

Peripheral Lymphocyte-to-Monocyte Ratio as a Predictive Factor for Early Neurological Deterioration in Patients with Acute Ischemic Stroke

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Purpose: Previous studies have reported that lymphocyte-to-monocyte ratio (LMR) is associated with the prognosis of patients with acute ischemic stroke (AIS); however, the relationship between LMR and early neurological deterioration (END) in AIS patients has not been elucidated.

Patients and Methods: Patients were divided into two groups according to LMR by using receiver operating characteristic (ROC) curve analysis. Patients with END were confirmed as the National Institutes of Health Stroke Scale (NIHSS) increased ≥ 4 points between hospital days 0 and 5. Multivariate logistic regression analysis was used to analyze the factors independently related to END in patients with AIS.

Results: In total, 202 patients diagnosed with AIS were enrolled in this retrospective study. Using ROC curve analysis, patients were divided into two groups according to LMR: low LMR group (LMR < 3.24 , $n = 95$) and high LMR group (LMR ≥ 3.24 , $n = 107$). The frequencies of END were significantly higher in the low LMR group compared to the high LMR group (41.05 vs. 15.89%, $p < 0.001$). Multivariate logistic regression showed that age (OR = 1.03, 95% CI 1.01–1.06, $p = 0.04$), infarct volume (OR = 1.01, 95% CI 1.00–1.02, $p = 0.001$), neutrophil count (OR = 1.17, 95% CI 1.03–1.33, $p = 0.018$), and LMR (OR = 2.49, 95% CI 1.01–9.11, $p = 0.018$) were independently associated with END in AIS patients.

Conclusion: A peripheral LMR levels at admission were significantly associated with END and LMR < 3.24 is an independent predictive factor of END in patients with AIS.

Keywords: lymphocyte-to-monocyte ratio, acute ischemic stroke, early neurological deterioration, national institutes of health stroke scale

Introduction

Stroke is a serious threat to human health worldwide, and it has become one of the most common leading causes of death in China.¹ There are more than 13 million cases of stroke in China, of which 70 to 80% are ischemic stroke (IS).² Many efforts have been made to treat early acute ischemic stroke (AIS), including intravenous rt-PA thrombolysis and load-based anti-platelet aggregation therapy under the guidance of the CHANCE study.³ However, despite regular treatment, there are still some patients with early neurological deterioration (END).⁴

Although the exact definition of END is still controversial, current studies agree that END appears to be associated with long-term neurological impairment and is a predictor of poor functional outcome in stroke patients. Therefore, such patients should be given full medical attention in the course of treatment.⁵ Many factors have been reported that may influence END, including neurological deficits at admission, hyperglycemia, diabetes, fibrinogen level and systolic blood pressure.^{6–9} However, there are no peripheral blood indicators that can predict the development of END.

A previous study found that a lower lymphocyte-to-monocyte ratio (LMR) value was independently related to the severity of coronary artery disease.¹⁰ Qi et al suggested that LMR on admission could be a predictive indicator for neurological deterioration in the initial week after spontaneous intracerebral hemorrhage.¹¹ Ren et al reported that

decreased LMR could predict poor prognosis of AIS in patients with thrombolysis.¹² Park et al found that LMR was significantly lower on days 1 and 7 in patients with AIS and pointed out that LMR was related to infection after stroke.¹³ However, few studies have determined the relationship between LMR and END in patients with AIS. Therefore, this study explored factors associated with END and evaluated the predictive value of LMR as a prognostic biomarker of END in AIS patients.

Materials and Methods

Study Population

After reviewing AIS patients admitted to our institute between January 2023 and December 2023, we eventually enrolled 202 patients with AIS in this retrospective cross-sectional study. The inclusion criteria were as follows: (1) AIS confirmed by diffusion-weighted imaging (DWI), (2) onset of AIS symptoms within 24 h preceding admission and (3) timely assessment of NIHSS score in hospital. Patients with persistent neurological deficits caused by non-ischemic reasons were excluded, including cerebral hemorrhage, brain tumors, and traumatic brain injury; in addition, patients with infectious diseases, rheumatic immune diseases, severe liver or kidney impairment and malignant tumors were excluded. This study complied with the Ethical Guidelines for Medical and Health Research Involving Human Subjects endorsed by the Chinese government.

