Platelet-to-lymphocyte ratio at 24h after thrombolysis is a prognostic marker in acute ischemic stroke patients

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Abstract

Introduction: The role of Platelet-to-lymphocyte ratio (PLR) in outcomes of acute ischemic stroke, especially before and after intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA), has not been elucidated. Thus, the aim of this study was to evaluate the effect of PLR before and after rtPA on clinical outcomes.

Methods: A total of 582 consecutive patients who had acute ischemic stroke diagnosed and received intravenous thrombolysis with rtPA were included in this study. We collected demographics, vascular risk factors, previous history of drugs and other clinical information for all patients. Specifically, blood samples for PLR values were collected on admission and at 24 hours after stroke. Multivariate logistic regression analysis was used to assess the association between PLR with the risk of poor outcome ($mRS \geq 3$), death and hemorrhagic transformation (HT).

Results: Of 582 patients, 191 (32.8%) had a poor outcome, 40 (6.9%) died and 82 (14.1%) had HT. After adjustment for potential confounders, multivariate logistic regression analysis showed that higher PLR at 24h after rtPA was independently associated with an increased risk of poor outcome ($OR=1.004$; 95% CI:1.001-1.007; $P=0.009$) and the occurrence of death ($OR=1.009$; 95% CI:1.004-1.013; $P<0.001$), but not associated with the risk of HT ($OR=1.003$; 95% CI:0.999-1.007; $P=0.165$). In addition, PLR on admission was not associated with the risk of poor outcome, death and HT (all $P>0.05$).

Conclusions: We found that PLR at 24h after rtPA can predict the risk of poor outcome and death in acute ischemic stroke patients, but PLR on admission cannot.

Introduction

Stroke is one of the most common causes of disability and death worldwide and ischemic stroke accounts for 80% of all cases[1, 2]. Intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA) is the most effective therapy and has been widely used in acute ischemic stroke patients within 4.5 hours[3]. However, it also may cause some complications, such as hemorrhagic transformation (HT), that affect the functional outcomes[4, 5]. Therefore, it is important to understand what clinical indicator can predict patients' prognosis and do what is possible to control the risk factors at an earlier stage.

Previous research suggested that inflammatory response plays an important role in the whole process of acute ischemic stroke[6]. Platelet-to-lymphocyte ratio (PLR), as a combination of platelets and lymphocytes, is a new biomarker to reflect the thrombus formation pathway and inflammation pathway. Several pieces of evidence have confirmed that PLR was a potential marker to predict increased inflammation, the risk of myocardial infarction and ischemic stroke[7–12]. However, the predictive value of PLR on the outcomes of ischemic stroke with rtPA treatment are largely unknown. Thus, the aim of this study was to evaluate the relationship between the PLR before and after thrombolysis treatment and poor outcome, death and HT in acute ischemic stroke patients.

Materials And Methods

Study Population

This retrospective study included patients who had acute ischemic stroke diagnosed and received intravenous thrombolysis with rtPA in our department from April 2015 to March 2019. The inclusion criteria were diagnosis of acute ischemic stroke and treatment with standard-dose rtPA (0.9-mg/kg) within 4.5 hours. The exclusion criteria

were missing clinical data or failure of follow-up. A flow chart of the study is given in **Figure 1**. The study was approved by the Ethics Review Committee of the First Hospital of Jilin University, and written informed consent was obtained from the patient or an appropriate surrogate.

Data Collection

Baseline clinical data were collected for all patients, including demographic information (age, gender), vascular risk factors (smoking, alcohol consumption, hypertension, diabetes, previous stroke), previous history of drugs (antihypertensive drugs, hypoglycemic agents, antiplatelet agents), as well as other clinical information. Patients were all treated with standard-dose thrombolysis (0.9-mg/kg). Hypertension was defined as systolic blood pressure of 140-mmHg, a diastolic blood pressure of 90-mmHg, the reported use of antihypertensive medications, or a history of diagnosed hypertension[13]. Diabetes was defined as fasting serum glucose of ≥ 126 -mg/dL (7-mmol/L), a non-fasting glucose of ≥ 200 -mg/dL (11.1-mmol/L), use of diabetic medications, or a previously established diagnosis[13]. Blood samples for platelet and lymphocyte counts of all patients were collected on admission and at 24 hours after thrombolysis. PLR was calculated as the ratio of platelet count to lymphocyte count.

