

An increase in neutrophil-to-lymphocyte ratio predicts poor functional outcomes in older patients with acute ischemic stroke: a retrospective study

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The neutrophil-to-lymphocyte ratio has emerged as a predictor of functional outcome in stroke patients. However, less is known about the value of neutrophil to lymphocyte ratio in older patients. This clinical study evaluated whether the neutrophil-to-lymphocyte ratio is associated with stroke severity and early clinical outcomes in older patients with acute ischemic stroke. This observational study included acute ischemic stroke patients aged 80 years or older. The patients were divided into three groups, and information was collected, including demographic, clinical and laboratory data. The neutrophil associations to lymphocyte ratio with stroke severity and early clinical outcomes were assessed with logistic regression. Overall, 356 older patients were enrolled in this study, with a median age of 85.0 (82.0–88.0). Split by tertiles of neutrophil-to-lymphocyte ratio, 118 patients were in the bottom tertile (<2.17), 118 patients were in the middle tertile (2.17–3.36), and 120 patients were in the top tertile (>3.36). After multivariable analysis, patients in the highest tertile were likely to have moderate to severe stroke on admission (OR 4.87, 95% CI, 1.93–12.30, $P = 0.001$), higher risks of primary unfavorable outcome (OR 2.70, 95% CI, 1.09–6.69, $P = 0.032$) and secondary unfavorable outcome (OR 2.00, 95% CI, 1.00–4.00, $P = 0.050$) compared to the lowest tertile. Our finding demonstrated that the neutrophil-to-lymphocyte ratio is an independent predictor of stroke severity and early clinical outcomes in older patients with acute ischemic stroke.

Keywords

Ischemic stroke; Inflammation; Neutrophils-to-lymphocytes ratio; Neurology; Hematology cerebral ischemia; Cerebral hypoxia

1. Introduction

Ischemic stroke is the most common subtype of stroke. Its main characteristics are cerebral ischemia and hypoxia, causing brain damage [1, 2]. Inflammation is a critical process in ischemic stroke [3], and many inflammatory biomarkers have been identified in stroke patients [4]. Following ischemic stroke, immune mediators such as chemokines and cytokines are activated and promote peripheral blood leukocytes [5]. Neutrophils are first responders recruited in hypoxic-ischemic tissues and release inflammatory mediators into neural tissues [6]. As a critical immune cell, the lymphocytes also participate in acute ischemic stroke [7, 8].

Recently, associations between blood-based biomarkers and ischemic stroke were reviewed [9]. As an important inflammatory marker, the neutrophil-to-lymphocyte ratio (NLR) has been identified and described in several coronary artery diseases [10–12], bacterial sepsis [13–15], pulmonary embolism [16] acute pancreatitis [17–20], appendicitis [21], acute physiological stress [22], and systematic inflammation and restless legs syndrome [23].

NLR was associated with in-hospital mortality, disability at discharge, delirium, and adverse functional outcome in patients with ischemic stroke [24–27]. This ratio appears to be a better predictive factor than the neutrophil count in ischemic stroke [28]. Several studies observed that NLR was associated with stroke subtypes, especially with atherosclerosis and cardioembolic stroke [29–31].

Switonska and colleagues [32, 33] reported that NLR was a predictive factor of stroke severity, and ischemic stroke patients with higher NLR had a higher risk of symptomatic hemorrhagic transformation after intravenous thrombolysis or mechanical thrombectomy. With the recent trend of population aging, the number of people aged 80 years or above is increasing. However, there are few reports regarding the association between NLR and acute ischemic stroke in older patients. We aimed to assess the association between NLR and stroke severity and early clinical outcomes in ischemic stroke patients aged 80 years and above.

2. Methods

2.1 Participants

This study was conducted in the Department of Neurology, Yangpu Hospital, Tongji University School of Medicine. The patients with age equal to or greater than 80 years old diagnosed with acute ischemic stroke were included. Patients were excluded if they were: (1) diagnosed with infection at admission or within 72 hours after admission, (2) had a history of the hematologic disorder, (3) or using immunosuppressive agents. The ethics committee approved this study of the Yangpu Hospital Tongji University School of Medicine.

