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The role of red blood cell distribution width to platelet ratio in predicting hemorrhagic transformation after mechanical thrombectomy therapy in acute ischemic stroke patients

Weiwei Tao *MD*, Dan Yu *MD*, Gang Wu *PhD*, Wanfen Wang *MD*, Xiaofei Hu *MD*

Department of Neurology, Taizhou Hospital, Affiliated Hospital of Wenzhou Medical College, Taizhou, Zhejiang Province, China

Abstract

Objective: Hemorrhagic transformation (HT) is common complication after mechanical thrombectory (MT) for acute ischemic stroke (AIS). To our knowledge, there has been no study on the correlation between baseline red blood cell distribution width (RDW) to platelet ratio (RPR) and HT after MT. *Methods:* This study recruited 126 AIS patients with anterior or posterior circulation large-vessel occlusion who underwent MT therapy at the Department of Neurology, Taizhou Hospital, Zhejiang province between September 2019 and April 2021. Patients were divided into two groups: patients with HT and those without HT (wHT), and their laboratory and clinical data were compared. *Results:* We found no significant differences in sex, age, alcohol consumption, diabetes mellitus, atrial fibrillation, systolic blood pressure, diastolic blood pressure, triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, serum creatinine, blood urea nitrogen, fibrinogen, neutrophil count, lymphocyte count, neutrophil-to-lymphocyte ratio (NLR), National Institutes of Health Stroke Scale (NIHSS) score, Alberta Stroke Program Early Computed Tomography Score (ASPECTS), whether intravenous thrombolysis was accepted, and TOAST classification between the two groups. Compared with patients without HT, we found that the admission blood glucose, RDW and RPR levels were higher in patients with HT after MT in AIS patients, multivariate logistic regression analysis revealed that baseline RPR (odds ratio (OR), 1.290; 95% CI, 1.062–1.567; P=0.010) and glucose level (OR, 1.177; 95% CI, 1.013–1.369; P=0.034) are independent predictors for HT after MT. *Conclusion:* Higher baseline RPR and higher admission blood glucose levels might be related to HT in AIS patients who received MT therapy.

Keywords: Mechanical thrombectomy, hemorrhagic transformation, red blood cell distribution width to platelet ratio, blood glucose

INTRODUCTION

Acute ischemic stroke (AIS) is the leading reason of disability, cognitive impairment, and mortality worldwide.[1] Recently, mechanical thrombectomy (MT) has become the standard therapy for AIS caused by large artery occlusion (LAO).[2] Hemorrhagic transformation (HT) is a severe and common complication after MT for AIS, which is usually related to poor prognosis.[3] The possible risk factors of HT after MT in AIS patients include a higher baseline neutrophil ratio, cardioembolic stroke, history of intravenous thrombolysis, oral anti-coagulation and/or anti-platelet drugs, increased systolic blood pressure, poor collateral circulation, delayed endovascular treatment, a higher National Institutes of Health Stroke Scale (NIHSS) score, and a lower Alberta Stroke Program Early Computed Tomography Score (ASPECTS).[4-6] However, most of these risk factors are complex and subjective, and were assessed through clinical and imaging data; therefore, the identification of blood biomarkers that can precisely predict HT following MT is essential.

Several studies have been designed to identify biomarkers for predicting HT in AIS patients. Inflammation and oxidative stress,[7] white blood

Address correspondence to: Dan Yu, M.D., Department of Neurology, Taizhou Hospital, Affiliated Hospital of Wenzhou Medical College, 150# Xi Men street, Taizhou 317000, Zhejiang Province, China. Tel: +86-576-85199876, email: 932905687@qq.com

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cells and neutrophils/lymphocytes,[8] lipid profiles, blood glucose, aminotransferase, bilirubin, globulin, and alkaline phosphatase [9] are associated with HT in ischemic stroke. Nevertheless, studies on the novel blood biomarkers of HT in patients with AIS after MT therapy are relatively limited.

Red blood cell distribution width (RDW) and platelets are common and available blood biomarkers in clinical practice and can be obtained from a complete blood cell count. RDW is an indicator of the volume heterogeneity of red blood cells (RBCs) in peripheral blood, and was originally used to identify the subtypes of anemia.[10] Elevated RDW reflects blood hypercoagulation and oxidative stress, which may result in damage to the erythrocyte membrane and increased erythrocyte fragility.[11] Recently, it has been confirmed that RDW increases the risk of cerebrovascular and cardiovascular disease.[12] Wang *et al*. found that in AIS patients without reperfusion therapy, a higher level of RDW was associated with a higher risk of HT.[13] Platelets and inflammation play important roles in the pathogenesis of AIS . The activation and aggregation of platelets can lead to stenosis and blockage of the vessels.[14-15] The RDW to platelet ratio (RPR) is a composite biomarker combining the message of RDW and platelets; therefore, it has higher specificity and sensitivity compared to the single index and can, to some extent, indicate the severity of inflammation.[16] Therefore, this study was designed to examine the value of RPR in predicting HT in patients with AIS after MT.

