

Neutrophil-to-Lymphocyte Ratio, Lymphocyte-to-Monocyte Ratio and Platelet-to-Lymphocyte Ratio as Predictors of Short- and Long-Term Outcomes in Ischemic Stroke Patients with Atrial Fibrillation

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Purpose: Inflammatory response plays essential roles in the pathophysiology of both ischemic stroke and atrial fibrillation (AF). We aimed to investigate whether composite inflammatory markers, including neutrophil to lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR) and platelet-to-lymphocyte ratio (PLR), can serve as early predictors of short- and long-term outcomes in ischemic stroke patients with AF.

Patients and Methods: Ischemic stroke patients with AF were enrolled in this cohort study. The primary outcome was 1-year functional dependence or death (modified Rankin scale (mRS) score 3–6). Secondary outcomes included hemorrhagic transformation (HT) and early neurological deterioration (END, increase in the National Institutes of Health Stroke Scale (NIHSS) ≥ 4 within 7 days). Partial correlations were performed to assess the correlation between systemic inflammation markers and admission NIHSS scores. Univariate and multivariate logistic analyses were performed to investigate whether systemic inflammatory markers were independent predictors of adverse outcomes.

Results: A total of 408 patients were included. Partial correlation analysis revealed statistically significant but weak correlations between the NLR ($r = 0.287$; $P < 0.001$), PLR ($r = 0.158$; $P = 0.001$) and admission NIHSS score. Compared with patients without HT or END, patients who developed HT or END had higher NLR and PLR, and lower LMR. Patients in the functional dependence or death group had significantly higher NLR and PLR, and lower LMR than those in the functional independence group (all $P < 0.001$). Multivariate logistic analysis indicated that NLR, LMR and PLR were independent predictors of HT (OR = 1.069, 0.814 and 1.003, respectively), END (OR = 1.100, 0.768 and 1.006, respectively) and adverse 1-year functional outcome (OR = 1.139, 0.760 and 1.005, respectively).

Conclusion: NLR, LMR and PLR were independent predictors for in-hospital HT, END and long-term functional outcome in ischemic stroke patients with AF. Close monitoring of these inflammatory markers may help guide risk stratification and clinical treatment strategies.

Keywords: inflammation, ischemic stroke, atrial fibrillation, hemorrhagic transformation, early neurological deterioration, functional outcome

Introduction

Atrial fibrillation (AF) is the most common arrhythmia and is a significant contributor to ischemic stroke and mortality.¹ Ischemic stroke patients with AF are often more severely ill and have a greater risk of a poor prognosis than those

without AF.² Moreover, treatment decision-making is usually more difficult in ischemic stroke patients with AF. The optimal antithrombotic strategy and timing to restart remain intractable problems since the relative benefit and hemorrhagic transformation (HT) should be considered. Identifying reliable biomarkers that can predict HT and functional outcomes is essential for risk stratification and determining possible means of controlling the risk factors at an early stage in ischemic stroke patients with AF.

Inflammatory response has been found to play essential roles in the pathogenesis and progression of both ischemic stroke and AF.^{3–7} Several studies have reported that inflammatory reactions are related to the triggering and maintenance of AF.⁸ Moreover, it has been suggested that inflammatory state in AF may promote the formation of left atrial thrombus and the detachment of an already formed thrombus and further contribute to an increased risk of thromboembolism and poor prognosis.^{9,10} Meanwhile, in patients with ischemic stroke, evidence has shown that neuronal cell death and disruption of the blood–brain barrier caused by inflammation may result in hemorrhagic transformation and poor functional outcomes.¹¹ This is particularly important for ischemic stroke patients with AF since the decision to prescribe therapeutic anticoagulation is challenging in clinical practice. Taken together, the role of inflammation in outcomes of ischemic stroke patients with AF may require extra attention, and may serve as an important predictor of HT and functional outcomes. However, there is limited evidence to support this.

Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) represent novel systemic inflammation biomarkers that combine various inflammatory parameters. These composite inflammatory markers can be easily assessed at disease onset via routine blood tests, and may provide more information about immunological activity than traditional individual inflammatory markers.¹² A previous study showed that NLR was an independent predictor of 90-day prognosis in acute ischemic stroke patients, and had a better predictive value than traditional individual inflammatory markers including C-reactive protein and white cell count.¹³ Another study demonstrated that NLR, PLR and LMR were associated with post-thrombolysis early neurological deterioration (END) in patients with acute ischemic stroke.¹⁴ Higher NLR levels has also been found to have predictive value for adverse functional outcomes in ischemic stroke patients after endovascular therapy or thrombolysis.^{15,16} However, whether NLR, LMR and PLR can be predictors of HT and functional outcomes in ischemic stroke patients with AF remains unclear.

In this study, we primarily aimed to investigate the associations of composite inflammatory markers, including NLR, LMR and PLR, with long-term functional outcome at 1 year in ischemic stroke patients with AF. Additionally, we explored the relationships between these inflammatory markers and stroke severity, in-hospital HT and END.

