

# Increased Platelet-to-Lymphocyte Ratio is an Independent Predictor of Hemorrhagic Transformation and In-Hospital Mortality Among Acute Ischemic Stroke with Large-Artery Atherosclerosis Patients

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**Background:** The platelet-to-lymphocyte ratio (PLR) is an inflammation marker of acute ischemic stroke, but its significance in patients with hemorrhage transformation (HT) after acute ischemic stroke with large-artery atherosclerosis (AIS-LAA) is unclear, and we also identified the relationship between PLR and in-hospital mortality of HT after AIS-LAA.

**Methods:** This was a retrospective analysis of patients with AIS-LAA. The PLR was calculated according to platelet and lymphocyte counts on admission. HT was defined on follow-up magnetic resonance imaging or computed tomography when neurologic deterioration worsened during hospitalization. The univariate analysis and multivariate logistic regression were performed to assess the association of PLR, HT and in-hospital mortality of HT after AIS-LAA.

**Results:** We included 328 Chinese AIS-LAA patients (mean age  $67.2 \pm 11.1$  years; 70.4% male). HT occurred in 38 patients (11.6%). After multivariate regression analyses, NRL (odds ratio [OR] 1.354, 95% confidence interval [CI] 1.176–1.559,  $P < 0.001$ ) and PLR (odds ratio [OR] 3.869, 95% confidence interval [CI] 2.233–5.702,  $P < 0.001$ ) were independently associated with HT after AIS-LAA. The area under the ROC curve (AUC) value of PLR (0.72, 95% CI (0.64–0.80),  $P < 0.001$ ) tested a greater discriminatory ability compared with neutrophil-lymphocyte ratio (NLR) (0.67, 95% CI (0.58–0.76),  $P < 0.001$ ). Meanwhile, PLR was found to be significantly related to HT after AIS-LAA, including in subtypes of artery-to-artery embolization (aOR 1.699, 95% CI 1.298–3.215,  $P < 0.001$ ), in-situ thrombosis (aOR 4.499, 95% CI 1.344–9.054,  $P < 0.001$ ) and branch atheromatous disease (aOR 3.239, 95% CI 1.098–8.354,  $P < 0.001$ ). Increased PLR predicts high in-hospital mortality of HT after AIS-LAA (OR 1.041, 95% CI (1.006–1.077),  $P = 0.020$ ; aOR 1.053, 95% CI (1.004–1.104),  $P = 0.034$ ).

**Conclusion:** High PLR is associated with greater risk of HT in AIS-LAA patients, including in artery-to-artery embolization, in-situ thrombosis and branch atheromatous disease. Meanwhile, increased PLR predicts high in-hospital mortality of HT after AIS-LAA.

**Keywords:** acute ischemic stroke, large-artery atherosclerosis, hemorrhagic transformation, platelet-to-lymphocyte ratio, in-hospital mortality

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Acute ischemic stroke (AIS) is one of the most common reasons for high mortality and morbidity in Chinese adults. AIS is classified by large-artery atherosclerosis (LAA), small-artery occlusion, cardio-embolism, undetermined etiology and other



etiology according to The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification system.<sup>1,2</sup> Although intravenous thrombolysis demonstrates efficacy, there are still several patients whose symptoms would worsen because of hemorrhagic transformation (HT). Meanwhile, HT is a part of AIS natural progression; it occurs in 10–40% of AIS, and contributes to early mortality and adversely affects functional recovery of AIS.<sup>3–5</sup> Previous researches indicate that patients with AIS-LAA are prone to early neurological deterioration, especially HT.<sup>6</sup> Therefore, it is significant to explore an easy measurable diagnostic biomarker of HT after AIS-LAA which may further improve the recovery of patients.

The pathogenesis of AIS with large-artery atherosclerosis is much more complex, with a key role for inflammation.<sup>7,8</sup> Several studies investigating inflammatory response have regarded as valuable HT after AIS, such as neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR) and neutrophil-platelet ratio (NPR).<sup>9–16</sup> Recently, platelet-to-lymphocyte ratio (PLR) has been reported as a potential biomarker in various diseases, including AIS, carotid artery stenosis, and post-stroke depression.<sup>17–20</sup> To our interest, it has been mentioned that high PLR may be associated with poor prognosis after intravenous thrombolysis in AIS.<sup>17</sup> However, the relationship between PLR and HT after AIS-LAA remains unclear; we are even unclear about the relationship between PLR and in-hospital mortality of HT after AIS-LAA. Therefore, in our single-center cross-sectional study, we aim to analyse the association between PLR, HT after AIS-LAA and in-hospital mortality of HT after AIS-LAA.

## Materials and Methods

### Study Population

This retrospective study was based on consecutive AIS-LAA patients at Department of Neurology in Beijing Friendship Hospital, Capital Medical University from February 2018 to March 2019. Patients were included if they met the following criteria: (1) they were diagnosed with AIS within 3 days of onset; (2) they underwent brain CT on admission; and (3) magnetic resonance imaging (MRI), magnetic resonance angiography (MRA) or CT angiography (CTA) within 3 days after admission immediately revealed worsening or abrupt neurological changes within 24 hours. This diagnosis of AIS was made based on World Health Organization criteria.<sup>21</sup> Patients with AIS-

LAA were classified into four groups: artery-to-artery embolization, in-situ thrombosis, hypoperfusion, and branch atheromatous disease<sup>39</sup> (Figure 1).

