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ORIGINAL RESEARCH

Association of Red Blood Cell Distribution Width with Stroke Prognosis Among Patients with Small Artery Occlusion: A Hospital-Based Prospective Follow-Up Study

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Objective: Stroke is the leading cause of mortality and disability worldwide. However, there is no study on the relationship between red blood cell distribution width and the prognosis of small artery occlusion, which is a stroke subtype. This study aimed to assess the association of red blood cell distribution width at admission with outcomes among patients with small artery occlusion.

Methods: In this hospital-based follow-up study, all included patients were diagnosed with small artery occlusion. Outcomes included death, recurrence, and dependency at 3, 12, and 36 months after stroke onset. Multivariate analysis was performed to explore the association of red blood cell distribution width with stroke outcomes.

Results: This study included 1576 patients with small artery occlusion who were followed up at 3, 12, and 36 months. For every unit increase in red blood cell distribution width, the risk of stroke recurrence and dependency increased by 5.1% (95% CI 1.002–1.102, P=0.039) at 3 months after stroke onset. At the 12-month follow-up, for every unit increase in red blood cell distribution width, the risk of stroke recurrence increased by 3.4% (95% CI 1.000–1.069, P=0.047). However, the relationship between red blood cell distribution width and mortality rate was not significant at 36 months after stroke onset after adjustment of covariates.

Conclusion: Red blood cell distribution width is an important hematological index of small artery occlusion. It may be used to predict the recurrence of acute ischemic stroke in small artery occlusion. Therefore, patients with higher baseline values of red blood cell distribution width may need more risk factor control to reduce recurrence and dependency.

Keywords: red blood cell distribution width, stroke prognosis, risk factors, small artery occlusion, prospective follow-up study

Introduction

According to the Global Burden of Diseases, Injuries, and Risk Factors Study, stroke is the leading cause of mortality and disability worldwide.[1,2] The situation is even more serious in China, with over 2 million new cases annually.[3] Small artery occlusion (SAO) is an ischemic stroke subtype according to the Trial of ORG10172 in Acute Stroke Treatment (TOAST) classification.[4] A study showed that SAO accounted for approximately 22% of all stroke types worldwide.[5] A recent study indicated that small-vessel-disease stroke increased from 15.5% to 39.6% over 10 years in China,[6] and this increase was higher than noted globally. Progressive neurological decline occurs after SAO, including cognitive impairment, vascular dementia, gait disorder, urinary incontinence, and affective disorders. Some patients have early

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neurological deterioration and a poor prognosis.[7] Therefore, a simple and effective biomarker for predicting the prognosis of SAO is necessary.

Recent studies have shown that a higher red blood cell distribution width (RDW) is associated with cardio-cerebrovascular disease, cancer, and mortality.[8–11] Moreover, RDW was a potential predictor of mortality in patients with first stroke.[12–14] An RDW study of the short-term prognosis after stroke showed that higher RDW was associated with poor function at discharge or 3 months later and that RDW had a dose-dependent relationship with 3-month mortality.[15–18] There have also been studies on the relationship between RDW and the prognosis of patients with large artery cerebral infarction. These found that RDW is associated with 1-month mortality in patients with malignant middle cerebral artery infarction[19] and that high RDW is a poor prognostic factor.[20] However, to our knowledge, there is no study on the relationship between RDW and the prognosis of the stroke subtype—SAO. Moreover, previous studies investigated the prognostic indicators of mortality and poor function, but there were no studies related to recurrence.

Therefore, in this hospital-based prospective study, we attempted to determine the correlation of RDW with the prognosis of SAO and whether RDW is a predictor of recurrence in AIS caused by SAO.

Methods

Participants and Study Design

This was a hospital-based follow-up study conducted in the stroke unit of Tianjin Huanhu Hospital, China. The study design has been previously described.[21] Briefly, all patients diagnosed with SAO according to the TOAST classification were recruited in this study. Patients diagnosed with transient ischemic attacks were excluded.

The study was approved by the medical research ethics committee at Tianjin Huanhu Hospital; written informed consent was obtained from each participant during recruitment.

