Red Cell Distribution Width: a Novel Predictive Biomarker for Stroke Risk After Transient Ischemic Attack

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Research

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Abstract

Objective: Predicting the prognosis of transient ischemic attack (TIA) is difficult for many frontline clinicians. The purpose of this study was to determine whether subsequent stroke in TIA patients can be predicted via the red blood cell distribution width(RDW).

Material and methods: A total of 309 consecutive age- and sex-matched patients with new onset TIA, in our stroke center, were enrolled over the period studied. The patients were divided into two groups :103 TIA patients and 206 patients who had a stroke within 7 days after TIA. Complete blood count, biochemical parameters and brain imaging were performed in all patients.

Results: The mean RDW values of patients with stroke after TIA were significantly higher than patients with TIA (12.84 ±1.19, 13.35 ±1.59, p= 0.001). In a multivariate model, RDW was independently associated with stroke after TIA (OR=2.52, 95% CI 1.46 to 3.35, P= 0.002). We also found that the higher levels of RDW, the earlier the stroke onset (p=0.024). Compared to $ABCD^2$ score, the diagnostic power of RDW in the differentiation of patients with stroke after TIA is better (AUCs:0.613vs0.731, p= 0.015). When an RDW cut-off value of 13.95% is accepted for differentiating patients with stroke after TIA from TIA, the sensitivity and specificity were 73.7% and 74.3%, respectively.

Conclusions: The early determination of RDW is a promising, rapid, easy and inexpensive biomarker to predict the subsequent stroke in TIA patients.

Introduction

up to 20% of patients with acute ischemic stroke (AIS) suffered a previous transient ischemic attack (TIA) [1]. Early identification of patients at high risk for stroke after TIA and selection of appropriate treatment can reduce the risk of stroke by 80% and improve prognosis[2]. Although several factors have been combined in different scores (such as $ABCD^2$ score: age, blood pressure, the presence of clinical weakness or speech disturbance, the duration of symptoms, and the presence or absence of diabetes) in order to stratify the risk after a TIA[3].Recent data suggest that their clinical value is controversial[4, 5]. The National Institute for Health and Care Excellence (NICE) guidelines, updated in 2019, no longer recommend clinical classification using scoring systems such as $ABCD^2$ score[6].

Many studies have been devoted to finding factors that predict subsequent stroke in TIA patients. In addition to improving risk stratification, some researchers suggest that new prognostic markers could further clarify the underlying pathophysiology or timely adjustment of treatment regimens[7]. Therefore, we need an inexpensive, easy, available, and sensitive laboratory marker that allow us to reliably predict the prognosis after TIA.

Cumulative evidence suggested that elevated red blood cell distribution width(RDW) was an important prognostic biomarker for predicting functional outcomes and mortality in patients with cerebral infarction[8, 9]. Recent studies have found that RDW may reflect the underlying inflammatory state and

oxidative stress damage[10],and therefore is related to the incidence, progression and prognosis of stroke[11, 12].The complex pathophysiological mechanisms behind TIA and stroke are similar[6].Perhaps, RDW can predict subsequent strokes in TIA patients.

For all we know, no studies have explored the relationship between RDW and TIA prognosis. Therefore, we tested the hypothesis that whether TIA and stroke after TIA can be predicted via the RDW.

Materials And Methods

Study Setting and Participants

From January 2015 to December 2020, 309 patients with TIA at our hospitals were enrolled in this study. All patients were hospitalized and classified in two groups: TIA and stroke after TIA groups.

The inclusion criteria for this study were TIA aged 18 to 80 years within 48 hours of symptom onset. Diagnostic criteria of TIA or AIS was based on clinical manifestations and confirmed by brain CT and MRI + MRA + DWI. The diagnosis of TIA was based on the clinical features of a presumed vasogenic focal neurological deficit of less than 24 hours duration[13]. Stroke after a TIA was defined as evidence of acute neurological impairment or acute infarction lasting 24 hours within 7 days of a TIA based on abnormalities in DWI.

Inclusion and Exclusion Criteria

Patients were excluded due to: (1) posterior circulation or cardioembolic stroke and TIA; (2) intracerebral hemorrhage, epileptic seizure, migraine with aura, peripheral vestibule disease, somatic form disorder, idiopathic facial palsy, transient impaired vision, brain tumour; (3) severe renal, liver, or heart failure, infection, immunologic diseases, and cancer ; (4) history of cardiovascular and cerebrovascular disease, trauma, and surgery within 3 months.