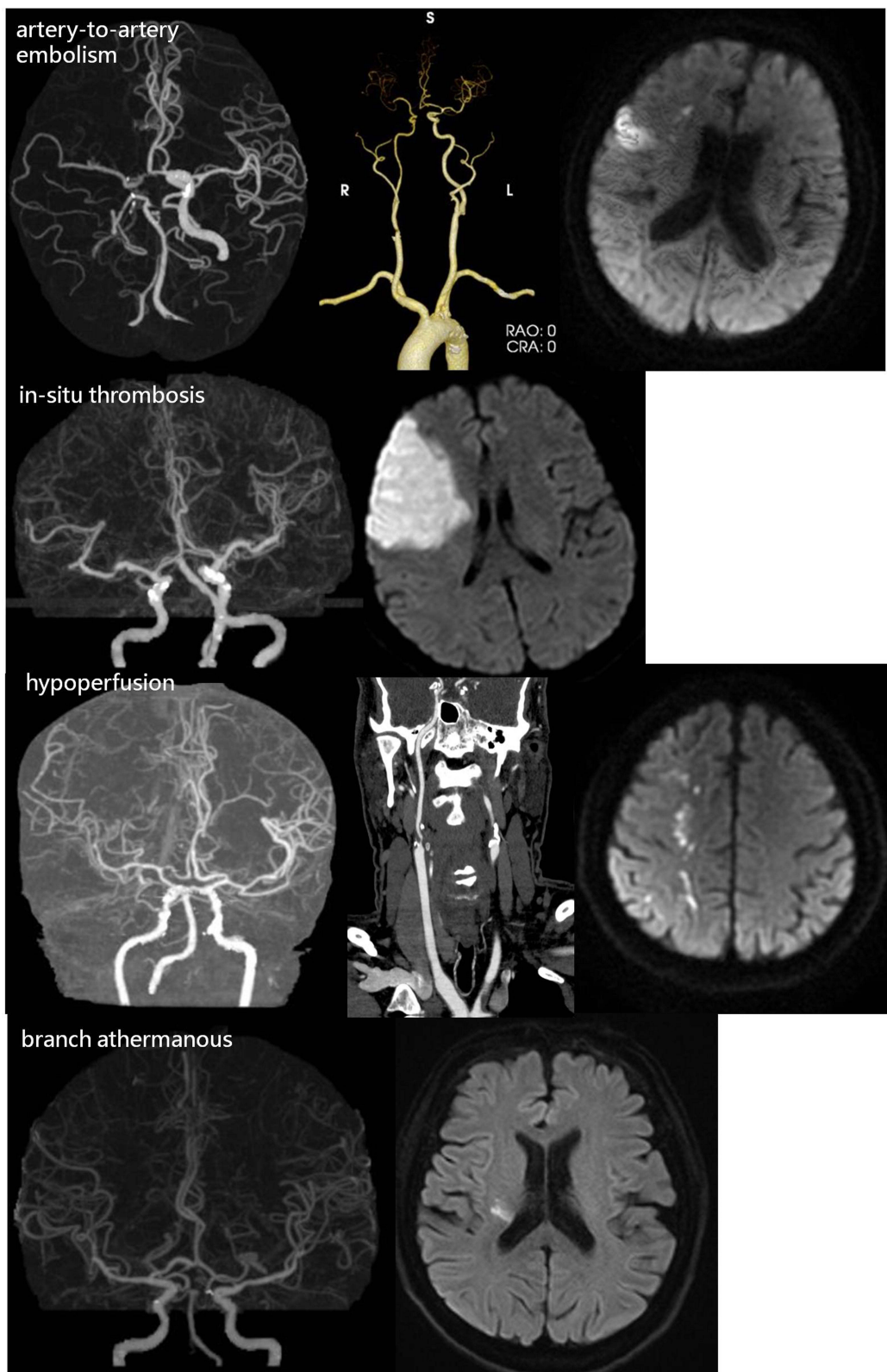
Patients were excluded if they (1) had hemorrhage detected on initial CT; (2) had acute or chronic infection, systemic immune diseases, liver and kidney diseases, hematological diseases, or cancer; or (3) had received endovascular thrombectomy (Figure 2).

This study was approved by the Ethics Committee of Beijing Friendship Hospital (2021-P2-167-01). This is a retrospective study, and all participants' information is protected. The study does not involve personal privacy or commercial interests. It is difficult to trace the recruitment and sign informed consent, so ethics committee of Beijing Friendship Hospital agreed to waive informed consent in this clinical trial. All procedures were carried out in accordance with the code of ethics of the 1975 Declaration of Helsinki.