Outcome

In this study, we included three clinical outcome indicators to assess the predictive value of PLR on the outcomes of ischemic stroke with rtPA treatment.

Modified Rankin Scale (mRS): the mRS was assessed at three months with a score ranging from 0 (no symptoms) to 6 (death)[14]. We defined mRS >2 as a poor outcome and mRS ≤ 2 as a favorable outcome.

Death: was defined as death associated with the stroke within three months of thrombolysis.

HT: was defined as any visible hemorrhage on brain CT or MRI 22–36h after thrombolysis[15].

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics 20. Distribution normality was tested by the Kolmogorov-Smirnov test. We found all continuous variables were nonparametrically distributed variables. So the Mann-Whitney U-test was used for the comparison of continuous variables. The chi-squared test was used for comparison of categorical variables. Median with interquartile range (IQR) and percentages were used to describe the distribution of continuous and categorical variables respectively. Multivariate analysis was performed using logistic regression analysis which adjusted for other variables. The area under the curve of receiver operating characteristics curve (ROC) was produced to determine accuracy and threshold of PLR values for poor outcome, death and HT. $P < 0.05$ was set as the statistical significance level.

Results

Baseline characteristics of patients

In our study, a total of 616 patients treated with rtPA were included according to the inclusion criteria. After 34 patients were excluded according to exclusion criteria, 582 patients were finally included and the baseline clinical characteristics of participants are presented in **Table 1** and **Figure 1**. The mean age of patients was 61 (interquartile range, 53-69) and 158 (27.1%) were women. The NIHSS score was 9 (interquartile range, 5–13). The time to treat

was 180min (interquartile range, 141–230min). Of 582 patients, 191 patients (32.8%) had poor outcome, 40 patients (6.9%) died and 82 patients (14.1%) had HT.

Patients with poor outcome were more likely to have a higher age, a higher prevalence of hypertension, higher systolic blood pressure, higher NIHSS scores and a higher level of PLR at 24h after rtPA (all $P<0.05$) than those with a favorable outcome ($mRS\leq 2$). Patients with death after stroke within three months were older, more likely to suffer from diabetes and atrial fibrillation, and had a higher proportion of antiplatelet agents, higher NIHSS scores and a higher level of PLR at 24h after rtPA (all $P<0.05$). Patients who had HT or non-HT were similar in most characteristics except for age, diabetes, atrial fibrillation, antiplatelet agents and NIHSS scores (all $P<0.05$). There was no significant difference in other listed variables between these groups (**Table 1** and **2**).

Association between PLR at 24h after thrombolysis and outcomes

After adjustment for potential confounders, multivariate logistic regression analysis disclosed that higher PLR at 24h after thrombolysis was independently associated with an increased risk of poor outcome (OR=1.004; 95% CI:1.001-1.007; $P=0.009$) and the occurrence of death (OR=1.009; 95% CI:1.004-1.013; $P<0.001$), but not associated with the risk of HT (OR=1.003; 95% CI:0.999-1.007; $P=0.165$) (**Table 3**).

ROC curve analysis was performed and the results showed that the ability of the areas under the curve (AUC) for the PLR at 24h after thrombolysis to predict clinical outcome was 0.617 with a sensitivity of 55.0% and a specificity of 64.2%, while the ability to predict death was 0.699 with a sensitivity of 77.5% and a specificity of 55.9%. But no significant threshold of PLR at 24h after thrombolysis was found to predict HT (**Table 4**).

Association between PLR on admission and outcomes

After adjustment for potential confounders, multivariate logistic regression analysis disclosed that PLR on admission was not associated with the risk of poor outcome (OR=1.001; 95% CI:0.998-1.003; $P=0.617$), death (OR=0.999; 95% CI:0.993-1.004; $P=0.658$) and HT (OR=1.000; 95% CI:0.999-1.001; $P=0.740$) (**Table 3**). In addition, no significant threshold of PLR on admission was found to predict these outcomes (**Table 4**).