Assessment

Clinical data collected in our study included the following: demographic data, medical history, traditional vascular risk factors, baseline laboratory results, whether or not treated with rt-PA thrombolytic therapy, infarct volume, NIHSS scores in initial 5 days after AIS onset and mRS at discharge.

In the present study, END was defined as a NIHSS score that increased by 4 or more points between 0 and 5 days (or new neurological symptoms, which means that a subsection of the previous score of 0 was subsequently scored as 1 point or more).¹⁴ NIHSS score was obtained from our hospital electronic medical record system or by two experienced neurologists to calculate and reach a consensus.

Assessment of Infarction Volume

The areas of DWI abnormalities were summed and multiplied by the section thickness (mm) and intersection gap (mm) by a neurologist who was blinded to all clinical information. The mean of the volume measurements was used as the AIS lesion volume.¹⁵

Laboratory Tests and LMR Calculation

Blood samples were obtained from the patients at admission between 6:00 a.m. and 7:00 a.m. after overnight fasting. Peripheral blood lymphocyte and monocyte counts were performed using an automatic hematology analyzer and LMR was calculated.

Statistical Analysis

Continuous variables were compared using the Student's *t*-test or Mann–Whitney *U*-test. Categorical variables were compared using a chi-square test and expressed as frequencies and percentages. The LMR cutoff level was evaluated by ROC curve analysis. The factors associated with END in AIS patients were determined by forward conditional binary logistic regression analysis and odds ratios (ORs), and the corresponding 95% confidence intervals (CIs) were calculated. Spearman correlation analysis was used to evaluate the relationship between LMR and infarct volume and mRS at discharge. SPSS 22.0 software (IBM SPSS Inc., Chicago, IL, USA) was used to analyze the data, and $p < 0.05$ was considered statistically significant.

Results

Sample Characteristics

In total, 202 patients with onset of AIS symptoms within 24 h preceding admission were enrolled in our study. Patients had a mean age of 64.76 ± 12.61 years, and 63.86% were men. ROC curve analysis was used to determine LMR in predicting END in patients with AIS. The area under ROC curve (AUC) was 0.685 (95% CI 0.601–0.770, $p < 0.001$) (Figure 1), and the cutoff value of LMR was 3.24, with a sensitivity of 61.60% and specificity of 69.60%. According to the LMR cutoff, patients were divided into two groups: a low LMR group (< 3.24 , $n = 95$) and a high LMR group (≥ 3.24 , $n = 107$) (Table 1).

There was no difference in age between the two groups, and the patients in the low LMR group compared to high LMR group had a higher proportion of males (74.74 vs 54.21%; $p = 0.002$), higher percentage of alcohol drinking (51.58 vs 29.91%; $p = 0.002$), higher infarction volume (37.81 ± 83.59 vs 18.41 ± 48.60 mm³; $p = 0.043$), lower total cholesterol (4.57 ± 1.40 vs 4.97 ± 1.11 ; $p = 0.027$), lower low density lipoprotein cholesterol (2.82 ± 0.89 vs 3.25 ± 0.94 ; $p = 0.001$), higher white blood cell count (9.15 ± 3.82 vs $7.56 \pm 2.23 \times 10^9/L$; $p < 0.001$), higher neutrophil count (6.95 ± 3.52 vs $4.99 \pm 2.03 \times 10^9/L$; $p < 0.001$), lower lymphocyte count (1.45 ± 0.64 vs $1.95 \pm 0.70 \times 10^9/L$; $p < 0.001$), higher monocyte count (0.63 ± 0.26 vs $0.43 \pm 0.15 \times 10^9/L$; $p < 0.001$), higher neutrophil/lymphocyte ratio (5.72 ± 4.55 vs 2.90 ± 1.87 ; $p < 0.001$) and higher platelet/lymphocyte ratio (177.46 ± 101.81 vs 122.92 ± 49.91 ; $p < 0.001$) (Table 1).