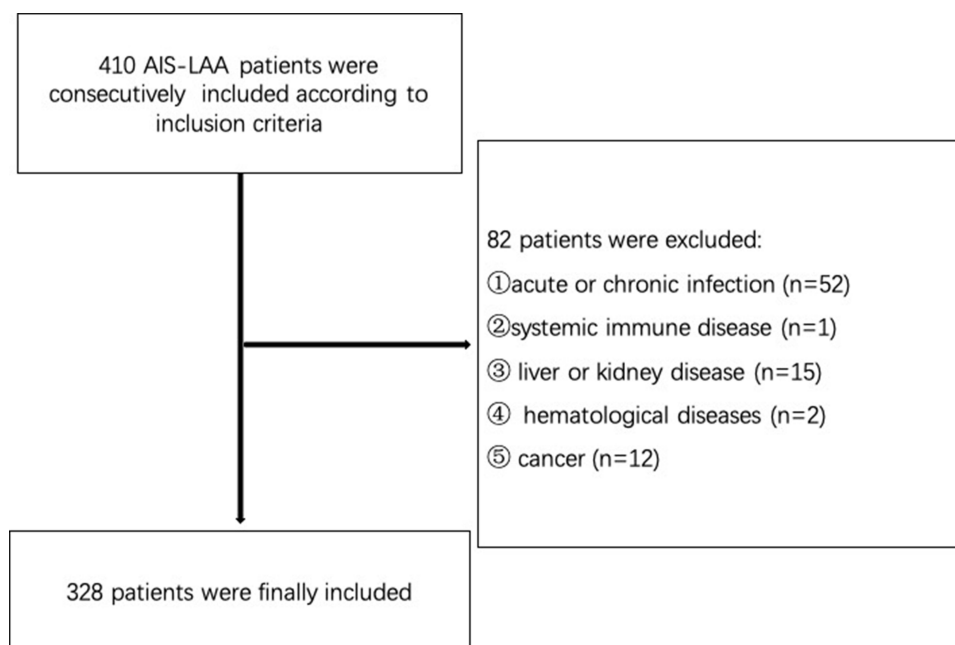
### Data Collection

Data were collected on the admission day, containing demographic characteristics (age and sex), cerebrovascular accident risk factors (hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, prior stroke or TIA, smoking, alcohol drinking), admission NIHSS, systolic blood pressure (SBP), diastolic blood pressure (DBP), and treatment in hospital (antiplatelet, anticoagulation, thrombolysis). According to MRI, MRA or CTA within 3 days after admission, we identified AIS-LAA patients who had stenosis greater than 50% in the relevant vessels. Mechanisms of AIS-LAA were classified into four subtypes: artery-to-artery embolization, in-situ thrombosis, hypoperfusion, and branch atheromatous disease. According to the area of the DWI infarction, the infarct volume was calculated using the Pullicino formula:  $t \text{ (mL)} = \pi/6 \times L \text{ (maximum long axis)} \times L \text{ (short axis)} \times \text{slice (layer thickness) (cm)}$ .<sup>40</sup> All laboratory examinations were collected next morning (5:00am) after admission, so we collected laboratory data including white blood cell counts (WBC), neutrophil counts (N), lymphocyte counts (L), platelet counts (P), NLR (calculated as neutrophil-to-lymphocyte ratio), and PLR (calculated as platelet-to-lymphocyte ratio).

HT which was not detected in initial CT or MRI on admission but later presented on the following CT and MRI because of worsened neurologic deterioration emergence in hospitalization was classified into hemorrhagic infarction (HI) and parenchymal hematoma (PH).<sup>22</sup>



**Figure 1** Representative cases of the four types of LAA mechanism (diffusion-weighted image and CTA images of the four types of LAA mechanism).



**Figure 2** Study flow diagrams.

## Statistical Analysis

All patients were divided into the HT and non-HT groups. Continuous variables were expressed as means (standard deviation, SD) or medians (interquartile range, IQR). Categorical variables were expressed as percentages. Univariate analysis using the student's *t*-test or Mann–Whitney *U*-test evaluated possible predictors of HT events, while the chi-square test or Fisher's exact test were applied for proportions. We used the violin plots in Python to show the distribution of PLR among groups in mechanism subtypes of LAA. Receiver operating characteristic (ROC) curves were used to test predictive indicators for HT and to determine the optimal cutoff value at which the total sensitivity and specificity was highest. The area under the ROC curve (AUC) was considered a critical diagnostic index because the prognosis is more accurate when the AUC is larger. Furthermore, multiple logistic regression analysis was adjusted for all potential confounders and assessed whether PLR was associated with incidence of HT after AIS-LAA and in-hospital mortality of HT after AIS-LAA. In the study, variables with  $P < 0.05$  were considered statistically significant and all statistical analyses were performed using SPSS version 23 (IBM SPSS, Chicago, IL, USA).

## Results

### Patient Characteristics

A total of 38 HT patients and 290 non-HT patients after AIS-LAA were admitted to the Neurology Department of Beijing Friendship Hospital between February 2018 and March 2019. The basic demographic and clinical characteristics and laboratory tests of the enrolled patients are shown in Table 1. Patients in the HT group were older ( $68.4 \pm 11.2$  vs  $67.0 \pm 11.0$ ,  $P = 0.572$ ), contained a smaller proportion of males ( $68.4\%$  vs  $70.7\%$ ,  $P = 0.774$ ), had more severe admission NIHSS scores ( $6[4-8]$  vs  $4[2-10]$ ,  $P = 0.187$ ), higher systolic blood pressure (mmHg) ( $150.9 \pm 16.7$  vs  $142.2 \pm 18.0$ ,  $P = 0.005$ ) and higher diastolic blood pressure (mmHg) ( $85.5 \pm 11.2$  vs  $83.3 \pm 13.5$ ,  $P = 0.058$ ), and infarct volume (mL) ( $9.6[6.8-12.2]$  vs  $8.4[6.4-10.6]$ ,  $P = 0.202$ ); more patients in the HT group received anticoagulation ( $15.8\%$  vs  $5.2\%$ ,  $P = 0.012$ ) and thrombolysis ( $13.2\%$  vs  $4.5\%$ ,  $P = 0.027$ ) treatment compared with those in the non-HT group. Compared to the patients in the non-HT group, the patients in the HT group possessed a significantly higher white blood cell level ( $10^9/L$ ) ( $7.52[6.00-10.01]$  vs  $6.87[5.60-7.99]$ ,  $P = 0.021$ ), a significantly higher neutrophil count level ( $10^9/L$ ) ( $5.20[3.58-8.61]$  vs  $4.39[3.50-5.85]$ ,  $P = 0.017$ ), and a significantly lower lymphocyte count level ( $10^9/L$ ) ( $1.45[1.18-1.78]$  vs  $1.76$