Clinical and Laboratory Parameters

Complete blood counts were measured at patients' arrival at the emergency room using Toshiba, with ethylene diamine tetraacetic acid blood samples. RDW-CV has been extensively studied and calculated according to the following formula: RDW-CV=(standard deviation of red blood cell(RBC) volume/mean RBC volume)×100[14]. The normal reference values for RDW in the laboratory are between 11% and 14%.In the present research, we reported the RDW-CV and represented it with RDW.

Serum albumin(ALB),alanine aminotransferase (ALT), uric acid(UA),total bilirubin(TBIL) levels, homocysteine(HCY),creatinine(CR), and fasting blood glucose (FBG)were measured using the Hitachi LST008 analyzer (Hitachi High Technologies, Tokyo, Japan) within the first 12 hours after the onset of TIA and after fasting for 8–10 hours. The concentrations of total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL) and C-reactive protein were

measured by the same method. Fibrinogen(FIB) was measured using the Wolfen ACL-TOP-700 automatic coagulation analyzer (Spanish).

Data collection and outcome assessment

All participants were interviewed using a standardized questionnaire to assess medical histories. Neuroimaging studies were evaluated by two neurologists who were blinded to the clinical data and independently identified TIA and stroke after TIA. Disputes were resolved by consensus.

Statistical Analysis

Normally distributed continuous variables were compared by the Student's T-tests and expressed as the mean standard deviations. Continuous variables that were not normally distributed were represented by the median (IQR) and compared by the Mann-Whitney U test. Categorical variables were expressed as absolute and relative frequencies and were compared using a chi-square test. In order to identify determinants of stroke after TIA, all possible variables with $P < 0.05$ in univariate analysis were then input into a forward logistic regression model. The results were expressed as adjusted OR with the corresponding 95% confidence interval(CI). If RDW is an independent risk factor for stroke after TIA, the receiver operating characteristic curve(ROC) for predicting TIA progression with RDW is drawn. When Youden index is the largest, the optimal diagnostic cutoff point for RDW is calculated, and then the sensitivity and specificity are calculated respectively. We compared $ABCD^2$ scores and RDW levels under the ROC curve. $P < 0.05$ was defined as statistically significant, and all statistical analyses were performed with IBM SPSS statistical version 24 (SPSS Inc. Chicago, IL, USA).

Ethical Considerations

This was a retrospective, cross-sectional study that did not involve clinical or animal studies and would not have had any effect on patient outcomes. According to the statement on ethics approval by the ethics committee composed of our hospital, the requirement for ethics approval was exempted.

Results

General characteristics of the subjects.

Patient baseline characteristics and clinical properties are summarized in Table 1. A total of 309 age- and gender-matched patients were include in the study: 103 patients with TIA and 206 patients with stroke after TIA. Of the patients studied, 57% were men and the average age was 58.94 ± 10.54.

Systolic and diastolic blood pressure ($p = 0.000$), diabetes($p = 0.03$) were significantly higher in stroke patients. Compared to TIA, stroke patients had significantly higher ABCD2 score($p = 0.001$) and thrombolysis treatment($p = 0.001$). No differences were found in history of smoking, history of drinking, hypertension, coronary heart disease, BMI, medication history(antihypertensive, antiglycemic, antiplatelet, and statin therapy) and time from onset to hospital between the TIA and stroke groups.

For hematologic and metabolic indicators, the RDW value of stroke group was significantly higher than TIA group, compared with TIA (13.35% versus 12.84%, $p = 0.001$). Significant differences in Neu/lym(2.72 versus 2.70, $p = 0.016$), CRP(8.32 versus 8.15, $p = 0.000$) were observed between two groups. However, serum TBIL(12.31 $p = 0.002$), HCY(12.28 versus 10.36, $p = 0.040$), and FBG(7.22 versus 6.09versus 13.72, $p = 0.038$) and ALB(40.84 versus 42.08, $p = 0.001$) were significantly lower in stroke patients than TIA.

