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The Prognosis of Neutrophil-to-Lymphocyte Ratio and Lymphocyte-to-Monocyte Ratio in Elderly with Acute Ischemic Stroke

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Background: Neutrophil-to-lymphocyte ratio (NLR) and Lymphocyte-to-monocyte ratio (LMR) have been reported to be associated with outcomes in acute ischemic stroke. However, research on elderly populations remains relatively scarce. We investigated the prognosis of NLR and LMR in elderly with acute ischemic stroke(AIS).

Methods: Based on the modified Rankin Score (mRS) on the 90th day after stroke, patients were divided into group and bad prognosis groups. Multivariate logistic regression analysis and receiver operating curves were used to identify prognostic factors and their predictive powers.

Results: In total, 824 elderly patients with AIS were enrolled between November 2021 and December 2023. Significant differences emerged in the NLR, LMR, and lymphocyte count between the two groups ($P<0.05$). Binary logistic regression identified NLR, LMR and neutrophil count as independent risk factors for an unfavorable prognosis in elderly patients with AIS. The areas under the curve (AUCs) of NLR, LMR, and the combination of NLR and LMR to discriminate poor function prognosis were 0.703, 0.672, and 0.706, respectively. ROC analysis also showed that combination of NLR and LMR was superior to NLR and LMR alone for predicting AIS.

Conclusion: NLR and LMR independently contribute to an unfavorable prognosis in elderly patients with AIS. The area under the ROC curve (AUC) for the combined NLR and LMR was higher than that for NLR and LMR individually, suggesting that combining these two indicators can improve the predictive ability for clinical outcomes in elderly patients with AIS.

Keywords: neutrophil to lymphocyte ratio, lymphocyte to monocyte ratio, acute ischemic stroke, elderly patients

Introduction

Given its high and increasing prevalence, acute ischemic stroke (AIS) has a profoundly detrimental impact on public health.[1,2] In 2019 alone, there were 12.2 million new cases of stroke, leading to 6.55 million deaths, making it the second leading cause of death globally.[3] Identifying biomarkers for adverse outcomes in ischemic stroke patients is crucial, as it allows for early targeted care and the implementation of comprehensive medical interventions to improve patient prognosis.[4]

Extensive research has demonstrated that neuroinflammatory responses are key in the pathophysiology of ischemic stroke.[5] The neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR) are recognized as potential biomarkers of inflammation and are promising for predicting outcomes in acute ischemic stroke patients.[6] Both NLR and LMR have been associated with stroke prognosis. Elevated NLR levels have been linked to poor short-term outcomes in AIS patients, as reported by Zhu et al[7] while Mao et al found that higher LMR at admission predicts poor prognosis at three months.[8] The prognostic value of NLR and LMR in elderly AIS patients, however, remains underexplored.

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In elderly, changes in inflammatory responses, possibly due to immunosenescence, various comorbidities, and physiological decline, may differ significantly from those in younger patients.[9] This study aims to evaluate the prognostic significance of NLR and LMR in elderly with acute ischemic stroke.

Method

Patients and Participants

Patients with AIS within 24 hours were recruited from the People's Hospital of Lu'an. The research protocol was approved by the People's Hospital of Lu'an Ethics Committee (approval number CAAE: 2022L (postgraduate) 007). Written informed consent was obtained from all the participants or their legally authorized surrogates, emphasizing their voluntary participation in the study. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients were included if they met the following criteria: age ≥ 65 years, confirmed World Health Organization diagnostic criteria for stroke, and First onset of illness within 24 hours. Patients were excluded if they met the following criteria: history of malignant tumor, asymptomatic cerebral infarction or transient ischemic attack, active infection within 2 weeks before admission, use of immunosuppressants, and cerebral infarction due to bleeding and trauma.

Clinical Assessment

Data collected from patients included medical history, modified Rankin Score (mRS), stroke subtype according to TOAST criteria,[10] hypertension, diabetes, hyperlipidemia, and current smoking and drinking statuses. Laboratory tests, including routine blood work, were conducted within 24 hours of admission. Neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR) were calculated using the equations: NLR = neutrophil count/lymphocyte count, LMR = lymphocyte count/monocyte count.

The mRS was employed to assess 3-month outcomes through telephone interviews. Functional outcomes of patients with AIS at the end of 3 months were gauged using the mRS, with scores ranging from 0 to 6.[11] A good outcome was defined as an mRS score of 0–2, and a poor outcome was defined as an mRS score of 3–6. Patients with an mRS score of 6 were defined as dead and categorized in the poor prognosis group. For patients who died during follow-up, we recorded the time and cause of death. This inclusion ensured that all outcomes, including death, were systematically considered in the final analysis.

