Neuroendocrinology Letters Volume 47 No. 1 2026
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

ORIGINAL ARTICLE

Neutrophil-to-Lymphocyte Ratio after Intravenous Thrombolysis Is a Prognostic Marker in Acute Ischemic Stroke

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Submitted: 2025-07-18 Accepted: 2025-12-12 Published online: 2026-01-08

Key words: **Acute ischemic stroke; Intravenous thrombolysis; 90-day outcome; Neutrophil-to-lymphocyte ratio; Platelet-to-lymphocyte ratio**

Neuroendocrinol Lett 2026; **47**(1):1–11 **PMID:** 41915923 47012601

Abstract

OBJECTIVES: The neutrophil-to-lymphocyte ratio (NLR) is an easily accessible biomarker that has been shown to predict the prognosis of acute ischemic stroke (AIS) patients. This study aimed to investigate the association between NLR on admission and within 24 hours after thrombolysis in A IS patients receiving intravenous thrombolysis (IVT) and the severity of stroke, infarction volume, hemorrhagic transformation (HT), and 90-day outcome.

METHODS: Retrospective cohort study of 171 consecutive patients, the NLR value was calculated according to neutrophil and lymphocyte counts both on admission and after IVT. We defined the NLR value on admission as pre-IVT NLR and after IVT within 24 hours was defined as post-IVT NLR. We used the modified Rankin scale (mRS) to assess the 90-day outcome for AIS patients. Regression analyses were performed, adjusting for confounders.

RESULTS: (1) Post-IVT NLR level was increased in the poor prognosis group, the moderate to severe group, large infarct volume group, and HT group. (2) In multivariate logistic regression analysis, the level of post-IVT NLR and post-IVT platelet-to-lymphocyte ratio (PLR) were correlated with the 90-day prognosis of AIS. Post-IVT NLR was an independent risk factor for predicting the prognosis of AIS patients with an adjusted OR of 1.212 (p = 0.001). Post-IVT NLR demonstrated superior prognostic accuracy compared to post-IVT PLR (AUC 0.738 vs. 0.601, p = 0.001), though remained inferior to NIHSS score (AUC 0.793) and infarction volume (AUC 0.808).

CONCLUSION: Post-IVT NLR is related to the severity of stroke, infarction volume, HT, and 90-day outcome in AIS patients receiving IVT. Post-IVT NLR was an independent predictor (p = 0.001, OR 1.212) for predicting the prognosis of AIS.

Abbreviations:

IVT	- intravenous thrombolysis
AIS	- acute ischemic stroke
HT	- hemorrhagic transformation
CNS	- central nervous system
WBC	- white blood cells
NLR	- neutrophil-to-lymphocyte ratio
rt-PA	- recombinant human tissue plasminogen activator
BMI	- body mass index
AF	- atrial fibrillation
FBG	- fasting blood glucose
HbA1c	- glycated hemoglobin
Scr	- serum creatinine
TG	- triglycerides
NIHSS	- National Institutes of Health Stroke Scale
mRS	- modified Rankin Scale
PNR	- platelet-to-neutrophil ratio
PLR	- platelet-to-lymphocyte ratio
CT	- Computed Tomography
MRI	- Magnetic Resonance Imaging
IQR	- interquartile range
ROC	- receiver operating characteristic
AUC	- area under the curve
TOAST	- Trial of Org 10,172 in Acute Stroke Treatment
CRP	- C-reactive protein
FIB	- fibrinogen
LDL	- low-density lipoproteins
OR	- odds ratio
BP	- blood pressure
TC	- total cholesterol
HDL	- high-density lipoproteins
HCY	- homocysteine
MMP9	- matrix metalloproteinase-9
BBB	- blood-brain barrier
iNK	- invariant natural killer

INTRODUCTION

Globally, cerebrovascular diseases are the leading cause of adult mortality second only to ischemic heart diseases, with a high disability rate (Collaborators 2022; Krishnamurthi *et al.* 2020). Ischemic stroke accounts for about 80%-85% of cerebrovascular diseases, caused by cerebral embolism or arterial thrombosis, resulting in cerebral ischemia and hypoxia (Allen & Bayraktutan 2009). Intravenous thrombolysis (IVT) is one of the effective treatment methods for acute ischemic stroke (AIS), suitable for patients with disabling deficits presenting within 4.5 hours from symptom onset (Prabhakaran *et al.* 2015). About 1/3 of patients treated with IVT had improved symptoms, while the rest had no effect or had hemorrhagic transformation (HT) (Karaszewski & Wyszomirski 2021). Therefore, it is of great clinical significance to study the risk factors that may affect the prognosis of AIS patients receiving IVT.

Cerebral ischemia after stroke triggers a strong inflammatory reaction (Jayaraj *et al.* 2019), and ischemic reperfusion after IVT may further aggravate inflammation (Alonso de Leciñana *et al.* 1996). Neutrophils are the primary response to injury in inflammatory diseases of the central nervous system (CNS) (Easton 2013). During the first few hours of stroke onset, the number of neutrophils in peripheral blood increases (Jickling *et al.* 2015). The injury of brain tissue promotes the infiltration of white blood cells (WBC) in peripheral blood to the site of cerebral ischemia, among which neutrophils are the first blood-derived immune cells to invade ischemic tissue (Herz *et al.* 2015). Neutrophils promote ischemia by releasing inflammatory mediators and inducing thrombosis in the ischemic brain area, further exacerbating brain injury (Ruhnau *et al.* 2017). Lymphocytes begin to rise 3-6 days after the onset of ischemic stroke (Kim *et al.* 2014). Lymphocytes play an important role in inhibiting inflammatory responses (Liesz *et al.* 2009; Prabhu & Frangogiannis 2016). Clinical evidence suggests that lower lymphocyte counts are associated with poor early neurological improvement and poor long-term functional outcomes (Kim *et al.* 2012).

