

Elevated Red Blood Cell Distribution Width Levels at Admission Predicts Depression After Acute Ischemic Stroke: A 3-Month Follow-Up Study

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Purpose: Red blood cell distribution width (RDW) is closely related to inflammatory-related disease markers. The present study aimed to investigate the association between the red blood cell distribution width (RDW) and post-stroke depression (PSD).

Patients and Methods: A total of 414 patients with acute ischemic stroke (AIS) admitted to our hospital from June 2018 to July 2021 were consecutively enrolled and received 3 months' follow-up. According to the 17-item Hamilton Depression Scale (HAMD) assessment, they were divided into PSD group and non-PSD group. Diagnosis of PSD was made in accordance with DSM-IV. RDW was recorded within 24 hours of admission.

Results: Among the included 414 patients, 95 (22.95%) patients were diagnosed as having PSD at 3 months after stroke. The results showed significantly higher level of RDW in patients with depression (13.69 (IQR13.24–13.88) vs. 13.56 (IQR 12.67–13.77), $P < 0.001$) at admission than patients without depression. After adjustment for potential confounding factors, the odds ratio of PSD was 5.707 (95% CI, 2.717–11.989) for the highest tertile of RDW compared with the lowest tertile. Moreover, based on the receiver operating characteristic (ROC) curve, the optimal cutoff of RDW levels as an indicator for the prediction of PSD was projected as 13.01, which yielded a sensitivity of 83% and a specificity of 41.0%, with an area under the curve (AUC) of 0.643 (95% CI, 0.585–0.701; $P = 0.012$).

Conclusion: Higher RDW levels at admission were found to be correlated with PSD 3 months after stroke.

Keywords: inflammation, red blood cell distribution width, depression, stroke

Introduction

Post-stroke depression (PSD) is a frequent complication of acute ischemic stroke (AIS), which can occur in the acute and recovery phases of stroke, with prevalence ranging from 8% to 46%.¹ The appearance of PSD has been related to negative impact on neurological function and cognitive function, delayed the recovery process, increased the risk of stroke recurrence and mortality, and affected the prognosis of patients.^{2–4} Nevertheless, the underlying neurobiological mechanisms of PSD have not yet been completely explored. Here, the early diagnosis and rational treatment of PSD is vital for the reduction of stroke complications and mortality, as well as for better functional rehabilitation.

Many research findings have demonstrated that proinflammatory factors are of vital importance in the development of stroke and psychosomatic disorders.^{5,6} For instance, previous extensive numerous studies had documented that patients with a poor prognosis after stroke had a significant increase in inflammatory markers including pentraxin 3, interleukin-18 (IL-18), interleukin-6, interleukin-8, and high-sensitivity C-reactive protein (hs-CRP).^{7–9} Many studies have shown

that higher levels of inducible nitric oxide synthase (iNOS), systemic immune-inflammation index, macrophage inflammatory protein 1 α (MIP-1 α), and hs-CRP are positively associated with increased risk for PSD.^{10–12} In another study, IL-18 has also been shown to be correlated with PSD and plays an important role in the development of depression-like behaviors through the IL-18 receptor/NKCC1 signaling pathway.^{13,14} In the final analysis, it is considered that the above proinflammatory mediators could contribute to foundation of PSD diagnosis.

Recently, the red blood cell distribution width (RDW), an easily available marker of inflammatory-related disease, has been reported to be associated with various diseases, including cardiovascular disease, but the detailed mechanisms have not been completely explored.¹⁵ Besides, a large number of studies have appeared a near affiliation between poor clinical outcomes and high RDW levels in the intense stage of maladies such as stroke, and hemorrhagic transformation in acute ischemic stroke patients who have experienced intravenous thrombolysis.^{16,17} Similarly, Kim et al found that higher RDW levels at admission were related to a 3-month poor functional prognosis in patients with AIS treated with intravenous thrombolysis.¹⁸ Additionally, a close association has been shown between depression and RDW. Shafiee and Demircan et al found that RDW levels were essentially higher in depressive patients.^{19,20} Therefore, given the involvement of RDW in depression and the higher RDW levels may contribute to poor functional outcomes among stroke patients, whether RDW is correlated with the advancement of PSD at 3 months after stroke was investigated.