Incidence of END in the Low and High LMR Groups

Thirty-nine (41.05%) patients in the low LMR group had an END compared with 17 (15.89%) patients in the high LMR group. The incidence of END was thus significantly higher in the low LMR group ($p < 0.001$).

Relationship Between LMR and Infarction Volume and mRS at Discharge

To further investigate the relationship between LMR and factors associated with AIS, we used Spearman correlation analysis to analyze the relationship of LMR with infarct volume and mRS scores at discharge. The results showed that LMR was negatively correlated with infarct volume ($r = -0.176$, $p = 0.012$) and mRS score at discharge ($r = -0.199$, $p = 0.006$) (Figure 2).

Demographic, Clinical, and Laboratory Data of AIS Patients with or Without END

In the initial five days after onset of AIS, 56 patients (27.72%) developed END. These patients had older ages (68.75 ± 13.35 vs 63.23 ± 12.0 years; $p = 0.005$), higher percentage of atrial fibrillation (32.14% vs 21.23%; $p =$

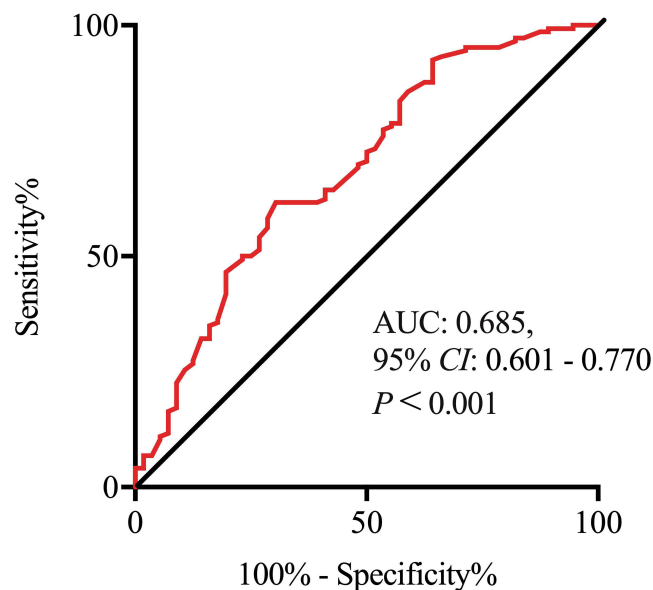


Figure 1 Receiver operating characteristic curve analysis of LMR and END of patients with AIS (area under the curve 0.685, 95% confidence interval 0.601–0.770, $p < 0.001$).

Table 1 Demographic, Clinical, and Laboratory Data in Patients with LMR < 3.24 and LMR ≥ 3.24

