

The Association of the Neutrophil-to-Lymphocyte Ratio, Platelet-to-Lymphocyte Ratio, Lymphocyte-to-Monocyte Ratio and Systemic Inflammation Response Index with Short-Term Functional Outcome in Patients with Acute Ischemic Stroke

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Background and Purpose: The aim of this study was to explore the relationship between functional prognosis and the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR) and systemic inflammatory response index (SIRI) in patients with acute ischemic stroke (AIS) at discharge.

Methods: A total of 861 patients with AIS were enrolled between January 2019 and December 2021. Blood cell counts were collected on admission. Logistic regression analysis was performed to assess the relationship between NLR, PLR, LMR, SIRI and adverse functional outcomes (modified Rankin scale score of 3–6) at discharge. We also used receiver operating characteristic (ROC) curves to estimate the overall ability of NLR, PLR, LMR and SIRI to judge short-term functional outcomes. Associations between NLR, PLR, LMR, and SIRI with length of hospital stay were analyzed by Spearman correlation test.

Results: A total of 194 patients (22.5%) had poor functional outcomes at discharge. Multivariate logistic regression analysis showed that NLR (odds ratio [OR], 1.060; 95% confidence interval [CI] 1.004–1.120, $P=0.037$), PLR (OR, 1.003; 95% CI 1.000–1.005, $P=0.018$), LMR (OR, 0.872; 95% CI 0.774–0.981, $P=0.023$) and SIRI (OR, 1.099; 95% CI 1.020–1.184, $P=0.013$) were independent factors for poor functional outcome. The odds ratios of the highest versus lowest quartiles of NLR, PLR and SIRI were 2.495 (95% CI 1.394–4.466), 1.959 (95% CI 1.138–3.373) and 1.866 (95% CI 1.106–3.146), respectively. The odds ratio of the lowest versus highest quartile of LMR was 2.300 (95% CI 1.331–3.975). The areas under the curve (AUCs) of the NLR, PLR, LMR, and SIRI to discriminate poor functional prognosis were 0.644, 0.587, 0.628, and 0.651, respectively. NLR, LMR, and SIRI were related with the length of hospital stay ($P<0.05$).

Conclusion: NLR, PLR, LMR, and SIRI were associated with functional outcome at discharge in AIS patients. NLR, LMR and SIRI were related to hospitalization days in patients with AIS.

Keywords: acute ischemic stroke, short-term functional outcome, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, systemic inflammatory response index

Introduction

Stroke is the second leading cause of death and a major cause of disability worldwide. China bears the largest burden of stroke in the world and is the country with the highest risk of stroke. The incidence of stroke in China is about 343.4/100

000 person-years.^{1–3} Patients with acute ischemic stroke (AIS) often experience early neurological deterioration and poor functional outcome during hospitalization, which further prolongs the length of hospital stay and has a long-term impact on the patient's quality of life.⁴ Identifying patients with a high risk of short-term functional prognosis as soon as possible can help doctors provide intensive treatment for patients and alleviate their adverse functional outcomes during hospitalization. Therefore, it is essential to identify rapidly available and reliable markers to optimize risk stratification for functional outcome in acute ischemic stroke.

Many studies have shown that inflammation is a major factor affecting the pathophysiology and prognosis of AIS.^{5–7} The inflammatory cascade after cerebral ischemia is a dynamic process in which various cells interact in the ischemic region, which can cause secondary brain injury.⁸ Inflammatory markers (including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR), and systemic inflammatory response index (SIRI)) are excellent predictors of functional outcome in AIS. These indexes are readily available, and previous studies have shown that NLR, PLR, LMR, and SIRI correlate with stroke severity on admission, 3-month functional outcomes, and mortality.^{9–13} In addition, a retrospective study found that NLR, PLR, and LMR were associated with early neurological deterioration after intravenous thrombolysis in patients with AIS, NLR and PLR predicted early neurological deterioration after thrombolysis, and NLR was an independent factor of early neurological improvement after thrombolysis.¹⁴ However, few studies have investigated the relationship between inflammatory markers and clinical outcomes at discharge in patients with acute ischemic stroke. The length of hospital stay is an important indicator of disease severity in AIS, but few studies have linked the length of hospital stay with inflammatory markers.

To better evaluate the early risk predictive value of inflammatory composite indicators (including NLR, PLR, LMR and SIRI), we not only explore the relationship between inflammatory composite indicators and the poor functional outcome of patients with AIS at discharge, but also analyzed the association between inflammatory composite indicators and hospitalization days.

Method

Study Participants

We screened stroke patients who presented to the First Hospital of Hebei Medical University from January 2019 to December 2021. According to the inclusion and exclusion criteria, 861 patients with AIS were finally included. Finally, 861 AIS patients were eligible for this analysis (Figure 1).

