and anticoagulant molecules and increased incidence of cardiovascular and cerebrovascular events[23,24].

Our study was novel in that it was the first to examine a population of patients with acute ischemic stroke older than 80 years, which to some extent lessens the deficiency of available data for this population; second, our study recorded the survival time of patients in detail and analyzed the prognosis of patients through survival outcome and survival time. However, this study had the following shortcomings: first, it was a single-center, retrospective study; second, the span of image data was long, and the collection of infarct area data was limited, but the NIHSS score can indirectly indicate a certain degree of infarct area. Third, the dynamic evolution of the NLR in the occurrence of ischemic stroke was not included. Fourth, the cause of death was not recorded during the follow-up. Finally, the results should be further verified through prospective experiments.

Conclusion

This study showed that a high NLR can be an independent factor for the 90-day prognosis of patients ≥ 80 years old with acute ischemic stroke and that the NLR has predictive value for poor 90-day outcomes in this patient population. The peripheral-blood NLR is an indicator of inflammation and is closely related to the occurrence, development, and prognosis of AIS. It also has predictive value for patients aged ≥ 80 years, and clinicians should pay attention to this non-economic indicator.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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