Materials and Methods

Patients and Study Design

Patients with AIS were enrolled consecutively from the First Affiliated Hospital of Anhui University of Science and Technology between June 2018 and July 2021. The exclusion criteria were as follows for the participants: (1) patients with a history of depression or other psychiatric disorders; (2) patients with serious dysarthria or aphasia; (3) patients taking antidepressant drugs prior to stroke onset; (4) patients with a history of dementia; (5) patients with a history of tumors; (6) patients with severe hepatic or renal disease; (7) patients with an active infection history 2 weeks before stroke onset; (8) patients with other central nervous system diseases; (9) patients diagnosed with transient ischemic attacks (TIA); (10) patients with blood system diseases; and (11) patients with extreme stroke condition that they might not follow up in 3 months.

The participants who were accepted for consideration met the following criteria: (1) age greater than 18 years and less than 80 years; (2) the ability and eagerness to provide informed consent; and (3) verified from computed tomography or magnetic resonance imaging of 1.5-T or 3.0-T framework reports performed inside 24 h after admission. Ultimately, 414 patients with AIS were included in this study (Figure 1). This study was approved by the Ethics Committee of the First Affiliated Hospital of Anhui University of Science and Technology, and all participants signed an informed consent form before participation, according to the Helsinki Declaration of 1975.

Data Collection

At baseline, demographic data (gender, age), marital status (married or single), level of education, and vascular risk factor (hypertension, diabetes mellitus, coronary heart disease, atrial fibrillation, current smoking, alcohol consumption, prior stroke) were collected from standardized surveys, which were given in face-to-face interviews by professionally trained physicians. AIS severity was assessed by certified neurologist using the National Institutes of Health Stroke Scale (NIHSS) on the first day (time 1) and on day 90 (time 2) after admission.²¹ The Barthel index (BI), modified Rankin Scale (mRS) and the Mini-Mental State Exam (MMSE) were used to evaluate functional outcome and cognitive functions, respectively, at 3 months after stroke.^{22–24}

Neuropsychiatric Assessment

All participants were interviewed or telephone interviews for depressive symptoms using the 17-item Hamilton Depression Scale at 3 months, unless they died or were lost.²⁵ Patients with a HAMD score ≥ 8 were considered to be diagnosed corresponding to the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental*

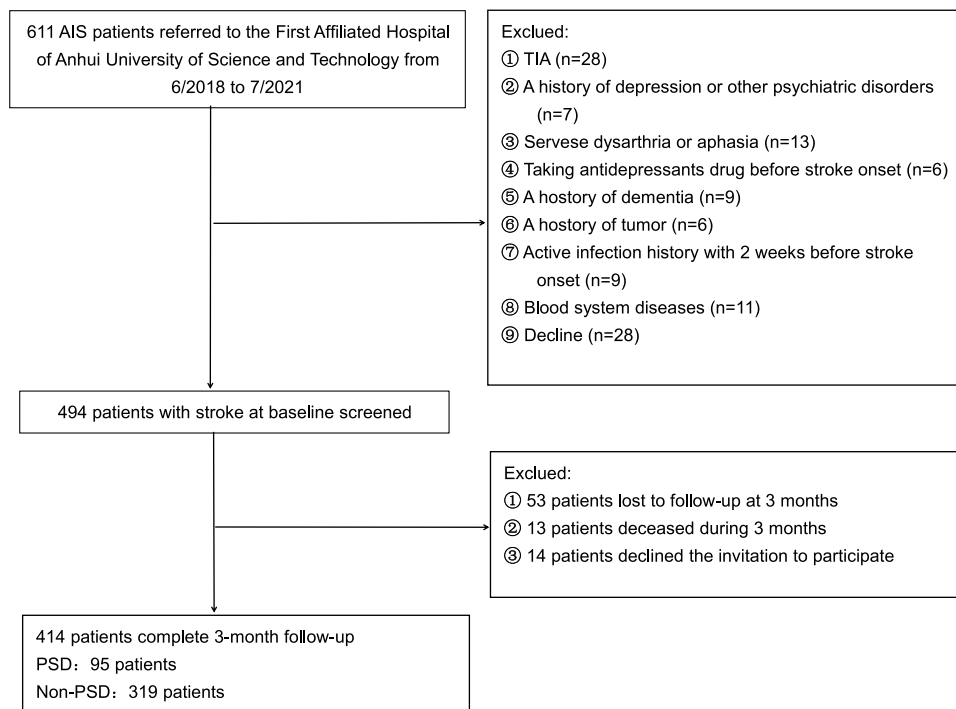


Figure 1 Study recruitment profile.