Material and Methods

Study Population

This retrospective cohort study was performed using prospectively collected data. Ischemic stroke patients with AF from all over the country admitted to Beijing Tiantan Hospital from February 2021 to January 2023 were screened. This study was approved by the ethics committee of Beijing Tiantan Hospital, Capital Medical University (No. KY2023-163-01). Written informed consent was obtained from all patients or their legal guardians. This study was conducted according to the Declaration of Helsinki and institutional guidelines.

The inclusion criteria included (1) age greater than or equal to 18 years, (2) a diagnosis of ischemic stroke according to the WHO criteria¹⁷ within 72 h of symptom onset, and (3) a documented history or in-hospital diagnosis of AF. The exclusion criteria were as follows: (1) had iatrogenic stroke, venous infarction or stroke due to head trauma; (2) had a prestroke modified Rankin scale (mRS) score ≥ 2 ; (3) had major comorbidities or late-stage disease with a life expectancy of <3 months; (4) had complications such as infectious diseases, inflammatory diseases, immune system disorders, or were receiving immunotherapy; (5) had comorbidities that may have increased inflammation indicators including tumors, myocardial infarction, trauma, recent surgery and anaphylaxis; (6) lacked neutrophil, lymphocyte, monocyte or platelet count data; and (7) lacked follow-up data.

Data Collection

Clinical data, including demographic variables, medical history, preonset medication and in-hospital treatment, were collected by a trained neurological physician. The severity of neurological impairment was assessed by the National Institute of Health Stroke Scale (NIHSS) score on the first three days and seventh day of admission. CT/MRI scans were performed on admission whenever neurologic worsening was detected and before discharge at the discretion of the treating physicians.

Neutrophil counts, lymphocyte counts, monocyte counts and platelet counts were assessed in the emergency room on admission with an autoanalyzer via standard procedures (BC-5390 CRP, Mindray, China). These counts were used to determine the systemic inflammatory markers listed below. NLR was calculated as neutrophil count/lymphocyte count. PLR was calculated as platelet count/lymphocyte count. LMR was calculated as lymphocyte count/monocyte count.

Outcome Measurements

The primary outcome was 1-year functional dependence or death, which was defined as an mRS score of 2–6. Secondary outcomes included END (increase in NIHSS score ≥ 4 within 7 days) and HT (any hemorrhage found on the follow-up CT during hospitalization but not detected on initial head CT). The outcomes were collected through clinical interviews or telephone follow-up by trained investigators who were blinded to the baseline information.

Statistical Analysis

All statistical analyses were performed using SPSS software (version 25.0 for Windows, IBM). The χ^2 test or Fisher's exact test was used for comparisons of categorical variables, and Student's *t* test and the Mann–Whitney *U*-test were used for comparisons of continuous variables. To assess the association between the composite inflammatory markers and the NIHSS score, partial correlation analyses were performed adjusted for age, sex, prior stroke or TIA, diabetes mellitus, hypertension, coronary heart disease, current smoking and AF type. Univariate and multivariate logistic regression model analyses were performed to assess the associations of the composite inflammatory markers with patient outcomes. Potential confounding factors for adjustments were selected based on their statistical significance in the univariate analysis and clinical importance. Model 1 was adjusted for age and sex. Model 2 was adjusted for Model 1 plus NIHSS score on admission, stroke etiology, prior hypertension, diabetes mellitus, stroke or TIA, coronary heart disease, current smoking status, use of antiplatelet agents, anticoagulant agents, and AF type. The composite inflammatory markers were analyzed as continuous variables and dichotomous variables, respectively. All the statistical analyses were two-tailed, and statistical significance was indicated if the *P* value was <0.05 .

Results

Demographic and Clinical Characteristics

A total of 422 ischemic stroke patients with AF met the inclusion criteria. We excluded two patients with infectious disease and 12 patients without follow-up data. Ultimately, a total of 408 patients with a mean age of 70.5 years (257 males, 63.0%) were included in the analysis (Figure 1). During hospitalization, 79 (19.4%) patients developed END, and 158 (38.7%) patients developed HT. At the 1-year follow-up, the primary outcome (functional dependence or death) occurred in 215 (52.7%) patients. The baseline characteristics of the study participants are shown in Table 1. Compared to patients with favorable functional outcome, patients with functional dependence or death were older (67.0 vs 74.0, $P < 0.001$), a lower proportion were male (68.9% vs 57.7%, $P = 0.019$); had higher NIHSS score on admission (5.0 vs 13.0, $P < 0.001$); were more likely to have nonparoxysmal AF (39.4 vs 66.0, $P < 0.001$); had higher levels of white blood cell counts (7.9 vs 8.5, $P = 0.018$), neutrophil counts (5.8 vs 6.6, $P < 0.001$), C-reactive protein (2.1 vs 3.1, $P < 0.001$), NLR (3.9 vs 6.1, $P < 0.001$) and PLR (140.7 vs 184.4, $P < 0.001$); and had lower levels of lymphocyte counts (1.5 vs 1.0, $P < 0.001$), platelet counts (206.0 vs 184.0, $P = 0.002$) and LMR (3.4 vs 3.0, $P < 0.001$).

