The Association of Neutrophil-Lymphocyte Ratio, Platelet-Lymphocyte Ratio and Lymphocyte-Monocyte Ratio With Post-Thrombolysis Early Neurological Outcomes in Patients With Acute Ischemic Stroke

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Research

**Keywords:** acute ischemic stroke, early neurological deterioration, early neurological improvement, intravenous thrombolysis, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, lymphocyte-monocyte ratio

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Abstract

Background and Purpose: To investigate the association of neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and lymphocyte-monocyte ratio (LMR) with post-thrombolysis early neurological outcomes including early neurological improvement (ENI) and early neurological deterioration (END) in patients with acute ischemic stroke (AIS).

Methods: AIS patients undergoing intravenous thrombolysis were enrolled from April 2016 to September 2019. Blood cell counts were sampled before thrombolysis. Post-thrombolysis END was defined as National Institutes of Health Stroke Scale (NIHSS) score increase of ≥4 within 24 hours after thrombolysis. Post-thrombolysis ENI was defined as NIHSS score decrease of ≥4 or complete recovery within 24 hours. Multivariable logistic regression analyses were performed to explore the relationship of NLR, PLR and LMR to post-thrombolysis END and ENI. We also used receiver operating characteristic curve analysis to assess the discriminative ability of three ratios in predicting END and ENI.

Results: Among 1060 recruited patients, a total of 193 (18.2%) were diagnosed with ENI and 398 (37.5%) were diagnosed with END. Multivariable logistic models indicated that NLR (odds ratio [OR], 1.652; 95% confidence interval [CI] 1.510-1.807, P=0.001) and PLR (OR, 1.015; 95% CI 1.012-1.018, P=0.001) were independent factors for post-thrombolysis END. Moreover, NLR (OR, 0.686; 95% CI 0.631-0.745, P=0.001), PLR (OR, 0.997; 95% CI 0.994-0.999, P=0.006) and LMR (OR, 1.170; 95% CI 1.043-1.313, P=0.008) served as independent factors for post-thrombolysis ENI. Area under curve (AUC) of NLR, PLR and LMR to discriminate END were 0.763, 0.703 and 0.551, respectively. AUC of NLR, PLR and LMR to discriminate ENI were 0.695, 0.530 and 0.547, respectively.

Conclusions: NLR and PLR were associated with and may predict post-thrombolysis END. NLR, PLR and LMR were related to post-thrombolysis ENI.

Introduction

Stroke is one of the main reasons for mortality and morbidity at the national level in China [1, 2]. The efficacy of thrombolysis with intravenous recombinant tissue plasminogen activator was demonstrated for the patients with acute ischemic stroke (AIS) [3–5]. It has been reported that rapid recovery, which is described as early neurological improvement (ENI), can be observed in a significant proportion of AIS patients within the first 24 hours after intravenous thrombolysis [3, 4]. However, there are still several patients whose symptoms would worsen and neurological deficits may aggravate within 24 hours after intravenous thrombolysis, named as early neurological deterioration (END) [6–8]. Previous researches indicate that post-thrombolysis early neurological outcomes, including post-thrombolysis END as well as post-thrombolysis ENI, are relevant to the prognosis of patients treated with intravenous thrombolysis [9, 10]. Post-thrombolysis ENI can promote acceptable long-term outcomes for the patients with AIS [9], and END results in the increasing likelihood of mortality and morbidity [10]. Therefore, it is significant to
explore the risk factors and the measurable biomarkers of post-thrombolysis early neurological outcomes in AIS patients.

Numerous studies have demonstrated that neuroinflammatory response play an essential role in the pathophysiology of ischemic stroke [11–14]. Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and lymphocyte-monocyte ratio (LMR) have recently been reported as potential novel biomarkers of baseline inflammatory process and could serve as outstanding predictors in patients with ischemic stroke [15, 16]. NLR, PLR and LMR may have the ability to predict functional outcome in AIS patients treated with intravenous thrombolysis [17–19]. Our previous research manifested that NLR and PLR might be connected with stroke-associated infection after endovascular treatment [20]. Goyal and colleagues found NLR on admission may be able to function as a prognostic biomarker of outcomes in patients with large vessel occlusion stroke [21]. What is more, previous studies showed these three novel composite inflammatory ratios, which were mentioned above, could have superior predictive capacity to those of traditional inflammatory factors [22]. Nevertheless, the relationship between these composite inflammatory ratios and post-thrombolysis early neurological outcomes in AIS patients remains uncertain and worth exploring.

In this study, we aimed to investigate the association of composite inflammatory ratios before thrombolysis, including NLR, PLR and LMR, with post-thrombolysis END as well as ENI in AIS patients. Furthermore, we planned to explore the utility of these composite inflammatory ratios in predicting post-thrombolysis END and post-thrombolysis ENI.

**Methods**

**Study design and participants**

AIS patients undergoing intravenous thrombolysis within 4.5 hours were recruited from Nanjing First Hospital, Haimen Hospital Affiliated to Nantong University and Nantong Third Peoples Hospital. All the patients were treated in the stroke units and received standard treatments, for instance, antiplatelet therapy and statin therapy. Eligible participants were enrolled in the final analysis if they met the following criteria. Informed consent was obtained from participants or their legal representatives. This study was approved by the Ethics Committee of Nanjing First Hospital, Haimen Hospital Affiliated to Nantong University as well as Nantong Third Peoples Hospital.