Abbreviations: PSD, post-stroke depression; AIS, acute ischemic stroke; TIA, transient ischemic attack.

Disorders, 4th edition (DSM-IV). Evaluations were conducted by professional researchers to whom the patients' laboratories were completely unknown.

Blood Collection and Laboratory Test

The 3 mL venous blood of patients was collected into the EDTA containing tube (Becton, Dickinson and Company, USA) from the antecubital vein within 24 h after admission. Routine blood examination (hemoglobin, white blood cell count, platelet count, and RDW) were measured using a Sysmex XE-2100 Hematology Automated Analyzer (Sysmex, Kobe, Japan) at our hospital's laboratory by investigators blinded to the clinical outcomes and neuroimaging findings. Biochemical measurements (Glucose, TG, TC, HDL-C, LDL-C, ApoA, ApoB, Hcy) were performed using standard laboratory methods at admission. All methods and procedures used in this study followed the relevant instructions strictly.

Statistical Analysis

The data was processed and analyzed by SPSS22.0 statistical software (SPSS, Inc., Chicago, IL, USA). Continuous variables were exhibited as mean \pm SD or median and interquartile range [M (p25, p75)]. When the continuous variables were tested for abnormal distribution, the Kolmogorov-Smirnov test and Mann-Whitney *U*-test were used to assess differences in three-group and two-group comparisons, respectively. The continuous variables of normal distribution were analyzed with Student's *t*-test or one-way analysis of variance. Proportions were compared using the Chi-square test or Fisher exact test for as appropriate. Pearson or Spearman rank correlation analyses were used to evaluate the linear correlations between HAMD scores and other factors (NIHSS1 score, NIHSS2 scores, mRS score, BI score). Multivariable regression analyses were exhibited using 3 models to recognize the predictive factors of PSD, among which model 1 was adjusted for age and sex, model 2 was adjusted for model 1 and vascular risk factors (hypertension, diabetes mellitus, coronary heart disease, atrial fibrillation, current smoking, alcohol consumption, prior stroke), and model 3 was further adjusted for variables with $P < 0.05$ upon univariate analysis (basal ganglia lesions, baseline NIHSS score, NIHSS2 scores, mRS score, BI score). The results were expressed as adjusted odds ratios (OR) with the

corresponding 95% confidence intervals (CI). In addition, a receiver operating characteristic (ROC) curve analysis was used to identify the cutoff point on the RDW levels on admission with the greatest sensitivity and specificity to predict PSD at the 3-month follow-up. The area under the curve (AUC) of RDW levels was calculated as a measurement of the test's accuracy. Statistical significance was considered as $P < 0.05$.

Results

A total of 611 patients with AIS at the First Affiliated Hospital of Anhui University of Science and Technology between June 2018 and July 2021 were admitted in the study. Ultimately, 494 patients were eligible for the study, excluding 28 cases with a final diagnosis of TIA, 7 cases with pre-onset diagnosis of depression, 13 cases with severe aphasia who were unable to complete the examination, 6 cases who were taking antidepressants drug before stroke onset, 9 cases with history of dementia, 6 cases with history of tumors, 9 cases with active infection history 2 weeks before stroke onset, 11 cases with blood system diseases, and 28 cases with incomplete data due to missed visits or withdrawal.