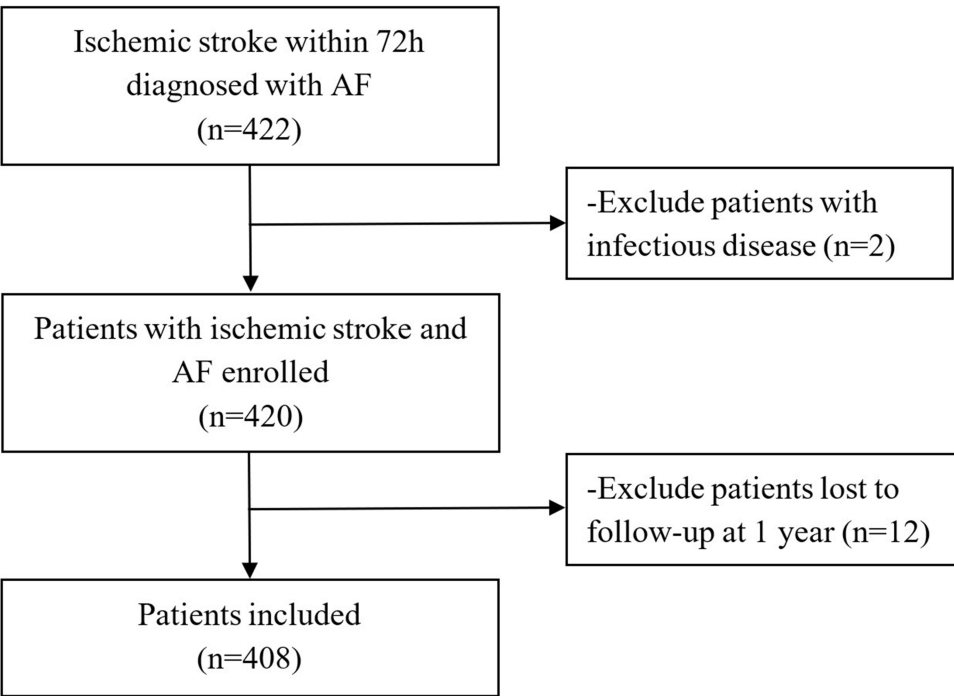


Figure 1 Study flow chart.

Partial Correlation Analysis Between Systemic Inflammatory Markers and Admission NIHSS Score in Ischemic Stroke Patients with AF

As shown in Figure 2, partial correlation analysis revealed a weak but significant correlation between systemic inflammatory markers and stroke severity on admission. After adjusting for age, sex, prior stroke or TIA, diabetes, hypertension, coronary disease, smoking status and AF type, higher NLR ($r = 0.287$; $P < 0.001$) and PLR ($r = 0.158$; $P = 0.001$) were associated with higher NIHSS score on admission. LMR was not significantly associated with NIHSS score after adjusting for potential covariates ($r = -0.085$; $P = 0.089$).

Table 1 Baseline Characteristics of the Study Population According to Functional Outcome

Baseline Characteristics	Functional independence	Functional dependence or death	P value
N (%)	193 (47.3)	215 (52.7)	
Age, y	67.0 (60.5–74.5)	74.0 (67.0–80.0)	<0.001
Male, n (%)	133 (68.9)	124 (57.7)	0.019
Current smoker, n (%)	51 (26.4)	45 (20.9)	0.191
Stroke or TIA, n (%)	45 (23.3)	61 (28.4)	0.245
Coronary heart disease, n (%)	40 (20.7)	62 (28.8)	0.059
Hypertension, n (%)	128 (66.3)	137 (63.7)	0.583
Diabetes mellitus, n (%)	63 (32.6)	73 (34.0)	0.779
Dyslipidemia, n (%)	28 (14.5)	30 (14.0)	0.873

(Continued)

Table 1 (Continued).