Table 1
The clinical characteristics of the study samples

Characteristics	TIA (n = 103)	Stroke after TIA (n = 206)	*P* value
Age(years),mean(SD)	58.94(10.54)	58.94(10.54)	——
Male, n(%)	59(57)	118(57)	——
Alcohol consumption, n(%)	19(17)	42(20)	0.461
Current smoking, n(%)	23(22)	67(33)	0.084
Hypertension, n(%)	64(62)	145(70)	0.157
Diabetes mellitus, n(%)	26(25)	82(40)	0.030*
Coronary heart disease, n(%)	11(11)	28(14)	0.586
BMI, mean (SD)	24.97(3.44)	25.36(3.03)	0.155
SBP(mm Hg), mean (SD)	144.70(3.46)	155.67(25.17)	0.000***
DBP(mm Hg), mean (SD)	89.43(15.45)	96.22(14.94)	0.000***
WBC(103/Ul), mean (SD)	7.20(2.04)	7.49(1.95)	0.130
Neu/lym, mean (SD)	2.70(1.46)	2.72(1.47)	0.016*
HGB (10^9 /L), mean (SD)	141.06(13.34)	141.79(15.66)	0.715
RBC(10^9 /L), mean (SD)	4.68(0.56)	4.74(0.47)	0.082
RDW (%)	12.84(1.19)	13.35(1.59)	0.001 **
PLT(10^9 /L), mean (SD)	232.56(54.74)	236.11(61.30)	0.615
ALT(U/L) ,median (IQR)	20.37(9.82)	20.50(9.57)	0.970
TBIL, (μmol/L), mean (SD)	13.72(4.92)	12.31(5.91)	0.038*
CR(μmol/L), mean (SD)	70.56(20.60)	68.66(17.59)	0.748
CRP (mg/L) ,median (IQR)	8.15(2.80)	8.32(3.90)	0.002*

BMI: body mass index, defined as weight in kilograms divided by the square of height in metres; SBP: systolic blood pressure; DBP: diastolic blood pressure; WBC: white blood cells; Neu/lym :Neutrophilic /lymphocytes; HGB: haemoglobin; RBC: red blood cell ; RDW: red blood cell distribution width; PLT: blood platelet; ALT: alanine transaminase; TBIL: total bilirubin; CR: creatinine; CRP: c reactive protein; FIB: fibrinogen;ALB: albumin; UA: uric acid; HCY: Homocysteine; TG: triglycerid; TC: total cholesterol; LDL: low-density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol; FBG: fasting blood-glucose; $ABCD^2$: Age, Blood Pressure, Clinical Features, Duration, and Diabetes; Values are expressed as Mean ± SD, median (IQR). The differences were considered significant if *P* value < 0.05. *** *p* value < 0.001, ** *p* value < 0.01,* *p* value < 0.05.

Characteristics	TIA (n = 103)	Stroke after TIA (n = 206)	*P* value
FIB(g/L), median (IQR)	2.64(0.73)	2.80(0.79)	0.111
ALB(g/L), median (IQR)	42.08(3.13)	40.84(3.07)	0.001 **
UA(μmol/L), mean (SD)	365.24(102.49)	344.44(91.79)	0.187
HCY(mmol/L), mean (SD)	10.36(4.50)	12.28(6.96)	0.040*
TG(mmol/L), mean (SD)	1.53(0.76)	1.65(0.87)	0.193
TC(mmol/L), mean (SD)	4.98(1.05)	5.07(1.17)	0.660
LDL(mmol/L), mean (SD)	3.04(0.89)	3.20(1.03)	0.259
HDL(mmol/L), mean (SD)	1.29(0.27)	1.24(0.27)	0.179
FBG(mmol/L), mean (SD)	6.09(1.79)	7.22(2.97)	0.000***
Medication history			
Antihypertensive therapy, n(%)	50(49)	117(57)	0.184
Antiglycemic therapy, n(%)	12(11)	45(22)	0.573
Antiplatelet therapy, n(%)	36(35)	94(46)	0.095
statin therapy, n(%)	5(5)	16(8)	0.713
Thrombolysis treatment, n(%)	29(28)	92(45)	0.001**
Time from onset to hospital(hours)	19.52(8.00)	21.20(12.00)	0.258
$ABCD^2$ score	4.87(1.71)	5.54(1.45)	0.001 **

BMI: body mass index, defined as weight in kilograms divided by the square of height in metres; SBP: systolic blood pressure; DBP: diastolic blood pressure; WBC: white blood cells; Neu/lym :Neutrophilic /lymphocytes; HGB: haemoglobin; RBC: red blood cell ; RDW: red blood cell distribution width; PLT: blood platelet; ALT: alanine transaminase; TBIL: total bilirubin; CR: creatinine; CRP: c reactive protein; FIB: fibrinogen;ALB: albumin; UA: uric acid; HCY: Homocysteine; TG: triglycerid; TC: total cholesterol; LDL: low-density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol; FBG: fasting blood-glucose; $ABCD^2$: Age, Blood Pressure, Clinical Features, Duration, and Diabetes; Values are expressed as Mean ± SD, median (IQR). The differences were considered significant if *P* value < 0.05. *** *p* value < 0.001, ** *p* value < 0.01,* *p* value < 0.05.