Inclusion criteria:

1. Eighteen years or older.
2. The patient was admitted within 7 days of onset.
3. AIS was diagnosed by CT or MRI.

Exclusion criteria:

1. Severe inflammatory diseases or infectious diseases.
2. Patients with insufficient laboratory data and discharge modified Rankin scale (mRS) score data.

Data Collection and Outcome Assessment

Experienced doctors collected the participants' demographic characteristics (age, sex, smoking and drinking), clinical characteristics (systolic blood pressure, diastolic blood pressure and NIHSS score at admission), TOAST classification, medical history (hypertension, diabetes, stroke, atrial fibrillation and coronary heart disease), past medication history (lipid-lowering drugs, hypoglycemic drugs, antihypertensive drugs and antiplatelet drugs) and time from onset to admission. Stroke severity was assessed by the National Institutes of Health Stroke Scale (NIHSS). All patients who participated in the study had routine blood tests on admission to measure neutrophil, lymphocyte, platelet, and monocyte counts. After fasting for at least 8 hours within 24 hours of admission, fasting blood samples were collected to measure

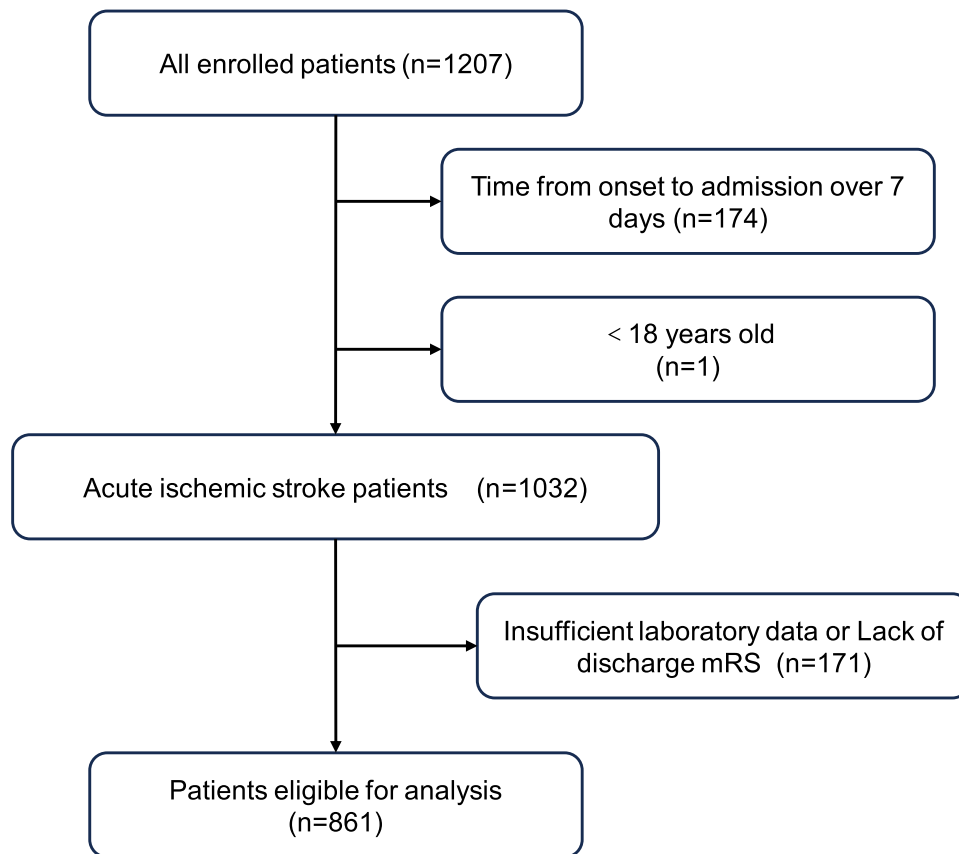


Figure 1 Flow chart of the present study participants.

total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and blood glucose (GLU).

Inflammatory indicators (including NLR, PLR, LMR, and SIRI) were calculated. The NLR was calculated as the neutrophil count/lymphocyte count. PLR was calculated as the platelet count/lymphocyte count. LMR was calculated as the lymphocyte count/monocyte count. SIRI was calculated as the neutrophil count * monocyte count/lymphocyte count. Short-term functional outcomes were assessed using the mRS scores at discharge. The mRS scores ranged from 0 to 6, with a score of 0 indicating no symptoms, a score of 3 indicating moderate disability, a score of 4 indicating moderate to severe disability, a score of 5 indicating severe disability, and a score of 6 indicating death. The primary outcome was poor functional outcome, defined as having an mRS score of 3–6 at discharge.