	All (n=202)	LMR < 3.24 (n = 95)	LMR ≥ 3.24 (n = 107)	P value
Men, n (%)	129 (63.86)	71 (74.74)	58 (54.21)	0.002*
Age, (years, mean ± SD)	64.76 ± 12.61	66.05 ± 12.44	63.62 ± 12.71	0.171
Smoking, n (%)	95 (47.03)	51 (53.68)	44 (41.12)	0.074
Alcohol drinking, n (%)	81 (40.10)	49 (51.58)	32 (29.91)	0.002*
Hypertension, n (%)	128 (63.37)	63 (66.32)	65 (60.75)	0.412
Diabetes mellitus, n (%)	56 (27.72)	28 (29.47)	28 (26.17)	0.60
Hyperlipemia, n (%)	41 (20.30)	14 (14.74)	27 (25.23)	0.064
CHD, n (%)	27 (13.37)	11 (11.58)	16 (14.95)	0.482
Atrial fibrillation, n (%)	36 (17.82)	20 (21.05)	16 (14.95)	0.258
History of stroke, n (%)	45 (22.27)	26 (27.37)	19 (17.76)	0.101
Systolic pressure (mmHg)	151.39 ± 22.22	153.21 ± 22.01	149.77 ± 22.38	0.273
Diastolic pressure (mmHg)	85.82 ± 11.94	87.38 ± 12.76	84.44 ± 11.04	0.081
Epilepsy, n (%)	3 (1.49)	2 (2.10)	1 (0.93)	0.492
Imaging of HT, n (%)	13 (6.44)	6 (6.32)	7 (6.54)	0.948
Infarct volume	27.49 ± 67.79	37.81 ± 83.59	18.41 ± 48.60	0.043*
FBG (mmol/L)	6.25 ± 2.09	6.44 ± 2.24	6.08 ± 1.94	0.213
HbA1c (%)	6.27 ± 1.49	6.30 ± 1.55	6.25 ± 1.44	0.838
Cys C (mg/L)	1.08 ± 0.35	1.11 ± 0.40	1.05 ± 0.29	0.191
Urea (mmol/L)	6.08 ± 2.42	6.37 ± 2.97	5.82 ± 1.77	0.103
Creatinine (μmol/L)	75.07 ± 35.49	79.66 ± 42.92	71.0 ± 26.81	0.084
Triglycerides (mmol/L)	2.05 ± 4.81	1.81 ± 2.23	2.25 ± 6.28	0.521
Total cholesterol (mmol/L)	4.78 ± 1.27	4.57 ± 1.40	4.97 ± 1.11	0.027*
HDL (mmol/L)	1.97 ± 12.73	1.06 ± 0.27	2.78 ± 1.69	0.340
LDL (mmol/L)	3.04 ± 0.94	2.82 ± 0.89	3.25 ± 0.94	0.001*
Hcy	15.61 ± 7.26	15.83 ± 6.93	15.42 ± 7.57	0.687
White blood cell count (10 ⁹ /L)	8.31 ± 3.18	9.15 ± 3.82	7.56 ± 2.23	<0.001*
Neutrophil count (10 ⁹ /L)	5.91 ± 2.99	6.95 ± 3.52	4.99 ± 2.03	<0.001*
Lymphocyte count (10 ⁹ /L)	1.72 ± 0.72	1.45 ± 0.64	1.95 ± 0.70	<0.001*
Monocyte count (10 ⁹ /L)	0.53 ± 0.23	0.63 ± 0.26	0.43 ± 0.15	<0.001*
Platelet count (10 ¹² /L)	215.93 ± 61.42	214.42 ± 60.29	217.27 ± 62.65	0.743
Mean platelet volume	9.14 ± 1.51	8.92 ± 1.30	9.34 ± 1.65	0.047
MCV	92.21 ± 5.94	92.77 ± 6.51	91.70 ± 5.36	0.201
MCH	30.81 ± 2.32	30.87 ± 2.61	30.75 ± 2.05	0.712
RDW	13.24 ± 1.57	13.56 ± 2.11	12.95 ± 0.76	0.005*
MPV/PLT	0.05 ± 0.02	0.05 ± 0.02	0.05 ± 0.02	0.564
Neutrophil/lymphocyte ratio (%)	4.23 ± 3.67	5.72 ± 4.55	2.90 ± 1.87	<0.001*
Platelet/lymphocyte ratio (%)	148.57 ± 83.10	177.46 ± 101.81	122.92 ± 49.91	<0.001*

Notes: Figures in parentheses are percentages, unless indicated otherwise. *Indicates p value less than 0.05 level.

Abbreviations: CHD, coronary heart disease; FBG, fasting blood-glucose; HbA1c, glycosylated hemoglobin; Cys, C Cystatin C; HDL, high density lipoprotein, HT, hemorrhagic transformation; LDL, Low density lipoprotein; Hcy, homocysteine; RDW, red cell distribution width; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MPV, mean platelet volume; PLT, platelet; LMR, lymphocyte to monocyte ratio.

0.001), higher percentage of hemorrhagic transformation (14.29% vs 3.42%; $p = 0.005$), higher infarct volume (70.99 ± 108.42 vs 1.10 ± 31.19 ; $p < 0.001$), higher white blood cell count (9.83 ± 3.99 vs $7.72 \pm 2.59 \times 10^9/L$; $p < 0.001$), higher neutrophil count (7.47 ± 3.75 vs $5.31 \pm 2.39 \times 10^9/L$; $p < 0.001$), higher monocyte count (0.61 ± 0.27 vs $0.49 \pm 0.21 \times 10^9/L$; $p = 0.002$), higher red blood cell distribution width (13.69 ± 2.35 vs 13.06 ± 1.11 ; $p = 0.011$), higher neutrophil/lymphocyte ratio (5.90 ± 5.40 vs 3.59 ± 2.48 ; $p < 0.001$) and higher platelet/lymphocyte ratio (172.25 ± 112.92 vs 139.49 ± 66.60 ; $p = 0.012$) (Table 2).

