Red Cell Distribution Width Before Intravenous Thrombolysis in Prediction of 1-year Outcome and Mortality in Patients with Acute Ischemic Stroke

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Abstract

Background: It is well known that red blood cell distribution width(RDW)is a parameter reflecting the heterogeneity of red blood cell volume，which recently may be associated with the development of cardiovascular events or mortality in patients after myocardial infarction .However, little is known about the association between RDW and stroke, especially regarding indisputable endpoints such as death. The purpose of the study was to explore the prognostic value of RDW and its effect on mortality among patients with acute ischemic stroke (AIS) undergoing Intravenous thrombolysis (IVT). Methods: We carried out retrospective analysis of acute anterior ischemic strokes cases treated with IVT between January 2016 and March 2018.The effect of RDW on poor outcome (modified Rankin score 3-6) and mortality in 1 year were assessed. Use multivariate logistic regression to explore the predictors. Receiver operating characteristic (ROC) curve was used to evaluate the predictive capability of variables, furthermore, we applied Cox proportional-hazards models to analyze the impact of factors on survival. Results: RDW (Multivariate OR 1.179;95%CI 0.900-1.545,p=0.232) was not associated with clinical outcome. Surviving patients have lower baseline RDW compared with patients who later died. Adding RDW to NIHSS could improve the prediction of the mortality of stroke clinical outcomes. Conclusions: The finding of our study implied that higher RDW was a potential predictive factor of mortality in 1 year in patients with AIS undergoing IVT，but RDW might not be associated with worse survival function among stroke survivors.

Background

RDW are the most reliable discrimination indices in differentiation between Iron deficiency anemia (IDA) and thalassemia trait(TT) [1], has recently considered to predict mortality in patients with severe sepsis or septic shock [2],acute kidney injury[3],acute heart failure patients and acute myocardial infarction[4,5],using data extended to a general population, such as critically ill patients and the elderly[6,7].As we all know, stroke is the second leading cause of death and third leading cause of disability worldwide[8],although the previous studies failed to identify the prognostic impact of RDW on stroke patients. The present study designed to assess the prognostic value of RDW in patient with acute anterior circulation ischemic strokes and correlation with death.

Methods

Study design and population

We retrospectively analyzed the clinical information and relevant imaging of consecutive patients with AIS who were treated with IVT in The First Affiliated Hospital of Wenzhou Medical University between January 2016 and March 2018.The diagnosis of AIS was determined by a neurologist specializing in stroke and further assessment of whether patients with acute neurological deficits require thrombolytic therapy.

The main inclusion criteria were:age≥18 ;onset-to-treatment time (OTT) within than 4.5 hours; Symptoms of neurological impairment caused by acute cerebral infarction; and Informed consent signed by patient or family member.

Exclusion criterion included : Active internal hemorrhage, intracranial tumor, cerebral aneurysm, cerebrovascular malformation or recent cerebral hemorrhage; evidence of active bleeding or trauma (such as fracture) on physical examination, major surgery in the past two weeks; serious heart, Liver, kidney and other parenchymal diseases.

The NIH Stroke Scale（NIHSS）score, which is used to assess the degree of neurological deficit in stroke patients, with a score range of 0-42. The higher the score, the more severe the neurological damage. We recorded NIHSS scores on admission and discharge from patients（Trial of Org 10 172 in Acute Stroke Treatment (TOAST) classification were also collected .

Primary predictor variable

Emergency blood samples including RDW count were collected on admission, using automated hematology analyzers.

Follow up and study endpoints

In current study, all patients were followed up for 1 year after admission. We classified Modified Rankin Scale scores (MRS)of 0-2 as good and 3-6 as a poor outcome,1-year all-cause mortality as primary endpoints. The follow up data were collected through outpatient visits or using standardized telephone questionnaire.

Statistical analysis

Continuous variables are expressed as means ± standard（SD）or median (interquartile ranges（IQR）)and categorical variables are expressed as percentage numbers. Differences in baseline clinical data were examined by 1-way analysis of continuous variables and $\chi 2$ test of categorical variables. Variables that differed significantly with a P value less than 0.05 were selected as covariates for univariate and multivariate logistic regression analysis. Odds-ratio(OR) and their 95% confidence intervals were calculated. The optimal cutoff values are calculated based on ROC area under the curve. The independent effect of variables on primary outcome was calculated using Cox multivariate proportional hazards regression analysis. All statistical analyses with P values <0.05 were considered statistically significant. We conducted all statistical analyses using SPSS version 25.0 (SPSS Inc., Chicago, Illinois, USA) .