Statistical Analysis

The patients were divided into two groups based on mRS scores at discharge, with good functional outcomes (mRS: 0–2) and poor functional outcomes (mRS: 3–6). Continuous variables are represented by the mean (standard deviation, SD) or median (interquartile interval, IQR), and categorical variables are expressed as frequency (%). We tested for normality for continuous variables using the Kolmogorov–Smirnov test. Differences in the baseline characteristics between the groups were analyzed by t tests for normally distributed variables, Mann–Whitney tests for nonnormally distributed variables, and chi-square tests for categorical variables. Associations between NLR, PLR, LMR, and SIRI with short-term functional outcome and length of hospital stay were analyzed by Spearman correlation test. Univariate logistic regression and multivariate logistic regression analyses were performed to assess the association between the NLR, PLR, LMR, SIRI and clinical outcomes, generating odds ratios (ORs) and 95% confidence interval (95% CI). In the multivariate logistic regression analysis, we constructed two models: Model 1 was adjusted for age, sex, length of hospital stay, NIHSS score at admission, TOAST classification, and stroke history; Model 2 was further adjusted for TG,

smoking, drinking, medical history (hypertension, diabetes, atrial fibrillation), thrombolysis and glucose-lowering drugs. We also divided the participants into four groups according to the quartiles of NLR, PLR, LMR, and SIRI, and logistic regression models were used to calculate the ORs and 95% CI for the high quartile versus the lowest quartile or the low quartile versus the highest quartile. A receiver operating characteristic (ROC) curve was used to test the overall ability of the NLR, PLR, LMR and SIRI to predict the short-term functional outcome of patients with AIS. The Youden Index was calculated as the sensitivity +specificity–1. All statistical analyses were performed using IBM SPSS Statistics version 25 and GraphPad Prism 9.0. A two-tailed value of $P < 0.05$ was considered significant.

Result

Baseline Characteristics

The study included 861 patients (552 males and 309 females) with an average age of 63.4 ± 12.1 years. According to the mRS score at the time of discharge, the patients were divided into a good functional outcome group (mRS: 0–2) and a poor functional outcome group (mRS: 3–6). The baseline characteristics of the participants are shown in Table 1. The participants with poor functional outcomes were older (66 versus 64 years; $P=0.019$) and less likely to be male (57.2 versus 66.1%; $P=0.027$) and had higher NIHSS scores on admission (6 versus 2; $P<0.001$), longer hospitalization days (12 versus 11; $P<0.001$), and a higher prevalence of stroke (37.6% versus 27.9%; $P=0.010$). Those with poor functional

Table 1 Demographics and Clinical Characteristics of the Subgroup According to Functional Outcome at Discharge

	Good Functional Outcome N=667	Poor Functional Outcome N=194	P values
Demographic			
Age, years, (median [IQR])	64[54,71]	66[58,73]	$P=0.019$
Age, years, female (median [IQR])	68[60,75]	71[63,77]	$P=0.046$
Male, n (%)	441(66.1%)	111(57.2%)	$P=0.027$
Smoker, n (%)	235(35.2%)	62(32.0%)	$P=0.440$
Alcohol user, n (%)	205(30.7%)	47(24.2%)	$P=0.089$
Clinical features, (median [IQR])			
Hospitalization days, d	11[9,13]	12[10,15]	$P<0.001$
SBP, mmHg	150[136,164]	151[138,162]	$P=0.496$
DBP, mmHg	90[81,99]	89[82,100]	$P=0.892$
Admission NIHSS score	2[1,4]	6[4,11]	$P<0.001$
Laboratory data, (median [IQR])			
TC, mmol/L	4.56[3.83,5.33]	4.42[3.72,5.36]	$P=0.426$
TG, mmol/L	1.33[0.96,1.86]	1.20[0.91,1.66]	$P=0.017$
HDL-C, mmol/L	0.99[0.84,1.14]	0.98[0.81,1.19]	$P=0.904$
LDL-C, mmol/L	2.87[2.35,3.45]	2.83[2.32,3.49]	$P=0.961$
GLU, mmol/L	5.40[4.82,6.86]	5.63[4.84,7.38]	$P=0.445$
NLR	2.50[1.88,3.60]	3.34[2.42,5.38]	$P<0.001$
PLR	129.38[101.03,176.10]	150.45[112.67,209.17]	$P<0.001$
LMR	4.00[3.00,5.25]	3.34[2.26,4.50]	$P<0.001$
SIRI	1.02[0.74,1.62]	1.60[0.92,2.65]	$P<0.001$
Medical history, n (%)			
Hypertension	460(69.0%)	133(68.6%)	$P=0.930$
Diabetes	186(27.9%)	59(30.4%)	$P=0.527$
Stroke	186(27.9%)	73(37.6%)	$P=0.010$
Atrial fibrillation	29(4.3%)	12(6.2%)	$P=0.337$
Coronary heart disease	62(9.3%)	21(10.8%)	$P=0.580$

(Continued)

Table 1 (Continued).