Discussion

This study attempted to evaluate the effect of PLR before and after thrombolysis treatment on the outcomes in acute ischemic stroke patients. We found that PLR at 24 h after rtPA treatment, but not on admission, was an independent risk factor for poor outcome and death. In addition, we found PLR had no significant interaction with the risk of HT, no matter whether the index was calculated before or after thrombolysis.

Previous studies have shown that PLR has a strong relationship with ischemic events in general. For example, in a recent study, researchers suggested that PLR can be used in clinical practices for prediction of no reflow in patients with acute ST-segment elevation myocardial infarction after primary percutaneous intervention[8]. Simultaneously, the study by Tekesin A et al. [9] showed a significant association between PLR and cerebral vein thrombosis in suspected patients. Another study by Altintas O et al.[10] found that, in patients with acute ischemic stroke who underwent endovascular therapy, low-PLR values were shown to be correlated with better clinical outcome ($mRS\leq 2$). In addition, in a retrospective study of 56 patients who had acute ischemic stroke diagnosed and underwent mechanical thrombectomy, researchers found that PLR had no relationship with clinical outcome, but PLR was lower in the group with a dramatic improvement in the 24th hour[11]. Compared with previous studies, the sample

size of our study is relatively large and we further found that the patients with high-PLR values at 24 h after thrombolysis had poorer outcome (mRS > 2) and a higher occurrence of death compared with the patients with low-PLR values at the same time.

Platelets play an important role in prothrombotic status. A high platelet count may represent a higher tendency to thrombosis, leading to poor prognosis[16]. Moreover, platelets can release a variety of inflammatory factors and recruit leukocytes to the sites of inflammation and injury, which leads to the aggravation of inflammatory reaction in thrombus sites[17]. In a previous study, it was suggested that the increase of platelet count in patients with thrombus may be due to multiple inflammatory mediators that stimulate megakaryocyte proliferation and thus produce more platelets[18]. In contrast, lymphocytes are known to control inflammatory pathways[19, 20]. A decreased lymphocyte count may aggravate the injury of cerebral infarction and neurological deficits[21]. On the one hand, regulatory T cells, specific subtypes of lymphocytes, play a key role in eliminating inflammatory response, and act as the main brain protective immunomodulator in the process of acute stroke[22, 23]. On the other hand, a decrease in lymphocyte count may be an index to reflect the stress level of the body, which can reflect the production of cortisol-induced stress response and the activation of the renin–angiotensin system which further increases the production of pro-inflammatory cytokines promoting ischemic injury[21, 24, 25]. In general, lymphocytes have an important role in the healing and repairing inflammation[26].

PLR, as a combination of platelets and lymphocytes, has the advantage of reflecting not only the thrombus formation pathway, but also the inflammation pathway[27]. There are two main reasons why PLR may be superior to absolute platelet or lymphocyte count in predicting prognosis. First, PLR represents two inversely related predictors and immunologic pathways[20]. Second, previous studies have suggested that PLR is more stable compared with single platelet and lymphocyte counts, because platelet or lymphocyte counts could be altered by many physiologic and pathologic conditions[28–30]. Therefore, the PLR is more useful, rational and reliable for predicting the risk of poor outcome and death in patients. However, we did not find a significant association between PLR and HT in acute ischemic stroke patients after thrombolysis in this study. We think the association between PLR and HT needs further investigation in the future.

Also, the AUC for the PLR after 24 h appeared to be greater than that at baseline, and the mechanisms have not been well established. We suspect that there may be two reasons to explain this phenomenon. One reason is that, within 24 hours of stroke, the lymphocytes accumulate in cerebral vessels at a later time [31]. So we speculated that the PLR values after 24 h was more valuable than the PLR at baseline for reflecting the patients' conditions. The other reason is that the recent study suggested that the lymphocyte count after ischemic stroke exhibited a significant temporal variation which was characterized by “dynamic” changes[22, 32]. Moreover, thrombolysis also has a significant impact on the PLR. Thus, the PLR values on admission may be unable to dynamically and comprehensively reflect the patients' conditions.