Results

Association between RDW values and Clinical prognosis

The integrity of follow-up was 92%.Finally,a total of 480 patients were included in the current study. Of the 480 patients, 242(MRS 0-2)had a good prognosis and 238(MRS 3-6)had a poor prognosis. In our analysis, RDW values(13.95±1.37vs.13.57±0.99,p=0.00was differed significantly between poor- and good-outcome patients(Table 1).

To identify the independent prognostic factors, we performed a logistic regression analysis with variables that differed significantly(P<0.05).Only three factors screened out which were Discharged NIHSS score(multivariate analysis OR 1.400;95% CI 1.268-1.546;p<0.001),age(multivariate analysis OR 1.058;95% CI1.028-1.088;p<0.001)and stroke history or TIA (multivariate analysis OR 2.533;95% CI 1.279-5.016;p=0.008)(Table 2).In our regression model, RDW did not show significant correlation with clinical outcome after 1 yearit univariate analysis OR 1.331;95% CI1.123–1.579;p=0.001; multivariate analysis OR 1.179;95% CI0.900–1.545;p=0.232.

Association between RDW values and mortality

The primary endpointdeathwas observed in 55 patients. Admission NIHSS value(OR 1.110, 95% CI 1.074-1.146,p<0.001), discharged NIHSS value (OR1.155, 95% CI 1.114-1.196,p<0.001),age(OR1.083,95%CI 1.051-1.116,p<0.001),diabetes(OR1.826,95% CI 1.074-3.107,p=0.026),bleeding transformation (OR1.990, 95%CI 1.172-3.379 , p=0.011), RDW(OR1.969 , 95% CI 1.418-2.736,p<0.001) and RBC(OR0.483,95%CI 0.310-0.754,p=0.001) were filtered out in the univariate analysis. On the multivariate analysis, discharged NIHSS value(OR1.211,95% CI 1.129-1.299,p<0.001),age(OR 1.087,95% CI 1.048-1.128,p<0.001)remained important prognostic factors of mortality, beyond that, individuals with higher RDW(OR 1.371,95% CI 1.109-1.696,p=0.004)had a higher greater risk of all-cause mortality. The final multivariable model is shown in Table3. On the basis of receiver-operating characteristic (ROC) analysis, the best cut-off value for RDW was 14.65% [area under the ROC curve (AUC)= 0.649; 95%CI 0.569-0.730; p <0.001].At this threshold the sensitivity of 42.0% and specificity of 88.3% were obtained (Table 4). According to the optimal cutoff value, the continuous variables and clinical features were categorized as high(>14.65)and low(<=14.65)group. As we see in Table5,admitted NIHSS score(p=0.037),discharge NIHSS score(p=0.006),age(p<0.001) and all-cause mortality(p<0.001) were different among two groups patients, Besides ,as expected, higher RDW was associated with lower Red blood cell(4.51±0.54vs.4.31±0.84,p=0.006).We drew a ROC curve based on the traditional markers of risk (basic NHISS, age) and another RDW-rich model (Fig. a) .After adding new risk markersthere were a higher significant correlations with unfavorable clinical outcome(AUC= 0.813; 95%CI 0.767-0.859; p <0.001). Univariate cox hazard regression model analyses were further performed to determine independent variables. By adjusting the possible confounding effect, multivariate Cox regression proportional hazard model analyses were performed, as predicted, RDW(HR2.860;95%CI 1.724-4.745;P <0.001was revealed as an independent predictor in the overall population(Table 6).

Age was highly significant in death assessment. For further discussion, we divide the age into 2 groups high: age>70,low:age<=70according to the average value. Then we evaluate the relationship between RDW and death outcomes respectively. Interestingly, after adjusting for various confounding variablesit

seems that in both age groups, RDW value was significant differences.(age>70 group: multivariate OR 1.342;95% CI1.008-1.788;p=0.044;age<=70 group: multivariate OR 1.445;95% CI1.034-2.021;p=0.031) (Table 7).