	Good Functional Outcome N=667	Poor Functional Outcome N=194	P values
Medication use history, n (%)			
Lipid lowering drugs	95(14.2%)	29(14.9%)	P=0.817
Hypoglycemic drugs	132(19.8%)	49(25.3%)	P=0.109
Antihypertensive drugs	292(43.8%)	82(42.3%)	P=0.742
Antiplatelet drugs	126(18.9%)	39(20.1%)	P=0.756
Thrombolysis	27(4.0%)	14(7.2%)	P=0.068
TOAST classification, n (%)			P<0.001
Large-artery atherosclerosis	294(44.1%)	129(66.5%)	
Small-artery occlusion	346(51.9%)	54(27.8%)	
Cardio-embolism	19(2.8%)	8(4.1%)	
Other etiology	7(1.0%)	3(1.5%)	
Undetermined etiology	1(0.1%)	0(0.0%)	

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; NIHSS, National Institute of Health Stroke Scale; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; GLU, Plasma glucose; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; SIRI, systemic inflammation response index.

outcomes were more likely to have lower levels of triglycerides (1.20 versus 1.33; $P=0.017$). The baseline characteristics according to the quartiles of NLR, PLR, LMR and SIRI are detailed in [Additional files: Tables S1–S4](#), respectively.

Inflammatory Composite Index and Unfavorable Functional Outcome

Table 1 shows that the patients with poor functional outcomes had a higher NLR (3.34 versus 2.50; $P < 0.001$), higher PLR (150.45 versus 129.38; $P < 0.001$), higher SIRI (1.60 versus 1.02; $P < 0.001$) and lower LMR (3.34 versus 4.00; $P < 0.001$).

Table 2 presents the results of the univariate logistic regression analysis of poor functional prognosis. The univariate logistic regression analysis showed that age, sex, NIHSS score at admission, length of stay, TOAST classification, stroke history, NLR, PLR, LMR and SIRI were correlated with the prognosis of adverse function ($P < 0.05$).

Table 3 shows the results of the multivariate logistic regression analysis for poor functional outcome. After adjusting for age, sex, NIHSS score at admission, length of hospital stay, TOAST classification and stroke history, NLR (ORs, 1.062; 95% CI 1.006–1.121, $P = 0.028$), PLR (ORs, 1.003; 95% CI 1.001–1.005, $P=0.014$), LMR (ORs, 0.863; 95% CI

Table 2 Univariate Logistic Regression Analysis for Risk Factors with Poor Functional Prognosis

Variable	Poor Functional Outcome (mRS Score 3–6)	
	OR (95% CI)	P values
Demographic		
Age, years	1.016[1.003–1.030]	P=0.018
Male	0.685[0.494–0.950]	P=0.023
Smoker	0.863[0.614–1.214]	P=0.399
Alcohol user	0.721[0.499–1.040]	P=0.080
Clinical features		
Hospitalization days	1.077[1.038–1.118]	P<0.001
SBP	1.000[0.997–1.003]	P=0.869
DBP	0.999[0.989–1.010]	P=0.919
Admission NIHSS score	1.375[1.300–1.455]	P<0.001

(Continued)

Table 2 (Continued).

Variable	Poor Functional Outcome (mRS Score 3–6)	
	OR (95% CI)	P values
Laboratory data		
TC	0.960[0.840–1.096]	P=0.547
TG	0.891[0.747–1.063]	P=0.199
HDL	1.132[0.576–2.226]	P=0.719
LDL	1.019[0.841–1.234]	P=0.851
GLU	1.019[0.960–1.081]	P=0.546
NLR	1.101[1.049–1.156]	P<0.001
PLR	1.003[1.002–1.005]	P<0.001
LMR	0.783[0.705–0.869]	P<0.001
SIRI	1.144[1.055–1.240]	P=0.001
Medical history		
Hypertension	0.981[0.695–1.385]	P=0.914
Diabetes	1.130[0.797–1.603]	P=0.493
Stroke	1.560[1.115–2.184]	P=0.010
Atrial fibrillation	1.451[0.726–2.900]	P=0.293
Coronary heart disease	1.185[0.702–1.998]	P=0.526
Medication use history		
Lipid lowering drugs	1.058[0.674–1.660]	P=0.805
Hypoglycemic drugs	1.370[0.941–1.994]	P=0.101
Antihypertensive drugs	0.940[0.680–1.299]	P=0.709
Antiplatelet drugs	1.080[0.723–1.613]	P=0.706
Thrombolysis	1.844[0.947–3.590]	P=0.072
TOAST classification	0.552[0.413–0.738]	P<0.001

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; NIHSS, National Institute of Health Stroke Scale; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; GLU, Plasma glucose; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; SIRI, systemic inflammation response index.