Baseline Characteristics	Functional independence	Functional dependence or death	P value
CHA2DS2-VASc score	3.0 (2.0–4.0)	3.0 (2.0–5.0)	<0.001
Atrial fibrillation type			<0.001
Paroxysmal	117 (60.6)	73 (34.0)	
Nonparoxysmal	76 (39.4)	142 (66.0)	
NIHSS on admission	5.0 (2.0–11.0)	13.0 (9.0–18.0)	<0.001
Stroke etiology, n (%)			0.092
Cardioembolism only	128 (66.3)	159 (74.0)	
Additional competing etiologies	62 (32.1)	56 (26.0)	
Prior medication use, n (%)			
Antiplatelet agents	45 (23.3)	56 (26.0)	0.523
Anticoagulant agents	36 (18.7)	48 (22.3)	0.360
Treatment during hospitalization, n (%)			
Thrombolysis	64 (33.2)	67 (31.2)	0.666
Thrombectomy	41 (21.2)	63 (29.3)	0.062
Anticoagulant agents	134 (69.4)	147 (68.4)	0.818
Antithrombotics on discharge			
Anticoagulant agents	130 (67.4)	129 (60.0)	0.801
Antiplatelet agents	68 (35.2)	43 (20.0)	0.004
Systolic blood pressure, mmHg	150.0 (134.5–166.0)	154.0 (134.0–168.0)	0.249
Diastolic blood pressure, mmHg	85.0 (77.0–97.0)	89.0 (79.0–98.0)	0.147
White blood cell, 10 ⁹ /L	7.9 (6.5–9.4)	8.5 (6.7–11.2)	0.018
Lymphocyte, 10 ⁹ /L	1.5 (1.1–1.9)	1.0 (0.8–1.5)	<0.001
Monocyte, 10 ⁹ /L	0.4 (0.3–0.5)	0.4 (0.3–0.5)	0.457
Neutrophil, 10 ⁹ /L	5.8 (4.5–7.4)	6.6 (4.9–9.0)	<0.001
Platelet, 10 ¹² /L	206.0 (170.5–246.0)	184.0 (153.0–233.0)	0.002
C-reactive protein, mg/L	2.1 (0.9–4.8)	3.1 (1.5–8.0)	<0.001
NLR	3.9 (2.8–6.3)	6.1 (3.9–10.3)	<0.001
LMR	3.4 (2.7–4.9)	3.0 (2.0–4.0)	<0.001
PLR	140.7 (105.9–206.6)	184.4 (126.8–253.1)	<0.001

Notes: Continuous variables are expressed as median with interquartile range. Categorical variables are expressed as frequency with percentage.

Abbreviations: TIA, transient ischemic attack; NIHSS, The National Institutes of Health Stroke Scale; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-lymphocyte ratio.

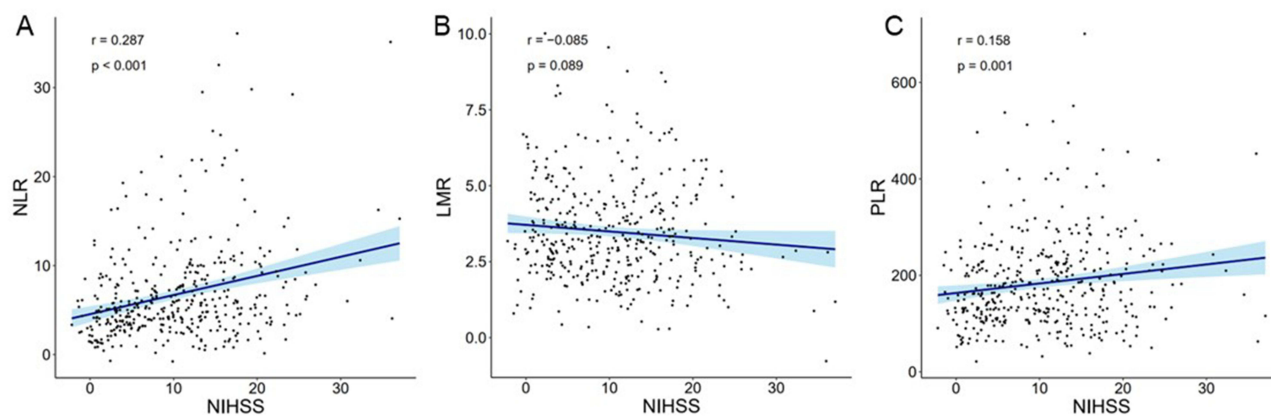


Figure 2 Relationships between composite systemic inflammatory markers and NIHSS score on admission after adjusting for potential covariates in ischemic stroke patients with atrial fibrillation. The blue line and shadow depict linear regressions with 95% confidence intervals, respectively. **(A)** NLR; **(B)** LMR; **(C)** PLR.

Between-Group Differences in Levels of Systemic Inflammatory Markers

Figure 3 shows the violin plots of systemic inflammatory markers between patients with different outcomes. Patients in the functional dependence or death group had significantly higher levels of NLR (6.1 vs 3.9, $P < 0.001$), PLR (184.4 vs 140.7, $P < 0.001$) and lower levels of LMR (3.0 vs 3.4, $P < 0.001$) than patients in the functional independence group. Compared with those without HT, patients who developed the secondary outcome of HT had significantly higher levels of NLR (4.1 vs 6.6, $P < 0.001$), PLR (151.3 vs 187.8, $P < 0.001$) and lower levels of LMR (3.4 vs 2.8, $P < 0.001$). Patients with the secondary outcome of END had significantly higher levels of NLR (7.3 vs 4.6, $P < 0.001$), PLR (212.1 vs 151.7, $P < 0.001$) and lower levels of LMR (2.7 vs 3.3, $P < 0.001$) than those without END.