Discussion

The study suggests that baseline RDW may be an independent marker for death in patients with AIS treated with IVT.

RDW reflects the heterogeneity of cell volume in hematopoietic processes and is not only used for early diagnosis and therapeutic observation of iron deficiency anemia. In an analysis of a large examination of 15852 community-dwelling adults The principal founding was that higher RDW was strongly associated with risk of all-cause mortality[9].Another two studies have shown that high RDW values may increase cardiovascular event rate in people with coronary disease or heart failure [10,11].Furthermore, A lot of evidence also shows that RDW could be a novel prognostic marker in esophageal and hepatocellular cancer[12,13]. Other field of research have reported RDW, for example, two studies published RDW in acute stroke patients[14,15],although the results in this study have not been confirmed.

The cause and mechanism underlying RDW and mortality risk are not yet clear. Salvagno and Sanchis-Gomar recently summarized the several biological and metabolic abnormalities associated with clinical significance of RDW in health and disease, include shorter telomere lengths, increased erythrocyte fragmentation and the iron contained in the hemoglobin molecules released[16], Felker provided a variety of novel insights into relate to RDW and outcome such as nutritional deficiencies, renal dysfunction, hepatic congestion and inflammatory stress [10]. In addition, oxidative stress might also contribute importantly to anisocytosis [17].

As mentioned above we found an inverse association of RDW with red blood cell, numerous studies have reported anemia and RBC levels are considered strong predictors of cardiovascular disease and mortality development in different populations[18,19,20].Besides, A number of functional outcome measures have been proposed, the strongest including the patients age and a scale to measure the severity of neurological deficits, such as NIHSS[21,22],risk of stroke increases with age[23],older age is inversely associated with good functional outcome after IAT in patients with AIS[24]. The results of the current study are consistent with other published studies, with RDW rising with aging, which is a main determinant of survival. From these aspects, RDW has its feasibility as a potential predictor.

Nonetheless, the exact physiologic mechanism of RDW and mortality from ischemic stroke after IVT remains unclear. RDW has been recently related to adverse outcomes in patients with atherosclerosis[25,26]. RDW value is positively correlated with cholesterol content of erythrocyte membranes[27], which increases the volume of the necrotic lipid core, leading to rupture of atherosclerotic plaque[28]. Erythrophagocytosis promote foam cell and ceroid, help plaque expansion and promote plaque vulnerability[29].Inflammation is critical in atherosclerosis, ischemia and ischemic stroke[30,31]. RDW increases the level of plasma inflammatory markers such as interferon γ and colony-

forming unit erythroid cells to reduce endothelial nitric oxide production [32]. Studies in recent years showed RDW was correlated with CRP[17,33,34].What is puzzling is there was no apparent difference in the level of Leukocytes in the two groups of RDW, it indicates whether the association between RDW and mortality is inflammation as the main mechanism worthy of further investigation. Meanwhile, recent studies reported the response of patients with AIS to IVT [35,36], RBC can affect clot-stabilizing and tPA-induced fibrinolysis [37], High RDW reflect the increased RBC aggregability, deformability and adherence to the vessel wall, affect blood flow and contribute to thrombosis formation [38],However, there are little research about RDW on IVT reactivity and lysis of blood clots, and more experiments are needed to confirm or deny these findings.

We acknowledge that our experiment has some limitations. First, due to the treatment differences of discharged individuals, unknown factors might have confounded the results. Second ,small sample size may lead to selection bias, we have collected as much data as possible to reduce errors. Third, we did not discuss in depth the relationship between the RDW and age, which limited the generalizability of the study's results. At last, we did not further explore the role of RDW in inflammatory. In future experiments, we will avoid the above limitations to get more reliable results.

Conclusions

Our study confirms that RDW before thrombolysis is an independent predictor of 1-year mortality in patients with AIS , rather than a prognostic factor for the severity of stroke clinical outcomes, which may be one of the future development areas that help us to further understand the mechanism of thrombolysis and improve the management of patients with AIS.