Table 3 Multinomial Logistic Regression Models for Poor Function Outcome

	Model 1		Model 2	
	OR (95% CI)	P values	OR (95% CI)	P values
NLR	1.062[1.006–1.121]	P=0.028	1.060[1.004–1.120]	P=0.037
PLR	1.003[1.001–1.005]	P=0.014	1.003[1.000–1.005]	P=0.018
LMR	0.863[0.768–0.970]	P=0.013	0.872[0.774–0.981]	P=0.023
SIRI	1.101[1.022–1.186]	P=0.012	1.099[1.020–1.184]	P=0.013

Notes: Model 1: adjusted for age; sex; length of hospital stay; NIHSS score at admission; TOAST classification and stroke history. Model 2: further adjusted for TG, smoking, drinking, medical history (hypertension, diabetes, atrial fibrillation), thrombolysis and glucose-lowering drugs.

Abbreviations: NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; SIRI, systemic inflammation response index; TG, triglyceride.

0.768–0.970, P=0.013) and SIRI (ORs, 1.101; 95% CI 1.022–1.186, P=0.012) were determined to be independent factors for poor functional outcome. Model 2 was further adjusted for TG, smoking, drinking, medical history (hypertension, diabetes, atrial fibrillation), thrombolysis and glucose-lowering drugs. NLR (ORs, 1.060; 95% CI 1.004–1.120, P=0.037), PLR (ORs, 1.003; 95% CI 1.000–1.005, P=0.018), LMR (ORs, 0.872; 95% CI 0.774–0.981, P=0.023) and SIRI (ORs, 1.099; 95% CI 1.020–1.184, P=0.013), which were still independent factors for poor functional outcome.

Table 4 shows the results of the multivariate logistic regression analysis based on the NLR, PLR, LMR, and SIRI quartile grouping. In Model 2, the ORs for poor functional outcome at discharge increased with the NLR, PLR, and SIRI quartiles and decreased with the LMR quartiles. The ORs of unfavorable functional outcome at discharge with NLR ranged from 1.463 (95% CI 0.795–2.694) in quartile 2 to 2.495 (95% CI 1.394–4.466) in quartile 4. The ORs of unfavorable functional outcome at discharge with PLR ranged from 1.421 (95% CI 0.811–2.491) in quartile 2 to 1.959 (95% CI 1.138–3.373) in quartile 4. The ORs of unfavorable functional outcome at discharge with SIRI ranged from 0.682 (95% CI 0.372–1.251) in quartile 2 to 1.866 (95% CI 1.106–3.146) in quartile 4. The ORs of unfavorable functional outcome at discharge with LMR ranged from 1.509 (95% CI 0.850–2.679) in quartile 3 to 2.300 (95% CI 1.331–3.975) in quartile 1.

Table 4 Multivariate Logistic Regression Analysis According to Quartiles of NLR, PLR, LMR, and SIRI

Clinical Outcome	NLR				P values
	Q1 (<1.96) N=214	Q2 (1.96–2.63) N=216	Q3 (2.64–3.99) N=215	Q4 (≥4.00) n=216	
Poor functional outcome					
Cases, n (%)	25(11.7%)	41(19.0%)	52(24.2%)	76(35.2%)	P<0.001
Model 1	1.00	1.538(0.841–2.812)	2.269(1.273–4.047)	2.607(1.463–4.644)	
Model 2	1.00	1.463(0.795–2.694)	2.197(1.227–3.934)	2.495(1.394–4.466)	
PLR					
Clinical outcome	Q1 (<103.19) N=215	Q2 (103.19–134.96) N=215	Q3 (134.97–180.92) N=216	Q4 (≥180.93) n=215	
Poor functional outcome					
Cases, n (%)	35(16.3%)	44(20.5%)	52(24.1%)	63(29.3%)	P=0.010
Model 1	1.00	1.429(0.820–2.492)	1.706(0.975–2.985)	1.962(1.149–3.351)	
Model 2	1.00	1.421(0.811–2.491)	1.694(0.963–2.980)	1.959(1.138–3.373)	
LMR					
Clinical outcome	Q1 (<2.90) N=213	Q2 (2.90–3.79) N=209	Q3 (3.80–4.99) N=198	Q4 (≥5.00) n=241	
Poor functional outcome					
Cases, n (%)	73(34.3%)	48(23.0%)	41(20.7%)	32(13.3%)	P<0.001
Model 1	2.384(1.386–4.098)	1.651(0.946–2.882)	1.607(0.912–2.833)	1.00	
Model 2	2.300(1.331–3.975)	1.539(0.876–2.704)	1.509(0.850–2.679)	1.00	
SIRI					
Clinical outcome	Q1 (<0.77) N=214	Q2 (0.77–1.11) N=213	Q3 (1.12–1.79) N=214	Q4 (≥1.80) n=220	
Poor functional outcome					
Cases, n (%)	35(16.4%)	28(13.1%)	49(22.9%)	82(37.3%)	P<0.001
Model 1	1.00	0.730(0.401–1.331)	1.359(0.791–2.337)	1.932(1.150–3.248)	
Model 2	1.00	0.682(0.372–1.251)	1.304(0.754–2.255)	1.866(1.106–3.146)	