**Inclusion criteria:**

(1) admission within 4.5 hours after onset;

(2) treated with intravenous thrombolysis;

(3) 18 years or older.
Exclusion criteria:

1. severe inflammatory diseases or infectious diseases;

2. incomplete clinical data;

3. The neurological deficits of patients cannot be evaluated over the following 24 hours after admission.

Data acquisition

On the day of admission, all the participants underwent standard assessments of demographic characteristics (age, sex and body mass index), vascular risk factors (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, current smoking, current drinking, previous stroke, Peripheral artery disease and coronary artery disease), medication use history (previous antiplatelet, previous anticoagulation and previous statin), clinical assessment (stroke severity, blood pressure, hemorrhagic transformation [HT], onset to treatment time [OTT], proximal arterial occlusion [PAO] and endovascular treatment), stroke subtype, lesion location, and laboratory data. Systolic blood pressure and diastolic blood pressure were measured and recorded immediately after admission. Computed tomography, magnetic resonance, electrocardiogram, echocardiography, carotid ultrasonography and transcranial doppler were performed for assessing the lesion location, stroke subtype, HT as well as PAO. Stroke subtype was classified according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [23]. Laboratory data included total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), fasting blood glucose (FBG) and hypersensitive C-reactive protein (Hs-CRP), NLR, PLR and LMR.

Measurement of composite inflammatory ratios from blood cell counts

Blood cell counts, including total leukocyte counts, neutrophil counts, lymphocyte counts, monocyte counts as well as platelet counts, were sampled from each participant in emergency room on admission before intravenous thrombolysis. Then, the cell counts were analyzed by an auto-analyzer (XE-2100, Sysmex, Kobe, Japan) and utilized to calculate composite inflammatory ratios (including NLR, PLR and LMR). NLR was calculated as neutrophil counts/lymphocyte counts. PLR was calculated as platelet counts/lymphocyte counts. LMR was calculated as lymphocyte counts/monocyte counts.

Definition of post-thrombolysis early neurological deterioration and early neurological improvement

Stroke severity was assessed using NIHSS score on the day of admission and continued 2–3 times every day over the following 24 days after admission by two certified neurologists. All the certified neurologists in the three centers underwent unified training for NIHSS score evaluation and were blind to our study. In case of disagreement about the NIHSS score evaluation, a third neurologist in this center was invited for a final decision. Post-thrombolysis END was defined as an increase in the NIHSS score by ≥ 4 points in the total score within 24 hours after thrombolysis [7, 24, 25]. Meanwhile, post-thrombolysis ENI was
defined as a decrease in the NIHSS score by ≥ 4 points in the total score or a complete resolution of neurological deficits within 24 hours after thrombolysis [26–28].

**Statistical analysis**

Statistical analyses were performed using R version 4.0.3 software (http://www.R-project.org/). All participants were categorized into 3 groups according to post-thrombolysis early neurological outcomes (END group, without END or ENI group as well as ENI group). Categorical variables were expressed as n (%) and continuous variables were expressed as means (standard deviation, SD) or medians (interquartile range, IQR). Differences in baseline characteristics between groups were analyzed using one-way ANOVA test or Mann-Whitney U test for continuous variables as well as the Chi-squared test or Fisher’s exact test for categorical variables, as appropriate. We used the violin plots to show the distribution of NLR, PLR and LMR among END group, without END or ENI group as well as ENI group. We also used univariate logistic regression analysis to detect the risk factors of END and ENI. Multivariable analysis was adjusted for all potential confounders with statistically significant association at \( P < 0.1 \) in univariate regression analysis. In the model 1 for post-thrombolysis END and model 4 for post-thrombolysis ENI, ‘composite inflammatory ratio’ means NLR. In the model 2 for post-thrombolysis END and model 5 for post-thrombolysis ENI, ‘composite inflammatory ratio’ means PLR. In the model 3 for post-thrombolysis END and model 6 for post-thrombolysis ENI, ‘composite inflammatory ratio’ means LMR. A MedCalc 15.6.0 (MedCalc Software Acacialaan 22, B-8400 Ostend, Belgium) packet program was used to obtain receiver operating characteristic (ROC) curve to test the overall discriminative ability of NLR, PLR and LMR for post-thrombolysis END as well as post-thrombolysis ENI. Youden Index was calculated as the Sensitivity + Specificity−1.

**Results**

From April 2016 to September 2019, a total of 1235 AIS patients treated with intravenous thrombolysis were screened for 24 hours in this study (Additional file 1: Figure S1). Ninety-two patients’ neurological deficits could not be evaluated over the following 24 hours after admission. Meanwhile, eighty-three patients were excluded for the following reasons: nineteen patients were excluded for severe inflammatory or infectious diseases, and sixty-four patients were excluded for incomplete data. A total of 1060 subjects were included for the final analysis.

After admission, post-thrombolysis END was observed in 193 patients (18.2%), and ENI was observed in 398 patients (37.5%), respectively. Baseline characteristics of the study participants according to post-thrombolysis early neurological outcomes (END group, without END or ENI group as well as ENI group) are provided in Table 1. Significant differences among the three group are described as follows: age \((P = 0.001)\), previous antiplatelet \((P = 0.002)\), NIHSS \((P = 0.001)\), diastolic blood pressure \((P = 0.034)\), HT \((P = 0.001)\), OTT \((P = 0.002)\), PAO \((P = 0.002)\), stroke subtype \((P = 0.001)\), FBG \((P = 0.001)\), Hs-CRP \((P = 0.001)\), NLR \((P = 0.001)\), PLR \((P = 0.001)\) and LMR \((P = 0.014)\). Figure 1 showed the violin plots of NLR, PLR and LMR among three groups. NLR decreased gradually among END group, without END or ENI group as well as ENI group \((6.09 [4.43, 8.02] versus 4.15 [3.14, 5.26] versus 3.17 [2.54, 4.22], P = 0.001, Fig. 1A)\). PLR
also exhibited different among three groups (179.1 [122.1, 251.1] versus 126.7 [98.8, 158.0] versus 133.1 [102.5, 168.2], \( P = 0.001 \), Fig. 1B). LMR increased gradually among three groups (3.03 [2.50, 4.13] versus 3.36 [2.48, 4.34] versus 3.63 [2.61, 4.52], \( P = 0.014 \), Fig. 1C).
Table 1  
Demographics and Clinical Characteristics of the subgroup according to early neurological outcome