2.2 Clinical data

Clinical data collected included demographics (age, gender, body mass index (BMI)), medical history (systolic blood pressure (BP), diastolic BP, hypertension, diabetes mellitus, atrial fibrillation (AF), coronary heart disease, hyperlipidemia, smoking, and alcohol intake) and laboratory parameters. Venous blood samples were collected from all participants within 24 hours after admission, and laboratory parameters were evaluated in the hospital's biochemistry department. NLR was defined as the neutrophil count divided by the lymphocyte count. $NLR = \text{neutrophil count} / \text{lymphocyte count}$. According to their NLR on admission, patients were grouped into tertiles based on a previous study [25].

2.3 Stroke severity and early clinical outcomes

Based on the National Institutes of Health Stroke Scale (NIHSS) at admission, patients were categorized into two groups with moderate to severe stroke (≥ 6 points) and mild stroke (< 6 points) [34]. We assessed early clinical outcomes at discharge by the modified Rankin scale (mRS) and Barthel index (BI). Patients with the mRS of 3–6 points were defined as primary unfavorable outcomes, whereas a BI score below 85 was a secondary unfavorable outcome.

2.4 Statistical analysis

Continuous variables are presented as median (interquartile range) or mean (standard deviation). Categorical variables are described as percentages. Kolmogorov Smirnov test was used to analyze the distribution normality. Differences between mean values were analyzed using an unpaired *t*-test or analysis of variance. The comparison of non-normally distributed variables were evaluated with Kruskal-Wallis and Mann-Whitney U tests. The chi-square test was used for the comparison of categorical variables. Correlation between two variables was assessed with the Spearman correlation test. After adjusting for the confounders, multivariate logistic regression was performed analyzing the relationship between NLR level and outcome in acute ischemic stroke. Potential confounding variables included age, gender, BMI, systolic BP, diastolic BP, diabetes mellitus, AF, coronary heart disease, hyperlipidemia, smoking, alcohol intake and laboratory findings. A two-sided probability value less than 0.05 was defined as statistically significant. SPSS Statistics 22.0 software (SPSS Inc., Chicago, IL) was used for all statistical analyses.

3. Results

3.1 Baseline characteristics

Three hundred fifty-six older patients were included in the current study, 202 (56.7%) were female with a median age of 85.0 (82.0–88.0) years, ranging from 80 to 96 years. Based on tertiles of NLR, 118 patients were in the bottom tertile ($NLR < 2.17$), 118 patients were in the middle tertile ($NLR 2.17\text{--}3.36$), and 120 patients were in the top tertile ($NLR > 3.36$). Hyperlipidemia was more common in the bottom NLR tertile. Compared with the bottom group, platelet

count, WBC count, Hs-CRP level, and fasting blood glucose were higher in the top tertile, while TC, TG and LDL were significantly decreased (Table 1).

3.2 Clinical outcomes

There were 61 (17.1%) patients with moderate to severe stroke on admission, whereas 63 patients (17.7%) with a primary unfavorable outcome ($mRS \geq 3$) and 118 patients (33.1%) with a secondary unfavorable outcome ($BI < 85$). Significant differences among the tertile groups were identified, where the patients in the top tertile had the highest percentage of moderate to severe stroke ($P < 0.001$). Worse primary and secondary clinical outcomes at discharge were also observed in the highest tertile group (Table 2).

In the univariate analysis, the top tertile patients had a higher risk of moderate to severe stroke on admission (OR 4.79, 95% CI, 2.18–10.52, $P < 0.001$) when compared with the bottom tertile. After adjustments for age, gender, BMI, systolic BP, diastolic BP, hypertension, diabetes mellitus, AF, coronary heart disease, hyperlipidemia, smoking, alcohol intake, platelet count, WBC count, Hs-CRP level, fasting blood glucose, TC, TG and LDL, higher NLR was an independent risk factor of moderate to severe stroke (OR 4.87, 95% CI, 1.93–12.30, $P = 0.001$). In the multivariable mode, the top tertile group had a higher risk of a primary unfavorable outcome (OR 2.70, 95% CI, 1.09–6.69, $P = 0.032$) and secondary unfavorable outcome (OR 2.00, 95% CI, 1.00–4.00, $P = 0.050$) compared to the bottom tertile group (Table 3).