By the time of follow-up, at 3 months after stroke, 2.63% ($n=13$) of patients had died, 2.83% ($n=14$) of patients declined the invitation to participate, and 10.73% ($n=53$) of patients were lost to follow-up, leaving 414 participants (Figure 1). Of all patients followed up, 179 (43.24%) were female, with a mean age of (66.23 ± 8.43) years. Overall, the number of patients who were diagnosed with depression at the 3-month follow-up was 95 (22.95%). The basic characteristics of the 414 patients with and without PSD were presented in Table 1. There were no significant difference in age, gender, educational level, marital status, vascular risk factors (hypertension, diabetes mellitus, coronary heart disease, atrial fibrillation, current smoking, alcohol consumption, prior stroke), stroke location (frontal lobe, parietal lobe, temporal lobe, occipital lobe, brainstem, cerebellum), laboratory index (white blood cell count, platelet, blood glucose, blood lipid, homocysteine) and neuropsychological function (MMSE score) between the two groups ($P > 0.05$, Table 1). Compared with non-PSD, PSD patients had higher NIHSS1 scores ($P < 0.001$), NIHSS2 scores ($P < 0.001$), higher mRS scores ($P < 0.001$), lower BI scores ($P < 0.001$), and higher RDW levels ($P < 0.001$). Moreover, among lesion locations, the basal ganglia ($P = 0.012$, Table 1) demonstrated a notable association with the risk of PSD. Correlation analyses revealed that NIHSS1 scores on the first day after admission were positively correlated with the HAMD scores 90 days after admission in all patients ($r = 0.293$, $P < 0.001$), and NIHSS2 scores were also positively correlated with HAMD scores 90 days after admission in all patients ($r = 0.329$, $P < 0.001$).

In addition, there was a significantly positive correlation between HAMD scores and mRS scores ($r = 0.258$, $P < 0.0001$). There was a negative correlation between HAMD scores and BI scores ($r = -0.247$, $P < 0.0001$).

Baseline clinical characteristics of the study population stratified by the RDW tertile were shown in Table 2. Ascending tertiles of RDW were associated with basal ganglia ($P = 0.001$), NIHSS1 score ($P = 0.023$), NIHSS2 score ($P = 0.008$), and mRS score ($P = 0.034$). There were significant differences between the PSD and non-PSD groups in RDW tertiles of patients ($\chi^2 = 23.47$, $P < 0.001$). Indeed, the percentage of patients in the lowest tertile (10.96–12.70) was significantly lower in the PSD group, while the percentage of patients in the highest tertile (13.75–14.65) was notably higher in the PSD group. The numbers of patients with depression after stroke were 13 (13.68%), 36 (37.89%) and 46 (48.42%) in Tertile 1, Tertile 2 and Tertile 3, respectively (Table 3).

In Table 4, all patients were considered as a whole, and the incidence of PSD was used as a dependent variable. In multivariate regression analysis, when RDW levels were categorized into tertiles, patients in the highest tertile had elevated risk of PSD compared to patients in the lower tertile (non-adjusted: OR 4.808, 95% CI 2.455–9.414, $P < 0.001$). And after adjusting for confounders including age, sex, education years, married, vascular risk factors (hypertension, diabetes mellitus, coronary heart disease, atrial fibrillation, current smoking, alcohol consumption, prior stroke), baseline NIHSS1 scores, BI score, NIHSS2 scores, basal ganglia lesions, and modified Rankin Scale scores, the highest tertile of RDW was independently associated with the prevalence of PSD (model 1: OR = 5.398, 95% CI = 2.713–10.738, $P < 0.001$; model 2: OR = 6.069, 95% CI = 2.998–12.286, $P < 0.001$; model 3: OR = 5.707, 95% CI = 2.717–11.989, $P < 0.001$).

According to the ROC curve, the optimal cutoff of RDW levels as an indicator for the prediction of PSD was projected to be 13.01, which yielded a sensitivity of 83% and a specificity of 41.0%, with an AUC of 0.643 (95% CI, 0.585–0.701; $P = 0.012$, Figure 2).

Table 1 Clinical and Demographic Characteristics of Patients with PSD and Non-PSD