METHODS

Study Subjects

This study recruited 204 AIS patients from the Department of Neurology, Taizhou Hospital of Zhejiang Province, between September 2019 and April 2021, and 126 patients satisfied the inclusion and exclusion criteria. The inclusion criteria were as follows: age > 18 years; NIHSS score ≥ 6; ASPECTS score ≥ 6; Modified Rankin Scale (mRS) score ≤ 1 before AIS; anterior or posterior circulation large-vessel occlusion determined by digital subtraction angiography (DSA) or CT angiography (CTA); MT operated within 24 h of symptom onset with or without intravenous thrombolysis; successful recanalization, modified Thrombolysis in Cerebral Infarction (mTICI) scale grade 2b or 3; patients with routine blood examinations prior to MT and subsequent CT 24 hours after MT. The exclusion criteria were as follows: skull CT showing intracranial hemorrhage (ICH); evident hemorrhagic tendency elsewhere in the body; severe heart, liver, and kidney disease; and no baseline laboratory data or subsequent CT imaging.

The present study was approved by the Ethics Committee of Taizhou Hospital of Zhejiang Province.

Data collection

The patients' laboratory and clinical data including age, sex, alcohol consumption, smoking, atrial fibrillation (AF), diabetes mellitus (DM), stroke subtypes, systolic blood pressure (SBP), diastolic blood pressure (DBP), NIHSS score, ASPECTS, RDW, platelet (PLT) count, neutrophil count, lymphocyte count, high-density lipoprotein cholesterol (HDLC), total cholesterol (TC), low-density lipoprotein cholesterol (LDLC), triglycerides (TG), blood urea nitrogen (BUN), serum creatinine (Scr), glucose, fibrinogen, neutrophil-to-lymphocyte ratio (NLR), and RPR were obtained. The RDW was divided by the platelet count, and multiplied by 100 to calculate the RPR and divide the neutrophil count by lymphocyte count to calculate the NLR. HT was classified and diagnosed according to the European Cooperative Acute Stroke Study (ECASS)II classification.[17] Patients were divided into two groups: patients with HT and those without HT (wHT).

Statistical analysis

The data are presented as mean±standard deviation (SD) if normally distributed and as median (interquartile range, IQR) otherwise. The Mann-Whitney U test was used for non-normally distributed data, and the chi-square test was performed to compare categorical variables. The means were compared using the t-test for independent samples. Statistical significance was set at $P < 0.05$. Receiver operating characteristic (ROC) curve analysis was used to determine the effectiveness of the variables in predicting HT.

RESULTS

Comparison between the clinical and laboratory data of AIS patients with HT and without HT.

A comparison of the clinical and laboratory data between AIS patients with HT and without HT is shown in Table 1. A total of 126 patients with AIS who underwent MT were included in this study, including 28 patients with HT and 98 patients without HT. There were more smokers in patients without HT (P<0.05), and the level of RDW, RPR, and admission blood glucose levels were higher in patients with HT (P<0.05). Furthermore, there were no significant differences between the two groups in terms of age, sex, alcohol consumption, DM, AF, SBP, DBP, TG,

Table 1: Comparison of the clinical and laboratory data between AIS patients with HT and without HT