Treatment Modalities

All patients received standard care for acute ischemic stroke based on the current guidelines. Acute phase treatments included intravenous thrombolysis and/or mechanical thrombectomy, depending on patient eligibility. Intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) was administered within 4.5 hours of symptom onset for eligible patients, while mechanical thrombectomy was performed for those with large-vessel occlusions within 6 hours of onset. Patients who were not candidates for acute interventions received standard supportive treatment, including antiplatelet therapy (eg, aspirin), anticoagulant therapy for atrial fibrillation, blood pressure management, and glucose control according to standard protocols. Secondary prevention strategies, such as statin therapy, were also implemented in eligible patients.

Statistical Analysis

Continuous variables are presented as medians (interquartile ranges, IQRs) and were compared using the Mann–Whitney *U*-test, when appropriate. Categorical variables were presented as frequencies and percentages and were compared using the chi-square test, when appropriate. NLR, LMR, Age, and variables that differed significantly in the univariate analysis were included in the multivariable logistic regression models to identify potential risk factors. Two-sided P values<0.05 were considered statistically significant. The predictive ability was determined based on the area under the receiver operating characteristic curve (AUC). The best cut-off as the point was defined as that which the Youden index was maximized. Statistical analyses were performed using IBM SPSS 26.0.

Results

Baseline Characteristics

The baseline characteristics of the favorable and unfavorable prognosis groups are detailed in Table 1. Patients with unfavorable outcomes were significantly older (P = 0.001), had a higher neutrophil count (P < 0.001), and elevated NLR (P < 0.001), while showing a lower lymphocyte count (P < 0.001) and LMR (P < 0.001) compared to the favorable prognosis group.

Other clinical and laboratory parameters, such as sex, diabetes, hypertension, blood pressure, LDL, and triglyceride levels, did not show significant differences between the two groups (P > 0.05), indicating limited prognostic value in predicting 3-month outcomes.

Multivariate logistic regression analysis (Table 2) identified NLR (OR = 1.200, 95% CI: 1.053–1.360, P = 0.006), LMR (OR = 0.822, 95% CI: 1.005–1.370, P = 0.043), and age (OR = 1.029, 95% CI: 1.002–1.057, P = 0.038) as independent predictors of poor outcomes. Atrial fibrillation (OR = 2.838, 95% CI: 1.415–5.692, P = 0.003) and neutrophil percentage (P = 0.000) were also significantly associated with unfavorable prognoses.

The ROC curve analysis identified an optimal NLR cut-off value of 4.155, achieving a sensitivity of 53.5% and a specificity of 81.7% (area under the curve [AUC] = 0.703; 95% CI: 0.660–0.746). For LMR, the optimal cut-off was 0.308, with a sensitivity of 53.8% and a specificity of 77.9% (AUC = 0.672; 95% CI: 0.625–0.719). The combined NLR and LMR optimal cut-off value was determined to be 0.293, with a sensitivity of 52.1% and specificity of 83.8% (AUC = 0.706; 95% CI: 0.662–0.750). As shown in Table 3 and Figure 1.

Table 1 Baseline Characteristics of AIS Patients with Favorable Prognosis Group and Unfavorable Prognosis Group

Characteristics	Favorable Prognosis Group (n=611)	Unfavorable Prognosis Group (n=213)	P
Age, median (IQR), y	74(69.0,79.0)	76(70.0,83.0)	0.001
Smoking, n(%)	185(76.1)	58(23.9)	0.401
Drinking, n(%)	191(78.6)	52(21.4)	0.059
Blood Sugar (mmol/l), median (IQR) C	5.46(4.946.45)	6.05(5.19,7.3)	0.000
Reactive protein	10.5(2.04,10.5)	10.5(2.86,10.)	0.005
Blood homocysteine	15.7(12.2,17.6)	16.0(12.1,18.0)	0.300
Hypertension, n(%)	525(73.5)	189(26.5)	0.190
Diabetes, n(%)	112(72.7)	42(27.3)	0.600
Atrial fibrillation	85(61.2)	54(38.8)	0.000
Stroke etiology (TOAST), n (%)			0.001
Large-artery atherosclerosis	409(75.3)	134(24.7)	
Cardioembolic	19(29.2)	46(70.8)	
Small-vessel disease	183(84.7)	33(15.3)	
Sex			0.030
Male	360(76.9)	108(23.1)	
Female	251(70.5)	105(29.5)	
Leukocyte (10^9/L), median(IQR)	6.30(5.26,7.30)	7.50(6.20,9.55)	0.001
Neutrophils (10^9/L), median(IQR)	4.18(3.2, 5.30)	4.90(4.05,6.80)	0.001
Lymphocytes (10^9/L), median(IQR)	1.47(1.17,1.80)	1.28(0.97,1.70)	0.001
Monocyte (10^9/L), median(IQR)	0.45(0.35,0.54)	0.46(0.34,0.63)	0.150
Neutrophil percentage, median(IQR)	66.7(60.0,72.4)	72.8(66.0,81.2)	0.001
NLR, median(IQR)	2.87(2.09,4.11)	4.23(2.96,7.11)	0.001
LMR, median(IQR)	3.64(2.91,4.41)	2.79(1.94,3.87)	0.001
TC (mmol/l), median(IQR)	4.70(4.01,5.35)	4.80(4.11,5.57)	0.118
TG (mmol/L), median(IQR)	1.11(0.79,1.47)	1.09(0.76,1.40)	0.301
HDL (mmol/L), median(IQR)	1.29(1.12,1.51)	1.34(1.12,1.54)	0.200
LDL (mmol/L), median(IQR)	2.91(2.38,3.49)	2.99(2.51,3.48)	0.147