Variables	Total (n=414)	Depression After Stroke		P value
		Depression (n=95)	Non-Depression (n=319)	
Demographic characteristics				
Gender, female, n (%)	179 (43.24)	50 (53.63)	129 (40.44)	0.035
Age, years, mean±SD	66.23±8.43	65.53±9.12	66.45±8.22	0.352
Education years, median (IQR)	5 (3–8)	5 (2–7)	5 (2–8)	0.689
Married, n (%)	390 (74.64)	89 (93.7)	301 (94.36)	0.904
Vascular risk factors (%)				
Hypertension	267 (64.49)	62 (65.26)	205 (64.26)	0.858
Diabetes mellitus	134 (32.37)	36 (37.89)	98 (30.72)	0.190
Coronary heart disease	53 (12.80)	14 (14.74)	39 (12.23)	0.520
Atrial fibrillation	14 (3.38)	2 (2.11)	12 (4.39)	0.423
Current smoking	111 (26.33)	24 (30.52)	87 (25.08)	0.586
Alcohol consumption	132 (31.88)	30 (31.58)	102 (34.97)	0.942
Prior stroke	77 (18.60)	17 (17.89)	60 (19.05)	0.841
Laboratory findings (IQR)				
WBC, ×10 ⁹ /L, median (IQR)	6.35 (5.28–7.53)	6.38 (5.58–7.70)	6.33 (5.24–7.5)	0.307
RBC, ×10 ¹² /L, median (IQR)	4.94 (4.56–5.31)	4.67 (4.52–5.29)	4.98 (4.58–5.32)	0.059
Hb, g/L	139 (134–145)	138 (131–144)	140 (134–145)	0.039
PLT, ×10 ⁹ /L, median (IQR)	209 (167–241)	212 (171–234)	207 (167–243)	0.914
Glucose, mmol/L	5.3 (4.7–6.8)	5.4 (4.8–7.4)	5.2 (4.7–6.7)	0.171
TG, mmol/L	1.36 (0.95–1.93)	1.41 (0.97–1.92)	1.34 (0.94–1.99)	0.782
TC, mmol/L	4.51 (3.78–5.35)	4.51 (3.67–5.48)	4.51 (3.81–5.32)	0.793
HDL-C, mmol/L	1.01 (0.84–1.22)	0.99 (0.83–1.29)	1.02 (0.84–1.22)	0.921
LDL-C, mmol/L	2.52 (1.96–3.17)	2.51 (1.99–3.34)	2.52 (1.93–3.16)	0.469
ApoA, g/L	1.26 (1.10–1.43)	1.28 (1.12–1.43)	1.26 (1.09–1.44)	0.330
ApoB, g/L	0.86 (0.69–1.02)	0.85 (0.68–1.12)	0.86 (0.69–1.0)	0.536
Hcy, μmol/L	12.6 (10.24–16.31)	13.49 (10.96–16.8)	12.32 (10.02–16.18)	0.062
RDW, %	13.59 (12.73–13.79)	13.69 (13.24–13.88)	13.56 (12.67–13.77)	<0.001
Lesion location, n (%)				
Frontal lobe	78 (18.84)	20 (21.05)	58 (18.18)	0.530
Parietal lobe	78 (18.84)	15 (15.79)	63 (19.75)	0.386
Temporal lobe	89 (21.49)	27 (28.42)	62 (20.38)	0.061
Occipital lobe	61 (14.73)	12 (12.63)	49 (15.36)	0.510
Basal ganglia	111 (26.81)	16 (16.84)	95 (29.78)	0.012
Brainstem	77 (18.60)	21 (22.11)	56 (17.55)	0.317
Cerebellum	25 (21.50)	9 (9.47)	16 (5.02)	0.109
Neuropsychological function				
NIHSS 1 score, median (IQR)	6 (4–9)	8 (6–10)	6 (4–8)	<0.001
NIHSS 2 score, median (IQR)	3 (1–5)	5 (3–7)	2 (1–5)	<0.001
MMSE score, median (IQR)	22 (17–26)	21 (17–25)	22 (17–26)	0.311
BI score, median (IQR)	75 (50–90)	60 (40–80)	80 (60–95)	<0.001
mRS score, median (IQR)	3 (2–4)	3 (3–4)	2 (2–3)	<0.001
HAMD score, median (IQR)	5 (2–7)	12 (9–18)	3 (2–5)	<0.001

Abbreviations: WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; PLT, platelet; TG, total triglyceride; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; ApoA, apolipoprotein A; ApoB, apolipoprotein B; Hcy, homocysteine; RDW, red blood cell distribution width; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; MMSE, Mini-Mental State Examination; IQR, interquartile range; 1, on admission; 2, three months after stroke.