**Table 1** Baseline Characteristics of Patients with and without HT

Characteristics	Total, n=328	Without HT, n=290	With HT, n=38	P
Age, years (SD)	67.2(11.1)	67.0(11.0)	68.4(11.2)	0.572
Male, n (%)	231(70.4)	205(70.7)	26(68.4)	0.774
Hypertension, n (%)	182(55.5)	160(55.2)	22(57.9)	0.754
Diabetes, n (%)	102(31.1)	89(30.7)	13(34.2)	0.672
Dyslipidemia, n (%)	32(9.8)	27(9.3)	5(13.2)	0.512
Coronary artery disease, n (%)	36(11.0)	31(10.7)	5(13.2)	0.675
Prior stroke or TIA, n (%)	20(6.1)	17(5.9)	3(7.9)	0.664
Smoking, n (%)	141(43.0)	121(41.7)	20(52.6)	0.203
Alcohol consumption, n (%)	167(50.9)	150(51.7)	17(44.7)	0.425
Admission NIHSS, median (IQR)	4[2–10]	4[2–10]	6[4–8]	0.187
SBP (mmHg), mean±SD	143.5±18.2	142.2±18.0	150.9±16.7	0.005
DBP (mmHg), mean±SD	83.6±13.3	83.3±13.5	85.5±11.2	0.058
Infarct volume (mL), median (IQR)	8.6[6.5–11.2]	8.4[6.4–10.6]	9.6[6.8–12.2]	0.202
Treatment in hospital, n (%)				
Antiplatelet, n (%)	320(97.6)	283(97.6)	37(97.3)	0.938
Anticoagulation, n (%)	21(6.4)	15(5.2)	6(15.8)	0.012
Thrombolysis, n (%)	18(5.5)	13(4.5)	5(13.2)	0.027
Mechanism, n (%)				
Artery-to-artery embolization	144(43.9)	121(41.7)	23(60.5)	0.028
In-situ thrombosis	46(14.0)	36(12.4)	10(26.3)	0.020
Hypoperfusion	37(11.3)	36(12.4)	1(2.3)	0.073
Branch atheromatous disease	101(30.8)	97(33.4)	4(10.5)	0.004
Laboratory tests				
WBC (10 <sup>9</sup> /L), median (IQR)	6.96[5.63–8.16]	6.87[5.60–7.99]	7.52[6.00–10.01]	0.021
Neutrophil (10 <sup>9</sup> /L), median (IQR)	4.47[3.56–6.05]	4.39[3.50–5.85]	5.20[3.58–8.61]	0.017
Lymphocyte (10 <sup>9</sup> /L), median (IQR)	1.74[1.42–2.17]	1.76[1.35–2.18]	1.45[1.18–1.78]	0.004
Platelet (10 <sup>9</sup> /L), median (IQR)	210.56[174.65–257.32]	211.64[179.92–253.78]	209.25[169.30–272.65]	0.734
NLR, median (IQR)	2.63[1.92–3.68]	2.56[2.05–3.71]	3.86[2.33–6.61]	<0.001
PLR, median (IQR)	122.37[93.15–157.58]	118.77[88.96–150.36]	153.11[119.96–250.65]	<0.001

**Abbreviations:** SBP, systolic blood pressure; DBP, diastolic blood pressure; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to lymphocyte ratio; SD, standard deviation; IQR, interquartile range.