Notes: Data are presented as medians (interquartile ranges) or as counts (percentages).
Abbreviations: NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte to monocyte ratio; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low density lipoprotein.

Table 2 Binary Logistics Regression Analysis for an Unfavorable Outcome

Variables	B	S.E.	Wald	P	OR	95% CI
NLR	0.180	0.065	7.617	0.006	1.200	(1.053, 1.360)
LMR	0.160	0.079	4.112	0.043	0.822	(1.005, 1.370)
Leukocyte	−0.032	0.083	0.149	0.700	0.968	(0.823, 1.139)
Neutrophils	0.208	0.046	20.375	0.000	2.231	(1.125, 1.348)
Lymphocytes	0.614	0.420	2.136	0.144	1.848	(0.811, 4.212)
Age	0.028	0.014	4.291	0.038	1.029	(1.002, 1.057)
Sex	0.366	0.193	3.588	0.058	1.443	(0.987, 2.108)
Atrial fibrillation	1.043	0.355	8.634	0.003	2.838	(1.415, 5.692)
Neutrophil percentage, median	0.026	0.022	1.298	0.255	1.026	(0.982, 1.072)
Blood Sugar	0.048	0.030	2.547	0.110	1.049	(0.989, 1.113)
C Reactive protein	0.011	0.006	3.116	0.078	1.011	(0.999, 1.024)
Large-artery atherosclerosis	−0.293	0.236	1.546	0.214	0.746	(0.470, 1.184)
Small-vessel disease	2.278	0.444	26.280	0.000	9.754	(4.083, 23.301)

Table 3 In the Receiver Operating Characteristic (ROC) Curve Analysis Show NLR, LMR

Variables	AUC	Sensitivity (%)	Specificity (%)	Optimal Cut-off Value	95% CI
NLR	0.703	0.535	0.817	4.155	0.660–0.746
LMR	0.672	0.535	0.779	0.308	0.625–0.719
NLR and LMR	0.706	0.521	0.838	0.293	0.662–0.750

Discussion

Our findings demonstrate that both NLR and LMR independently contribute to unfavorable prognoses in this demographic. Additionally, the combined analysis of NLR and LMR increases sensitivity beyond that of using either marker alone in predicting outcomes for elderly AIS patients. This study suggests that evaluating NLR and LMR can effectively predict clinical outcomes, including mortality and functional recovery, in patients. These biomarkers yield crucial