| Variable                        | END group (n = 193) | Without END or ENI group (n = 469) | ENI group (n = 398) | P     |
|--------------------------------|---------------------|------------------------------------|---------------------|-------|
| Demographic characteristics    |                     |                                    |                     |       |
| Age, years                     | 73.2 ± 11.5         | 69.6 ± 12.0                        | 68.1 ± 12.1         | 0.001 |
| Male, n (%)                    | 121 (62.7)          | 319 (68.0)                         | 260 (65.3)          | 0.303 |
| BMI, kg/m²                      | 24.4 ± 3.6          | 24.1 ± 3.5                         | 23.9 ± 3.6          | 0.242 |
| Vascular risk factors, n (%)   |                     |                                    |                     |       |
| Hypertension                   | 132 (68.4)          | 315 (67.2)                         | 275 (69.1)          | 0.816 |
| Diabetes mellitus              | 51 (26.4)           | 116 (24.7)                         | 77 (19.3)           | 0.079 |
| Dyslipidemia                   | 51 (26.4)           | 120 (25.6)                         | 114 (28.6)          | 0.592 |
| Atrial fibrillation            | 49 (25.4)           | 96 (20.5)                          | 75 (18.8)           | 0.180 |
| Current smoking                | 59 (30.6)           | 149 (31.8)                         | 129 (32.4)          | 0.903 |
| Current drinking               | 69 (35.8)           | 145 (30.9)                         | 129 (32.4)          | 0.482 |
| Previous stroke                | 38 (19.7)           | 114 (24.3)                         | 80 (20.1)           | 0.238 |
| Peripheral artery disease      | 11 (5.7)            | 30 (6.3)                           | 30 (7.5)            | 0.662 |
| Coronary artery disease        | 38 (19.7)           | 83 (17.7)                          | 81 (20.4)           | 0.603 |
| Medication use history, n (%)  |                     |                                    |                     |       |
| Previous antiplatelet          | 21 (10.9)           | 88 (18.8)                          | 91 (22.9)           | 0.002 |
| Previous anticoagulation       | 15 (7.8)            | 49 (10.4)                          | 42 (10.6)           | 0.521 |
| Previous statin                | 5 (2.6)             | 11 (2.3)                           | 5 (1.3)             | 0.391 |

Abbreviation: END, early neurological deterioration; ENI, Early neurological improvement; BMI, body mass index; NIHSS, national institute of health stroke scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; HT, hemorrhagic transformation; OTT, onset to treatment time; PAO, proximal arterial occlusion; LAA, large-artery atherosclerosis; CE, cardioembolism; SAO, small-artery occlusion; SOE: stroke of other determined etiology; SUE: stroke of undetermined etiology; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein; HDL, high density lipoprotein; FBG, fasting blood glucose; Hs-CRP, hyper-sensitive c-reactive protein; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio.
| Variable                          | END group (n = 193) | Without END or ENI group (n = 469) | ENI group (n = 398) | P   |
|----------------------------------|---------------------|-------------------------------------|---------------------|-----|
| **Clinical assessment**          |                     |                                     |                     |     |
| NIHSS, score                     | 11 (5, 17)          | 5 (3, 12)                           | 8 (4, 14)           | 0.001 |
| SBP, mmHg                        | 146.9 ± 23.6        | 151.8 ± 25.7                       | 148.3 ± 22.6        | 0.171 |
| DBP, mmHg                        | 87.8 ± 16.2         | 89.4 ± 14.4                        | 86.8 ± 14.6         | 0.034 |
| HT, n (%)                        | 32 (16.6)           | 37 (7.9)                           | 13 (3.3)            | 0.001 |
| OTT, minute                      | 165.00 (120.00, 200.00) | 160.00 (115.00, 200.00)       | 130.00 (90.00, 180.00) | 0.001 |
| PAO, %                           | 77 (39.9)           | 134 (28.6)                         | 91 (22.9)           | 0.001 |
| **Endovascular treatment, %**    | 43 (22.2)           | 77 (16.4)                          | 65 (16.3)           | 0.148 |
| **Stroke subtype, n (%)**        |                     |                                     |                     | 0.001 |
| LAA                              | 73 (37.8)           | 169 (36.0)                         | 147 (36.9)          |     |
| CE                               | 62 (32.1)           | 120 (25.6)                         | 132 (33.2)          |     |
| SAO                              | 27 (14.0)           | 138 (29.4)                         | 83 (20.9)           |     |
| SOE                              | 8 (4.1)             | 16 (3.4)                           | 8 (2.0)             |     |
| SUE                              | 23 (12.0)           | 26 (5.6)                           | 28 (7.0)            |     |
| **Lesion location, n (%)**       |                     |                                     |                     | 0.616 |
| Anterior circulation             | 149 (77.2)          | 357 (76.1)                         | 294 (73.9)          |     |
| Posterior circulation            | 44 (22.8)           | 112 (23.9)                         | 104 (20.1)          |     |
| **Laboratory data**              |                     |                                     |                     |     |
| TC, mmol/L                       | 4.41 ± 1.11         | 4.38 ± 1.11                        | 4.32 ± 1.10         | 0.591 |
| TG, mmol/L                       | 1.14 (0.82, 1.68)   | 1.19 (0.86, 1.70)                  | 1.20 (0.85, 1.75)   | 0.744 |
| HDL, mmol/L                      | 1.21 ± 0.68         | 1.14 ± 0.36                        | 1.13 ± 0.49         | 0.214 |
| LDL, mmol/L                      | 2.53 (1.95, 3.20)   | 2.63 (1.98, 3.23)                  | 2.59 (1.96, 3.27)   | 0.733 |