The neutrophil-to-lymphocyte ratio (NLR) is an easily accessible biomarker that has been shown to predict the prognosis of AIS patients. Xue *et al.* found that the NLR in the peripheral blood of AIS patients was associated with the occurrence of poor prognosis and the recurrence of cerebral infarction (Xue *et al.* 2017). Pektezel *et al.* reported that the NLR in patients with AIS receiving IVT, which increased during the first 24 hours, was a predictor of poor prognosis (Pektezel *et al.* 2019).

In this study, we aimed to investigate the association between NLR on admission and within 24 hours after thrombolysis in AIS patients receiving IVT and the severity of stroke, infarction volume, HT, and 90-day outcome.

MATERIALS AND METHODS

Study Population

This study retrospectively collected AIS patients admitted to Wenzhou People's Hospital from January 2019 to October 2023. The inclusion criteria were: (1) meeting the diagnosis of AIS (Stroke--1989. Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on Stroke and other Cerebrovascular Disorders 1989); (2) age ≥ 18 years old; (3) receiving IVT within 4.5 h after symptom onset (by recombinant human tissue plasminogen activator [rt-PA] at the dose of 0.9 mg/kg). The exclusion criteria were: (1) recent history of confirmed infection, severe trauma, or major surgery; (2) severe liver or kidney dysfunction; (3) patients with tumors, rheumatism, or blood diseases; (4) patients with a history of stroke within 6 months; (5) lack complete clinical data. A total of 182 patients that met the inclusion criteria were recruited and 171 of them completed follow-up (11 patients could not be reached).

Data collection and definition

Baseline clinical characteristics were collected for all patients. Including demographic information (age,

gender, body mass index [BMI]), risk factors (smoking habits, alcohol abuse, hypertension, diabetes mellitus, atrial fibrillation [AF], hyperlipidemia, history of stroke), laboratory examination within 24 hours of admission (such as fasting blood glucose [FBG], glycated hemoglobin [HbA1c], serum creatinine [Scr], triglycerides [TG]), the National Institutes of Health Stroke Scale (NIHSS) score on admission, etiological classification, and modified Rankin Scale (mRS) score at 90-day.

Venous blood samples were collected both on admission and within 24 hours after IVT. The NLR value was calculated according to neutrophil and lymphocyte counts both on admission and after IVT. We defined the NLR value on admission as pre-IVT NLR and after IVT within 24 hours was defined as post-IVT NLR. The platelet-to-lymphocyte ratio (PLR) value was calculated according to platelet and lymphocyte counts both on admission and after IVT. We defined the PLR value on admission as pre-IVT PLR and after IVT within 24 hours was defined as post-IVT PLR. The platelet-to-neutrophil ratio (PNR) value was calculated according to platelet and neutrophil counts both on admission and after IVT. We defined the PNR value on admission as pre-IVT PNR and after IVT within 24 hours was defined as post-IVT PNR.

If there was a definite medical history or the disease was diagnosed at discharge, hypertension, diabetes mellitus, AF, and hyperlipidemia were determined. And the definition of smoking and drinking, smokers were defined as smoking more than 1 cigarette a day for 6 months; heavy drinkers were defined as the average male drinking 2 U/d or female average drinking 1 U/d (Fu *et al.* 2015).

Outcomes

Clinical outcome indicators included the severity of stroke, infarction volume, HT, and 90-day outcome. Neurologists used the NIHSS score to measure the severity of AIS patients on admission (Brott *et al.* 1989). We defined the mild group as NIHSS score < 5 and the moderate to severe group as NIHSS score ≥ 5 (Yakhkind *et al.* 2016). 171 cases were examined with Computed Tomography (CT) scans or Magnetic Resonance Imaging (MRI), according to the formula 0.5 x a x b x c (a: maximum longitudinal diameter; b: maximum transverse diameter perpendicular to a; c: 10 mm slices with infarction) to calculate the infarct volume (French *et al.* 2014). A small infarct volume was defined as less than 5 cm^3, while a large infarct volume was larger than 5 cm^3 (Li *et al.* 2019). HT was defined as any visible bleeding on brain CT within 24 hours after IVT. Measure clinical outcomes at 90-day using mRS score through telephone interviews or outpatient services (Sulter *et al.* 1999). We defined the mRS score for the group with a good prognosis as 0-2, while the mRS score for the group with a poor prognosis was of 3-6 (Huybrechts & Caro 2007).