Our study has some limitations. First, the study was retrospective and the data included patients only treated at one hospital, which might lead to selection bias. Second, we only examined PLR at two time points, which was before thrombolysis and 24 h after thrombolysis. The dynamic change of PLR during the whole process of ischemic injury and its definite mechanisms have not been fully elucidated. Further investigations are needed to explore the relevant mechanisms of this study. Lastly, some other inflammatory markers such as neutrophils, CRP, and IL-2 were not taken into consideration.

In conclusion, we found that the PLR at 24 h after rtPA thrombolysis, rather than before thrombolysis, was associated with the risk of poor outcome and death in acute ischemic stroke patients, which can be used as a simple, novel and inexpensive method for predicting patients' prognosis.

Declarations

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Competing interest:

There are no competing interests for all the other authors of this manuscript.

Consent for publication:

For each subject, an informed consent form was obtained. The document included consent for the use of individual data for academic purposes and publications.

Data Availability Statement:

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

Authors' contributions:

Yi Yang and Zhen-Ni Guo were responsible for study design. Material preparation, data collection and analysis were performed by Ying-Ying Sun, Mei-Qi Wang and Yan Wang. The first draft of the manuscript was written by Ying-Ying Sun and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate:

This study was approved by the Ethics Review Committee of the First Hospital of Jilin University. Written informed consent was obtained from all study participants. The privacy rights of all study participants always be observed. All patients consent to participate.

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Tables

Table 1 Baseline characteristics of patients according to presence/absence of poor outcome and death

	Total	Favorable outcome	Poor outcome	P	Alive	Dead	P
N	582	391	191		542	40	
Age, years, median (IQR)	61(53-69)	60(52-68)	63(54-71)	0.010	61(53-69)	68(58-75)	0.003
Females, %	158(27.1)	108(27.6)	50(26.2)	0.713	147(27.1)	11(27.5)	0.959
Smoking, %	327(56.2)	226(57.8)	101(52.9)	0.261	302(55.7)	25(62.5)	0.404
Alcohol consumption, %	254(43.6)	171(43.7)	83(43.5)	0.949	235(43.4)	19(47.5)	0.610
Hypertension, %	302(51.9)	190(48.6)	112(58.6)	0.023	283(52.2)	19(47.5)	0.565
Diabetes, %	189(32.5)	117(29.9)	72(37.7)	0.06	170(31.4)	19(47.5)	0.035
Coronary artery disease, %	116(19.9)	75(19.2)	41(21.5)	0.517	110(20.3)	6(15.0)	0.419
Atrial fibrillation, %	27(4.6)	20(5.1)	7(3.7)	0.435	22(4.1)	5(12.5)	0.014
Previous stroke, %	88(15.1)	52(13.3)	36(18.8)	0.079	82(15.1)	6(15.0)	0.982
Antihypertensive drugs, %	200(34.4)	124(31.7)	76(39.8)	0.054	188(34.7)	12(30.0)	0.547
Hypoglycemic agents, %	102(17.5)	65(16.6)	37(19.4)	0.413	93(17.2)	9(22.5)	0.391
Antiplatelet agents, %	73(12.5)	45(11.5)	28(14.7)	0.281	64(11.8)	9(22.5)	0.049
SBP, mmHg, median (IQR)	154(138- 165)	152(138- 164)	157(142- 169)	0.012	154(138- 165)	155(135- 169)	0.881
DBP, mmHg, median (IQR)	89(80-98)	89(80-98)	89(81-98)	0.596	89(80-98)	89(80-99)	0.758
Blood glucose, mmol/L, median (IQR)	6.92(6.13- 8.65)	6.8(6.0- 8.6)	7.1(6.3- 8.7)	0.156	6.9(6.1- 8.6)	7.0(6.3-9.0)	0.636
Time to treat, min, median (IQR)	180(141- 230)	182(144- 231)	175(135- 230)	0.165	180(140- 230)	180(158- 236)	0.405
Baseline NIHSS score, median (IQR)	9(5-13)	8(4-11)	12(8-15)	<0.001	9(5-12)	13(10-16)	<0.001
PLR on admission	120.7(91.6- 155.7)	122.7(92.0- 155.5)	118(90.4- 156.2)	0.874	120.7(91.6- 155.7)	127.2(90.3- 154.3)	0.803
PLR at 24h after rtPA	116.9(92.0- 154.6)	110.7(88.4- 147.9)	134(103.3- 172.8)	<0.001	115.3(91.0- 152.0)	148.8(121.3- 208.7)	<0.001

IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; PLR, platelet-to-lymphocyte ratio; mRS, modified Rankin Scale scores.