Abbreviation: END, early neurological deterioration; ENI, Early neurological improvement; BMI, body mass index; NIHSS, national institute of health stroke scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; HT, hemorrhagic transformation; OTT, onset to treatment time; PAO, proximal arterial occlusion; LAA, large-artery atherosclerosis; CE, cardioembolism; SAO, small-artery occlusion; SOE: stroke of other determined etiology; SUE: stroke of undetermined etiology; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein; HDL, high density lipoprotein; FBG, fasting blood glucose; Hs-CRP, hyper-sensitive c-reactive protein; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio.
| Variable | END group (n = 193) | Without END or ENI group (n = 469) | ENI group (n = 398) | P      |
|----------|---------------------|-------------------------------------|---------------------|--------|
| FBG, mmol/L | 7.30 ± 2.95 | 6.28 ± 2.47 | 6.86 ± 3.19 | 0.001  |
| Hs-CRP, mg/L | 7.25 (2.66, 14.55) | 4.28 (2.11, 7.55) | 4.85 (2.16, 8.61) | 0.001  |
| NLR | 6.09 (4.43, 8.02) | 4.15 (3.14, 5.26) | 3.17 (2.54, 4.22) | 0.001  |
| PLR | 179.1 (122.1, 251.1) | 126.7 (98.8, 158.0) | 133.1 (102.5, 168.2) | 0.001  |
| LMR | 3.03 (2.50, 4.13) | 3.36 (2.48, 4.34) | 3.63 (2.61, 4.52) | 0.014  |

Abbreviation: END, early neurological deterioration; ENI, Early neurological improvement; BMI, body mass index; NIHSS, national institute of health stroke scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; HT, hemorrhagic transformation; OTT, onset to treatment time; PAO, proximal arterial occlusion; LAA, large-artery atherosclerosis; CE, cardioembolism; SAO, small-artery occlusion; SOE: stroke of other determined etiology; SUE: stroke of undetermined etiology; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein; HDL, high density lipoprotein; FBG, fasting blood glucose; Hs-CRP, hyper-sensitive c-reactive protein; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio.

Table 2 illustrated the results of univariate logistic regression analysis for post-thrombolysis END and post-thrombolysis ENI. Univariate logistic regression analysis for END showed that age, atrial fibrillation, previous antiplatelet, NIHSS, HT, OTT, PAO, endovascular treatment, stroke subtype, FBG, Hs-CRP, NLR, PLR and LMR might be associated with post-thrombolysis END (P < 0.1). Furthermore, Univariate logistic regression analysis also exhibited that age, diabetes mellitus, previous antiplatelet, diastolic blood pressure, HT, OTT, PAO, NLR, PLR and LMR might be related to post-thrombolysis ENI (P < 0.1).
Table 2
Univariate Logistic regression analysis for risk factors with post-thrombolysis END and post-thrombolysis ENI

| Variable                        | Crude model for post-thrombolysis END |   | Crude model for post-thrombolysis ENI |   |
|--------------------------------|--------------------------------------|---|--------------------------------------|---|
|                                | OR (95%CI)                           | P | OR (95%CI)                           | P |
| Demographic characteristics    |                                      |   |                                      |   |
| Age, years                     | 1.033 (1.018–1.048)                  | 0.001 | 0.982 (0.972–0.993)                  | 0.002 |
| Male, n (%)                    | 0.813 (0.587–1.125)                  | 0.211 | 0.950 (0.729–1.237)                  | 0.702 |
| BMI, kg/m2                     | 1.032 (0.987–1.079)                  | 0.169 | 0.974 (0.940–1.010)                  | 0.159 |
| Vascular risk factors, n (%)   |                                      |   |                                      |   |
| Hypertension                   | 1.033 (0.737–1.447)                  | 0.851 | 1.070 (0.819–1.399)                  | 0.629 |
| Diabetes mellitus              | 1.254 (0.877–1.794)                  | 0.215 | 0.711 (0.524–0.964)                  | 0.028 |
| Dyslipidemia                   | 0.972 (0.682–1.383)                  | 0.873 | 1.153 (0.872–1.523)                  | 0.317 |
| Atrial fibrillation            | 1.385 (0.962–1.995)                  | 0.080 | 0.828 (0.606–1.130)                  | 0.235 |
| Current smoking                | 0.933 (0.665–1.308)                  | 0.687 | 1.047 (0.802–1.366)                  | 0.737 |
| Current drinking               | 1.204 (0.868–1.671)                  | 0.226 | 1.004 (0.770–1.309)                  | 0.977 |
| Previous stroke                | 0.847 (0.574–1.249)                  | 0.402 | 0.848 (0.625–1.150)                  | 0.288 |
| Peripheral artery disease      | 0.813 (0.419–1.577)                  | 0.540 | 1.235 (0.758–2.012)                  | 0.397 |
| Coronary artery disease        | 1.049 (0.708–1.555)                  | 0.810 | 1.140 (0.833–1.561)                  | 0.412 |
| Medication use history, n (%)  |                                      |   |                                      |   |
| Previous antiplatelet          | 0.469 (0.290–0.760)                  | 0.002 | 1.504 (1.102–2.053)                  | 0.010 |
| Previous anticoagulation       | 1.415 (0.512–3.909)                  | 0.504 | 0.514 (0.187–1.413)                  | 0.197 |
| Previous statin                | 0.848 (0.638–1.127)                  | 0.256 | 1.050 (0.855–1.289)                  | 0.642 |