Notes: Model 1: adjusted for age, sex, length of hospital stay, NIHSS score at admission, TOAST classification and stroke history. Model 2: further adjusted for TG, smoking, drinking, medical history (hypertension, diabetes, atrial fibrillation), thrombolysis and glucose-lowering drugs.

Abbreviations: NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; SIRI, systemic inflammation response index; NIHSS, National Institute of Health Stroke Scale; TG triglyceride.

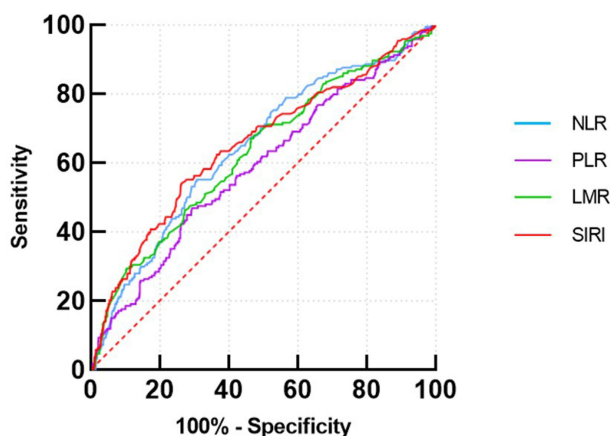


Figure 2 Receiver operating characteristic curve of inflammatory composite indicators. The AUC was 0.644 (0.599–0.688) in blue line for NLR, 0.587 (0.540–0.633) in purple line for PLR, 0.628 (0.582–0.674) in green line for LMR, 0.651 (0.605–0.697) in red line for SIRI.

Abbreviations: AUC, area under the curve; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; SIRI, systemic inflammation response index.

ROC curves were plotted to evaluate the efficiency of NLR, PLR, LMR, and SIRI in predicting the outcome of poor function in patients with AIS, as shown in Figure 2 and Table 5. We observed that the area under the curve (AUC) of the NLR, PLR, LMR, and SIRI was 0.644 (95% CI, 0.599–0.688), 0.587 (95% CI, 0.540–0.633), 0.628 (95% CI, 0.582–0.674), and 0.651 (95% CI, 0.605–0.697), respectively. The optimal diagnostic cutoff point of NLR was 3.16, the sensitivity was 55.2%, and the specificity was 69.3%. The optimal diagnostic cutoff point of PLR was 162.92, the sensitivity was 46.9%, and the specificity was 70.6%. The optimal diagnostic cutoff point of LMR was 3.95, the sensitivity was 52.6% and the specificity was 68.0%. The optimal diagnostic cutoff point of SIRI was 1.55, the sensitivity was 54.1%, and the specificity was 73.6%.

Table 6 shows that the NLR, PLR and SIRI were positively correlated with poor functional outcome ($P < 0.001$), and the LMR was negatively correlated with poor functional outcome ($P < 0.001$). The NLR and SIRI were positively correlated with the length of hospital stay ($P < 0.05$), the LMR was negatively correlated with the length of hospital stay ($P < 0.05$), and the PLR was not significantly correlated with the length of hospital stay ($P = 0.063$).

Table 5 The Ability of NLR, PLR, LMR and SIRI to Predict Poor Functional Prognosis at Discharge

Variable	AUC	P-value	95% CI	Se (%)	Sp (%)	Cutoff
NLR	0.644	$P < 0.001$	0.599–0.688	55.2	69.3	3.16
PLR	0.587	$P < 0.001$	0.540–0.633	46.9	70.6	162.92
LMR	0.628	$P < 0.001$	0.582–0.674	52.6	68	3.95
SIRI	0.651	$P < 0.001$	0.605–0.697	54.1	73.6	1.55

Abbreviations: AUC, area under curve; Se, sensitivity; Sp, specificity; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; SIRI, systemic inflammation response index.