Statistical analysis

All data were statistically analyzed using SPSS 26.0. Measurement data conforming to the normal distribution were expressed as mean ± SD, and the comparison between groups was by independent sample T-test; measurement data with skewed distribution were expressed by the median and interquartile range (IQR), and the comparison between groups was performed using the Mann-Whitney U test; enumeration data were expressed as case (%), and comparisons between groups were performed using the $\chi 2$ test or Fisher test. After adjusting for confounding factors in univariate analysis, the multivariate logistic regression equation was used to analyze the influencing factors on the prognosis of AIS patients receiving IVT. The receiver operating characteristic (ROC) curve was used to evaluate the sensitivity and specificity of post-IVT NLR in predicting the 90-day outcome of AIS after thrombolysis, and the area under the curve (AUC) was calculated as the standard for testing accuracy. $p < 0.05$ was considered a statistically significant difference.

RESULTS

Baseline data of study samples

Across all patients, 53 (31.0%) were female, with an average age of 65.0 (IQR, 52.0-76.0) years, ranging in age from 30 to 91 years, NIHSS score on admission average 6 (IQR, 3-13). According to the criteria of the Trial of Org 10,172 in Acute Stroke Treatment (TOAST)(Adams *et al.* 1993), 171 patients had 120 patients with large-artery atherosclerosis, 21 patients with cardioembolism, 12 patients with small-artery occlusion, 0 patients with stroke of other determined etiology, 18 patient with stroke of undetermined etiology. 117 patients (68.4%) had good prognosis, and 54 patients (31.6%) had poor prognosis.

Compared with good prognosis group, age, NIHSS score on admission, infarct volume, HT, diabetes mellitus, pre-IVT C-reactive protein (CRP), post-IVT WBC, post-IVT neutrophil count, post-IVT CRP, post-IVT PLR level, post-IVT NLR level, FBG, HbA1c, fibrinogen (FIB) and D-Dimer were all higher in poor prognosis group, while low-density lipoproteins (LDL), pre-IVT platelet count, post-IVT lymphocyte count, post-IVT platelet count and post-IVT PNR level were significantly decreased, the differences between two groups were statistically significant (all $p < 0.05$). The differences in other clinical characteristics and baseline data between the two groups were not statistically significant (all $p > 0.05$) (Table 1).

The correlation between levels of NLR, PLR, and PNR and the severity of AIS

According to the NIHSS score on admission, there were 63 (36.8%) patients in the mild group (NIHSS < 5), and 108 (63.2%) patients in the moderate

Tab. 1. Baseline characteristics of patients with good and poor prognosis group

Characteristics	Patients	Good prognosis group	Poor prognosis group	*p*
N (%)	171	117	54	
Age (y)	65.0(52.0-76.0)	61.0(50.5-73.0)	72.5(59.5-81.0)	0.002
Gender (female), n (%)	53(31.0)	35(30.0)	18(33.3)	0.653
Stroke onset to treat time (min)	161.0(116.0-215.0)	164.0(115.5-215.0)	151.0(116.0-220.5)	0.959
Weight (kg)	65.5(55.9-74.6)	66.0(56.0-73.0)	65.0(54.9-75.3)	0.599
BMI (kg/m^2)	24.3±3.7	24.3±3.5	24.2±4.2	0.930
NIHSS score on admission	6.0(3.0-13.0)	5.0(3.0-8.0)	13.5(8.0-21.3)	<0.001
Smoking, n (%)	65(38.0)	45(38.5)	20(37.0)	0.858
Alcohol drinking, n (%)	43(25.1)	30(25.6)	13(24.1)	0.826
Systolic BP (mmHg)	148.7±19.7	147.3±18.8	152.1±21.3	0.146
Diastolic BP (mmHg)	86.3±14.2	87.3±12.8	84.4±16.7	0.214
Hypertension, n (%)	138(80.7)	91(77.8)	47(87.0)	0.154
Diabetes mellitus, n (%)	59(34.5)	32(27.4)	27(50.0)	0.004
AF, n (%)	55(32.2)	33(28.2)	22(40.7)	0.103
Hyperlipidemia, n (%)	60(35.1)	42(35.9)	18(33.3)	0.744
History of stroke, n (%)	23(13.5)	13(11.1)	10(18.5)	0.187
Stroke etiologic subtypes, n (%)				0.892
Large-artery atherosclerosis	120(70.2)	80(68.4)	40(74.1)	
Cardioembolism	21(12.3)	15(12.8)	6(11.1)	
Small-artery occlusion	12(7.0)	9(7.7)	3(5.6)	
Other determined etiology	0(0.0)	0(0.0)	0(0.0)	
Undetermined etiology	18(10.5)	13(11.1)	5(9.3)	
HT, n (%)	27(15.8)	11(9.4)	16(29.6)	0.001
Infarction volume (cm^3)	3.6(0.6-32.5)	1.8(0.3-12.0)	26.9(5.0-261.1)	<0.001
Laboratory tests				
Pre-IVT WBC (10^9/L)	7.6(6.3-9.6)	7.6(6.4-9.6)	7.8(6.3-9.6)	0.938
Pre-IVT neutrophils (10^9/L)	4.7(3.6-6.2)	4.6(3.7-6.1)	4.8(3.4-6.5)	0.928
Pre-IVT lymphocytes (10^9/L)	1.9(1.2-2.8)	2.0(1.3-2.8)	1.7(1.1-2.5)	0.086
Pre-IVT RBC (10^{12}/L)	4.7±0.6	4.7±0.5	4.6±0.7	0.236
Pre-IVT CRP (mg/L)	2.1(1.0-4.7)	1.8(0.9-3.6)	3.1(1.5-7.6)	0.006
Pre-IVT NLR	2.4(1.5-4.0)	2.3(1.5-3.9)	2.6(1.8-5.1)	0.216
Pre-IVT PLR	115.7(91.7-173.8)	115.0(77.2-177.6)	126.0(89.0-167.1)	0.357
Pre-IVT PNR	46.5(35.3-59.7)	47.6(35.7-61.0)	45.1(33.3-55.3)	0.247
Post-IVT WBC (10^9/L)	8.0(6.5-10.1)	7.5(6.3-9.2)	9.5(7.7-11.2)	<0.001
Post-IVT neutrophils (10^9/L)	5.6(4.2-7.6)	4.8(4.0-6.5)	7.0(5.6-9.9)	<0.001
Post-IVT lymphocytes (10^9/L)	1.5(1.1-2.0)	1.6(1.3-2.2)	1.2(0.8-1.7)	<0.001
Post-IVT RBC (10^{12}/L)	4.4±0.6	4.5±0.6	4.3±0.6	0.079
Post-IVT platelet (10^9/L)	211.7±57.5	219.8±56.7	195.5±56.7	0.010
Post-IVT CRP (mg/L)	3.3(1.5-9.1)	2.4(1.3-5.7)	8.2(3.3-18.8)	<0.001
Post-IVT NLR	3.5(2.3-6.2)	2.9(2.0-4.8)	5.8(3.2-9.8)	<0.001
Post-IVT PLR	137.0(98.6-195.2)	133.3(97.2-182.9)	156.4(102.7-235.3)	0.035
Post-IVT PNR	36.8(25.4-51.7)	43.2(31.2-57.8)	26.0(19.3-35.0)	<0.001
FBG (mmol/L)	5.8(5.1-7.8)	5.6(5.0-6.4)	7.4(5.5-10.0)	<0.001
HbA1c (%)	6.0(5.6-7.2)	6.0(5.0-6.5)	6.2(5.7-8.1)	0.036