Abbreviations

RDW: red blood cell distribution width；AIS: acute ischemic stroke; IVT: intravenous thrombolysis；IDA: iron deficiency anemia; TT: thalassemia trait; IQR, Interquartile Rang；CI: Confidence Interval; OR: Odds Ratio; SD: Standard Deviation; AUC: area under the ROC curve; HT：hemorrhagic transformation; CVD: cardiovascular Disease; IAT: intra-arterial treatment; RBC: red blood cell

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of The First Affiliated Hospital of Wenzhou Medical University. Due to the retrospective nature of this study no written informed consent was obtained. All patient data were anonymously analyzed.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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No funding was obtained.

Authors' contributions

WYY was responsible for the concept and design of the study, data collection and analysis and the first draft of the paper and further manuscript; WWX helped to collect the data; XL performed the statistically analysis; JL and YYW participated the design of the study and explanation of the data; XZY and XZ were responsible for overseeing the concept and design of the study. All authors read and approved the final manuscript.

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Tables

The tables could not be inserted due to technical limitations. They have been included as Excel files in the supplementary file section.

Figures

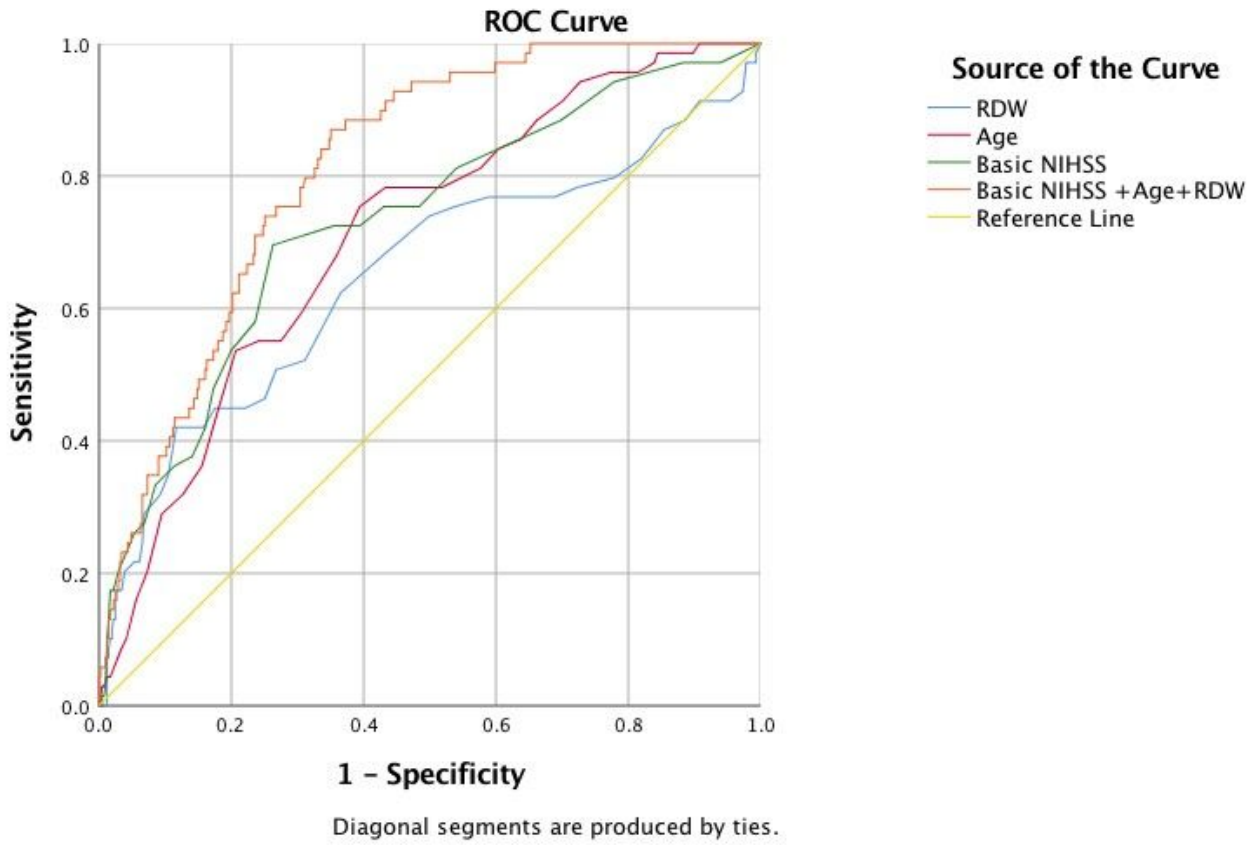

Figure 1

Fig. a Receiver-operating characteristic (ROC) curve display of multivariate model features. The receiver-operating characteristic (ROC) curve and related performance characteristics for model based on the classic risk factors (NIHSS, Age) and multivariable model enriched with red cell distribution width (RDW)