SAO Diagnostic Criteria

All patients with AIS diagnosed with SAO met the TOAST classification criteria as follows:[4] (1) presence of a traditional clinical lacunar syndrome without cerebral cortex dysfunction; (2) infarct located under the cortex or brainstem and with a diameter of < 1.5 cm as shown by computed tomography/magnetic resonance imaging within 24 h of admission; (3) history of diabetes or hypertension supporting the clinical diagnosis; (4) absence of potential cardiac embolism; and (5) presence of extracranial ipsilateral large artery stenosis < 50%. No patients in this study had received reperfusion therapy.

RDW Measurement

Blood samples were collected from peripheral veins with EDTA tubes within 24 h of admission and analyzed with an automatic blood cell analyzer (Sysmex, Kobe, Japan). Two RDW parameters were calculated: standard deviation (SD) and coefficient of variation (CV). RDW-CV has been widely studied and is calculated using the following formula: RDW-CV = (red blood cell volume/SD of average red blood cell volume) × 100. The reference range of RDW-CV is 11.5–14.5%.[16]

Clinical Features and Risk Factors

Clinical features included stroke severity, stroke risk factors (hypertension, diabetes mellitus, atrial fibrillation, obesity, smoking, and alcohol consumption), neurological function score, and laboratory values (fasting plasma glucose, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, C-reactive protein, and homocysteine).

Patients were categorized into three age groups: < 45, 45–65, and ≥ 75 years. The severity of stroke was divided into three groups according to the National Institutes of Health Stroke Scale (NIHSS) score: mild (≤ 7 points), moderate (8–16 points), and severe (≥ 17 points).

Outcome Assessments and Follow-Up

In this study, outcomes were defined as death, recurrence, and dependence within 3 years after stroke onset. Death was defined as all-cause death occurring within the 3-year follow-up period. Recurrence was defined as all new-onset vascular events, including stroke, myocardial infarction, and venous thrombosis. Dependency was defined as a modified Rankin scale (mRS) score of > 2.[22]

Follow-up assessments were conducted by trained senior neurologists, and all patients were followed up using face-to-face interviews at 3, 12, and 36 months, except for those who required telephone follow-up because they underwent re-examination at another hospital.

Statistical Analysis

Continuous variables are presented as means and SDs; differences between groups were compared with the Student's *t*-test and analysis of variance for two groups and more than two groups, respectively. Categorical variables are presented as numbers with frequencies and were compared with the chi-square test. Factors associated with death, recurrence, and dependency during the follow-up periods were assessed using logistic regression analyses. The results of the multivariate analyses are presented as adjusted relative risks and 95% confidence intervals (CIs) after adjusting for covariates that were statistically significant in the univariate analysis. Stroke outcomes were analyzed as dependent variables, while RDW and other variables were analyzed as independent variables in the logistic regression model. This study analyzed the relationship between RDW and stroke prognosis at 3, 12, and 36 months, with no longitudinal comparisons between the three time points. Statistical significance was set at $P < 0.05$. SPSS for Windows (version 22.0; SPSS, Chicago, IL, USA) was used for the statistical analyses.

Result

Demographic and Clinical Features in Patients with SAO at Baseline

This study included 1576 SAO patients (male, n=1050, 66.6%; female, n=526, 33.4%), who were followed up at 3, 12, and 36 months. The average age of the patients was 63.21±11.39 years, including 787 (49.9%) aged 45–64 years and 1312 (83.4%) with mild symptoms. The prevalence rates of hypertension, diabetes, atrial fibrillation, arteriosclerotic stenosis, smoking history, and drinking history were 74.9%, 32.0%, 2.2%, 14.3%, 37.3%, and 18.1%, respectively (Table 1). Moreover, the baseline characterization of patients according to distribution of red cell distribution width in quartiles was showed in Supplementary Table 1.