Characteristics	Patients	Good prognosis group	Poor prognosis group	*p*
TG (mmol/L)	1.3(0.9-1.8)	1.3(1.0-1.8)	1.1(0.8-1.8)	0.198
TC (mmol/L)	4.6±1.1	4.7±1.1	4.4±1.2	0.125
HDL (mmol/L)	1.1(0.9-1.2)	1.1(1.0-1.2)	1.1(0.9-1.3)	0.901
LDL (mmol/L)	2.8±0.9	2.9±0.8	2.6±1.0	0.042
HCY (μmol/L)	11.9(9.3-15.9)	11.6(9.1-14.7)	12.4(9.6-20.5)	0.079
Scr (μmol/L)	65.5(56.0-78.0)	66.0(56.0-78.5)	65.0(56.0-77.0)	0.931
PT (s)	11.4(11.0-11.8)	11.3(10.8-11.7)	11.5(11.0-12.2)	0.234
APTT (s)	30.6±3.1	30.5±3.2	30.9±3.2	0.443
TT (s)	14.8(14.1-15.6)	14.8(14.0-15.6)	14.8(14.2-15.7)	0.676
FIB (g/L)	3.1(2.8-3.6)	3.1(2.7-3.5)	3.3(3.1-3.7)	0.009
D-Dimer (mg/L)	0.4(0.2-0.8)	0.4(0.2-0.8)	0.5(0.3-1.1)	0.001

BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale; BP, blood pressure; AF, atria fibrillation; HT, hemorrhagic transformation; IVT, intravenous thrombolysis; WBC, white blood cell; RBC, red blood cell; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNR, platelet-to-neutrophil ratio; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; TG, triglycerides; TC, total cholesterol; HDL, high-density lipoproteins; LDL, low-density lipoproteins; HCY, homocysteine; Scr, serum creatinine; PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; FIB, fibrinogen.
Data are presented as means (± SD) and medians (IQR) or as number (percentage).

to severe group (NIHSS ≥ 5). Compared with the mild group, the post-IVT NLR level was higher in the moderate to severe group, while the post-IVT PNR level was significantly decreased, the differences between the two groups were statistically significant (all $p < 0.05$). The differences in pre-IVT PNR level, pre-IVT PLR level, pre-IVT NLR level, and post-IVT PLR level between the two groups were not statistically significant (all $p > 0.05$) (Table 2).

Levels of NLR, PLR, and PNR in relation to infarction volume

In 171 patients, MRI or CT scans were all available, and the median (quartiles) infarct volume was 3.6 (IQR, 0.6-32.5), including 92 (53.8%) patients with small infarct volume and 79 (46.2%) patients with large infarct volume. Post-IVT NLR level was significantly higher in patients with large infarct volume, while pre-IVT PNR level and post-IVT PNR level were increased significantly in the small infarct volume group (all $p < 0.05$) (Table 3).

The association of NLR, PLR, and PNR levels with HT

27 (15.8%) of all patients had HT and 144 (84.2%) patients did not have HT. It was found that higher post-IVT NLR levels ($p = 0.004$) and lower post-IVT PNR levels ($p < 0.001$) were associated with HT. In addition, pre-IVT NLR level was found to be increased in the HT patients although it did not reach significance ($p = 0.793$) (Table 4).

The correlation between NLR, PLR, and PNR levels and 90-day outcome

We found that post-IVT PNR level, post-IVT PLR level, and post-IVT NLR level were associated with 90-day outcome in the univariate logistic regression analysis, and the unadjusted odds ratio (OR) of post-IVT NLR level was 1.170 (95% CI, 1.081-1.267; $p < 0.001$).