Table 2 Baseline Characteristics of Patients with Acute Ischemic Stroke According to RDW Tertiles

Variables	RDW			
	Q1 (≤ 12.7 , n=138)	Q1 (12.98–13.74, n=138)	Q1 (>13.74 , n=138)	P value
Demographic characteristics				
Gender, female, n (%)	69 (50)	58 (42.03)	52 (37.68)	0.111
Age, years, median (IQR)	69 (64–72)	68 (60–71)	67 (60–71)	0.125
Education years, median (IQR)	5 (3–7)	6 (3–8)	5 (3–8)	0.209
Married, n (%)	133 (96.38)	129 (93.48)	128 (92.75)	0.395
Vascular risk factors (%)				
Hypertension	88 (63.77)	96 (69.57)	83 (60.14)	0.256
Diabetes mellitus	54 (39.13)	42 (30.43)	38 (27.54)	0.101
Coronary heart disease	15 (10.87)	21 (15.22)	17 (12.32)	0.546
Atrial fibrillation	6 (4.35)	4 (2.89)	4 (2.89)	0.744
Current smoking	38 (27.54)	43 (31.16)	30 (21.74)	0.204
Alcohol consumption	44 (31.88)	52 (37.68)	36 (26.09)	0.118
Prior stroke	29 (21.01)	22 (15.94)	26 (18.84)	0.554
Laboratory findings (IQR)				
WBC, $\times 10^9/L$, median (IQR)	6.24 (5.23–7.37)	6.21 (5.23–7.49)	6.70 (5.56–7.77)	0.159
RBC, $\times 10^{12}/L$, median (IQR)	4.98 (4.56–5.32)	4.96 (4.54–5.31)	4.94 (4.58–5.29)	0.544
Hb, g/L	142 (134–147)	139 (134–145)	138 (134–144)	0.264
PLT, $\times 10^9/L$, median (IQR)	206 (167–243)	213 (182–245)	201 (149–234)	0.128
Glucose, mmol/L	5.40 (4.7–7.85)	5.53 (4.8–6.9)	5.20 (4.7–6.1)	0.219
TG, mmol/L	1.34 (0.91–1.85)	1.32 (0.92–1.92)	1.41 (1.00–2.07)	0.395
TC, mmol/L	4.56 (3.81–5.44)	4.52 (3.63–5.53)	4.50 (3.91–5.17)	0.859
HDL-C, mmol/L	1.02 (0.88–1.22)	1.03 (0.82–1.28)	0.99 (0.81–1.18)	0.521
LDL-C, mmol/L	2.52 (1.96–3.19)	2.53 (1.81–3.20)	2.51 (1.99–3.06)	0.863
ApoA, g/L	1.27 (1.12–1.42)	1.25 (1.07–1.47)	1.26 (1.11–1.42)	0.866
ApoB, g/L	0.84 (0.70–1.06)	0.89 (0.67–0.98)	0.87 (0.73–1.02)	0.928
Hcy, $\mu\text{mol/L}$	12.68 (8.90–16.30)	11.93 (11.02–15.83)	13.01 (10.85–16.49)	0.264
RDW, %	12.3 (11.58–12.74)	13.59 (13.45–13.68)	13.88 (13.79–13.99)	<0.001
Lesion location, n (%)				
Frontal lobe	26 (18.84)	29 (21.01)	23 (16.67)	0.653
Parietal lobe	30 (21.74)	27 (19.57)	21 (15.22)	0.370
Temporal lobe	22 (15.94)	37 (26.81)	30 (21.74)	0.089
Occipital lobe	16 (11.59)	23 (16.67)	22 (15.94)	0.437
Basal ganglia	50 (36.23)	22 (15.94)	39 (28.26)	0.001
Brainstem	24 (17.39)	24 (17.39)	29 (21.01)	0.671
Cerebellum	5 (3.62)	8 (5.80)	12 (8.70)	0.211
Neuropsychological function				
NIHSS 1 score, median (IQR)	6 (4–8)	7 (5–9)	7 (4–10)	0.023
NIHSS 2 score, median (IQR)	3 (1–5)	3 (2–5)	3 (1–7)	0.008
MMSE score, median (IQR)	22 (17–26)	23 (17–26)	21 (17–25)	0.780
BI score, median (IQR)	80 (50–95)	70 (50–90)	75 (45–90)	0.067
mRS score, median (IQR)	2 (2–3)	3 (2–4)	3 (2–4)	0.034
HAMD score, median (IQR)	5 (2–6)	5 (3–8)	5 (2–9)	0.166

Abbreviations: WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; PLT, platelet; TG, total triglyceride; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; ApoA, apolipoprotein A; ApoB, apolipoprotein B; Hcy, homocysteine; RDW, red blood cell distribution width; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; MMSE, Mini-Mental State Examination; IQR, interquartile range; 1, on admission; 2, three months after stroke.