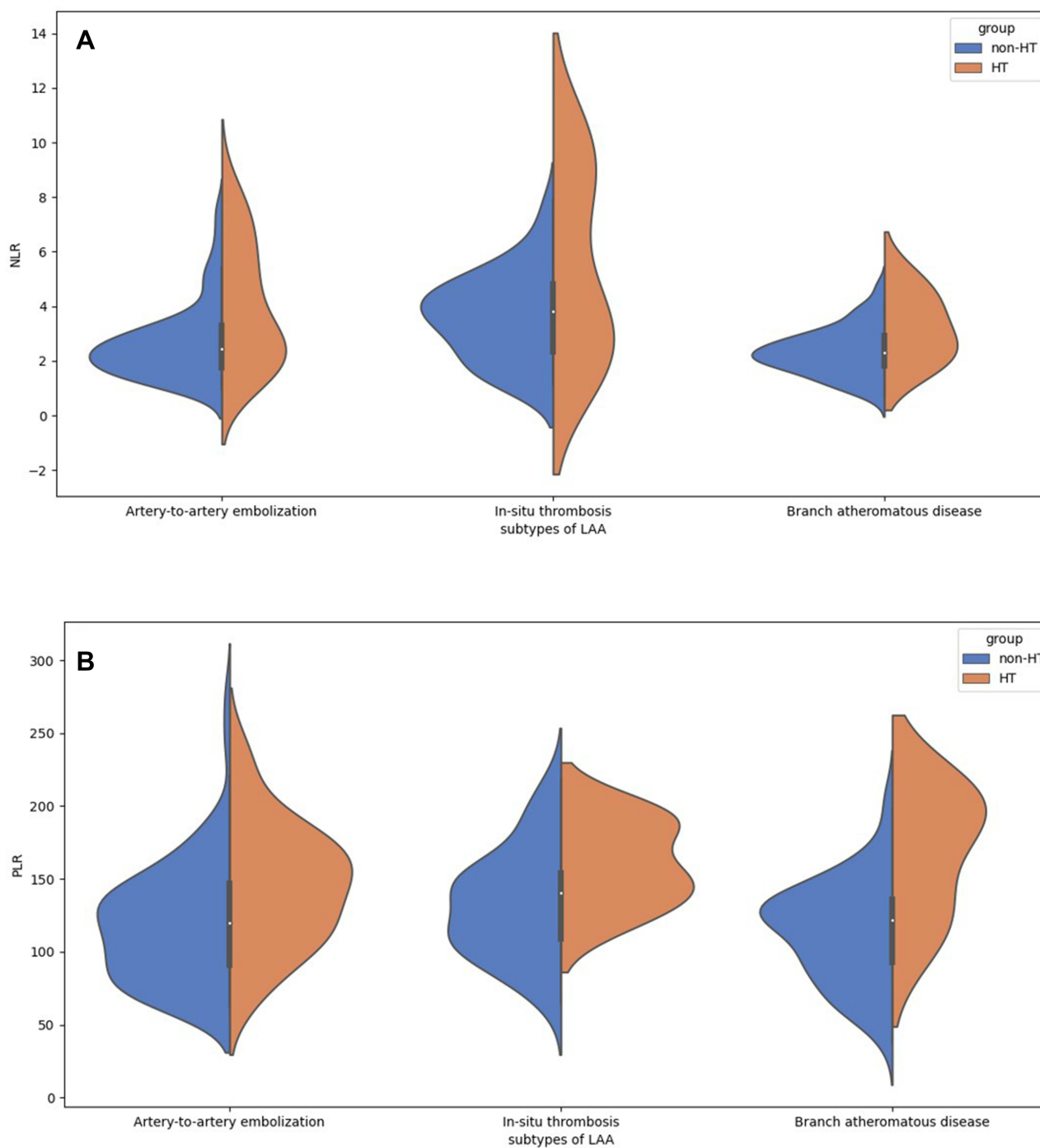
[1.35–2.18],  $P=0.004$ ). Both PLR (153.11[119.96–250.65] vs 118.77[88.96–150.36],  $P<0.001$ ) and NLR (3.86[2.33–6.61] vs 2.56[2.05–3.71],  $P<0.001$ ) were significantly higher in the patients with HT than those with non-HT. Figure 3 shows the violin plots of NLR and PLR among groups in mechanism subtypes of LAA (artery-to-artery embolization, in-situ thrombosis and branch atheromatous disease); we do not show hypoperfusion because of limited sample size. Both NLR and PLR in each subtype of LAA among groups were significantly different ( $P<0.005$ ).

HT patients are divided into PH group and HI group. Table 2 shows the baseline data of HT patients. There is no difference in age, sex, admission NIHSS, infarct volume,

systolic blood pressure, NLR and PLR between the two groups.

## PLR and HT

In binary logistic regression analysis, sex (aOR 0.594, 95% CI 0.262–1.343,  $P=0.210$ ), age (aOR 1.008, 95% CI 0.979–1.038,  $P=0.592$ ), systolic blood pressure (aOR 1.025, 95% CI 1.006–1.044,  $P=0.010$ ), white blood cell (aOR 1.228, 95% CI 1.000–1.456,  $P=0.050$ ), neutrophil (aOR 1.162, 95% CI 1.038–1.386,  $P=0.016$ ), lymphocyte (aOR 0.330, 95% CI 0.158–0.694,  $P=0.008$ ), platelet (aOR 0.550, 95% CI 0.233–1.298,  $P=0.183$ ), NLR (aOR 1.356, 95% CI 1.179–1.562,  $P<0.001$ ) and PLR



**Figure 3** The violin plot in distribution of composite inflammatory ratios (neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio) among different subtypes of LAA. **(A)** The violin plot in distribution of neutrophil-to-lymphocyte ratio among the different subtypes of LAA; each subtype has significant difference in two groups ( $P<0.005$ ). **(B)** The violin plot in distribution of platelet-to-lymphocyte ratio among different subtypes of LAA; each subtype has significant difference in two groups ( $P<0.005$ ).

(aOR 3.872, 95% CI 2.237–5.706,  $P<0.001$ ) were independently associated with HT after adjustment for possible confounders (Table 3).

The ROC curves predicting the value of NLR and PLR for HT after AIS-LAA are presented in Figure 4. The area under the curve (AUC) value of PLR (0.72, 95% CI (0.64–

**Table 2** Baseline Data of PH and HI

Characteristics	HI, n=24	PH, n=14	P
Age, years (SD)	69.4±10.9	66.7±11.9	0.276
Male, n (%)	16	10	0.761
Hypertension, n (%)	14	8	0.943
Diabetes, n (%)	8	5	0.881
Dyslipidemia, n (%)	3	2	0.875
Coronary artery disease, n (%)	2	3	0.249
Prior stroke or TIA, n (%)	2	1	0.896
Smoking, n (%)	12	8	0.671
Alcohol consumption, n (%)	10	7	0.618
Admission NIHSS, mean±SD	6.7±4.5	6.6±5.0	0.567
SBP (mmHg), mean±SD	153.7±15.1	147.3±18.6	0.082
DBP (mmHg), mean±SD	85.9±10.5	84.2±12.8	0.508
Infarct volume (mL), mean±SD	9.8±7.3	9.4±8.0	0.266
Treatment in hospital, n (%)			
Antiplatelet, n (%)	23	14	0.439
Anticoagulation, n (%)	4	2	0.846
Thrombolysis, n (%)	3	2	0.875
Mechanism, n (%)			
Artery-to-artery embolization	15	8	0.744
In-situ thrombosis	6	4	0.017
Hypoperfusion	1	0	0.439
Branch atheromatous disease	3	1	0.604
Laboratory tests			
WBC (10 <sup>9</sup> /L), mean±SD	7.2±2.2	8.8±2.5	0.044
Neutrophil (10 <sup>9</sup> /L), mean±SD	5.0±2.3	6.7±2.6	0.056
Lymphocyte(10 <sup>9</sup> /L), meanSD	1.4±0.46	1.5±0.64	0.372
Platelet (10 <sup>9</sup> /L), mean±SD	209.0±77.8	211.3±54.6	0.888
NLR, mean±SD	2.6±2.2	3.4±3.2	0.391
PLR, mean±SD	157.7±63.1	146±65.6	0.369