	HT	wHT	P
n	28	98	
Male : Female	18:10	63:35	1.000#
Age (year)	68.7 ± 11.7	67.7 ± 12.9	0.698*
Smoking (n) (%)	4 (14.3%)	34 (34.7%)	0.038#
alcohol consumption (n) (%)	5 (17.9%)	18 (18.4%)	0.951#
DM (n) (%)	7 (25.0%)	16 (16.3%)	0.295#
SBP (mmHg)	153.9 ± 20.6	150.5 ± 28.0	0.546*
DBP (mmHg)	88.6 ± 14.2	87.4 ± 14.9	0.714*
TG (mmol/L)	0.99 (0.73-1.53)	1.01 (0.74-1.59)	0.904^
TC (mmol/L)	4.17 ± 1.14	3.93 ± 1.02	0.285*
LDLC (mmol/L)	2.41 ± 0.91	2.21 ± 0.81	0.259*
HDLC (mmol/L)	1.18 ± 0.26	1.13 ± 0.24	0.369*
Scr (umol/L)	76.0 (53.2-86.5)	66.5 (59.8-79.0)	0.709^
BUN (mmol/L)	5.31 (3.88-6.39)	5.07 (4.12-5.95)	0.703^
Fibrinogen (g/L)	3.13 (2.70-3.58)	3.40 (3.00-3.88)	0.067c
Glucose (mmol/L)	9.05 ± 3.65	7.69 ± 2.55	0.026c
RDW (%)	13.3 (13.0-14.2)	12.9 (12.5-13.4)	0.037^
PLT (×10^12/L)	190.5 ± 71.0	219.4 ± 66.7	0.061*
RPR	8.02 ± 3.05	6.55 ± 2.04	0.022*
Neutrophil (×10^9/L)	6.5 ± 3.8	7.0 ± 3.7	0.490*
Lymphocyte (×10^9/L)	1.7 ± 0.9	1.7 ± 0.9	0.949*
NLR	3.7 (2.1-6.7)	3.9 (2.1-7.4)	0.438*
NIHSS	17.3 ± 7.8	17.2 ± 8.5	0.925*
ASPECTS	8 (6-10)	9 (7-10)	0.199^
intravenous thrombolysis (n) (%)	10 (35.7%)	27 (27.5%)	0.635#
TOAST classification (n) (%)			0.737#
Large-artery atherosclerosis	12 (42.9%)	49 (50.0%)	
Cardioembolism	15 (53.5%)	43 (43.9%)	
Stroke of undetermined etiology	1 (3.6%)	3 (3.06%)	
Stroke of other determined etiology	0 (0.0%)	3 (3.06%)	
AF (n) (%)	13 (46.4%)	40 (40.8%)	0.596#

chi-square test, * t-test, ^ Mann-Whitney U test.
HT- hemorrhagic transformation; wHT- without hemorrhagic transformation; DM- diabetes mellitus; SBP- systolic blood pressure; DBP- diastolic blood pressure; TG- triglycerides; TC- total cholesterol; LDLC- low-density lipoprotein cholesterol; HDLC- high-density lipoprotein cholesterol; Scr- serum creatinine; BUN- blood urea nitrogen; RDW- Red blood cell distribution width; PLT- platelets; RPR- RDW to platelet ratio; NLR- neutrophil-to-lymphocyte ratio (NLR); NIHSS- National Institutes of Health Stroke Scale; ASPECTS-Alberta Stroke Program Early Computed Tomography Score; TOAST- Trial of Org 10172 in Acute Stroke Treatment; AF- atrial fibrillation.

Table 2: Multivariate logistic regression analysis for HT in AIS patients after MT

Variables	*B*	*S.E.*	*P Value*	*OR*	*95%CI*	
					Lower	Upper
Smoking	-1.000	0.620	0.107	0.368	0.109	1.239
RDW	0.053	0.169	0.754	1.055	0.757	1.470
RPR	0.254	0.099	0.010	1.290	1.062	1.567
Glucose	0.163	0.077	0.034	1.177	1.013	1.369

S.E.- standard error; OR- Odds ratio; 95% CI- 95% confidence interval; RDW- Red blood cell distribution width; RPR- RDW to platelet ratio.

TC, LDLC, HDLC, Scr, BUN, fibrinogen, PLT, neutrophil count, lymphocyte count, NLR, NIHSS score, ASPECTS, acceptance of intravenous thrombolysis, and TOAST classification.

Multivariate logistic regression analysis for HT after MT in AIS patients

A multivariate logistic regression analysis revealed that admission blood glucose and RPR level are probable independent predictors for HT after MT, which is presented in Table 2.

The ROC curve analysis of the predictive value of RPR and blood glucose level

The results of the ROC curve analysis of the predictive value of RPR and blood glucose levels in predicting HT in patients after MT are shown in Fig. 1. The recommended cut-off value of RPR was 6.825, with a sensitivity of 60.7% and specificity of 64.3%. The Youden Index was 0.250, and the AUC was 0.642 (95%CI, 0.516–0.768). The recommended cut-off value of the blood glucose level was 8.375, with a sensitivity of 53.6% and specificity of 72.4%. The Youden Index was 0.260, and the AUC was 0.632 (95%CI, 0.512–0.751). (shown in Figure 1).