Table 3 RDW Tertiles of Patients

Variables	Depression (n=95)	Non-Depression (n=319)	χ^2	P value
RDW				<0.001
Tertile1 (10.96–12.7)	13 (13.68%)	125 (37.76%)	19.54	<0.001
Tertile2 (12.98–13.74)	13 (37.89%)	13 (30.81%)	1.69	0.194
Tertile3 (13.75–14.65)	13 (48.42%)	13 (27.79%)	14.34	<0.001

Abbreviation: RDW, red blood cell distribution width.

Table 4 Multivariate Logistic Regression Analysis Model of RDW and PSD

	Tertile	OR ^a	95% CI	P value
Unadjusted	Middle	1.417	0.843–2.381	0.189
	Highest	4.808	2.455–9.414	P<0.001
Model 1 ^b	Middle	1.476	0.871–2.503	0.148
	Highest	5.398	2.713–10.738	P<0.001
Model 2 ^c	Middle	1.625	0.943–2.799	0.080
	Highest	6.069	2.998–12.286	P<0.001
Model 3 ^d	Middle	1.734	0.975–3.086	0.061
	Highest	5.707	2.717–11.989	P<0.001

Notes: ^aReference OR (1.000) is the lowest tertile of RDW for PSD. ^bModel 1: adjusted for age, sex, education years, married. ^cModel 2: adjusted for covariates from model 1 and further adjusted for vascular risk factors (hypertension, diabetes mellitus, coronary heart disease, atrial fibrillation, current smoking, alcohol consumption, prior stroke). ^dModel 3: adjusted for covariates from model 2 and further adjusted for variables with $p < 0.05$ in univariate analysis (basal ganglia lesions, baseline NIHSS score, NIHSS2 score, mRS score, BI score).

Abbreviations: RDW, red blood cell distribution width; CI, confidence interval; OR, odds ratio; CI, confidence level; PSD, post-stroke depression.

Discussion

As far as we know, this is the first report exploring the prospective association between RDW levels and the development of PSD. Our results indicated high levels of RDW at admission were significantly correlated with depression at 3 months after stroke and documented a 5.707-fold higher risk of PSD among individuals with the highest tertiles of RDW compared with those with the lowest tertiles of RDW after adjustment for potential confounders. Therefore, our findings have shown that the RDW levels could provide the vital predictive information for patients with PSD.

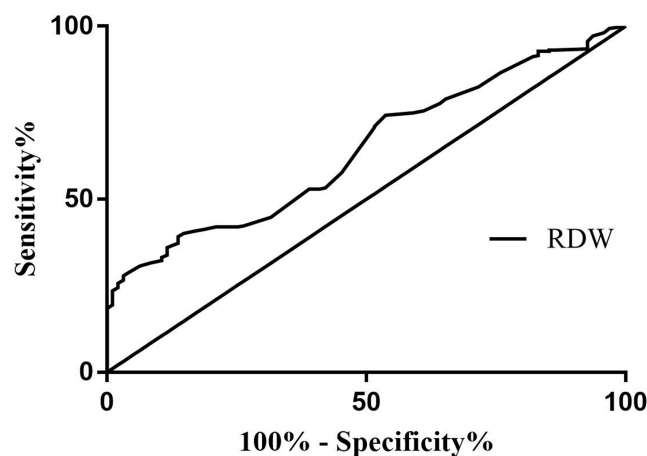


Figure 2 ROC curves for predicting of PSD. Receiver operator characteristic curve demonstrating sensitivity as a function of 100%–specificity% for predicting PSD within 3 months based on the RDW levels in stroke patients. Area under the curve 0.643 (95% CI, 0.585–0.701; $P = 0.012$) for RDW.

Abbreviations: RDW, red blood cell distribution width; CI, confidence interval.

