# The predictive value of red cell distribution width for stroke severity and outcome

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**Research note**

**Keywords:** Ischemic Stroke; Tissue Plasminogen Activator; Red Cell Distribution Width; Modified Ranking Score; National Institute of Health Stroke Scale; Prediction

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# Abstract

Objectives: In the present study, we sought to investigate the association of RDW with stroke severity and outcomes in patients who underwent anti-thrombolytic administration with tissue plasminogen activator (tPA). Results: This study was conducted during eighteen months at emergency department. During the time of study, 282 subjects were included. The categorization of RDW to <12.9 and >13 values revealed insignificant difference in stroke severity score, accounting for the mean 36-hour NIHSS of 8.19±8.2 in normal RDW values and 9.94±8.28in higher RDW group (p=0.64). In seventh day assessment, NIHSS was 6.46±7.28 in normal RDW group and was 8.52±8.35 in increased RDW group (p=0.058). Neither the thirty-six-hour, nor the seventh day and 3-month MRS demonstrated significant difference between those with normal and higher RDW values.



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# Introduction

Cerebral ischemic attack is a general term of ischemic stroke, including cerebral thrombosis, cerebral embolism and lacunar infarction. Seventy percent of cerebrovascular attacks are related to ischemic stroke which induced by the disorder in brain–blood supply of brain lesions. It is second common cause of death accounting for over 20 million morbidities worldwide (1,2). tPA anti-thrombolytic therapy is a recently introduced with promising results for the treatment of ischemic stroke (5,6).

Regarding the high incidence and mortality rate of ischemic stroke, a predictive parameter related to severity of stroke would enhance the pre-assumption in anti-thrombotic therapeutic approach (7,8). RDW is a hematologic parameter to indicate the divergence of the red blood cell volume. The rise in RDW has been shown in different physiological and pathological conditions. Primarily, it was generated for the diagnosis of different types of Anemia, while the recent evidence proved its prognostic role in cerebrovascular diseases (13).

There is still a lack of data regarding predictive value of RDW with severity of stroke among patients with ischemic stroke received tPA therapy. In the present study, we aimed to investigate the association of RDW with stroke severity and final outcome in patients who underwent anti-thrombolytic administration.

# Materials And Methods

This prospective study was conducted during eighteen months since April 2016. The participants were patients with definite diagnosis of stroke with specific criteria for tPA injection, who admitted to emergency department of Imam Reza University Hospital of Tabriz University of Medical sciences. Those with transient ischemic attack, intracerebral hemorrhage, cerebral sinus venous thrombosis, sub-arachnoidal hemorrhage, renal insufficiency and late admission (424 h after stroke onset) as well as pregnant females were excluded from the study population.

The blood samples were obtained at the time of admission for the measurement of RDW. The patients were followed during 3 months. The severity of stroke was assessed using National Institute of Health Stroke Scale (NIHSS) and the clinical outcome was measured by Modified Ranking Score (mRS) in 36 hour, 7 days and 3 months.

The RDW was calculated within 3 hours after admission and assessed by the Sysmex KX-21 automated cell counter (Sysmex Corporation, Kobe, Japan) from ethyl enediamine tetra acetic acid blood samples. RDW values of $\leq$12.9 were categorized as normal and $\geq$ 13.0 were considered as elevated. Stroke severity (NIHSS) was categorized as mild (0-6), moderate (7-15), and severe (16-38). mRS<<2 (0, 1 and 2) was defined as fine outcome.

The statistical analysis was performed by SPSS software version 19.0 (IBM Corp., Armonk, N.Y., USA). Categorical variables were calculated as percentages and continuous variables calculated as mean ± standard deviation. Continuous variables were compared using independent t-test and categorical variables were compared by qui-square test. The ROC was performed for the accuracy detection of RDW, in which the AUC closer to 1 was considered as a test with high predictive value. The P-value less than 0.05 was regarded as significant.

# Results

General Findings

Two-hundred and eighty two patients including 155 men and 127 women aged 65.20 ± 12.70 years (17-90) were enrolled.

The mean NIHSS score was 13.16 ± 6.39 at time of arrival, and it took averagely 55.99 ± 30.12 hours for tPA injection (5-184h). The NIHSS score improved significantly after the injection in 36 hours (p=0.027) with the mean thirty-six-hour score of 10.10 ± 8.93.

RDW values ranged from 10.4 to 20.5, with the mean value of 13.67 ± 1.17.

Mean values for RDW didnot significantly correlate with the severity of stroke (p = 0.11). In mild form of stroke (NIHSS = 0-6), the mean value for RDW was 13.60 ± 0.22 and in stroke of moderate severity (NIHSS = 7-15), it was 13.58 ± 0.11. For patients with severe stroke (NIHSS > 16), the mean RDW was higher than the mild to moderate cases with mean value of 13.854 ± 0.12.

Table 1 demonstrates patients' characteristics according to the severity of stroke.