4. Discussion

This brief report presented the predictive value of NLR patients aged 80 years or older with acute ischemic stroke and found that patients with higher NLR were associated with moderate to severe stroke and unfavorable clinical outcomes, suggesting that NLR might be an independent risk factor in older patients.

The inflammatory response following acute ischemic stroke exacerbates brain injury, despite the potential for beneficial contributions to neurological tissue repair and regeneration over time [3]. As a significant subtype of leukocytes, neutrophils initially arrive at ischemic brain tissues by binding various adhesion molecules within hours after stroke [5, 35] and exacerbate ischemic brain injury [36]. Neutrophils may release matrix metalloproteinase9 (MMP9), proteases, free oxygen radicals, and other inflammatory mediators, resulting in blood-brain barrier (BBB) damage, brain edema, and further brain damage [37–39]. Compared with other stroke subtypes, elevated levels of tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6) are detected in ischemic stroke patients with the cardioembolic subtype [40]. Furthermore, previous clinical studies suggest that increased neutrophil counts are related to stroke severity [41] and major disability [42].

The patterns and effects of lymphocyte activity following stroke are different from neutrophils [5], as lymphocytes accumulate in the ischemic tissue later than neutrophils [43,

Table 1. Baseline characteristics of patients according to tertiles of NLR.

	Total (356)	NLR on admission			P value
		T1 (n = 118, NLR <2.17)	T2 (n = 118, NLR 2.17–3.36)	T3 (n = 120, NLR >3.36)	
Age (years)	85.0 (82.0–88.0)	84.0 (82.0–87.0)	85.0 (82.0–88.0)	85.0 (83.0–88.0)	0.170
Gender (female)	202 (56.7)	76 (64.4)	65 (55.1)	61 (50.8)	0.097
BMI (kg/m ²)	23.5 (21.0–26.4)	22.9 (21.2–25.8)	23.5 (19.9–26.4)	24.3 (21.5–26.7)	0.258
Systolic BP, mmHg	146.0 (134.3–160.0)	148.0 (135.5–160.0)	146.0 (130.0–160.0)	148.5 (136.0–160.0)	0.639
Diastolic BP, mmHg	80.0 (74.0–86.8)	80.0 (72.8–86.0)	80.0 (73.8–86.0)	80.0 (75.0–88.0)	0.277
Hypertension (n)	283 (79.5)	93 (78.8)	89 (75.4)	101 (84.2)	0.242
Diabetes (n)	124 (34.8)	44 (37.3)	36 (30.5)	44 (36.7)	0.481
Hyperlipidemia (n)	61 (17.1)	34 (28.8)	11 (9.3)	16 (13.3)	<0.001
AF (n)	41 (11.5)	8 (6.8)	17 (14.4)	16 (13.3)	0.138
Coronary heart disease (n)	64 (18.0)	16 (13.6)	25 (21.2)	23 (19.2)	0.286
Smoking (n)	68 (19.1)	16 (13.6)	31 (26.3)	21 (17.5)	0.039
Alcohol intake (n)	11 (3.1)	1 (0.8)	5 (4.2)	5 (4.2)	0.246
Laboratory tests					
Hemoglobin (g/L)	126.0 (115.3–139.0)	126.0 (116.5–137.0)	125.5 (115.0–139.3)	128.5 (116.0–139.0)	0.735
Platelet (10 ⁹ /L)	204.0 (159.3–252.8)	190.0 (155.3–237.5)	208.0 (163.0–251.3)	215.0 (158.0–290.0)	0.046
WBC (10 ⁹ /L)	6.9 ± 1.9	6.2 ± 1.5	6.6 ± 1.8	7.9 ± 1.9	<0.001
Neutrophils (10 ⁹ /L)	4.5 (3.3–5.9)	3.3 (2.7–4.3)	4.4 (3.4–5.4)	6.3 (5.1–7.4)	<0.001
Lymphocytes (10 ⁹ /L)	1.7 ± 0.7	2.2 ± 0.7	1.7 ± 0.5	1.1 ± 0.5	<0.001
NLR	2.7 (2.0–4.1)	1.7 (1.4–2.0)	2.7 (2.4–3.0)	5.4 (4.1–9.5)	<0.001
Hs-CRP (mg/L)					<0.001
0 ≤ CRP < 5	170 (47.7)	75 (63.6)	55 (46.6)	40 (33.3)	
5 ≤ CRP ≤ 10	102 (28.7)	30 (25.4)	37 (31.4)	35 (29.2)	
10 < CRP	84 (23.6)	13 (11.0)	26 (22.0)	45 (37.5)	
FBG (mmol/L)	6.1 (5.1–7.7)	5.7 (4.9–7.3)	5.7 (5.1–7.9)	6.6 (5.0–8.0)	0.022
TC (mmol/L)	4.4 (3.8–5.1)	4.8 (4.0–5.4)	4.3 (3.7–5.1)	4.2 (3.5–5.0)	0.001
TG (mmol/L)	1.2 (0.9–1.6)	1.3 (0.9–1.9)	1.2 (0.9–1.6)	1.1 (0.8–1.5)	0.040
HDL (mmol/L)	1.0 (0.9–1.3)	1.1 (0.9–1.3)	1.0 (0.9–1.3)	1.0 (0.9–1.2)	0.288
LDL (mmol/L)	2.8 (2.3–3.4)	3.0 (2.6–3.6)	2.8 (2.2–3.3)	2.6 (2.2–3.3)	0.002