**Abbreviations:** SBP, systolic blood pressure; DBP, diastolic blood pressure; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to lymphocyte ratio; SD, standard deviation.

0.80),  $P<0.001$ ) showed a greater discriminatory ability compared with NLR (0.67, 95% CI (0.58–0.76),  $P<0.001$ ). The optimal cutoff value of PLR was 140.15, with a sensitivity of 66.9% and a specificity of 68%, but the optimal cutoff value of NLR was 3.28, with a sensitivity of 48.8% and a specificity of 75.5%. The binary logistic analysis, with PLR as a dichotomous variable,  $PLR \geq 140.15$  (OR 4.104, 95% CI (2.049–8.219),  $P<0.001$ ; aOR 4.721, 95% CI (2.204–9.110),  $P<0.001$ ) had a significant association with HT after AIS-LAA (Table 4).

**Table 3** Multivariate Analysis for the Association Between Indicators and HT

Indicators	Adjusted OR (95% CI)	P
Sex#	0.594(0.262–1.343)	0.210
Age <sup>†</sup>	1.008(0.979–1.038)	0.592
SBP <sup>**</sup>	1.025(1.006–1.044)	0.010
WBC <sup>*</sup>	1.228 (1.000–1.456)	0.050
Neutrophil <sup>*</sup>	1.162 (1.038–1.386)	0.016
Lymphocyte <sup>*</sup>	0.330 (0.158–0.694)	0.008
Platelet <sup>*</sup>	0.550 (0.233–1.298)	0.183
NLR <sup>*</sup>	1.356 (1.179–1.562)	<0.001
PLR <sup>*</sup>	3.872 (2.237–5.706)	<0.001

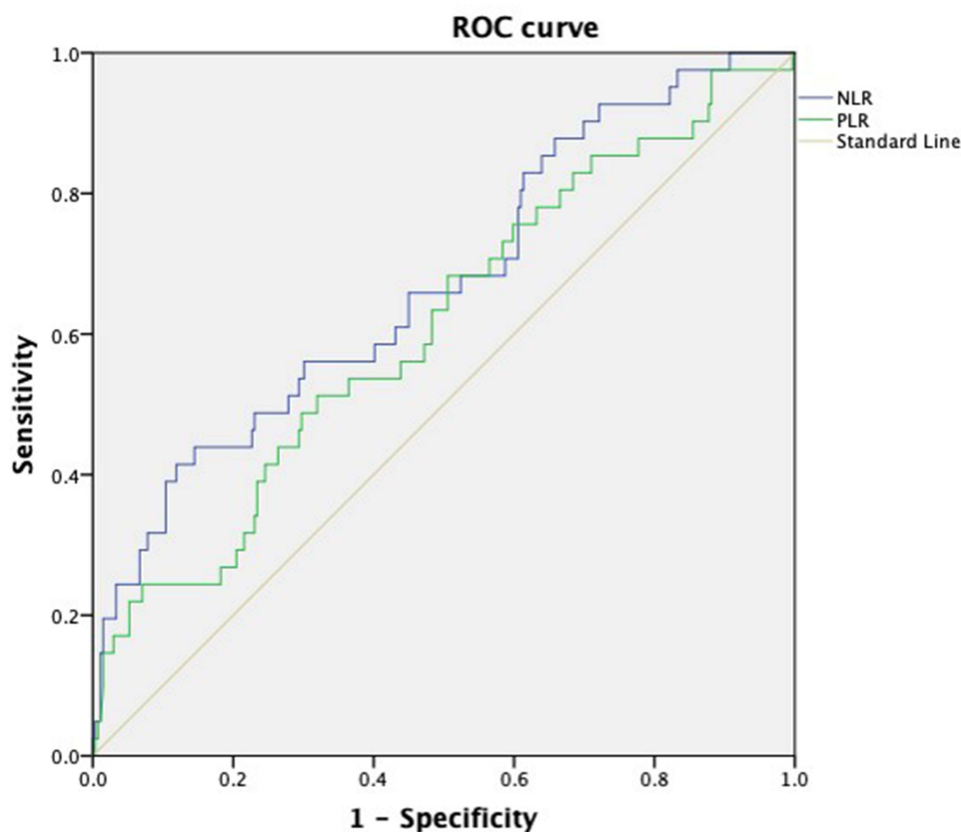
**Notes:** #As continuous variables adjustment for age, SBP, admission NIHSS, Infarct volume, anticoagulation, thrombolysis, Artery-to-artery embolization, In-situ thrombosis, Hypoperfusion, Branch atheromatous disease. <sup>†</sup>As continuous variables adjustment for sex, SBP, admission NIHSS, Infarct volume, anticoagulation, thrombolysis, Artery-to-artery embolization, In-situ thrombosis, Hypoperfusion, Branch atheromatous disease. <sup>\*</sup>As continuous variables adjustment for age, sex, admission NIHSS, Infarct volume, anticoagulation, thrombolysis, Artery-to-artery embolization, In-situ thrombosis, Hypoperfusion, Branch atheromatous disease. <sup>\*\*</sup>As continuous variables adjustment for age, sex, SBP, admission NIHSS, Infarct volume, anticoagulation, thrombolysis, Artery-to-artery embolization, In-situ thrombosis, Hypoperfusion, Branch atheromatous disease.