Association of RDW with SAO Outcomes During the Follow-Up Period: Univariate Analysis

The average RDW-SD was higher in the recurrence group than in the non-recurrence group (P=0.005). The average RDW-SD was greater in the dependency group than in the non-dependency group at 3 months after stroke onset (P=0.005). The average RDW-SD was higher in those with death, recurrence, and dependency at 12 months after stroke onset than in those without these outcomes. RDW-SD was higher among dead patients than among survivors (44.53 vs 43.19, P=0.015) during the 36-month follow-up (Table 2).

Predictive Value of RDW for SAO Outcomes During the Follow-Up Period: Multivariate Analysis

The multivariate analysis results showed that the RDW-SD value associated with the stroke outcomes after adjusted the covariates which were significant statistical in the univariate analysis (Supplementary Tables 2.1–2.3). For every unit increase in RDW-SD, the risk of SAO recurrence increased by 5.1% (95% CI 1.002–1.102, P=0.039), and the risk of dependency increased by 5.1% (95% CI 1.002–1.102, P=0.039) at the 3-month follow-up. At the 12-month follow-up, for every unit increase in RDW-SD, the risk of SAO recurrence increased by 3.4% (95% CI 1.000–1.069, P=0.047; Table 3).

Table 1 Baseline Characterization of Patients According to Distribution of Red Cell Distribution Width

Characteristics	Men	Women	Total
Cases, n (%)	1050 (66.6)	526 (33.4)	1576
Age, year, mean (SD)	61.94 (11.51)	65.75 (10.70)	63.21 (11.39)
Age group, n (%)			
< 45 years	54 (5.1)	11 (2.1)	85 (4.1)
45–64	562 (53.5)	225 (42.8)	787 (49.9)
≥ 65 years	434 (41.3)	290 (55.1)	724 (45.9)
Severity, n (%)			
Mild	891 (84.9)	421 (80.3)	1312 (83.4)
Moderate	140 (13.3)	85 (16.2)	225 (14.3)
Severe	19 (1.8)	18 (3.4)	37 (2.4)
Risk factors, n (%)			
Hypertension	777 (74.0)	403 (76.6)	1180 (74.9)
Diabetes mellitus	315 (30.0)	190 (36.1)	505 (32.0)
Atrial fibrillation	23 (2.2)	12 (2.3)	35 (2.2)
Cerebral atherosclerotic stenosis	153 (14.6)	72 (13.7)	225 (14.3)
Smoking	526 (50.1)	68 (12.9)	594 (37.3)
Drinking	277 (26.4)	8 (1.5)	285 (18.1)
Laboratory tests, mean (SD)			
FBG, mmol/L	6.40 (2.27)	6.65 (2.77)	6.48 (2.74)
TC, g/L	4.76 (0.95)	5.26 (1.03)	4.93 (1.01)
TG, g/L	1.66 (1.01)	1.73 (1.60)	1.68 (1.24)
HDL-C, g/L	1.05 (0.55)	1.16 (0.30)	1.09 (0.48)
LDL-C, g/L	2.91 (0.78)	3.14 (0.83)	2.99 (0.80)
CRP, mg/L	6.52 (21.61)	5.34 (11.88)	6.14 (18.98)
HCY, μmol/L	17.93 (13.07)	12.51 (6.92)	16.13 (11.67)
RDW-SD, fl	43.56 (4.51)	43.10 (4.01)	43.41 (4.35)
Neurological function, median (range):			
NIHSS	3 (0, 33)	4 (0, 32)	4 (0, 33)
BI	80 (0, 100)	70 (0, 100)	75 (1, 100)
mRS	2 (0, 5)	3 (0, 5)	2 (0, 5)

Table 2 The Average Levels of RDW in Patients with the Different Outcomes During Following-Up Periods

Outcomes	Yes	No	P
3 Months:			
Mortality	44.93 (4.02)	43.39 (4.37)	0.088
Recurrence	44.57 (4.32)	43.30 (4.36)	0.005
Dependence	44.57 (4.32)	43.30 (4.36)	0.005
12 Months:			
Mortality	44.78 (4.27)	43.34 (4.44)	0.031
Recurrence	44.13 (4.13)	43.12 (4.52)	<0.001
Dependence	44.06 (4.10)	43.12 (4.52)	0.001
36 Months			
Mortality	44.53 (5.95)	43.19 (4.63)	0.015
Recurrence	43.51 (4.62)	43.07 (4.89)	0.148
Dependence	43.30 (4.57)	43.10 (4.68)	0.519