Univariate and Multivariate Logistic Analyses of Systemic Inflammatory Markers and Adverse Clinical Outcomes

As shown in Table 2, according to the crude model of univariate logistic regression analysis, NLR (OR = 1.157, 95% CI: 1.097–1.221, $P < 0.001$), PLR (OR = 1.005, 95% CI: 1.002–1.007, $P < 0.001$) and LMR (OR = 0.763, 95% CI: 0.675–0.862, $P < 0.001$) were significant predictors of functional dependence or death at the 1-year follow-up. The associations between NLR (OR = 1.139, 95% CI: 1.067–1.216, $P < 0.001$), PLR (OR = 1.005, 95% CI: 1.002–1.008, $P = 0.001$) and LMR (OR = 0.760, 95% CI: 0.652–0.885, $P < 0.001$) and 1-year functional outcome remained significant even after adjustment for potential covariates.

The crude model of univariate logistic regression analysis showed that NLR (OR = 1.102, 95% CI: 1.058–1.149, $P < 0.001$), PLR (OR = 1.004, 95% CI: 1.002–1.006, $P < 0.001$) and LMR (OR = 0.791, 95% CI: 0.697–0.899, $P < 0.001$) were significant predictors of HT. After adjusting for all potential covariates, the NLR (OR = 1.069, 95% CI: 1.020–1.120, $P = 0.006$), PLR (OR = 1.003, 95% CI: 1.000–1.005, $P = 0.023$) and LMR (OR = 0.814, 95% CI: 0.703–0.944, $P = 0.006$) remained independent predictors of HT.

According to the crude model of univariate logistic regression analysis, NLR (OR = 1.100, 95% CI: 1.057–1.145, $P < 0.001$), PLR (OR = 1.006, 95% CI: 1.004–1.008, $P < 0.001$) and LMR (OR = 0.747, 95% CI: 0.629–0.886, $P = 0.001$) were significant predictors of END. Multivariate logistic analysis revealed that NLR (OR = 1.100, 95% CI: 1.051–1.151, $P < 0.001$), PLR (OR = 1.006, 95% CI: 1.003–1.008, $P < 0.001$) and LMR (OR = 0.768, 95% CI: 0.638–0.923, $P = 0.005$) were independent predictors of END.

When systemic inflammatory markers were analyzed as dichotomous variables, the associations between NLR, LMR and PLR remained unchanged (Table 3).