**Abbreviations:** HT, hemorrhagic transformation; SBP, systolic blood pressure; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to lymphocyte ratio; OR, odds ratio; CI, confidence interval.

We performed univariate and multivariate analysis to identify whether an association existed between PLR and the risk of HT after AIS-LAA in different LAA mechanism subtypes. Table 5 summarizes univariate and multivariate analysis for the association between PLR and HT in each LAA subtype. PLR was observed to be a predictor of HT in AIS with artery-to-artery embolization (OR 1.632, 95% CI (1.207–2.940),  $P=0.016$ ; aOR 1.702, 95% CI (1.300–3.218),  $P=0.024$ ), in-situ thrombosis (OR 3.178, 95% CI (1.244–8.114),  $P<0.001$ ; aOR 4.502, 95% CI (1.346–9.056),  $P<0.001$ ) and branch atheromatous disease (OR 3.452, 95% CI (1.123–8.652),  $P<0.001$ ; aOR 3.240, 95% CI (1.099–8.357),  $P<0.001$ ) (Table 5).

## PLR and In-Hospital Mortality of HT After AIS-LAA

The difference between all-cause in-hospital mortality rates is statistically significant ( $p=0.012$ ) in the two groups: 13.16% ( $n=5/38$ ) of patients with HT versus 3.79% ( $n=11/290$ ) of patients with non-HT. The causes of death were neurological in 5 patients in HT, including herniation of the brain in 2 (5.26%) and recurrent cerebral ischemia in 3 (7.89%). The cause of death in the non-HT group was as follows: 3 patients died from cerebral ischemia (1.03%), 4 patients died from



**Figure 4** Predictive value of NLR and PLR for HT. The receiver operating characteristic (ROC) curves were used to test predictive power of indicators for HT and to determine the optimal cutoff value. ROC curves demonstrated that the optimal cutoff value of PLR for HT was 140.15 (sensitivity 66.9%, specificity 68.0%); the area under the curve (AUC) value was 0.72 (0.64–0.80),  $P < 0.001$ . The optimal cutoff value of NLR was 3.28 (sensitivity 48.8%, specificity 75.5%); the AUC value was 0.67 (0.58–0.76),  $P < 0.001$ .

pulmonary complications (1.38%), and 4 patients died from cardiovascular issues (1.38%). Compared to the non-in-hospital mortality patients in the HT group, patients who died in hospital in the HT group possessed significantly higher levels of PLR (191.72 [114.82–275.08] vs 126.77[109.47–144.07],  $P < 0.001$ ). Univariate and multivariate analysis showed that increased PLR predicts high in-hospital mortality of HT after AIS-LAA (OR 1.041, 95% CI (1.006–1.077),

$P = 0.020$ ; aOR 1.055, 95% CI (1.007–1.106),  $P = 0.033$ ) (multivariate analysis was adjusted for age, sex, systolic blood pressure, infarct volume, anticoagulation, and thrombolysis).

### Discussion

To the best of our knowledge, PLR has not previously been assessed in HT after AIS. This is the first study to explore the association between PLR and HT in AIS-LAA,

**Table 4** Univariate and Multivariate Analysis for the Relationship Between NLR, PLR and HT, with NLR and PLR Dichotomized by the Optimal Cutoff Value in ROC Curves

Indicators*	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	P	Adjusted OR (95% CI)	P
NLR ( $\geq 3.28$ vs $< 3.28$ )	2.221 (1.147–4.300)	0.018	2.194 (1.053–4.574)	0.035
PLR ( $\geq 140.15$ vs $< 140.15$ )	4.104 (2.049–8.219)	$< 0.001$	4.721 (2.204–9.110)	$< 0.001$

**Notes:** \*Multivariate analysis adjusted for age, sex, SBP, admission NIHSS, infarct volume, anticoagulation, thrombolysis, artery-to-artery embolization, in-situ thrombosis, hypoperfusion, branch atheromatous disease.

**Abbreviations:** HT, hemorrhagic transformation; PLR, platelet-to lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; CI, confidence interval.



**Table 5** Univariate and Multivariate Analysis for the Association Between PLR and HT in Each Stroke with LAA Subtypes

Indicators*	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	P	OR (95% CI)	P
Artery-to-artery embolization	1.632(1.207–2.940)	0.016	1.702(1.300–3.218)	0.024
In-situ thrombosis	3.178(1.244–8.114)	<0.001	4.502(1.346–9.056)	<0.001
Hypoperfusion	–	–	–	–
Branch atheromatous disease	3.452(1.123–8.652)	<0.001	3.240(1.099–8.357)	<0.001

**Notes:** \*Multivariate analysis adjusted for age, sex, SBP, admission NIHSS, infarct volume, anticoagulation, thrombolysis.