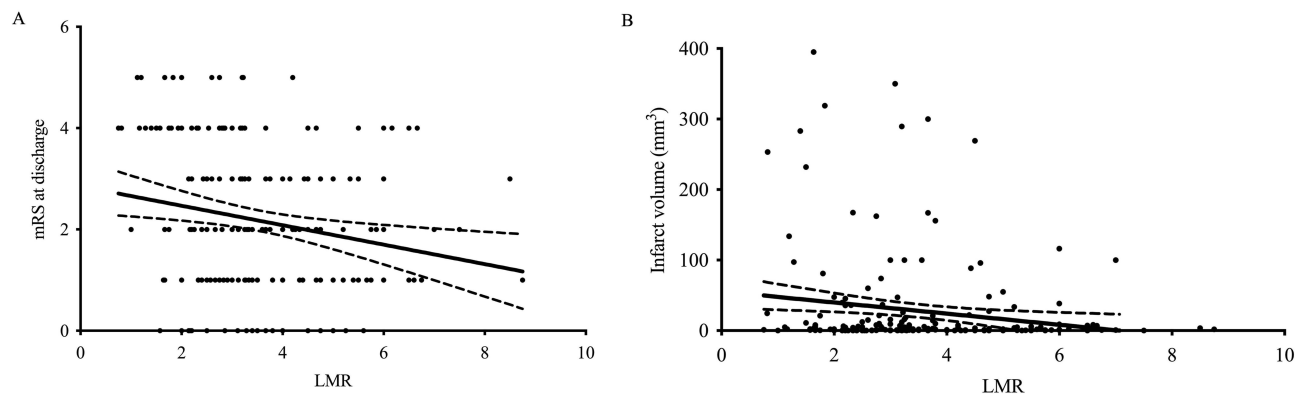


Figure 2 (A) Correlation between LMR and mRS score at discharge. (B) Correlation between LMR and the infarct volume.

Logistic regression analysis showed that age (OR = 1.03, 95% CI 1.01–1.06, $p = 0.04$), infarct volume (OR = 1.01, 95% CI 1.00–1.02, $p = 0.001$), neutrophil count (OR = 1.17, 95% CI 1.03–1.33, $p = 0.018$), and LMR <3.24 (OR = 2.49, 95% CI 1.01–9.11, $p = 0.018$) were independently associated with END in AIS patients (Table 3).