Table 2 Baseline characteristics of patients according to presence/absence of HT

	Total	No HT	HT	P
N	582	500	82	
Age, years, median (IQR)	61(53-69)	62(54-70)	57(50-66)	0.006
Females, %	158(27.1)	141(28.2)	17(20.7)	0.159
Smoking, %	327(56.2)	278(55.6)	49(59.8)	0.482
Alcohol consumption, %	254(43.6)	213(42.6)	41(50.0)	0.210
Hypertension, %	302(51.9)	260(52.0)	42(51.2)	0.896
Diabetes, %	189(32.5)	153(30.6)	36(43.9)	0.017
Coronary artery disease, %	116(19.9)	103(20.6)	13(15.6)	0.319
Atrial fibrillation, %	27(4.6)	16(3.2)	11(13.4)	<0.001
Previous stroke, %	88(15.1)	75(15.0)	13(15.9)	0.841
Antihypertensive drugs, %	200(34.4)	172(34.4)	28(34.1)	0.964
Hypoglycemic agents, %	102(17.5)	83(16.6)	19(23.2)	0.147
Antiplatelet agents, %	73(12.5)	56(11.2)	17(20.7)	0.016
SBP, mmHg, median (IQR)	154(138-165)	154(138-165)	154(140-165)	0.895
DBP, mmHg, median (IQR)	89(80-98)	89(80-98)	89(82-98)	0.391
Blood glucose, mmol/L, median (IQR)	6.92(6.13-8.65)	6.92(6.09-8.62)	6.91(6.18-9.56)	0.444
Time to treat, min, median (IQR)	180(141-230)	179(138-227)	203(154-236)	0.115
Baseline NIHSS score, median (IQR)	9(5-13)	8(5-12)	12(8-15)	<0.001
PLR on admission	120.7(91.6-155.7)	118.8(90.8-154.6)	130.8(96.1-163.7)	0.153
PLR at 24h after rtPA	116.9(92.0-154.6)	115.8(92.0-153.4)	127.2(94.5-183.4)	0.131

IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; PLR, platelet-to-lymphocyte ratio; mRS, modified Rankin Scale scores; HT, hemorrhagic transformation.

Table 3 Multivariable logistic regression analysis of PLR associated with the poor outcome, death and HT

	OR	95% confidence interval		p ^a
		Lower bound	Upper bound	
On admission				
Poor outcome	1.001	0.998	1.003	0.617
Death	0.999	0.993	1.004	0.658
HT	1.000	0.999	1.001	0.740
At 24h after rtPA				
Poor outcome	1.004	1.001	1.007	0.009
Death	1.009	1.004	1.013	<0.001
HT	1.003	0.999	1.007	0.165

^a Adjusting for age, sex, smoking, alcohol drinking, hypertension, diabetes, coronary artery disease, atrial fibrillation, previous stroke, antihypertensive drugs, hypoglycemic agents, antiplatelet agents, systolic blood pressure, diastolic blood pressure, blood glucose, time to treat and NIHSS score at baseline. HT, hemorrhagic transformation; rtPA, recombinant tissue plasminogen activator.

Table 4 Accuracy of PLR in prediction of outcomes

	Threshold	AUC (95% CI)	Sensitivity, %	Specificity, %	P
On admission					
Poor outcome	234.883	0.496(0.446-0.546)	9.9	93.9	0.874
Death	133.895	0.512(0.417-0.607)	47.5	63.5	0.802
HT	130.526	0.549(0.481-0.617)	51.2	61.6	0.153
At 24h after rtPA					
Poor outcome	126.995	0.617(0.568-0.666)	55.5	64.2	<0.001
Death	120.920	0.699(0.620-0.779)	77.5	55.9	<0.001
HT	199.194	0.552(0.482-0.622)	22.0	89.6	0.131

HT, hemorrhagic transformation; rtPA, recombinant tissue plasminogen activator.

Figures

Figure 1

The flow chart of the study HT, hemorrhagic transformation.