Note: T1: NLR at first tertile, T2: NLR at second tertile, T3: NLR at third tertile; BP, blood pressure; BMI, body mass index; AF, atrial fibrillation; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; Hs-CRP, highly sensitive C-reactive protein; FBG, fasting blood glucose; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoproteins; LDL, low-density lipoproteins.

44]. However, whether the overall effects of lymphocytes are harmful or protective in the pathogenesis of ischemic stroke remains unclear. Some studies postulate that lymphocytes increase pro-inflammatory cytokines and cytotoxic substances, aggravating ischemic injury [45, 46]. In contrast, lymphocytes have been reported to be major cerebrum-protective immunomodulators following acute ischemic stroke [47, 48].

NLR increased rapidly after a severe stroke, considered acute physiological stress [22]. The increase of NLR may be due to the influence of endogenous cortisol and catecholamine. Elevated cortisol levels increase neutrophil counts and decrease lymphocyte counts [49]. Similarly, endogenous catecholamines may cause leukocytosis and lymphopenia [50]. Additionally, NLR is a simple and easily acquired marker that reflects neutrophils and lymphocytes' relationship, indicating systemic inflammation [24]. Since the influence of lymphocytes involves a longer duration, NLR represents a better predictor [51]. Numerous studies have reported that NLR is an independent risk factor of stroke severity, mortality and 3-month functional outcomes in acute is-

chemic stroke [30, 31, 52]. A recent review concluded that NLR might be useful in specific classifications for cardioembolic and atherosclerosis etiologies [9].

Gokhan *et al.* [30] reported that the NLR ratio was higher in the atherosclerotic stroke subtype than the other etiologies groups. Tokgoz *et al.* [31] found that the atherosclerotic and cardioembolic stroke patients had higher NLR levels than the lacunar infarct patients. Additionally, NLR was proposed to have a predictive value associated with hemorrhagic transformation in acute ischemic stroke patients [53] and 30-day mortality in spontaneous intracerebral hemorrhage patients [54]. Recently, Yu *et al.* [25] observed that stroke patients with high NLR had a significant disability at discharge. However, the relationship between NLR and early clinical outcomes in older patients with acute ischemic stroke is still unclear. This study focused on patients aged 80 years or older and found that NLR is independently associated with stroke severity and early clinical outcome in older patients.