The higher RDW, the earlier the stroke onset after TIA

By categorizing the time from TIA to stroke, it can be concluded that the higher the baseline RDW, the shorter the stroke onset. (p=0.024) (Fig.1).

Utility of predictors for assessing the onset of stroke in TIA patients

To determine the independent association between RDW and stroke, these potential confounders were adjusted for in a multivariable regression analysis. Our multivariable regression analysis model (Table 2) suggested that RDW (OR = 2.52, 95%CI 1.46–3.35, $p = 0.002$) could independently predict the subsequent stroke in TIA patients.

Table 2
Risk factors for stroke using multiple logistic regression

Risk factors	OR	95% CI	*p* Value
RDW	2.523	1.464–3.345	0.002
CRP	1.098	1.035–1.164	0.007
ALB	0.844	0.766–0.930	0.001
HCY	1.062	1.010–1.116	0.019
GLU	1.240	1.062–1.449	0.007

The predictive value of RDW

The ROC curve analysis of RDW values for predicting the risk of stroke after TIA. The area under the ROC curve was 0.731 (95% CI, 0.648–0.814; $p = 0.000$; Fig. 2).The best predictive RDW value was found to be 13.95%(73.7% sensitivity and 74.3% specificity). Meanwhile, the AUC for $ABCD^2$ score was 0.613 (95% CI, 0.547–0.678; $p = 0.001$; Fig. 2). RDW was better than $ABCD^2$ score in predicting stroke after TIA (Z = 2.19, $p = 0.015$).

Discussion

The current study is, so far as we know, the first to clarify the predictive value of elevated baseline RDW level in patients with TIA. The most important result of our study is to show that(1) the higher RDW, the earlier the stroke onset and(2) RDW ≥ 13.95%has a 2.52-fold risk of stroke in TIA patients.

Previous studies found an association between RDW and the incident stroke in a general population, which was independent of anaemia[15]. The higher RDW values measured in stroke patients were associated with adverse functional outcomes and mortality[8].Moreover, increased RDW has proven to be a potent predictor of neuronal damage[16], hemorrhagic transformation[17], higher mortality after intravenous thrombolysis[18], and atrial fibrillation[19] in AIS patients.

The mechanism by which high RDW is associated with stroke progression and clinically poor prognosis is not fully understood. In fact, high RDW is known to reflect high oxidative stress and inflammation[10]. Oxidative stress can reduce RBC lifespan[20],and inflammation is closely related to suppressed RBC production[21], both of which may increase RDW levels. Lorente et al. found that patients with malignant middle cerebral artery infarction(MMACAI) and eventual death show higher RDW, higher blood malondialdehyde(MDA) levels, and higher tumor necrosis factor-α (TNF-α)levels than survivors, and these parameters are correlated. They suggest that the association between mortality and RDW in MMACAI patients may be due to higher oxidative status and higher inflammatory status[22].

As mentioned above, RDW is associated with the potential inflammatory state and oxidative damage, and may predict the incidence and prognosis of stroke patients. The explanation of correlation between an increased RDW level and stroke after TIA may be as follows.

First, higher oxidative stress status in stroke patients after TIA. Several studies have shown that patients with elevated RDW are more likely to suffer high oxidative stress and low antioxidant levels. Oxidative damage and antioxidant levels have been shown to be associated with neuronal damage/protection during cerebral ischemic and reperfusion, which play a role in functional outcome and mortality[23].

Ischemia and reperfusion injury can induce oxidative stress through production of reactive oxygen species(ROS)[24].The TIA animal model suggested that oxygen free radicals produced during reperfusion of ischemic brain injury might be the main cause of reperfusion injury[25]. A 24-month follow-up study of 786 women with moderate and severe disabilities found that their serum oxidant levels increased as RDW increased. Inversely, serum antioxidant concentrations decreased with RDW. An increased RDW level has been identified as a marker of greater oxidative stress status[26]. We found that the stroke patients in respect to the TIA patients had higher RDW, indicating higher oxidative stress.