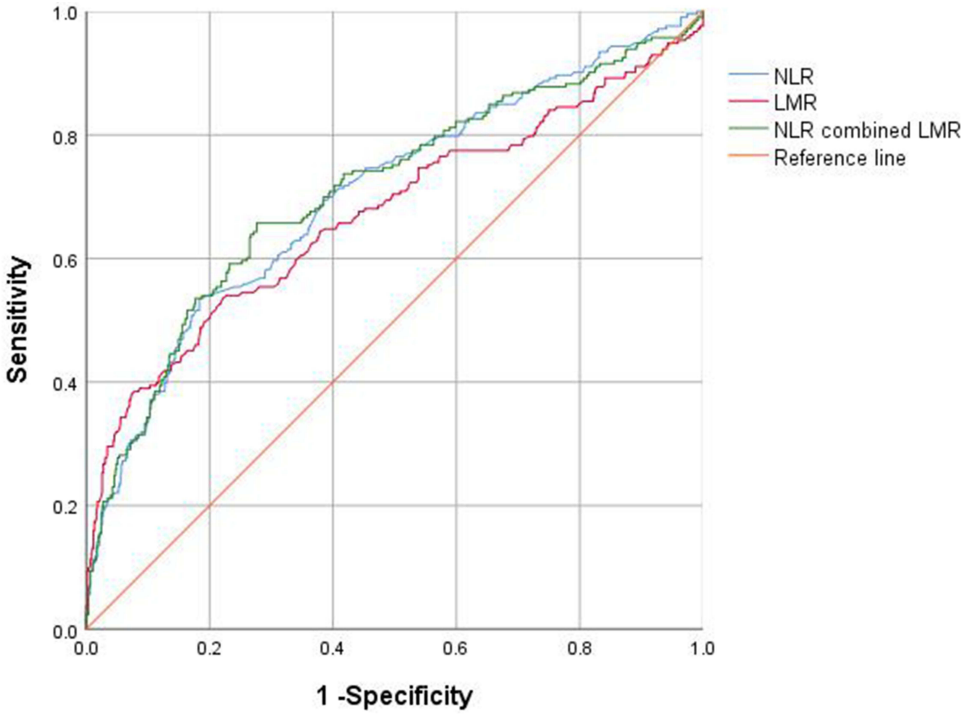

Figure 1 NLR, LMR, and NLR combined LMR receiver operating characteristic curve analysis.

insights into disease severity and potential clinical trajectories, offering valuable supplementary information for clinicians.

The NLR is a simple, readily obtainable marker reflecting neutrophil and lymphocyte interactions, indicating systemic inflammation. Elevated NLR levels signify a robust systemic inflammatory and weakened immune response in patients.[12,13] Extensive research links elevated NLR to various conditions, including cardiovascular diseases, tumors, strokes, and respiratory diseases.[11,14] Consistent with prior research, our study found higher NLR levels in patients with unfavorable prognoses compared to those with favorable outcomes.[15,16] Logistic regression analysis in our study identified NLR as an independent risk factor for the 3-month prognosis in elderly patients, aligning with previous findings.[17] Our results indicate that elderly patients with an NLR greater than 4.155 are at increased risk for poor 3-month outcomes. Previous studies have reported that high NLR levels within 24 h of admission are associated with an increased risk of adverse clinical outcomes in patients, with AIS, with a 3-month follow-up NLR cutoff value of 3.872 for mortality. Moreover, the NLR cutoff value for unfavorable outcomes was 2.846.[6] A higher NLR was associated with a higher risk of poor 3-month functional outcomes (OR = 1.64, 95% CI = 1.38–1.94, $P < 0.001$).[17] However, our findings suggest an optimal NLR cutoff of 4.155, in contrast to the 3.51 reported in earlier studies.[18] This suggests that post-AIS NLR values in patients aged ≥65 years are higher than those in younger populations. Consequently, higher NLR values in patients aged 65 and older may indicate that NLR is a valuable prognostic tool for identifying high-risk AIS patients.

In this study's univariate analysis, the median lymphocyte-to-monocyte ratio (LMR) in the good prognosis group was 3.64, significantly higher than the 2.79 observed in the poor prognosis group ($P < 0.05$), aligning with prior research.[8] Song et al studied consecutive AIS patients within seven days of stroke onset from January 2016 to October 2017, categorizing them into three groups by LMR levels. Multivariable logistic regression revealed that lower LMR independently predicted a higher risk of hemorrhagic transformation (HT) in these patients.[19] Daniele et al analyzed 121 patients with an average age of 66.4 ± 16.7 years, where poor functional prognosis was defined by a 3-month mRS of 3–6. Multivariable logistic regression showed that LMR measured 24 hours after end ovascular treatment could predict the 3-month functional prognosis, with lower LMR linked to worse outcomes (OR = −0.093).[6] Logistic regression in this study found the odds ratio (OR) for LMR to be 0.822 (95% CI 1.005–1.370, $P < 0.05$), suggesting that LMR serves as an independent protective factor in the prognosis of elderly AIS patients. This protective role may be due to lymphocytes secreting anti-inflammatory factors, thus inhibiting inflammation.

Our study has several potential limitations. First, it was conducted as a single-center retrospective study. Second, the large sample size may have introduced additional confounding factors that could affect the results. Third, we calculated NLR and LMR only at admission without ongoing monitoring, potentially impacting their prognostic association with AIS. Finally, functional outcomes were assessed solely using the mean mRS.

Data Sharing Statement

All data generated or analysed during this study are included in this published article.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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