DISCUSSION

Several studies have demonstrated that inflammation and oxidative stress play significant roles in the pathogenesis of ischemic stroke.[18-19] Oxidative stress may increase RBC fragility and decrease erythrocyte lifespan, leading to an increase in RDW.[20] Furthermore, increased RDW may also be caused by other abnormalities, including erythrocyte fragmentation, inflammation,

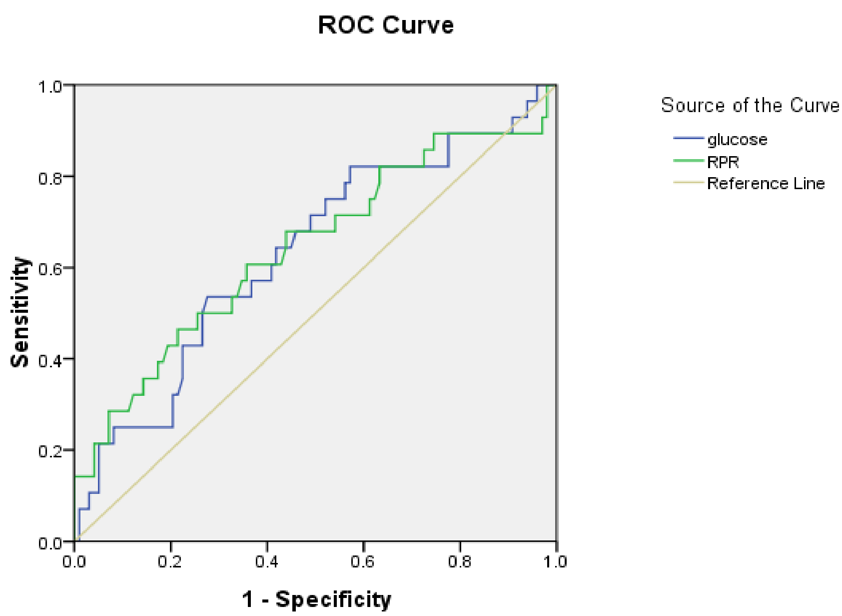

Figure 1. The ROC curve analysis of the predictive value of red blood cell distribution width (RDW) to platelet ratio (RPR) and blood glucose level.

hypertension, and dyslipidemia, all of which are significant factors affecting the prognosis of severe diseases. RDW may provide information on health status and diseases, and predict the prognosis of many acute or chronic diseases.[21] Platelets play critical roles in the physiological and pathological processes of thrombosis, and hemostasis and low platelet counts are often associated with hemorrhage.[22] RPR is a novel and composite biomarker that integrates inflammation, oxidative stress, and coagulation, which are important pathophysiological mechanisms in AIS. Hence, RPR can mirror cerebrovascular status more comprehensively and the risk of thrombosis in patients to a certain degree. Li et al. reported that a higher RPR and NLR might predict a 3-month poor prognosis in patients with AIS who underwent MT.[23] Lehmann et al. demonstrated that RPR is an independent inflammatory marker that might predict the prognosis of deep-seated ICH.[24] The present study investigated the connection between preoperative RPR and HT in the setting of MT for the first time, as a result, we found that RPR is a predictive factor for HT after MT in AIS patients. An RPR level > 6.825 might predict a higher risk for HT after MT treatment and provide new insight into the prediction of HT.

Furthermore, Lin *et al*. revealed that lower baseline platelet counts and fibrinogen levels were related to HT in AIS patients with anterior circulation large-vessel occlusion after MT.[25] However in our study, we found no relationship between baseline platelet counts, fibrinogen levels and HT in AIS patients with anterior or posterior circulation large-vessel occlusion after MT.

In addition, previous studies have confirmed that hyperglycemia and DM are risk factors for ICH and symptomatic intracranial hemorrhage (sICH) after endovascular therapy in AIS.[26-27] A higher glucose level may aggravate cerebral damage and lead to a poor prognosis, possibly involving blood-brain barrier disruption, intracellular acidosis,[28] accumulation of extracellular glutamate,[29] and brain edema.[30] The present study indicated that blood glucose level at admission is a probable independent predictor of HT after MT therapy, with a cutoff value of 8.375, consistent with previous studies.

Furthermore, some previous studies found no significant difference in smoking between HT and wHT in AIS patients after MT; however, according to our study, more smokers were observed in patients without HT, which contradicts previous studies.[23,25] Further studies are necessary to identify the probable role of smoking in HT among patients with AIS after HT.

In conclusion, a higher baseline RPR and higher admission blood glucose are related to HT among AIS patients after MT. Since RPR and blood glucose are convenient and inexpensive to measure in clinical practice, they could be used to identify patients who are at a high risk of developing HT after MT therapy.

DİSCLOSURE

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Conflict of interest: None

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