During the current study, we found that 22.95% of patients developed depression 3 months after stroke, which was similar to previous studies.^{26,27} The diagnosis of PSD is a dynamic process, and different time points have a significant impact on the prevalence of PSD in different studies, which may be related to the timing of PSD determination, discrepancies in design, psychological assessment methods, and different criteria for evaluation. Our results also showed that stroke severity and functional outcome were risk factors for the development of PSD, which was broadly consistent with the previous studies.^{28,29}

Several studies have found that the specific location of the lesion could influence the etiology of PSD: that is, PSD is more likely to occur when the lesions are adjacent basal nuclei or the located in the left frontal region.³⁰ We documented the location of the basal ganglia lesions in relation to the presence of patients with PSD. Consistently, Farner and Gong et al had demonstrated a close relationship between basal ganglia lesions and affective symptoms, including depression.^{31,32} Although numerous studies have demonstrated a possible relationship between stroke localization and depression after stroke, the issue remains controversial.

Although the mechanisms for the association between RDW and PSD remained largely unclear, some possible explanations should be considered. First, the study by Montagnana et al demonstrated that oxidative stress and inflammation were important determinants of RDW.³² And Marinkovic and Li et al reported that oxidative stress and inflammation were strongly associated with decreased erythrocyte lifespan and inhibited erythropoiesis, respectively, which could increase RDW levels.^{33,34} Furthermore, the elevated RDW was associated with increased oxidative stress. Elevated RDW might reflect high oxidative stress and low antioxidant levels, and oxidative stress could contribute to erythrocyte membrane damage, increase in erythrocyte fragility, and decrease in the rate of erythroid maturation and the lifespan of erythroid.³⁵

A second explanation was that oxidative stress had a significant role in the etiology of atherosclerosis and could lead to increased RDW by affecting the lifespan of hematopoietic stem cells and red blood cells.³⁶ The overproduction of reactive oxygen could contribute to oxidative stress in the brain and neurons after stroke, which eventually may lead to oxidative damage to lipid peroxidation and DNA, as well as nitrosative damage to proteins.³⁷ In specific brain regions (such as the limbic system), mitochondrial dysfunction and mitochondrial DNA damage could be disrupted by oxidative stress, which is one of the pathological mechanisms of major depression.^{38,39} The study by May et al reported an association between an elevated level of RDW and a subsequent diagnosis of depression, although this association persisted after adjustment for risk factors, medications, and other indicators of disease status.⁴⁰

Last but not the least, the inflammatory response is known to play a significant role in ischemic stroke. Once AIS occurs, the organism induces a systemic inflammatory response and increases the levels of RDW and CRP in AIS patients.⁴¹ Previous reports have investigated the correlation between high RDW and elevated indices of inflammation, such as C-reactive protein (CRP).⁴² Kowalska et al found that higher levels of CRP are associated with greater depressive symptoms after stroke.⁴³ A meta-analysis of previous prospective and retrospective studies showed that higher level of CRP in the acute phase of stroke suggested an increased risk for PSD.¹¹ Inflammation is conducive to dysfunction of synaptic plasticity and ultimately depression by mediating alterations in neurotransmitters, particularly the synthesis and metabolism of 5-hydroxytryptamine and glutamine.⁴⁴ RDW not only reflects the inflammatory state after stroke but also suggests a causal factor for the development of depression. Therefore, increasing RDW may be considered a high level of inflammation that most likely contributes to the occurrence of depression after stroke.

This study had several limitations regarding interpretation of its results. First, the RDW levels were only detected within 24 hours of admission, which restricted dynamic investigation of the relationship between the variation of RDW levels over time after stroke with PSD. Second, patients with severe aphasia, severe stroke conditions, and other central nervous system diseases were removed, which may have resulted in underestimation of the actual prevalence of PSD and contributed some bias to the results. Finally, this is a single-center-based prospective study. Although a relatively large sample size may reduce selection bias, future large-scale multicenter studies are necessary to support our findings and contribute to generalizability.

Conclusion

Our study reveals a significant association between higher RDW levels within 24 hours of admission and development of PSD at 3 months after stroke. RDW measured within 24 hours of admission can be used as a potential diagnostic

biomarker for the prediction of PSD. Further prospective studies are essential to explore whether the treatment to reduce RDW offers a potential preventive or therapeutic target for PSD.

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Disclosure

The authors report no conflicts of interest in this work.

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