Table 2 Demographic, Clinical, and Laboratory Data in END and Non-END Patients

	END (n = 56)	Non-END (n = 146)	P value
Man, n (%)	33 (58.93)	96 (65.75)	0.366
Age, (years, mean \pm SD)	68.75 \pm 13.35	63.23 \pm 12.0	0.005*
Smoking, n (%)	23 (41.07)	72 (49.32)	0.293
Alcohol drinking, n (%)	24 (42.86)	57 (38.26)	0.620
Hypertension, n (%)	38 (67.86)	90 (61.64)	0.412
Diabetes mellitus, n (%)	14 (25.0)	42 (28.77)	0.592
Hyperlipemia, n (%)	9 (16.07)	32 (21.92)	0.355
CHD, n (%)	11 (19.64)	16 (10.96)	0.104
Atrial fibrillation, n (%)	18 (32.14)	18 (12.33)	0.001*
History of stroke, n (%)	14 (25.0)	31 (21.23)	0.565
rt-PA treatment	10 (17.86)	18 (12.33)	0.309
Systolic pressure (mmHg)	155.57 \pm 24.30	149.78 \pm 21.24	0.097
Diastolic pressure (mmHg)	85.84 \pm 13.10	85.82 \pm 11.52	0.990
Epilepsy, n (%)	1 (1.79)	2 (1.37)	0.827
Imaging of HT, n (%)	8 (14.29)	5 (3.42)	0.005*
Infarct volume	70.99 \pm 108.42	11.10 \pm 31.19	$<0.001^*$
FBG (mmol/L)	6.71 \pm 2.20	6.08 \pm 2.02	0.057
HbA1c (%)	6.29 \pm 1.28	6.27 \pm 1.57	0.913
Cys C (mg/L)	1.11 \pm 0.35	1.07 \pm 0.34	0.401
Urea (mmol/L)	6.21 \pm 1.99	6.03 \pm 2.57	0.626
Creatinine (μ mol/L)	76.92 \pm 28.90	74.36 \pm 37.78	0.647
Triglycerides (mmol/L)	2.78 \pm 8.84	1.76 \pm 1.50	0.182
Total cholesterol (mmol/L)	4.68 \pm 1.36	4.82 \pm 1.24	0.460
HDL (mmol/L)	4.37 \pm 3.23	1.05 \pm 0.27	0.098
LDL (mmol/L)	2.91 \pm 0.92	3.10 \pm 0.95	0.196
Hcy	14.93 \pm 6.53	15.87 \pm 7.52	0.412
White blood cell count ($10^9/L$)	9.83 \pm 3.99	7.72 \pm 2.59	$<0.001^*$
Neutrophil count ($10^9/L$)	7.47 \pm 3.75	5.31 \pm 2.39	$<0.001^*$
Lymphocyte count ($10^9/L$)	1.61 \pm 0.80	1.76 \pm 0.69	0.205

(Continued)

Table 2 (Continued).

	END (n = 56)	Non-END (n = 146)	P value
Monocyte ($10^9/L$)	0.61 ± 0.27	0.49 ± 0.21	0.002*
Platelet count ($10^{12}/L$)	223.20 ± 66.18	213.14 ± 59.50	0.299
Mean platelet volume	8.87 ± 1.21	9.25 ± 1.59	0.117
MCV	92.56 ± 5.84	92.07 ± 5.99	0.606
MCH	30.64 ± 2.34	30.88 ± 2.32	0.516
RDW	13.69 ± 2.35	13.06 ± 1.11	0.011*
MPV/PLT	0.05 ± 0.02	0.05 ± 0.02	0.313
Neutrophil/lymphocyte ratio (%)	5.90 ± 5.40	3.59 ± 2.48	<0.001*
Platelet/lymphocyte ratio (%)	172.25 ± 112.92	139.49 ± 66.60	0.012*

Notes: Figures in parentheses are percentages, unless indicated otherwise. *Indicates p value less than 0.05 level.

Abbreviations: CHD, coronary heart disease; END, early neurological deterioration; FBG, fasting blood-glucose; HbA1c, glycosylated hemoglobin; Cys C, Cystatin C; HDL, high density lipoprotein; HT, hemorrhagic transformation; LDL, Low density lipoprotein; Hcy, homocysteine; RDW, red cell distribution width; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MPV, mean platelet volume; PLT, platelet.

Table 3 Logistic Regression Analysis of Parameters Associated with END

	OR	95% CI	P value
Age	1.03	1.01–1.06	0.04
Infarct volume	1.01	1.00–1.02	0.001
LMR	2.49	1.01–9.11	0.018
Neutrophil count	1.17	1.03–1.33	0.018

Abbreviation: LMR, lymphocyte to monocyte ratio.

Discussion

In the present study, 56 patients developed END in the initial 5 days after onset of AIS symptoms within 24 h preceding admission. Patients in the END group had a significantly lower LMR than that in the non-END group. In logistic regression analysis, age, infarct volume, neutrophil count and LMR <3.24 were independently associated with END in patients with AIS.