Tab. 2. Levels of NLR, PLR, and PNR in different groups of stroke severity

	Mild group	Moderate to severe group	*p*
N	63	108	
Pre-IVT NLR	2.1(1.7-3.7)	2.7(1.5-4.8)	0.338
Pre-IVT PLR	116.0(85.0-146.3)	116.2(81.0-181.8)	0.788
Pre-IVT PNR	47.7(36.6-60.0)	44.7(34.2-59.5)	0.593
Post-IVT NLR	2.8(1.9-4.4)	4.3(2.8-8.6)	<0.001
Post-IVT PLR	130.0(93.1-173.1)	146.2(101.1-202.1)	0.064
Post-IVT PNR	43.5(35.0-59.0)	32.9(22.3-45.9)	<0.001

IVT, intravenous thrombolysis; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNR, platelet-to-neutrophil ratio.
Data are presented as median (IQR).

Tab. 3. Levels of NLR, PLR, and PNR in different groups of infarction volume

	Small infarct volume group	Large infarct volume group	*p*
N	92	79	
Pre-IVT NLR	2.2(1.5-3.8)	2.6(1.7-5.2)	0.285
Pre-IVT PLR	115.7(83.2-175.3)	120.9(80.3-175.0)	0.927
Pre-IVT PNR	48.2(36.8-62.2)	43.3(31.1-53.6)	0.018
Post-IVT NLR	2.8(1.9-4.3)	4.9(3.2-8.9)	<0.001
Post-IVT PLR	134.9(98.0-181.3)	143.1(100.0-203.3)	0.334
Post-IVT PNR	45.2(36.1-60.0)	26.9(20.0-38.5)	<0.001

IVT, intravenous thrombolysis; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNR, platelet-to-neutrophil ratio.
Data are presented as median (IQR).

Tab. 4. Compare the levels of NLR, PLR, and PNR in groups with HT or not

	Non-HT group	HT group	*p*
N	144	27	
Pre-IVT NLR	2.4(1.6-4.6)	2.9(1.5-3.5)	0.793
Pre-IVT PLR	116.8(85.0-172.2)	104.5(72.1-175.7)	0.650
Pre-IVT PNR	46.5(35.5-59.7)	45.6(33.8-56.9)	0.906
Post-IVT NLR	3.3(2.2-5.9)	5.3(3.5-7.7)	0.004
Post-IVT PLR	137.0(98.3-190.8)	143.1(98.8-285.0)	0.355
Post-IVT PNR	38.6(27.3-54.1)	26.9(19.5-34.2)	<0.001

HT, hemorrhagic transformation; IVT, intravenous thrombolysis; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNR, platelet-to-neutrophil ratio.
Data are presented as median (IQR).

Multivariate Logistic regression was used to further assess all parameters of $p < 0.05$ in unadjusted models (age, NIHSS score on admission, diabetes mellitus, infarct volume, post-IVT WBC, post-IVT CRP, FBG, HbA1c, LDL, D-Dimer) and other key outcome predictors (gender, BMI, smoking, alcohol misuse, history of stroke, hypertension, AF, hyperlipidemia, admission systolic blood pressure [BP], admission diastolic BP, TG, total cholesterol [TC], high-density lipoproteins [HDL], Scr, homocysteine [HCY], FIB), post-IVT NLR level remained an independent predictor of poor prognosis in AIS patients, which adjusted OR was 1.212 (95% CI, 1.078-1.363; $p = 0.001$). Post-IVT NLR was an independent predictor ($p = 0.001$, OR 1.212) for predicting the prognosis of AIS, while post-IVT PLR was also an independent risk factor in functional outcome with an adjusted OR of 1.006 (95% CI, 1.000-1.012; $p = 0.041$). Furthermore, NIHSS score on admission and infarct volume were independent predictors of AIS outcome. After adjustment, the post-IVT PNR level was not related to poor outcome at 90 days (Table 5).

Prognostic accuracy: Area under ROC curve for post-IVT NLR and post-IVT PLR predicting 90-day functional outcome

According to the ROC curve, the optimal cutoff value of post-IVT NLR predicted 90-day prognosis of AIS patients was 4.9, the sensitivity was 59.3%, specificity was 76.9%, the AUC was 0.738 (95% CI, 0.659-0.817; $p < 0.001$). In addition, the AUC of post-IVT PLR was 0.601 (95% CI, 0.509-0.692; $p = 0.035$). Post-IVT NLR demonstrated superior prognostic accuracy compared to post-IVT PLR (AUC 0.738 vs. 0.601, $p = 0.001$), though remained inferior to NIHSS score (AUC 0.793) and infarction volume (AUC 0.808) (Table 6, Fig. 1).