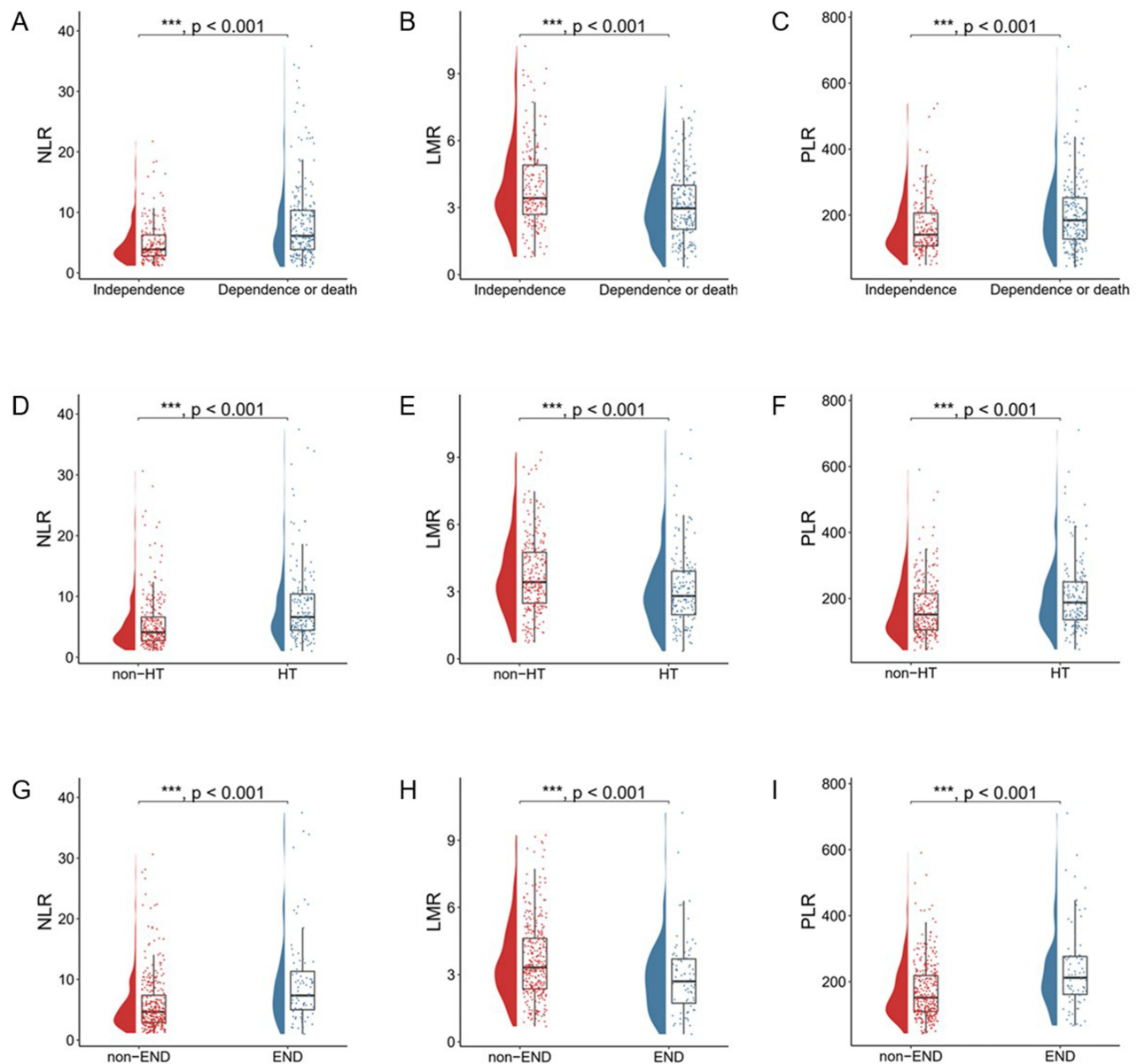


Figure 3 Violin and box plots of composite systemic inflammatory markers among different prognosis groups. **(A)** NLR among functional Independence vs functional dependence or death at 1-year follow-up; **(B)** LMR among functional independence vs functional dependence or death at 1-year follow-up; **(C)** PLR among functional independence vs functional dependence or death at 1-year follow-up; **(D)** NLR among non-HT vs HT; **(E)** LMR among non-HT vs HT; **(F)** PLR among non-HT vs HT; **(G)** NLR among non-END vs END; **(H)** LMR among non-END vs END; **(I)** PLR among non-END vs END. ***p values indicate $p < 0.001$.

Receiver Operating Characteristic Curves of Systemic Inflammatory Markers

ROC curves were used to assess the efficiency of novel composite inflammatory markers and a traditional individual inflammatory marker (C-reactive protein) in predicting outcomes in ischemic stroke patients with AF ([Supplementary Table 1](#) and [Figures 1–3](#)). The area under curve (AUC) of NLR, PLR and LMR in the prediction of 1-year functional outcome were 0.679 (95% CI: 0.625–0.733, $P < 0.001$), 0.625 (95% CI: 0.569–0.682, $P < 0.001$) and 0.625 (95% CI: 0.569–0.681, $P < 0.001$), respectively. Which were all greater than the AUC of C-reactive protein (0.603, 95% CI: 0.546–0.660, $P = 0.001$). The area under curve (AUC) of NLR, PLR and LMR for the prediction of HT were 0.673 (95% CI: 0.618–0.728, $P < 0.001$), 0.618 (95% CI: 0.561–0.675, $P < 0.001$) and 0.611 (95% CI: 0.552–0.670, $P < 0.001$), respectively. Which were all greater than the AUC of C-reactive protein (0.571, 95% CI: 0.512–0.631, $P = 0.002$). The area under curve (AUC) of NLR, PLR and LMR in the prediction of END were 0.687 (95% CI: 0.619–0.754, $P < 0.001$), 0.680 (95% CI: 0.613–0.746, $P < 0.001$) and 0.637 (95%

Table 2 Univariate and Multivariable-Adjusted Odds Ratios and 95% Confidence Intervals for Adverse Outcomes According to NLR, LMR and PLR as Continuous Variables

Outcomes	Crude	P value	Model 1	P value	Model 2	P value
I-year mRS 3–6 (n=215)						
NLR	1.157 (1.097–1.221)	<0.001	1.153 (1.093–1.216)	<0.001	1.139 (1.067–1.216)	<0.001
LMR	0.763 (0.675–0.862)	<0.001	0.779 (0.686–0.885)	<0.001	0.760 (0.652–0.885)	<0.001
PLR	1.005 (1.002–1.007)	<0.001	1.004 (1.002–1.007)	<0.001	1.005 (1.002–1.008)	0.001
HT (n=158)						
NLR	1.102 (1.058–1.149)	<0.001	1.105 (1.060–1.152)	<0.001	1.069 (1.020–1.120)	0.006
LMR	0.791 (0.697–0.899)	<0.001	0.778 (0.681–0.888)	<0.001	0.814 (0.703–0.944)	0.006
PLR	1.004 (1.002–1.006)	<0.001	1.004 (1.002–1.006)	<0.001	1.003 (1.000–1.005)	0.023
END (n=79)						
NLR	1.100 (1.057–1.145)	<0.001	1.100 (1.056–1.145)	<0.001	1.100 (1.051–1.151)	<0.001
LMR	0.747 (0.629–0.886)	0.001	0.748 (0.627–0.891)	0.001	0.768 (0.638–0.923)	0.005
PLR	1.006 (1.004–1.008)	<0.001	1.006 (1.004–1.009)	<0.001	1.006 (1.003–1.008)	<0.001

Notes: Model 1 was adjusted for age and sex. Model 2 was adjusted for model 1 plus NIHSS score on admission, stroke etiology, prior hypertension, diabetes mellitus, stroke or TIA, coronary heart disease, current smoker, use of antiplatelet agents, anticoagulant agents, and atrial fibrillation type.

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-lymphocyte ratio; HT, hemorrhagic transformation; END, early neurological deterioration; NIHSS, The National Institutes of Health Stroke Scale.