The antioxidant and oxidant systems were not balanced, and oxidative stress occurred when lots of ROS were produced or the antioxidant were exhausted[27].ALB and TBIL are the main antioxidants participating in removal of ROS and reactive nitrogen species (RNS) produced by various reactions[28]. Our study found lower serum TBIL and ALB levels in stroke patients, suggesting lower antioxidant status in stroke after TIA patients. To sump up, the stroke patients experience higher levels of oxidative stress than TIA both in terms of oxidative stress and antioxidant markers. Therefore, oxidative stress may participate in the pathology of high RDW in stroke after TIA.

Second, higher inflammation status in stroke patients after TIA. The role of inflammation in the ischemic cascade after TIA is well known. Inflammatory mechanisms are central to the pathogenesis and progression of atherosclerosis, plaque rupture[29],thrombosis[30], and stroke[31]. A rich body of literature demonstrates that inflammation is associated with increased stroke risk and may be an important determinant of outcomes[32]. Inflammatory biomarkers such as P-selectin have been considered to be predictors of stroke after TIA[33].

A study of 3845 adult outpatient subjects further supported this hypothesis. the scholars demonstrated a strong, hierarchical and independent relationship between RDW and hsCRP levels[34]. In addition, some scholars have found that RDW and CRP are positively correlated, which further confirmed the hypothesis that RDW is an inflammation marker[35]. Moreover, another study revealed that older women in higher quartile of RDW were associated with higher concentration of interleukin-6, suggesting predictive values of RDW in serum antoxidants and inflammation[36]. To some extent, our results are consistent with the conclusion of their researches. In our study, both the values of RDW, N/L and the CRP were significantly higher in stroke patients. It seems that stroke patients experience higher levels of inflammation than TIA.

Third, higher RDW means microcirculation disturbance and insufficient oxygen supply. With the increase of RDW, the size of RBC is not uniform, and its deformation causes changes in peripheral blood circulation function. This may be an independent or synergistic factor for increased circulatory resistance and the result of vascular occlusion[37].Increased RBC aggregation and reduced deformability are observed in the pathophysiology of circulatory disorders, including myocardial infarction, inflammation, and stroke[38]. These hemorheological parameters interrupt microcirculation through narrow capillaries in ischemic tissue[39].Some scholars found that elevated RDW can lead to poor collateral flow and increased final infarct volume in stroke patients[40].

In addition, elevated RDW levels were negatively correlated with blood oxygen saturation[41].Lower oxygen saturation and decreased erythrocyte deformability were observed in patients with increased RDW in previous studies[37]. With the increased of RDW value, oxygen supply in the brain is lower[42], which may directly contribute to the progression of TIA.

More importantly, the comparison of different AUCs(Fig. 2, 0.731 vs 0.613) supported that the use of RDW value could improve predictive power when compared with the $ABCD^2$ score. To further investigate the necessity of addition of RDW to a scoring system, larger-sample studies are needed.

As a conclusion, our finding confirmed the prognostic value of RDW in patients with TIA. Increased RDW likely reflects the presence of oxidative stress, inflammation, microcirculation underfilling and/or hyoxemia or a combination thereof. Based on the above evidence, we look forward to more studies confirming that RDW is a powerful predictor of subsequent stroke in TIA patients.

LIMITATIONS

One limitation of our study is that several markers of inflammation and oxidative stress, such as TNF-α, and MDA, were not adequately evaluated. Another limitation in our study was that the RDW was measured only once, which may increases the possibility of analyzing defects. Thirdly, the sample of this retrospective study is small, which may lead to biases in the results of the study. Therefore, large sample, multi-center studies are needed to verify our findings.

Conclusions

In summary, this study is the first to demonstrate that elevated RDW is an independent predictor of subsequent stroke in TIA patients. As an economic and accessible hematological marker, baseline RDW may serve as a useful biomarker for risk stratification in TIA patients.

Declarations

Ethics approval and consent to participate

This was a retrospective, cross-sectional study that did not involve clinical or animal studies and would not have had any effect on patient outcomes. According to the statement on ethics approval by the ethics committee composed of our hospital, the requirement for ethics approval was exempted.

Consent for publication

All authors have read and agreed to the published version of the manuscript.

Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Conflicts of interests

The authors declare that they have no conflict of interest.

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Authors' contributions

Conceptualization, Ke-Hang Xie.; Data curation, Ke-Hang Xie.; Formal analysis, Ling-Ling Liu.; Investigation, Yun-Ru Liang.; Project administration, Chu-Yin Su. and Hua Li.; Resources, Qing-Qing Chen.; Software, Run-Ni Liu.; Supervision, Wang-Kai He.; Validation, Yong-Kun Ruan.; Visualization, Jia-Sheng He.; Writing original draft, Yun-Ru Liang.; Writing review and editing, Ke-Hang Xie.

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Figures

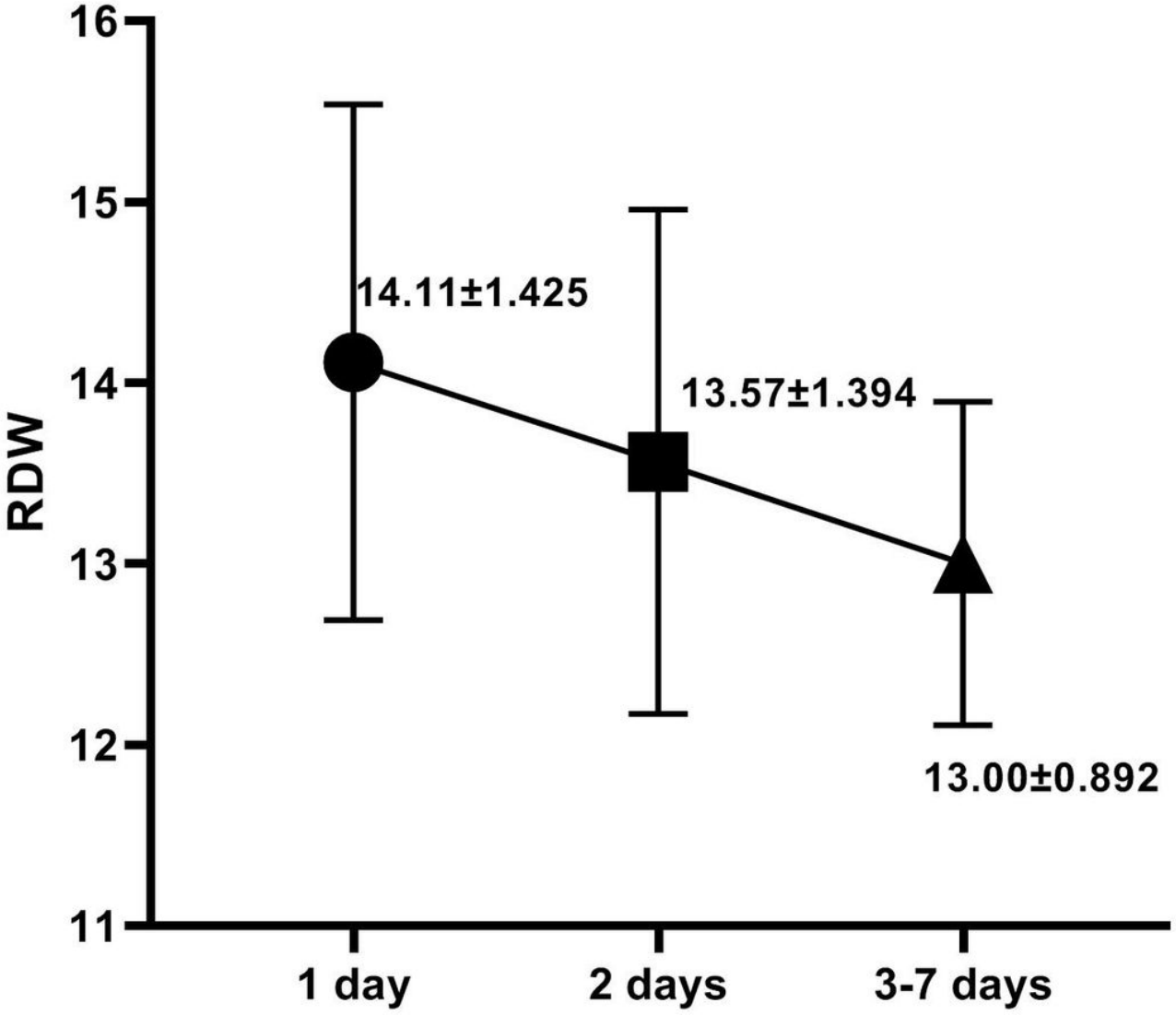

Fig. 1 The higher the RDW level,the earlier the stroke occurred.(*p*= 0.024).