**Abbreviations:** HT, hemorrhagic transformation; PLR, platelet-to-lymphocyte ratio; OR, odds ratio; CI, confidence interval.

including in patients with artery-to-artery embolization, in-situ thrombosis and branch atheromatous disease, and increased PLR predicts high in-hospital mortality of HT in AIS-LAA. The present study indicated that PLR was associated with an increased risk of HT after AIS-LAA. It was reported that an increased NLR at admission had a direct relationship with HT in AIS.<sup>11–16</sup> It was also reported that systemic immune-inflammation index (SII), based on peripheral neutrophil, lymphocyte, and platelet counts, was associated with hemorrhagic transformation in anterior circulation AIS patient with large-artery atherosclerosis.<sup>41</sup> However, as documented in our study, we found that PLR had more clinical utility and more accuracy for HT in AIS-LAA patients than did NLR.

As we all know, AIS with cardio-embolism accounts for approximately 25% of HT after AIS in white people, but LAA is a major contributor to HT after AIS in Chinese people.<sup>38</sup> In recent years, numerous studies have drawn more attention to inflammatory mechanisms in the pathogenesis of AIS.<sup>24</sup> PLR calculated by platelet count to lymphocyte count ratio has been reported as an effective predictor for severe atherosclerosis.<sup>23</sup> Both platelets and lymphocytes are predictors of prognosis in myocardial infarction and cerebral infarction.<sup>42,43</sup> HT was attributed to blood–brain barrier permeability, hemostatic dysfunction, oxidative stress, inflammation, and immunologic disorder.<sup>5</sup>

Why is PLR level related to risk of HT? The roles of platelet and lymphocytes in AIS and damage to the blood–brain barrier (BBB) may be the underlying mechanisms.<sup>25</sup> There is an autopsy study demonstrating that up-regulation of leukocytes and depletion of lymphopenia in 6 to 12 hours perfused cerebral infarction regions, which is associated with breakdown of BBB, endothelial activation, and complex neurohormonal responses.<sup>26–29</sup> Increased matrix metalloproteinase-9 (MMP-9) derived from peripheral leukocytes/neutrophils

at 6–8 hours after AIS degrade components of BBB and ultimately result in HT.<sup>30,31</sup> Lymphocytes, as a neuroprotective effector, contribute to neurological function improvement.<sup>32</sup> Ischemic stroke induces lymphopenia by mechanisms involving complex neurohormonal responses and facilitates HT.<sup>33</sup> AIS may lead to platelet function abnormality, and activated and hyper-responsive platelets may interact with platelet-binding T lymphocyte cells to produce cytokines, interferons, chemokines and altering adhesion molecules, and result in hampering AIS recovery.<sup>34–37</sup> Moreover, some factors released after AIS, including reactive oxygen species, cathepsin G, protease, myeloperoxidase, elastase, chemokines and cytokines, may also elevate permeability of BBB and risk of HT.<sup>4</sup>

A number of studies have indicated that PLR is an independent predictor of the incidence and mortality of in-hospital and long-term major adverse cardiovascular events in patients with acute myocardial infarction.<sup>44,45</sup> PLR is a combination of platelets and lymphocytes which provide the pathogenesis of AIS. Elevated level of PLR is associated with worse outcomes after intravenous thrombolysis in AIS, according to the study of Xu et al.<sup>17</sup> The finding of our research has provided new support for the role of PLR in HT after AIS-LAA.

Higher PLR on admission may indicate HT after AIS-LAA. In our study, we found PLR was an independent predictor of HT, and the risk of HT increased 4.719-fold when  $PLR \geq 140.15$ . PLR takes more clinical weight of parameters into consideration than NLR. Among the mechanism subtypes of LAA, HT after AIS patients with artery-to-artery embolization, in-situ thrombosis or branch atheromatous disease had higher PLR levels. We considered that PLR is a sensitive indicator of HT after AIS-LAA. Meanwhile, artery-to-artery embolization, in-situ thrombosis and branch atheromatous disease were independent risk factors for HT after AIS.

There is a trend that in-hospital mortality in HT after AIS-LAA is significantly higher than that in AIS-LAA, and the causes of recurrent cerebral ischemia in the HT group stop anti-thrombotic treatment. We also identified that increased PLR was an independent predictor of high in-hospital mortality in HT after AIS-LAA patients. Thus, the PLR plays multiple roles in patients with AIS-LAA as a predictor of HT and as a predictor of in-hospital mortality of HT after AIS-LAA.

Our study suggests that the PLR is a sensitive biomarker for HT after AIS-LAA, and predicts in-hospital mortality in patients with HT after AIS-LAA. However, there are several limitations in our study. First, the single-center retrospective observation study leads to selection bias because of limited sample size. In our study, we could not analyse the relationship between PLR and HT in the subgroup with hypoperfusion because of low case numbers. Meanwhile, patients in the HT group were older, contained a smaller proportion of males, had more severe admission NIHSS scores but showed no significant differences. We should enlarge the patient sample size to test this trend. Second, we need to conduct a follow-up study to confirm the relationship between PLR and HT. Third, our further study needs to observe the dynamic relationship of PLR in HT after AIS.

## Conclusion

In conclusion, high PLR is associated with greater risk of HT in Chinese patients with AIS-LAA, including in artery-to-artery embolization, in-situ thrombosis or branch atherosclerotic disease, and increased PLR predicts high in-hospital mortality in patients with HT after AIS-LAA. However, further investigation is needed into dynamic changes of PLR on the risk of HT after AIS-LAA in a larger cohort.

## Disclosure

The authors report no conflicts of interest in this work.

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