Table 3 Univariate and Multivariable-Adjusted Odds Ratios and 95% Confidence Intervals for Adverse Outcomes According to the Median of NLR, LMR and PLR

Outcomes	Crude	P value	Model 1	P value	Model 2	P value
I-year mRS 3–6 (n=215)						
NLR < 5.10	Reference		Reference		Reference	
NLR ≥ 5.10	3.303 (2.200–4.959)	<0.001	3.191 (2.095–4.860)	<0.001	3.307 (1.956–5.593)	<0.001
LMR < 3.21	Reference		Reference		Reference	
LMR ≥ 3.21	0.460 (0.310–0.684)	<0.001	0.521 (0.343–0.792)	0.002	0.429 (0.258–0.715)	0.001
PLR < 160.82	Reference		Reference		Reference	
PLR ≥ 160.82	2.360 (1.585–3.513)	<0.001	2.346 (1.549–3.551)	<0.001	2.597 (1.559–4.327)	<0.001
HT (n=158)						
NLR < 5.10	Reference		Reference		Reference	
NLR ≥ 5.10	3.162 (2.082–4.802)	<0.001	3.241 (2.125–4.943)	<0.001	2.544 (1.578–4.100)	<0.001
LMR < 3.21	Reference		Reference		Reference	
LMR ≥ 3.21	0.471 (0.313–0.707)	<0.001	0.446 (0.293–0.681)	<0.001	0.447 (0.276–0.724)	0.001
PLR < 160.82	Reference		Reference		Reference	
PLR ≥ 160.82	1.869 (1.248–2.800)	0.002	1.905 (1.268–2.863)	0.002	1.650 (1.036–2.627)	0.035

(Continued)

Table 3 (Continued).

Outcomes	Crude	P value	Model 1	P value	Model 2	P value
END (n=79)						
NLR < 5.10	Reference		Reference		Reference	
NLR ≥ 5.10	3.743 (2.156–6.500)	<0.001	3.701 (2.126–6.441)	<0.001	3.489 (1.916–6.354)	<0.001
LMR < 3.21	Reference		Reference		Reference	
LMR ≥ 3.21	0.510 (0.308–0.847)	0.009	0.523 (0.310–0.881)	0.015	0.563 (0.326–0.971)	0.039
PLR < 160.82	Reference		Reference		Reference	
PLR ≥ 160.82	4.057 (2.317–7.103)	<0.001	4.101 (2.335–7.203)	<0.001	3.692 (2.050–6.647)	<0.001

Notes: Model 1 was adjusted for age and sex. Model 2 was adjusted for model 1 plus NIHSS score on admission, stroke etiology, prior hypertension, diabetes mellitus, stroke or TIA, coronary heart disease, current smoker, use of antiplatelet agents, anticoagulant agents, and atrial fibrillation type.

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-lymphocyte ratio; HT, hemorrhagic transformation; END, early neurological deterioration; NIHSS, The National Institutes of Health Stroke Scale.

CI: 0.566–0.707, $P < 0.001$), respectively. Which were all greater than the AUC of C-reactive protein (0.530, 95% CI: 0.456–0.605, $P = 0.415$).

Discussion

In this cohort study, we systematically assessed the associations between composite systemic inflammatory markers and short- and long-term outcomes in ischemic stroke with AF. Several major findings emerged. First, systemic inflammatory markers, including NLR and PLR, showed positive but weak correlations with stroke severity on admission in ischemic stroke patients with AF, whereas the correlation between LMR and stroke severity was not significant. Second, NLR, LMR and PLR were associated with long-term adverse outcomes (functional dependence or death at 1-year follow-up) in ischemic stroke patients with AF, independent of stroke severity and other potential covariates. Third, NLR, LMR and PLR may serve as biomarkers indicative of in-hospital short-term outcomes, including HT and END. Assessment of these systemic inflammatory markers is important for risk stratification and therapeutic strategy development in ischemic stroke patients with AF.

In recent years, accumulating evidence has revealed that inflammation is involved in the pathophysiology of cardiovascular and cerebrovascular diseases and has significant prognostic value.^{18–21} NLR, LMR and PLR are composite inflammatory markers of different combinations of inflammatory parameters and thus may provide more information about immunological activities. It has been reported that composite inflammatory markers are more stable and superior to traditional individual markers in the prediction of stroke prognosis.¹² Additionally, these composite inflammatory markers can be easily calculated from blood cell counts, which are the most commonly used clinical tests and can be obtained via routine blood examination. Previous investigation of the relationship between composite inflammatory markers and outcomes of ischemic stroke demonstrated that inflammatory markers serve as independent prognostic indicators of functional outcome and mortality.^{13,22,23} A previous study reported that NLR, LMR and PLR were associated with END after thrombolysis in patients with ischemic stroke.¹⁴ Additionally, inflammation may also play an important role in the pathophysiology and prognostic outcomes of AF. Markers of systemic inflammation have been linked to atrial remodeling,²⁴ incident AF²⁵ and increased risk of stroke and all-cause mortality in patients with AF.^{26–28} Our study revealed similar results with the previous studies. And further provide evidence on the short- and long-term prognostic value of composite systemic inflammatory markers in ischemic stroke patients with AF, demonstrating that NLR, LMR and PLR were independent predictors of END and adverse functional outcome at 1-year follow-up.