Abbreviation: END, early neurological deterioration; ENI, Early neurological improvement; OR, odds ratio; CI, confidence interval; BMI, body mass index; NIHSS, national institute of health stroke scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; HT, hemorrhagic transformation; OTT, onset to treatment time; PAO, proximal arterial occlusion; LAA, large-artery atherosclerosis; CE, cardioembolism; SAO, small-artery occlusion; SOE: stroke of other determined etiology; SUE: stroke of undetermined etiology; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein; HDL, high density lipoprotein; FBG, fasting blood glucose; Hs-CRP, hyper-sensitive c-reactive protein; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio.
|                                   | Crude model for post-thrombolysis END |                  | Crude model for post-thrombolysis ENI |                  |
|-----------------------------------|---------------------------------------|-----------------|----------------------------------------|-----------------|
| NIHSS, score                      | 1.051 (1.030–1.072)                   | 0.001           | 1.007 (0.990–1.024)                    | 0.446           |
| SBP, mmHg                         | 0.995 (0.989–1.002)                   | 0.195           | 0.998 (0.993–1.002)                    | 0.359           |
| DBP, mmHg                         | 0.998 (0.993–1.009)                   | 0.737           | 0.990 (0.982–0.999)                    | 0.023           |
| HT, n (%)                         | 3.248 (2.020–5.221)                   | 0.001           | 0.290 (0.158–0.532)                    | 0.001           |
| OTT, minute                       | 1.004 (1.001–1.006)                   | 0.011           | 0.993 (0.990–0.995)                    | 0.001           |
| PAO, %                            | 1.894 (1.368–2.623)                   | 0.001           | 0.634 (0.476–0.843)                    | 0.002           |
| Endovascular treatment, %         | 1.464 (0.997–2.148)                   | 0.052           | 0.882 (0.633–1.228)                    | 0.456           |
| Stroke subtype, n (%)             |                                       |                 |                                        |                 |
| LAA                               | Reference                             |                 | Reference                              |                 |
| CE                                | 1.065 (0.731–1.552)                   | 0.743           | 1.194 (0.881–1.618)                    | 0.252           |
| SAO                               | 0.529 (0.329–0.849)                   | 0.008           | 0.828 (0.592–1.157)                    | 0.268           |
| SOE                               | 1.443 (0.623–3.341)                   | 0.392           | 0.549 (0.240–1.253)                    | 0.154           |
| SUE                               | 1.844 (1.063–3.197)                   | 0.029           | 0.941 (0.566–1.563)                    | 0.813           |
| Lesion location, n (%)            |                                       |                 |                                        |                 |
| Anterior circulation              | 1.124 (0.776–1.626)                   | 0.537           | 0.872 (0.654–1.161)                    | 0.347           |
| Posterior circulation             | 0.890 (0.615–1.288)                   | 0.537           | 1.147 (0.861–1.528)                    | 0.347           |
| Laboratory data                   |                                       |                 |                                        |                 |
| TC, mmol/L                        | 1.003 (0.996–1.010)                   | 0.447           | 0.999 (0.994–1.003)                    | 0.591           |
| TG, mmol/L                        | 1.000 (0.998–1.002)                   | 0.623           | 1.001 (0.996–1.005)                    | 0.655           |
| HDL, mmol/L                       | 1.255 (0.953–1.654)                   | 0.106           | 0.889 (0.664–1.190)                    | 0.428           |
| LDL, mmol/L                       | 0.999 (0.992–1.005)                   | 0.708           | 1.002 (0.998–1.005)                    | 0.415           |
| FBG, mmol/L                       | 1.084 (1.032–1.138)                   | 0.002           | 1.035 (0.991–1.080)                    | 0.119           |

Abbreviation: END, early neurological deterioration; ENI, Early neurological improvement; OR, odds ratio; CI, confidence interval; BMI, body mass index; NIHSS, national institute of health stroke scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; HT, hemorrhagic transformation; OTT, onset to treatment time; PAO, proximal arterial occlusion; LAA, large-artery atherosclerosis; CE, cardioembolism; SAO, small-artery occlusion; SOE, stroke of other determined etiology; SUE, stroke of undetermined etiology; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein; HDL, high density lipoprotein; FBG, fasting blood glucose; Hs-CRP, hyper-sensitive c-reactive protein; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio.
Table 3 displayed the results of the multivariate logistic regression model for post-thrombolysis END. In the multivariate logistic regression model including NLR (Model 1), NLR was identified as an independent factor for post-thrombolysis END (odds ratio [OR], 1.652; 95% confidence interval [CI] 1.510–1.807, \( P = 0.001 \)) after adjustment for all potential confounders. In the multivariate logistic regression model including PLR (Model 2), PLR remained an independent factor for post-thrombolysis END (OR, 1.015; 95% CI 1.012–1.018, \( P = 0.001 \)). However, in the multivariate logistic regression model including LMR (Model 3), it showed that LMR was not the independent factor for post-thrombolysis END (OR, 0.880; 95% CI 0.760–1.020, \( P = 0.090 \)).