There is no consensus on the definition of END. Recent studies have reported that the incidence of END is also very different, ranging from 5 to 40%, but regardless of the definition, the association of END with more severe fatality and worse functional outcome in patients with AIS for 3 months has been confirmed.^{16,17} Therefore, to clarify the risk factors and predictors of END, timely monitoring and treatment are an important challenge to improve AIS prognosis. Previous studies have shown that a variety of factors are associated with END, including hyperglycemia, neurological functional deficits at admission, systolic BP, and fibrinogen levels.^{6–9} Our study found that older age, larger infarct volume, elevated neutrophil count, and LMR decline were independently associated with END. Shkirkova et al showed that patients with ultra-END in IS were older than non-ultra-END patients.¹⁸ Scheetz et al believe that older adults with traumatic brain injury are more likely to develop END.¹⁹ Petrone et al studied changes in neutrophil and lymphocyte counts in peripheral blood of patients with AIS and found that elevated neutrophil counts were associated with poor prognosis.²⁰ Zhu et al suggested that higher neutrophil levels with intracranial artery stenosis significantly increase the risk of stroke recurrence after investigating the CHANCE trial.²¹ The conclusions of these studies are consistent with our results. However, there are few studies on the relationship between LMR and END.

Previous studies mainly focused on the prognostic effects of LMR on stroke patients, including the following: decreased LMR can predict poor prognosis of AIS in patients with thrombolysis at three months; LMR is significantly

lower on days 1 and 7 in patients with AIS; and LMR is related to infection after stroke.^{12,13} Our study showed that low LMR is independently associated with END, and that LMR <3.24 has predictive value for the development of END. Although the mechanism of LMR decline in the underlying pathophysiology of END following AIS is not clear, studies indicate that the inflammatory response after stroke is related to END. As a new systemic inflammatory response index, LMR can comprehensively reflect the body's inflammation and immune status.²² Inflammatory reaction and inflammatory mediators are closely related to the occurrence, development and prognosis of stroke. Leukocyte infiltration and release of various inflammatory mediators are important pathophysiological processes in AIS.^{23,24} Lymphocytes and monocytes are involved in the pathological process of IS. The decrease in lymphocyte count is related to disease severity. Lymphopenia can reduce the incidence of cerebral infarction and reduce neurological deficits. The phenomenon is generally considered to be a mechanism of endogenous self-protection. Sympathetic nerves excite too much catecholamines, and the hypothalamic-pituitary-adrenal system is excited, while a large number of hormones such as cortisol, catecholamine and acetylcholine are released, which together contribute to lymphocyte apoptosis.^{25–27} Monocytes are important immunoreactive cells in acute cerebral infarction. They can infiltrate the infarcted area and aggravate brain damage.²⁸ The increase in monocyte level in acute cerebral infarction is an independent risk of adverse prognosis of cerebral infarction.²⁹ This may be related to the release of cytokines such as interleukin-1, interleukin-6 and tumor necrosis factor- α by monocytes, which may play an inflammatory role.³⁰ Our study found that lymphocyte count decreased, and monocyte count increased in the END group, while LMR integrated the information on lymphocytes and monocytes, which may be more valuable in predicting END in patients with AIS. Moreover, these mechanisms may also explain the negative correlation between LMR and cerebral infarction volume and mRS at discharge in our results.

Single-center design and retrospective analysis were the main limitations of the present study. The relatively small sample size also increases the probability of selection bias. Although we obtained statistical support for the relationship between LMR and END, our conclusions will be more convincing if we can record the dynamic changes in LMR. Another limitation of our study is the lack of comparison of the predictive value of LMR with other inflammation-related biomarkers. A prospective study is needed, including larger samples and more time-points for LMR values.

Conclusion

Inflammation plays a crucial role in the pathogenesis and prognosis of AIS. It is a complex process involving various immune cells, cytokines, and signaling pathways. Decreased LMR is independently associated with END in patients with AIS. LMR <3.24 could be a promising predictor for development of END after AIS. Although the underlying mechanisms still need to be elucidated, monitoring LMR level could nonetheless be an inexpensive and practical predictor of END in patients with AIS.

Ethics Approval and Consent to Participate

Study approval statement: This study protocol was reviewed and approved by the Ethics Committee of the Shidong Hospital, approval number [IRB-AF37-V1.0]. Informed consent was waived because of retrospective design. During the study, patient data confidentiality and compliance with the Declaration of Helsinki were followed.

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Disclosure

The authors report no conflicts of interest in this work.

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