DISCUSSION

In this study, we measured NLR, PLR, and PNR levels on admission and within 24 hours after thrombolysis in AIS patients receiving IVT. We found that post-IVT NLR was related to the severity of stroke, infarction volume, HT, and 90-day outcome in AIS patients. Post-IVT NLR was an independent risk factor for predicting the prognosis of AIS. Meanwhile, the best estimate of post-IVT NLR for predicting 90-day adverse outcomes was proposed. We also found that post-IVT PLR was correlated with the 90-day prognosis of AIS. Post-IVT NLR demonstrated statistically significant but intermediate prognostic accuracy (AUC 0.738, 95% CI: 0.659–0.817) for predicting 90-day functional outcome. While NIHSS score (AUC 0.793) and infarction volume (AUC 0.808) remained superior predictors, post-IVT NLR independently associated with poor prognosis (adjusted OR 1.212, $p = 0.001$) outperformed post-IVT PLR (AUC 0.601) and may complement rather than

Tab. 5. Univariate and multivariate logistic regression analysis for 90-day outcome

Characteristics	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*	OR	95% CI	*p*
Age	1.037	1.012-1.062	0.003			
Gender	0.854	0.428-1.703	0.653			
Stroke onset to treat time	1.000	0.994-1.005	0.920			
Weight	0.996	0.970-1.024	0.790			
BMI	0.996	0.913-1.087	0.930			
NIHSS score on admission	1.140	1.084-1.199	<0.001	1.108	1.034-1.188	0.004
Smoking	0.941	0.483-1.832	0.858			
Alcohol drinking	0.920	0.435-1.945	0.826			
Systolic BP	1.013	0.996-1.030	0.147			
Diastolic BP	0.985	0.963-1.009	0.214			
Hypertension	1.918	0.775-4.746	0.159			
Diabetes mellitus	2.656	1.358-5.194	0.004			
AF	1.750	0.890-3.440	0.105			
Hyperlipidemia	0.893	0.452-1.763	0.744			
History of stroke	1.818	0.742-4.457	0.191			
TOAST subtype	0.917	0.704-1.196	0.524			
Infarction volume	1.014	1.007-1.021	<0.001	1.014	1.006-1.022	0.001
Pre-IVT WBC	0.970	0.849-1.109	0.656			
Pre-IVT neutrophils	0.975	0.852-1.117	0.718			
Pre-IVT lymphocytes	0.783	0.579-1.060	0.114			
Pre-IVT RBC	0.709	0.401-1.253	0.236			
Pre-IVT platelet	0.994	0.988-0.999	0.030			
Pre-IVT CRP	1.025	0.999-1.052	0.062			
Pre-IVT NLR	1.030	0.933-1.138	0.555			
Pre-IVT PLR	1.000	0.997-1.002	0.912			
Pre-IVT PNR	0.993	0.979-1.007	0.313			
Post-IVT WBC	1.302	1.136-1.493	<0.001			
Post-IVT neutrophils	1.355	1.184-1.551	<0.001			
Post-IVT lymphocytes	0.403	0.238-0.682	0.001			
Post-IVT RBC	0.601	0.339-1.065	0.081			
Post-IVT platelet	0.992	0.986-0.998	0.012			
Post-IVT CRP	1.036	1.013-1.060	0.002			
Post-IVT NLR	1.170	1.081-1.267	<0.001	1.212	1.078-1.363	0.001
Post-IVT PLR	1.004	1.001-1.007	0.017	1.006	1.000-1.012	0.041
Post-IVT PNR	0.964	0.944-0.985	0.001			
FBG	1.282	1.130-1.453	<0.001			
HbA1c	1.284	1.051-1.569	0.015			
TG	1.021	0.711-1.465	0.911			
TC	0.798	0.598-1.066	0.126			
HDL	0.673	0.196-2.309	0.529			
LDL	0.656	0.446-0.964	0.032			
HCY	1.023	0.995-1.052	0.101			

Characteristics	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*	OR	95% CI	*p*
Scr	1.004	0.997-1.012	0.279			
PT	1.114	0.852-1.458	0.430			
APTT	1.041	0.940-1.154	0.441			
TT	1.120	0.931-1.347	0.229			
FIB	1.588	0.982-2.568	0.059			
D-Dimer	1.850	1.129-3.033	0.015			

OR, odds ratio; CI, confidence interval; BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale; BP, blood pressure; AF, atria fibrillation; TOAST, Trial of Org 10 172 in acute stroke treatment; IVT, intravenous thrombolysis; WBC, white blood cell; RBC, red blood cell; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNR, platelet-to-neutrophil ratio; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; TG, triglycerides; TC, total cholesterol; HDL, high-density lipoproteins; LDL, low-density lipoproteins; HCY, homocysteine; Scr, serum creatinine; PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; FIB, fibrinogen.

replace established clinical and imaging markers for risk stratification in acute ischemic stroke patients receiving intravenous thrombolysis. In addition, pre-IVT NLR, pre-IVT PLR, pre-IVT PNR, and post-IVT PNR were not correlated with the prognosis of AIS.