Table 6 Association of NLR, PLR, LMR, and SIRI with Poor Functional Outcomes and Hospital Stay

	Poor Functional Outcome		Hospitalization Days	
	r	P	r	P
NLR	0.208	< 0.001	0.078	0.022
PLR	0.126	< 0.001	0.063	0.063
LMR	-0.186	< 0.001	-0.073	0.033
SIRI	0.219	< 0.001	0.085	0.012

Abbreviations: NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; SIRI, systemic inflammation response index.

Discussion

In this study, we comprehensively investigated the relationship between the NLR, PLR, LMR, and SIRI and functional outcome at discharge in a large sample of adult patients with AIS. Our study, involving 861 patients, showed that the NLR, PLR, LMR, and SIRI were correlated with functional outcome at discharge in patients with acute ischemic stroke. Multivariate logistic regression analysis showed that the NLR, PLR, LMR and SIRI remained independent factors for poor functional prognosis after adjusting for confounding factors. The higher the NLR, PLR, SIRI or lower the LMR, the more likely the occurrence of poor functional outcome. In addition, the area under the ROC curve of NLR, LMR and SIRI in predicting the prognosis of acute ischemic stroke is roughly similar. Therefore, this study suggests that the NLR, PLR, LMR and SIRI have important clinical value in identifying early unfavorable outcomes in patients with AIS. In addition, we also found that the NLR, LMR and SIRI were correlated with the length of hospital stay by Spearman correlation analysis.

Studies have indicated that inflammatory mechanisms play an important role in the onset and progression of AIS. After cerebral ischemia, damaged brain cells produce a large number of inflammatory cytokines, chemokines, reactive oxygen species (ROS) and other neurotoxic substances that mediate the destruction of the blood–brain barrier and the occurrence of inflammatory cascade reactions. At the same time, it guides immune inflammatory cells to enter the brain tissue, which further mediates secondary neuronal damage and aggravates neurological dysfunction.¹⁵ Neutrophils are the first blood-derived immune cells to invade ischemic brain tissue. After reaching the ischemic area, neutrophils release proinflammatory mediators, proteases, ROS and extracellular matrix metalloproteinases (MMPs), causing secondary damage to the ischemic tissue.¹⁶ Lymphocytes are thought to have neuroprotective and neurofunctional effects.⁶ Peripheral monocytes can serve as a source of MMP-9 and aggravate brain damage.¹⁷ Increased monocyte count has been shown to be an independent predictor of worse outcome after stroke.^{18,19} When acute ischemic stroke occurs, excessive activation and accumulation of platelets can lead to thrombosis and vascular obstruction, which in turn leads to vascular events.²⁰ NLR, PLR, LMR, and SIRI are four inflammatory complex markers of different combinations of inflammatory parameters and thus may provide more information about immune activity in the pathogenesis of ischemic stroke. More importantly, these four composite markers of inflammation can be calculated from blood cell counts, so they are relatively easy to obtain.

Previous studies have shown that a high NLR on admission may be a useful marker for predicting functional outcome at discharge in mild AIS patients receiving intravenous thrombolysis.²¹ Kim et al found that the higher the NLR, the worse the short-term functional prognosis of AIS patients.²² In addition, a study of 346 patients with AIS showed that the higher the NLR, the higher the incidence of adverse outcomes at discharge.²³ We included 861 AIS patients, and our findings suggested that the NLR was an independent risk factor for poor functional outcome at discharge, which was consistent with previous findings.

Altintas et al found that elevated PLR was associated with infarct volume and the occurrence of poor prognosis in AIS patients.²⁴ A previous study showed that PLR predicted 90-day clinical outcomes in patients with AIS.¹¹ Higher PLR before endovascular thrombectomy (EVT) was significantly associated with poor functional outcome at 90 days in AIS patients who successfully recovered after EVT.²⁵ A recent study found that PLR at 24 hours after thrombolysis was a marker of 3-month functional outcome in AIS patients.²⁶ To our knowledge, our study is the first to report the association of PLR with functional outcomes at discharge in AIS patients, and the finding is similar to the 90-day functional outcomes of previous studies.

Mao et al found that LMR was an independent predictor of progressive infarction in AIS patients.²⁷ Li et al demonstrated that the LMR 48 h after intravenous thrombolysis can be used as a biomarker of the functional outcome of discharged patients with AIS.²⁸ Our findings suggest that a low LMR increases the incidence of poor functional outcomes in AIS patients at discharge. This may be the first time that a correlation has been proposed between LMR at admission and functional outcome at discharge in patients with AIS. These findings may provide useful population-based information for researchers studying the PLR, LMR, and stroke short-term risk prediction, not only for research but also for clinical and public health applications.