The mechanisms underlying the relationship between systemic inflammation and adverse functional outcomes of ischemic stroke patients with AF may involve multiple pathways. First, damaged brain cells after ischemia triggers

inflammatory response, leading to the release of inflammatory mediators.²⁹ Conversely, peripheral leukocytes can induce the destruction of the blood–brain barrier, cause secondary neuronal damage and aggravate neurological dysfunction.^{30,31} Second, inflammation and thrombosis are closely linked processes.³² In patients with AF, NLR and PLR have been found to be independent risk factors for the presence of left atrial thrombosis,^{22,33} which may contribute to an acute exacerbation of neurological impairment and a greater risk of stroke recurrence and further lead to adverse functional outcomes after ischemic stroke.

Hemorrhagic transformation can occur as a part of ischemic stroke progression and may be another reason for the increased risk of adverse functional outcomes.³⁴ The optimal strategy and timing of resuming anticoagulation therapy after ischemic stroke with AF has always been an intractable clinical problem since resuming anticoagulation may contribute to HT in the acute phase of ischemic stroke.³⁵ Therefore, early and rapid identification of patients at high risk of HT is essential in ischemic stroke patients, especially for those with AF. A previous study demonstrated that NLR is an independent biomarker for major bleeding events.³⁶ Another study aimed at developing a model for predicting HT after ischemic stroke revealed that NLR was related to the risk of HT and enhanced the risk prediction for HT compared to the conventional risk model in real-world practice.³⁷ Our study adds to the emerging body of evidence on the utility of the composite systemic inflammatory markers, including NLR, LMR and PLR, as independent predictors of HT after ischemic stroke in patients with AF. Disruption of the blood–brain barrier by inflammatory mediators may be one of the reasons for the association between inflammatory markers and HT after stroke.¹¹ In addition, it has been reported that peripheral monocytes and neutrophils can act as sources of matrix metalloproteinase-9, which can lead to HT.^{38,39} Regardless, the results of the current study indicate that markers of systemic inflammation may be reliable biomarkers for identifying patients at high risk of HT in the acute phase of ischemic stroke among patients with AF, which may facilitate risk stratification and clinical decision-making.

The main innovations of the present study are as follows: This study revealed several novel composite systemic inflammation biomarkers (NLR, PLR and LMR), which can easily be obtained from routine clinical practice, and may be used as predictive biomarkers for predicting HT, END, and long-term adverse functional outcomes in ischemic stroke patients with AF. These findings indicate that early measurement of inflammatory markers may improve the identification of ischemic stroke patients with AF at greatest risk of END or HT and adverse long-term functional outcomes. Incorporation of these markers into clinical decision-making may allow us to choose patients who will benefit the most from intensive monitoring, early anticoagulant therapy and avoid exposing other patients with substantial HT risk. Whether treatments targeting inflammatory pathways can prevent HT, END and improve functional outcomes deserves further investigation. Our study has some potential limitations. First, we analyzed data of inflammatory markers only on admission. The systemic inflammatory indices might be dynamic and change over time. Although the current study revealed the important role of early inflammatory markers in ischemic stroke patients with AF, future studies are needed to assess the dynamic changes in these markers after stroke and determine their prognostic value in ischemic stroke patients with AF. Second, due to the observational nature of this study, the causal relationship between higher levels of inflammatory markers and adverse outcomes cannot be determined. Future studies should determine whether the associations between these composite inflammatory markers and adverse outcomes in ischemic stroke patients with AF are only epiphenomenon or whether they reflect causal relationships. Third, HT after ischemic stroke was assessed only during hospitalization, and HT may occur in some patients after discharge. Therefore, HT events may have been underestimated. Finally, information on stroke recurrence and its etiology was not available in the current study, and the association between systemic inflammatory markers and stroke recurrence awaits further study.

Conclusion

In summary, our study revealed that composite inflammatory markers (including NLR, PLR and LMR) can serve as simple and universally available independent prognostic biomarkers for HT, END and adverse functional outcomes at 1-year follow-up in ischemic stroke patients with AF. Close monitoring of these inflammatory markers may be necessary for risk stratification and clinical decision-making. Whether treatments for inhibiting inflammatory response can improve short- and long-term outcomes in ischemic stroke patients with AF deserves further investigation.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author (Jing Yan) on reasonable request.

Ethics Approval and Informed Consent

This study was approved by the ethics committee of Beijing Tiantan Hospital, Capital Medical University (No. KY2023-163-01). Written informed consent was obtained from all patients or their legal guardians. This study was conducted according to the Declaration of Helsinki and institutional guidelines.

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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. All authors have read and approved the final submitted manuscript.

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Disclosure

The authors report no conflicts of interest in this work.

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