| Abbreviation: END, early neurological deterioration; ENI, Early neurological improvement; OR, odds ratio; CI, confidence interval; BMI, body mass index; NIHSS, national institute of health stroke scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; HT, hemorrhagic transformation; OTT, onset to treatment time; PAO, proximal arterial occlusion; LAA, large-artery atherosclerosis; CE, cardioembolism; SAO, small-artery occlusion; SOE: stroke of other determined etiology; SUE: stroke of undetermined etiology; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein; HDL, high density lipoprotein; FBG, fasting blood glucose; Hs-CRP, hyper-sensitive c-reactive protein; NLR, neutrophil-lymphocyte ratio; PLR. platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio. | Crude model for post-thrombolysis END | Crude model for post-thrombolysis ENI |
|---|---|---|
| Hs-CRP, mg/L | 1.033 (1.018–1.048) | 0.001 | 0.997 (0.984–1.010) | 0.630 |
| NLR | 1.661 (1.528–1.807) | 0.001 | 0.678 (0.626–0.735) | 0.001 |
| PLR | 1.014 (1.011–1.017) | 0.001 | 0.997 (0.995–0.999) | 0.004 |
| LMR | 0.869 (0.758–0.996) | 0.043 | 1.152 (1.033–1.284) | 0.011 |
| Variable                  | Model 1: association of NLR with post-thrombolysis END |                  | Model 2: association of PLR with post-thrombolysis END |                  | Model 3: association of LMR with post-thrombolysis END |                  |
|--------------------------|--------------------------------------------------------|------------------|--------------------------------------------------------|------------------|--------------------------------------------------------|------------------|
|                          | OR (95%CI)                                             | P                | OR (95%CI)                                             | P                | OR (95%CI)                                             | P                |
| Age                      | 1.018 (1.001–1.035)                                    | 0.038            | 1.028 (1.011–1.045)                                    | 0.001            | 1.023 (1.007–1.039)                                    | 0.004            |
| Atrial fibrillation      | 1.014 (0.613–1.676)                                    | 0.957            | 1.185 (0.729–1.926)                                    | 0.494            | 1.038 (0.657–1.640)                                    | 0.874            |
| Previous antiplatelet    | 0.526 (0.302–0.915)                                    | 0.023            | 0.544 (0.320–0.927)                                    | 0.025            | 0.462 (0.278–0.767)                                    | 0.003            |
| NIHSS                    | 1.029 (1.004–1.056)                                    | 0.025            | 1.030 (1.005–1.056)                                    | 0.019            | 1.029 (1.006–1.053)                                    | 0.014            |
| HT                       | 1.973 (1.102–3.534)                                    | 0.022            | 2.892 (1.621–5.161)                                    | 0.001            | 2.581 (1.536–4.337)                                    | 0.001            |
| OTT                      | 1.004 (1.001–1.008)                                    | 0.011            | 1.005 (1.001–1.008)                                    | 0.007            | 1.004 (1.001–1.007)                                    | 0.012            |
| PAO                      | 1.890 (1.107–3.226)                                    | 0.020            | 2.014 (1.195–3.395)                                    | 0.009            | 2.032 (1.263–3.270)                                    | 0.003            |
| Endovascular treatment   | 0.631 (0.335–1.188)                                    | 0.154            | 0.661 (0.355–1.229)                                    | 0.191            | 0.623 (0.353–1.098)                                    | 0.102            |
| Stroke subtype           |                                                        |                  |                                                        |                  |                                                        |                  |
| LAA                      | Reference                                              |                  | Reference                                              |                  | Reference                                              |                  |
| CE                       | 0.954 (0.579–1.573)                                    | 0.854            | 0.823 (0.506–1.337)                                    | 0.437            | 0.829 (0.527–1.304)                                    | 0.417            |
| SAO                      | 0.671 (0.388–1.163)                                    | 0.155            | 0.701 (0.408–1.202)                                    | 0.197            | 0.644 (0.389–1.068)                                    | 0.088            |

* In the Model 1: ‘composite inflammatory ratio’ means NLR;

In the Model 2: ‘composite inflammatory ratio’ means PLR;

In the Model 3: ‘composite inflammatory ratio’ means LMR;

Abbreviation: NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; END, early neurological deterioration; OR, odds ratio; CI, confidence interval; NIHSS, national institute of health stroke scale; HT, hemorrhagic transformation; OTT, onset to treatment time; PAO, proximal arterial occlusion; LAA, large-artery atherosclerosis; CE, cardioembolism; SAO, small-artery occlusion; SOE: stroke of other determined etiology; SUE: stroke of undetermined etiology; FBG, fasting blood glucose; Hs-CRP, hyper-sensitive c-reactive protein.
| Model 1: association of NLR with post-thrombolysis END | Model 2: association of PLR with post-thrombolysis END | Model 3: association of LMR with post-thrombolysis END |
|------------------------------------------------------|------------------------------------------------------|------------------------------------------------------|
| **SOE**                                              | **SUE**                                              | **FBG**                                              |
| 2.576 (0.956–6.944)                                  | 2.074 (0.790–5.444)                                  | 1.686 (0.703–4.040)                                  |
| 0.061                                                | 0.139                                                | 0.242                                                |
| **SUE**                                              | **FBG**                                              | **Hs-CRP**                                           |
| 1.907 (0.967–3.764)                                  | 1.073 (1.009–1.141)                                  | 1.030 (1.012–1.047)                                  |
| 0.063                                                | 0.024                                                | 0.001                                                |
| **FBG**                                              | **Hs-CRP**                                           | **Composite inflammatory ratio***                   |
| 1.073 (1.009–1.141)                                  | 1.030 (1.012–1.047)                                  | 1.652 (1.510–1.807)                                  |
| 0.024                                                | 0.001                                                | 0.001                                                |
| **Hs-CRP**                                           | **Composite inflammatory ratio***                   | **Composite inflammatory ratio***                   |
| 1.030 (1.012–1.047)                                  | 1.652 (1.510–1.807)                                  | 1.015 (1.012–1.018)                                  |
| 0.001                                                | 0.001                                                | 0.001                                                |
| **Composite inflammatory ratio***                   | **Composite inflammatory ratio***                   | **Composite inflammatory ratio***                   |
| 1.652 (1.510–1.807)                                  | 1.015 (1.012–1.018)                                  | 0.880 (0.760–1.020)                                  |
| 0.001                                                | 0.001                                                | 0.090                                                |

* In the Model 1: ‘composite inflammatory ratio’ means NLR;

In the Model 2: ‘composite inflammatory ratio’ means PLR;

In the Model 3: ‘composite inflammatory ratio’ means LMR;

Abbreviation: NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; END, early neurological deterioration; OR, odds ratio; CI, confidence interval; NIHSS, national institute of health stroke scale; HT, hemorrhagic transformation; OTT, onset to treatment time; PAO, proximal arterial occlusion; LAA, large-artery atherosclerosis; CE, cardioembolism; SAO, small-artery occlusion; SOE: stroke of other determined etiology; SUE: stroke of undetermined etiology; FBG, fasting blood glucose; Hs-CRP, hyper-sensitive c-reactive protein.