Several limitations must be considered in this study. Most importantly, our study design was single-center retrospec-

Table 2. Comparison of stroke severity and early clinical outcomes according to tertiles of NLR.

Outcomes	NLR on admission				P value
	Total (356)	T1 (n = 118, NLR <2.17)	T2 (n = 118, NLR 2.17–3.36)	T3 (n = 120, NLR >3.36)	
Moderate to severe stroke severity (NIHSS ≥ 6)	61 (17.1)	9 (7.6)	18 (15.3)	34 (28.3)	<0.001
Primary unfavorable outcome (mRS ≥ 3)	63 (17.7)	10 (8.5)	21 (17.8)	32 (26.7)	0.001
Secondary unfavorable outcome (BI <85)	118 (33.1)	24 (20.3)	39 (33.1)	55 (45.8)	<0.001

Note: NLR, neutrophil to lymphocyte ratio; T1: NLR at first tertile, T2: NLR at second tertile, T3: NLR at third tertile; NIHSS, National Institutes of Health Stroke Scale; BI, Barthel index; mRS, modified Rankin Scale.

Table 3. Risks of stroke severity and early clinical outcomes according to tertiles of NLR.

Outcomes	NLR on admission		
	T1 (n = 118, NLR <2.17)	T2 (n = 118, NLR 2.17–3.36)	T3 (n = 120, NLR >3.36)
Moderate to severe stroke severity (NIHSS ≥ 6)			
Crude OR (95% CI)	ref	2.18 (0.94–5.08, $P = 0.071$)	4.79 (2.18–10.52, $P < 0.001$)
Adjusted OR (95% CI)	ref	1.92 (0.78–4.73, $P = 0.158$)	4.87 (1.93–12.30, $P = 0.001$)
Primary unfavorable outcome (mRS ≥ 3)			
Crude OR (95% CI)	ref	2.34 (1.05–5.21, $P = 0.038$)	3.93 (1.83–8.43, $P < 0.001$)
Adjusted OR (95% CI)	ref	2.00 (0.84–4.75, $P = 0.117$)	2.70 (1.09–6.69, $P = 0.032$)
Secondary unfavorable outcome (BI <85)			
Crude OR (95% CI)	ref	1.93 (1.07–3.49, $P = 0.028$)	3.31 (1.87–5.89, $P < 0.001$)
Adjusted OR (95% CI)	ref	1.57 (0.82–3.00, $P = 0.173$)	2.00 (1.00–4.00, $P = 0.050$)

Note: NLR, neutrophil to lymphocyte ratio; T1: NLR at first tertile, T2: NLR at second tertile, T3: NLR at third tertile; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; BI, Barthel index; OR, odd ratio; CI, confidence interval; Adjusts for age, gender, BMI, systolic BP, diastolic BP, diabetes mellitus, AF, coronary heart disease, hyperlipidemia, smoking, alcohol intake, Platelet, WBC, Hs-CRP, FBG, TC, TG, LDL.

tive observational, and the sample was relatively small, which might have introduced selection bias. Moreover, laboratory data were only available at admission, while the dynamic change of NLR during hospitalization would help understand the post-stroke inflammation response mechanisms. Furthermore, the time from stroke onset to admission was not evaluated in the present study. Moreover, the treatment of intravenous thrombolysis and thrombectomy was not taken into account. Ultimately, we did not consider some diseases and factors which could influence stroke in older patients.

Author contributions

YHY and ZWY conceived and designed the experiments; HYJ collected the data; XKC and DZ analyzed the data; JX and XGZ wrote the paper.

Ethics approval and consent to participate

The ethics committee approved this study of the Yangpu Hospital Tongji University School of Medicine.

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Conflict of interest

The authors declare no conflict of interest.

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