At present, it is known that immune response plays a major role in the pathological changes of AIS. Pathological changes such as necrotic cells, cell death fragments, and increased reactive oxygen species in the cerebral ischemic site promote the infiltration of peripheral blood WBC into the ischemic site (Easton 2013; Herz *et al.* 2015). Neutrophils, as the first cells recruited into the brain at the fastest rate (priority over other inflammatory cells such as macrophages, lymphocytes, and dendritic cells) (Ruhnau *et al.* 2017), are rapidly infiltrated into the ischemic site within a few hours after stroke under the action of chemokines and cytokines released by microglia and astrocytes at the ischemic site (Jayaraj *et al.* 2019), reach their peak 2-4 days after the onset of ischemic stroke, and then gradually decrease (Ross *et al.* 2007). After neutrophils reach the ischemic site, they quickly release multiple inflammatory mediators including matrix metalloproteinase-9 (MMP9), oxygen-free radicals, and proteases from the cytoplasmic granules, which cause brain edema and exacerbate brain injury (Ceulemans *et al.* 2010; Petrovic-Djergovic *et al.* 2016). The most important of these inflammatory mediators is MMP9, which participates in the biphasic opening of the blood-brain barrier (BBB) during ischemia-reperfusion injury, leading to BBB dysfunction, brain edema, neuronal death, and HT by disrupting the extracellular matrix surrounding the BBB (Maier *et al.* 2004; Zinnhardt *et al.* 2015). MMP9 activates microglia, macrophages, and neutrophils which secrete additional MMP9 further compromising cerebral vessels (Yang & Rosenberg 2015). The pro-inflammatory properties of neutrophils enhance tissue damage, and neutrophils promote thrombosis and ischemia by interacting with platelets, clotting factors, and the release of prothrombotic molecules (Jickling *et al.* 2015). Many studies have shown that an increase in neutrophils is associated with the severity of stroke, infarct volume, HT, and deterioration of neurological outcomes (Ruhnau *et al.* 2017; Herz *et al.* 2015).

The role of lymphocytes in ischemic stroke is complex, with both beneficial and harmful effects (Xie & Yang 2015; Brait *et al.* 2012). Recruitment of lymphocytes in ischemic brain injury is late (Jayaraj *et al.* 2019), usually beginning to increase 3-6 days after onset and decreasing around 14 days (Kim *et al.* 2014). The lymphocytes associated with cerebral infarction injury are mainly T-lymphocytes, including CD4 and CD8 T-cells, Foxp3 regulatory cells (Tregs), invariant natural killer (Ink) T-cells, and γδT-cells (Xie & Yang 2015). By day 3 of the onset of AIS, numerous T-lymphocytes have infiltrated the border zone around the lesion sparing the center (Jander *et al.* 1995). Different

Tab. 6. Prognostic accuracy: Area under ROC curve for post-IVT NLR and post-IVT PLR predicting 90-day functional outcome

Prediction	AUC	95% CI	*p*
NIHSS score on admission	0.793	0.714-0.873	<0.001
Infarction volume	0.808	0.739-0.877	<0.001
Post-IVT NLR	0.738	0.659-0.817	<0.001
Post-IVT PLR	0.601	0.509-0.692	0.035

AUC, area under the curve; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; IVT, intravenous thrombolysis; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

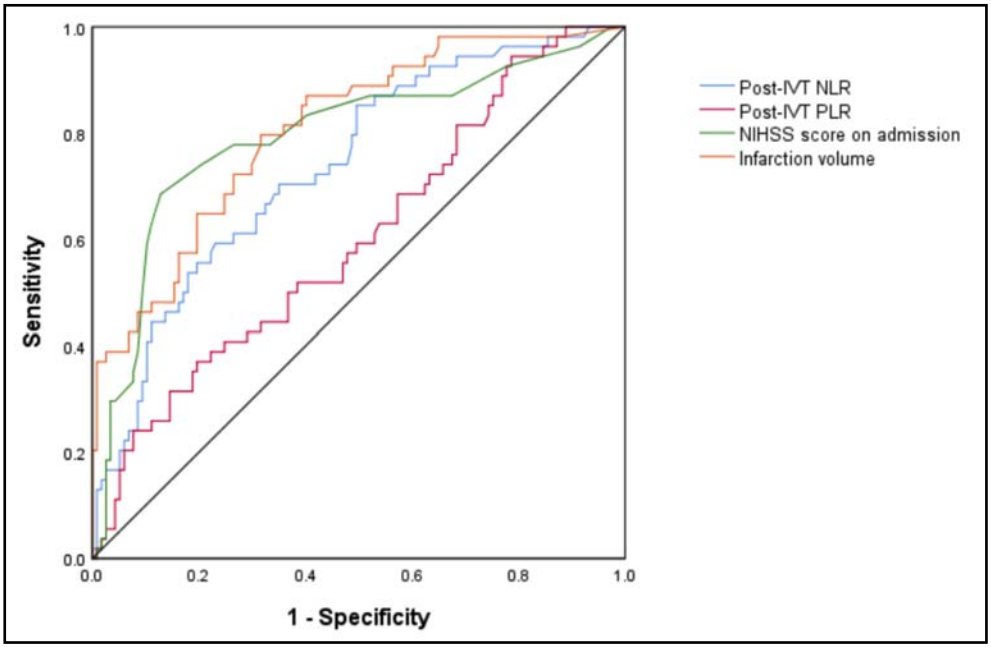

Fig. 1. Receiver operating characteristic (ROC) curves for post-IVT neutrophil-to-lymphocyte ratio (**NLR**), post-IVT platelet-to-lymphocyte ratio (**PLR**), **NIHSS** score on admission, and **infarction volume** in predicting 90-day poor functional outcome (mRS 3–6) after intravenous thrombolysis in acute ischemic stroke.