A previous study showed that SIRI was a promising low-grade inflammatory factor for predicting stroke outcome. SIRI was also found to be superior to the NLR, PLR and LMR in predicting mortality in stroke patients.²⁹ This is similar to our finding that SIRI exhibited better ability in predicting poor functional outcomes at discharge in AIS patients than NLR, PLR and LMR. Recently, a study showed that a higher SIRI was an independent risk factor for death in AIS patients.¹⁰ This suggests that SIRI is closely related to the prognosis of AIS patients. Huang's results indicated that SIRI was not associated with poor outcomes in AIS patients at discharge.⁹ This is not consistent with the results of our study. We included more patients than Huang's study, and through the comparison of baseline characteristics of patients, we found that the proportion of patients with diabetes in our included patients was slightly higher than that in Huang's study population (28.5% vs 22.6%). Previous studies have shown that hyperglycemia may worsen the acute outcome of ischemic stroke,³⁰ and perhaps for these reasons, different findings have been reported. Further studies with a larger sample size are needed to investigate the association between SIRI and functional outcomes at discharge in AIS patients.

A study has shown that an increase in the NLR can prolong the hospital stay of AIS patients.²³ Our study had similar results, with the NLR positively correlated with the length of hospital stay in AIS patients. At the same time, we also reported that the LMR was negatively correlated with the length of hospital stay, and SIRI was positively correlated with the length of hospital stay.

In summary, our study enriches the current epidemiological evidence on the relationship between the NLR, PLR, LMR, SIRI and short-term clinical outcomes in patients with ischemic stroke, supporting the hypothesis that the NLR, PLR, and SIRI are positively correlated with poor functional outcome and that the LMR is negatively correlated with poor functional outcome. Our findings suggest that the NLR, PLR, LMR, and SIRI are important for optimizing the risk stratification of short-term ischemic stroke outcomes and guiding clinical decision making.

The NLR, PLR, LMR, and SIRI were also associated with poststroke complications. Some studies have shown that the NLR, PLR, and LMR can predict hemorrhagic transformation (HT) after ischemic stroke.^{31–33} High NLR and PLR were associated with symptomatic internal carotid artery stenosis.³⁴ According to Hu et al, elevated levels of NLR and PLR are predictive of postischemic stroke depression.³⁵ High PLR was a relevant factor for stroke-related pneumonia in AIS patients.³⁶

These four inflammatory composite markers are relatively readily available biomarkers and are applied in clinical practice for the early identification of ischemic stroke patients with a higher risk of poor stroke outcome, and the findings suggest that close monitoring and management of inflammatory markers may be necessary. Furthermore, our study showed that NLR, LMR, and SIRI had similar predictive ability for short-term functional outcomes of ischemic stroke, with the best predictive ability of SIRI. The NLR, LMR, and SIRI were correlated with hospitalization days in ischemic stroke patients. This can also provide a reference for clinicians in the selection of indicators and the need for intensive treatment for patients.

There are several potential limitations to our study. First, we excluded patients without NLR, PLR, LMR, and SIRI data, which may have limited the generalizability of our findings. Second, this study only looked at the effect of inflammatory markers at admission on outcomes at discharge, whereas reports suggested that inflammation markers may change significantly during hospitalization. Future studies are needed to dynamically detect inflammatory composite markers, not just inflammatory markers at admission. Third, more than one neurologist assessed short-term functional outcomes, which may lead to bias in the assessment of mRS, even though the neurologists have received standardized training. Finally, all enrolled participants were Chinese patients, so the association between these inflammatory composite measures and short-term functional outcomes needs to be tested in populations from other countries.

Conclusion

Our findings indicated that increased levels of NLR, PLR, and SIRI in patients with AIS were associated with an increased risk of poor functional outcome at discharge, and decreased levels of LMR were associated with an increased risk of poor functional outcome at discharge. An increase in the NLR or SIRI or a decrease in the LMR may further prolong the length of hospital stay. The NLR, PLR, LMR, and SIRI may have the ability to predict short-term functional outcomes.

Abbreviations

AIS, acute ischemic stroke; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; SIRI, systemic inflammatory response index; mRS, modified Rankin scale score; NIHSS, National

Institutes of Health Stroke Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; GLU, plasma glucose; ROC receiver operating characteristic; AUC, areas under the curve.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of the First Hospital of Hebei Medical University (approval number: 20200908). The fully deidentified data on the patients enrolled in the current study and its retrospective study design enabled this study to be conducted under waiver of informed consent by the local institutional review board. Our study also complied with the Declaration of Helsinki.

Consent for Publication

All the authors agree to publish.

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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.

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Disclosure

The authors declare that they have no competing interests in this work.

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