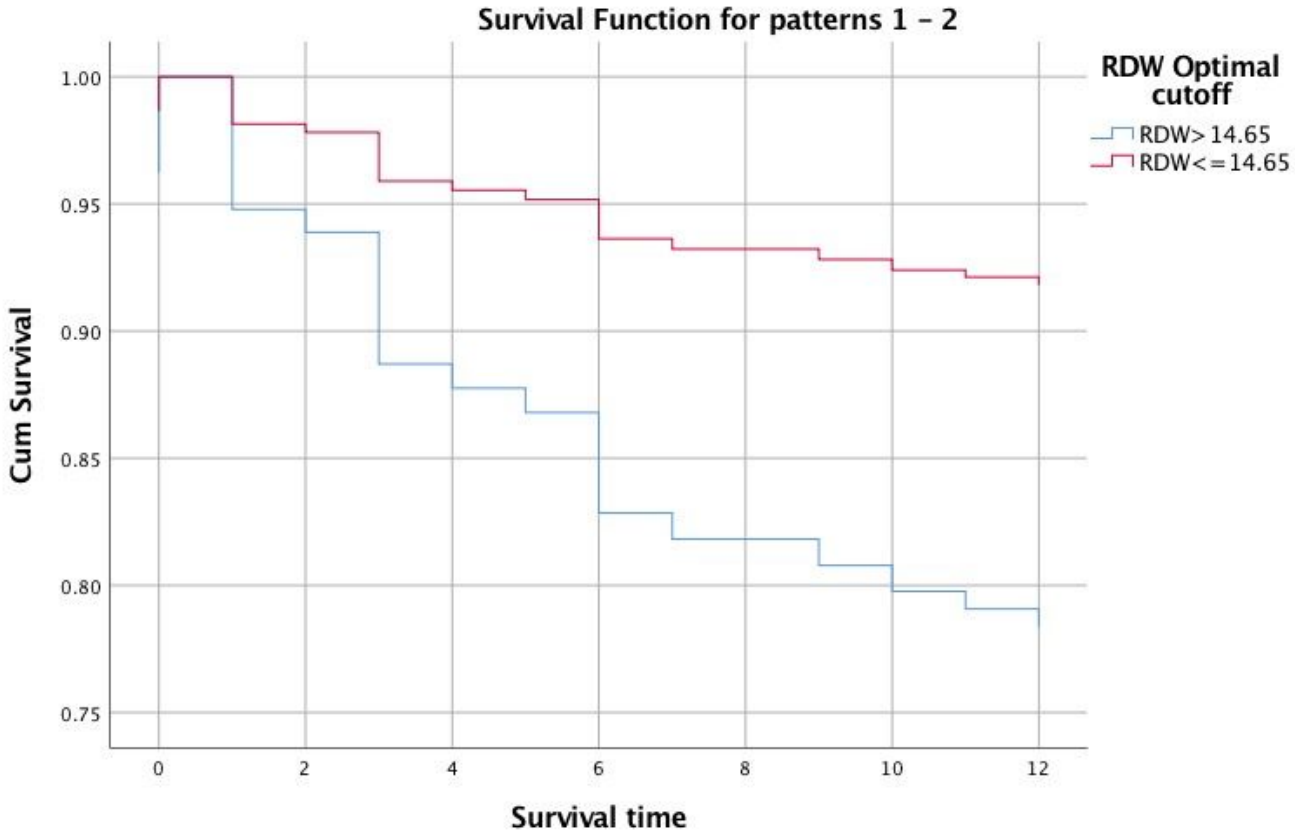

Figure 2

Fig. b Cox survival curves adjusted for classic risk factors according to RDW groups.

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