Table 4 manifested the results of the multivariate logistic regression model for post-thrombolysis ENI. In the multivariate logistic regression model including NLR (Model 4), NLR was identified as an independent factor for post-thrombolysis ENI (OR, 0.686; 95% CI 0.631–0.745, \( P = 0.001 \)) after adjustment for all potential confounders. In the multivariate logistic regression model including PLR (Model 5), PLR remained an independent factor for post-thrombolysis END (OR, 0.997; 95% CI 0.994–0.999, \( P = 0.006 \)). What is more, in the multivariate logistic regression model including LMR (Model 6), LMR was found to be the independent factor for post-thrombolysis ENI (OR, 1.170; 95% CI 1.043–1.313, \( P = 0.008 \)).
Table 4
Logistic regression NLR model, PLR model and LMR model of post-thrombolysis ENI

| Variable                        | Model 4: association of NLR with post-thrombolysis ENI | Model 5: association of PLR with post-thrombolysis ENI | Model 6: association of LMR with post-thrombolysis ENI |
|--------------------------------|--------------------------------------------------------|--------------------------------------------------------|--------------------------------------------------------|
|                                | OR (95%CI)     | P          | OR (95%CI)     | P          | OR (95%CI)     | P          |
| Age                            | 0.984 (0.973–0.995) | 0.006   | 0.982 (0.971–0.993) | 0.001   | 0.982 (0.972–0.993) | 0.001   |
| Diabetes mellitus              | 0.702 (0.503–0.978) | 0.036   | 0.684 (0.497–0.942) | 0.020   | 0.691 (0.502–0.951) | 0.023   |
| Previous antiplatelet          | 1.426 (1.008–2.015) | 0.045   | 1.522 (1.091–2.122) | 0.013   | 1.565 (1.123–2.181) | 0.008   |
| DBP                            | 0.986 (0.977–0.996) | 0.005   | 0.988 (0.979–0.997) | 0.011   | 0.989 (0.980–0.998) | 0.013   |
| HT                             | 0.417 (0.219–0.795) | 0.008   | 0.332 (0.177–0.620) | 0.001   | 0.326 (0.174–0.609) | 0.001   |
| OTT                            | 0.992 (0.990–0.995) | 0.001   | 0.993 (0.990–0.995) | 0.001   | 0.993 (0.990–0.995) | 0.001   |
| PAO                            | 0.714 (0.521–0.977) | 0.036   | 0.666 (0.492–0.900) | 0.008   | 0.667 (0.493–0.901) | 0.008   |
| Composite inflammatory ratio*  | 0.686 (0.631–0.745) | 0.001   | 0.997 (0.994–0.999) | 0.006   | 1.170 (1.043–1.313) | 0.008   |

* In the Model 4: ‘composite inflammatory ratio’ means NLR;

In the Model 5: ‘composite inflammatory ratio’ means PLR;

In the Model 6: ‘composite inflammatory ratio’ means LMR;

Abbreviation: NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; ENI, Early neurological improvement; OR, odds ratio; CI, confidence interval; NIHSS, national institute of health stroke scale; DBP, diastolic blood pressure; HT, hemorrhagic transformation; OTT, onset to treatment time; PAO, proximal arterial occlusion.

ROC curves, which were depicted in Fig. 2, were used to test the overall discriminative ability of these three composite inflammatory ratios for outcomes. We observed that the area under curve (AUC) of NLR, PLR and LMR to discriminate post-thrombolysis END were 0.763 (95% CI, 0.736–0.788), 0.703 (95% CI, 0.675–0.730) and 0.551 (95% CI, 0.521–0.581) (Fig. 2A). To predict post-thrombolysis END, AUC of NLR was superior to PLR (0.763 versus 0.703, \(P = 0.010\)) and LMR (0.763 versus 0.551, \(P = 0.001\)). Moreover, AUC of PLR was superior to LMR (0.703 versus 0.551, \(P = 0.001\)) Meanwhile, the AUC of NLR, PLR and LMR to discriminate post-thrombolysis ENI were 0.695 (95% CI, 0.666–0.722), 0.530 (95% CI, 0.499–0.560) and 0.547 (95% CI, 0.516–0.577) (Fig. 2B). To predict post-thrombolysis ENI, AUC of NLR was superior to PLR (0.695 versus 0.530, \(P = 0.001\)) and LMR (0.695 versus 0.547, \(P = 0.001\)). However, there
was not significant difference between the AUC of PLR and LMR (0.530 versus 0.547, \( P = 0.461 \)). We also established optimal cutoff values at which the Youden index was highest. The details of optimal cutoff values for NLR, PLR and LMR as predictors of post-thrombolysis END and ENI were described in Additional file 2: Table S1.

**Discussion**

To our knowledge, this is the first study with relatively large samples to investigate the association between composite inflammatory ratios before thrombolysis and post-thrombolysis early neurological outcomes. Our study showed that the prevalence of post-thrombolysis END and post-thrombolysis ENI were 18.2\% as well as 37.5\%, respectively. These prevalence are in line with the previous researches [25–29]. In this observational study, we found NLR as well as PLR were associated with post-thrombolysis END. Moreover, NLR, PLR and LMR were related to post-thrombolysis ENI. In general, a biomarker with 0.7 < AUC < 0.9 indicates a moderate diagnostic value. Therefore, NLR and PLR may be capable of predicting post-thrombolysis END.