Table 3 Association of the Average Levels of RDW in Patients with Outcomes During Following-Up Periods in the Multivariate Analysis

Outcomes	RR (95% CI)	Chi-Square	P
3 Months:			
Mortality	–	–	–
Recurrence	1.051 (1.002, 1.102)	4.256	0.039
Dependence	1.051 (1.002, 1.102)	4.256	0.039
12 Months:			
Mortality	1.054 (0.976, 1.139)	1.813	0.178
Recurrence	1.034 (1.000, 1.069)	3.957	0.047
Dependence	1.032 (0.998, 1.068)	3.391	0.066
36 Months			
Mortality	1.012 (0.958, 1.069)	0.186	0.666
Recurrence	–	–	–
Dependence	–	–	–

Notes: Adjusted risk factors: 12 months mortality (age group, severity, TG, CRP, FBG); 36 months mortality (age group, severity, TG, CRP); 3 months recurrence (age group, severity); 12 months recurrence (age group, severity, CRP); 3 months dependence (age group, severity); 12 months dependence (age group, severity, CRP).

Discussion

This hospital-based prospective study assessed the association of RDW with the prognosis of SAO. Patients with high RDW-SD had a poor prognosis, including a higher risk of death, recurrence, and dependency. High RDW-SD was associated with an increased risk of recurrence at 3 and 12 months and an increased risk of dependency at 3 months in patients with SAO.

RDW is considered a prognostic marker of vascular diseases, but the relationship between RDW and ischemic stroke outcomes is controversial. Some studies have shown that RDW is an independent predictor of stroke.[8] A population-based study showed that high RDW was associated with an increased incidence of cerebral infarction.[23] All the above studies observed a relationship between RDW and the first onset of ischemic stroke. However, to our knowledge, no study has observed the relationship between RDW and the recurrence of ischemic stroke, especially the recurrence of SAO. Our study noted that SAO patients with high RDW had a higher risk of recurrence. Increased RDW-SD was associated with an increased risk of recurrence at 3 and 12 months and was an independent predictor of recurrence at both time points.

Ritin et al analyzed the relationship between RDW and the severity of ischemic stroke. The results showed that the higher the RDW, the greater the severity of ischemic stroke. Thus, RDW may be an important prognostic index in patients with ischemic stroke.[11] Gianni et al used the mRS score to evaluate the prognosis of patients with AIS. Multivariate analysis showed that RDW was an important predictor of 3-month functional decline (mRS > 2) in patients with AIS, and each unit increase in RDW resulted in an increase in poor outcomes by 20.8%.[24] Another study assessed the association between RDW and neurological scoring systems (GCS, CNS, and NIHSS) in AIS patients.[24] This study showed that for stroke patients who have symptoms for < 24 h, RDW may be useful in predicting the severity and functional results of the stroke (area under the receiver operator characteristic curve = 0.760, 95% CI 0.676–0.844).[25] Consistent with the above findings, our results also showed that RDW-SD was associated with an increased risk of dependency at 3 months in patients with SAO. In contrast, the results of Kavous et al showed that RDW could not predict the severity and final outcome of stroke in patients receiving intravenous tissue plasminogen activator.[26]

The relationship between RDW and the prognosis of ischemic stroke is controversial. Pinho et al showed that RDW was an independent predictor of 1-year survival in patients with ischemic stroke treated with intravenous thrombolysis. Their study also revealed that RDW was not related to the severity of stroke at admission.[14] Another study showed that higher RDW was associated with a poorer prognosis in patients with ischemic stroke and with a greater risk of death in

1 year.[27] However, our results showed that the baseline RDW was not associated with the risk of death at 3, 12, and 36 months after onset. This may be because of the differences in patients because our study only focused on SAO and not all types of ischemic stroke. The cause of these differences needs to be explored in future studies.