Figure 1

See image above for figure legend.

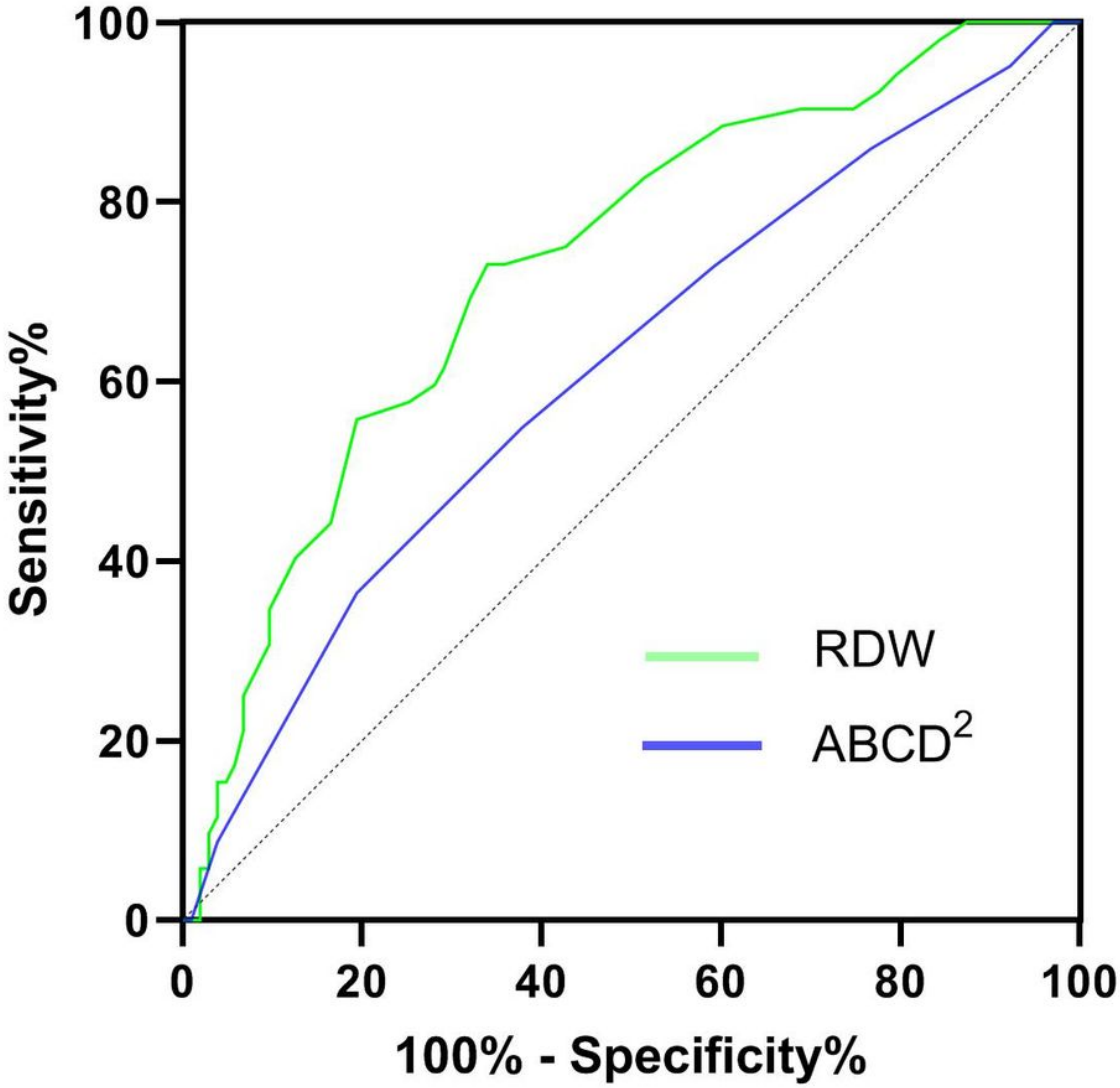

Fig.2 The ROC curve analysis of admission RDW for predicting the stroke after TIA.

Figure 2

See image above for figure legend.