During recent years, neuroinflammation has drawn more and more attention, and numerous studies have confirmed that inflammatory mechanisms play crucial roles in the pathogenesis and progression of ischemic stroke [30–35]. Peripheral leukocytes are guided by the inflammatory cytokines and chemokines, which are released from ischemic tissues [36]. Conversely, peripheral leukocytes may affect ischemic tissues as well [36]. Lymphocyte counts have been considered to have neuroprotective effect and contribute to neurological function improvement [36]. Both peripheral monocytes and neutrophils could perform as the source of matrix metalloproteinase-9, which would lead to HT and symptomatic deterioration [7, 37, 38]. Furthermore, it is reported that neutrophils can induce free oxygen radicals and cause brain injury [39]. Meanwhile, AIS may result in platelet function abnormality, and excessive activation and accumulation of platelets could hamper stroke recovery [40]. NLR, PLR and LMR are three composite ratios in the combination of different inflammatory parameters, hence they be able to provide more information immunological activities during the pathogenesis of ischemic stroke. What is more, these three composite inflammatory ratios can be calculated from blood cell counts, so that they are relatively accessible. Previous studies exhibited that NLR, PLR and LMR could predict the clinical outcome in AIS patients [41–43]. NLR and LMR can also foretell HT after ischemic stroke [44, 45]. Moreover, high NLR and PLR might be associated with symptomatic internal carotid artery stenosis [46]. Nam and colleagues found that upgraded NLR may portend stroke-associated pneumonia [47]. In addition, elevated levels of PLR are associated with post-stroke depression according to the study of Huang et al [48]. The findings of our study have supplemented the roles of NLR, PLR and LMR in cerebrovascular disease, and provide new ideas for clinical practice, too.

In this study, we also discovered that age, previous antiplatelet, baseline NIHSS, HT, FOTT, PAO, FBG and Hs-CRP were related to post-thrombolysis END in different multivariate regression models. In addition, diverse multivariate regression models showed that age, diabetes mellitus, previous antiplatelet, diastolic blood pressure, HT, OTT as well as PAO were connected with ENI. Previous researches confirmed that age,
diabetes mellitus and elevated levels of baseline NIHSS, OTT as well as FBG may be able to be the risk factors of neurological recovery [7, 8, 49]. Moreover, HT could serve as one reason for END [6, 50], and PAO may lead to symptoms worsening and poor prognosis in AIS patients [51]. Hu et al found that diastolic blood pressure might be associated with END [52]. We detected that previous antiplatelet treatment can be integrated into nomogram to predict END in AIS patients, who did not receive reperfusion therapy [49], and this research seemed to hint that previous antiplatelet might help AIS patients recover rapidly after thrombolysis. Serum Hs-CRP levels could also function as an inflammatory biomarker. Our previous study showed that Hs-CRP could predict progressive motor deficits, a subtype of END, in patients with penetrating artery infarctions [53]. Moreover, there were other studies that found serum Hs-CRP levels might be independently relevant with END, after adjustment for confounders [7, 54].

Our study has several potential limitations. Firstly, all the participants enrolled were Chinese patients treated with intravenous thrombolysis, so the associations between composite inflammatory ratios before thrombolysis and post-thrombolysis early neurological outcomes need to be tested in non-Chinese populations. Second, some risk factors that may be linked to END or ENI, such as serum homocysteine [55] and trimethylamine N-oxide levels [56], were unavailable in this study. These biomarkers might serve as potential independent predictors for END. Therefore, we attempt to collect these variables prospectively. Third, it is reported that composite inflammatory ratios might be able to vary significantly during hospitalization. Our future research needs dynamic examination of composite inflammatory ratios, not only composite inflammatory ratios before thrombolysis. Moreover, there were more than one neurologist that assessed stroke severity, which would led to bias on evaluation of NIHSS, even though these neurologists have undergone standardized training. Despite these limitations mentioned above, it is the first time to explore the relationship between composite inflammatory ratios before thrombolysis and post-thrombolysis early neurological outcomes, including END and ENI, with relatively large samples.

**Conclusion**

In summary, our study showed that NLR before thrombolysis as well as PLR before thrombolysis were associated with post-thrombolysis END. Meanwhile, NLR before thrombolysis, PLR before thrombolysis and LMR before thrombolysis were related to post-thrombolysis ENI. What is more, NLR and PLR may have the ability to predict post-thrombolysis END. NLR, PLR and LMR, which are easily available, might have utility as an inclusion criterion for future clinical trials about thrombolysis. Further investigations will be required to verify these results about post-thrombolysis early neurological outcomes.

**Abbreviations**

AIS: acute ischemic stroke; ENI: early neurological improvement; END: early neurological deterioration; NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; LMR: lymphocyte-monocyte ratio; HT: hemorrhagic transformation; OTT: onset to treatment time; PAO: proximal arterial occlusion; TOAST: Trial of Org 10172 in Acute Stroke Treatment; TC: total cholesterol; TG: triglyceride; HDL: high-density
lipoprotein; LDL: low-density lipoprotein; FBG: fasting blood glucose; Hs-CRP: hypersensitive C-reactive protein; OR: odds ratio; 95% CI: 95% confidence interval; AUC: area under curve.

Declarations

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Authors’ contributions

Pengyu Gong was mainly involved in study design, data analysis, data interpretation, and manuscript preparation. Yukai Liu was mainly involved in data acquisition and data analysis. Yachi Gong, Gang Chen, Feng Zhou, Siyu Wang, Rui Duan, Wenxiu Chen, Meng Wang, Ting Huang, Qiwen Deng and Hongchao Shi were mainly involved in data acquisition. Xiaohao Zhang were mainly involved in manuscript preparation. Junshan Zhou, Teng Jiang and Yingdong Zhang were mainly involved in study design, data interpretation, and manuscript preparation.

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Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Nanjing First Hospital, Haimen Hospital Affiliated to Nantong University as well as Nantong Third Peoples Hospital. Informed consent was obtained from participants or their legal representatives.

Consent for publication

All the authors agree to publish.
Availability of data and material

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

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