Elevated RDW can predict the incidence and prognosis of ischemic stroke, but the specific pathophysiological mechanisms remain unclear. Increased oxidative stress leads to damage to the vascular wall and increases the risk of stroke. Red blood cells have a strong antioxidant capacity and are vulnerable to oxidative stress. However, other studies suggest that ischemia-induced inflammation may be the mechanism underlying increased RDW during stroke. Our study only analyzed the relationship between baseline RDW and SAO prognosis and did not analyze the relationship between RDW and ischemia or blood flow recovery.[28–32]

This study showed that SAO patients with higher RDW were at higher risk of death, relapse, and dependence. The mechanism may be related to inflammatory response, oxidative stress, and microcirculation disturbance. RDW is a hallmark of systemic inflammation and oxidative stress;[33,34] inflammatory cytokines may contribute to elevated RDW levels by inhibiting erythrocyte maturation and releasing new and large reticulocytes into the circulation.[35] Inflammatory mechanisms are central to the pathogenesis and progression of atherosclerosis, plaque rupture,[36] thrombosis,[37] and stroke.[38] Inflammation is associated with an increased risk of stroke and may be an important determinant of outcome.[39]

Oxidative stress can lead to increased RDW by inhibiting erythropoiesis, increasing erythrocyte size imbalance, and altering the deformability of cell membranes.[40] Increased RDW levels lead to acute hypoxia, induction of EPO-driven erythropoiesis, and a rapid increase in erythrocyte size variability.[41] Hypoxia can also increase blood-brain barrier permeability, leading to uncontrolled vasogenic edema, microvascular ischemia, or hemorrhagic transformation.[42] Xie et al found that the RDW of stroke patients was higher than that of patients with transient ischemic attack, and the antioxidant capacity of stroke patients with higher RDW was lower.[43]

Oxidative stress injury and antioxidant levels have been shown to be associated with neuronal damage/protection during cerebral ischemia and reperfusion.[44] An imbalance between antioxidants and oxidants can lead to oxidative damage, which can lead to stroke. Stroke patients with high RDW have higher oxidative stress levels, have a lower antioxidant capacity, and are more prone to oxidative damage, which may lead to worse stroke prognosis and higher recurrence rates.

RDW is a parameter that reflects the heterogeneity and variability of peripheral blood erythrocyte volume. Increased RDW indicates an uneven size and reduced deformability of erythrocytes, which may lead to increased microcirculation resistance and interrupted microcirculation through narrowed capillaries in ischemic tissue,[45] thereby mediating an increase in ischemic vascular events.[46]

This study has some limitations. First, it was a single-center study, and the number of patients was relatively small. Second, RDW levels are affected by many factors and diseases, such as pregnancy, anemia, iron, vitamin B12, and folic acid deficiency. Iron, vitamin B12, and folic acid levels were not examined in this study. However, no patient in our study had pregnancy, severe anemia, or complex complications. Finally, this study did not collect patient-specific medication data, but all patients were administered secondary stroke prevention therapy and had good compliance.

In conclusion, the results of this study showed that RDW is an important hematological index of SAO patients. RDW may be related to the prognosis of SAO and should be used as a predictor of AIS recurrence in SAO. Therefore, patients with higher baseline RDW may need more risk factor control to reduce recurrence and dependency.

Abbreviations

DALYs, disability-adjusted life-years; SAO, small artery occlusion; TOAST, Trial of ORG10172 in Acute Stroke Treatment; RDW, red blood cell distribution width; RBC-SD, standard deviation of the red blood cell volume; MCV, mean corpuscular volume; AIS, acute ischemic stroke; CV, coefficient of variation; NIHSS, National Institutes of Health Stroke Scale; Cis, confidence intervals.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

The study was approved by the medical research ethics committee at Tianjin Huanhu Hospital and conducted in accordance with the Declaration of Helsinki. A written informed consent was obtained from each participant during recruitment.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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