cell subsets of T-lymphocytes may lead to different outcomes (Jayaraj *et al.* 2019; Prabhu & Frangogiannis 2016). Some studies have found that Tregs have a brain-protective effect in acute experimental stroke, and experimental reduction of Tregs function or quantity may aggravate ischemic injury (Hurn *et al.* 2007; Liesz *et al.* 2009). CD4 T-cells promote wound healing, inflammation resolution, and pro-inflammatory monocyte infiltration, as well as appropriate collagen matrix formation (Prabhu & Frangogiannis 2016), and CD4 T-cells have also been shown to contribute to the recruitment of pro-angiogenic macrophages and collateral artery formation (Stabile *et al.* 2003; Stabile *et al.* 2006). However, other studies hold different views, suggesting that T-lymphocytes cause neuronal damage by releasing cytokines, chemokines, and superoxides at the site of cerebral ischemia (Brait *et al.* 2012; Saino *et al.* 2010). Kleinschnitz *et al.* reported that selective depletion of Tregs in the mouse model dramatically reduced infarct size and improved neurologic function 24 hours after stroke, and they suggest that Tregs promote ischemic brain damage by causing microvascular dysfunction and thrombosis (Kleinschnitz *et al.* 2013). Little is known about the role of B-lymphocytes in brain inflammation. Clinical studies have shown that lower lymphocyte counts are associated with poor early nervous system improvement and poorer long-term functional outcomes (Kim *et al.* 2012; Brait *et al.* 2012).

In our study, we collected the ratio of different blood cells on admission and within 24 hours after thrombolysis in AIS patients receiving IVT. We dynamically analyzed the correlation between NLR, PLR, and PNR and the severity of stroke, infarction volume, HT, and 90-day outcome in AIS patients. We found that post-IVT NLR was related to the severity of stroke, infarction volume, HT, and 90-day outcome in AIS patients. Post-IVT NLR was an independent risk factor for predicting the prognosis of AIS. Pre-IVT NLR showed no prognostic value, consistent with post-reperfusion inflammatory amplification. Ischemia-reperfusion injury and time-dependent neutrophil recruitment (peak 2-4 days) and lymphocyte suppression likely explain this temporal pattern. Serial measurements at 48, 72 hours, and 2 weeks with concurrent inflammatory biomarkers (MMP9, IL-6) would clarify mechanistic pathways. Post-IVT PLR was also found to be associated with the 90-day prognosis of AIS, with higher post-IVT PLR in patients with poor prognosis. Patients with AIS experience a decrease in platelet count, accompanied by an increase in average platelet volume and platelet distribution width (Sansanayudh *et al.* 2015). However, the mechanism by which the increase in post-IVT PLR leads to adverse AIS outcomes remains unclear. In addition, we found that pre-IVT PNR and post-IVT PNR were not correlated with the prognosis of AIS, which was inconsistent with the study of Wang *et al.* (Wang *et al.* 2020). Part of the reason may be that there were differences in blood sample collection time and heterogeneity of patients.

Understanding the changes in different blood cell ratios at different periods of AIS after IVT in our study will contribute to the development of new post-stroke inflammation diagnosis, prognostic prediction, and therapeutic neuroprotective strategies. We found that higher post-IVT NLR suggests a poor prognosis of AIS. Strategies to reduce post-IVT NLR, such as by reducing neutrophils or modulating Tregs activity after reperfusion (Kim *et al.* 2014; Shekhar *et al.* 2018), appear to reduce brain injury and improve post-stroke outcomes, but these therapies have their challenges. Perhaps hypothermia to affect inflammatory response may be a good option to protect the brain (Kalisvaart

et al. 2019; Ceulemans *et al.* 2010). In experimental models of transient cerebral ischemic, moderate to mild hypothermia reduced infarct volume (Rewell *et al.* 2017).

STUDY LIMITATIONS

This study has several limitations. Single-center design (n = 171, 2019-2023) limits generalizability; external validation required. Only two NLR timepoints collected; serial measurements at 48, 72 hours, and 2 weeks needed to establish kinetic profiles. Unmeasured confounders include reperfusion quality (TIMI scores), collateral status, and thrombolytic protocols.

CONCLUSION

Our study suggests that post-IVT NLR is related to the severity of stroke, infarction volume, HT, and 90-day outcome in AIS patients receiving IVT. Post-IVT NLR was an independent predictor ($p = 0.001$, OR 1.212) for predicting the prognosis of AIS.

CREDIT AUTHOR CONTRIBUTIONS

PingPing Jin: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. SenXiang Wu: Data curation, Writing – original draft. MengYing Xu: Data curation, Investigation. Hua Ye: Conceptualization. QiaoWen Tong: Conceptualization, Methodology. QingYuan Zhang: Writing – original draft. HeHui Zhang: Conceptualization, Project administration, Supervision, Writing – review & editing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethics Committee of the Wenzhou People's Hospital (KY-2024-034). Patient consent forms were signed by each patient or their relatives before inclusion.

AVAILABILITY OF DATA AND MATERIALS

The dataset supporting the conclusions of this study is available upon request from the corresponding author.

CONSENT FOR PUBLICATION

All participants have agreed to publish this manuscript and signed the informed consent form.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no competing financial interests or personal relationships that could influence the work reported in this study.

ACKNOWLEDGMENTS

We would like to express our gratitude to all those who helped us during the writing of this manuscript. Thanks to all the peer reviewers for their opinions and suggestions.

FUNDING

The present study was funded by the Wenzhou Municipal Science and Technology Plan Project (grant no.Y20220827) and the Wenzhou People's Hospital Excellent Youth Talent Project (grant no.RC-PH202305 [QN]).

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