The patients were evaluated 7 days after the time of admission, however, the data was available only for 268 patients. The mean NIHSS was 2.7 ± 1.7 seven days after anti-thrombolytic therapy. The MRS was 3.14 ± 2.22 thirty-six hours after the treatment, which improved by 2.7 ± 1.73 in 7 days.

Classification of results based on the RDW values

The patients' characteristics according to the baseline RDW level is demonstrated in Table 2.

NIHSS

The categorization of RDW to <<12.9 and >13 values revealed insignificant difference in stroke severity score, accounting for the mean baseline NIHSS of 11.74 ± 6.39 in normal RDW values and 13.38 ± 0.49 in higher RDW group (p = 0.60). Similarly, the mean NIHSS of subjects with RDW<12.9 was lower than the patients with RDW>13 in each thirty-six-hour and seven-day evaluation, while the difference between them was statistically non-significant. The mean NIHSS was 8.19 ± 8.2 and 9.94 ± 8.28 in patients with normal and higher RDW values, respectively (p = 0.64). In seventh day assessment, NIHSS was 6.46 ± 7.28 in normal RDW group and was 8.52 ± 8.35 in increased RDW group (p = 0.058).

MRS

The categorization of final outcome according to RDW level demonstrated mean MRS of 2.74 ± 1.56 thirty-six hours after the time of tPA injection in the group of patients with normal RDW value, which was 3.25 ± 2.55 in increased RDW group. The final outcome results had a trend toward improvement in both RDW categories after seven days. The mean MRS was 2.33 ± 1.59 and 2.72 ± 1.75 in normal and increased RDW group, respectively.

Neither the thirty-six-hour, nor the seventh day MRS demonstrated significant difference between those with normal and higher RDW values.

Length of stay at hospital

The length of stay at hospital in patients with RDW<<12.9 was 14.34 ± 18.5 and in those with RDW > 13 was 15.08 ± 15.9. The results didn't differ significantly between two groups (p = 0.96).

SICH

SICH occurred in 14 patients, in 6 patients severe symptoms led to diagnosis and in 8 of them hemorrhage was asymptomatic. In patients with normal RDW level, 2.04% had symptomatic hemorrhage and 2.04% had asymptomatic hemorrhage. Among patients with elevated RDW, asymptomatic and symptomatic hemorrhage occurred in 4.69% and 3.35% of the patients. The analysis with Pearson's test did not reveal a correlation between SICH and RDW.

Mid-term Follow up

Out of 282 enrolled subjects, only 208 referred for the three-month follow up session, 98 of them had a good final outcome with mean baseline RDW of 13.57 ± 1.35 and 110 had poor outcome on MRS evaluation with score of 13.76 ± 1.06. The linear regression analysis didn't address any significant regression between final outcome results and baseline RDW values ($r = 0.04$, $p = 0.52$).

The sensitivity, specificity and AUC of baseline RDW for predicting final outcome within 36 hours were 77.6%, 69.8% and 0.51, respectively (Figure 1.A). In 7-day follow up, the sensitivity, specificity and AUC of baseline RDW were 75.0%, 74.3%, and 0.48, respectively (Figure 1.B). And during the period of 3 months the sensitivity, specificity and AUC of baseline RDW for MRS prediction were 74.4%, 71.4% and 0.57, respectively (Figure 1.C).

# Discussion

Principal findings

In this prospective cohort study, the association between RDW and severity of stroke as well as its final outcome was assessed to find a possible predictive value of RDW in patients with stroke who underwent anti-thrombolytic therapy with tPA. The results of the study revealed that stroke severity score in subjects with baseline RDW lower than 13 is lower than those with higher RDW values. The stroke severity improved after the injection of tPA, resulting in lower NIHSS results in each group after 36 hours and 7 days. On the other hand, the difference in severity score wasn't significant in each admission time, 36-hour and 7-day post injection time. The results of this study didn't address any significant correlation between stroke severity and RDW values in patients underwent tPA administration. RDW also didn't affect the final outcome neither after 36 hours nor after 7 days. The results also revealed that the final outcome scale in a mid-term follow up interval of 3 months is not correlated with baseline RDW values. RDW with 13 as cut-off didn't appeared as a predictive tool for predicting final stroke outcome with approximate AUC of 0.5.

Findings in relation to other studies

In a similar study by Kara *et al.*, RDW values in subjects with acute ischemic stroke were compared in clusters with different severity score. In contrast to our results, they reported a significant role of RDW for predicting stroke severity (9). They also reported a significant correlation between RDW and other parameters such as NIHSS and GCS and found that RDW with cutoff point of 14 had a high sensitivity

and specificity in differentiating stroke patients with normal subjects (ROC: 0.76). The reported cutoff point was higher than our study.

Jia et al studied 432 patients diagnosed with acute ischemic stroke confirms that RDW is closely related to the occurrence of ischaemic stroke. This study an important role of RDW in the progression of an ischaemic stroke, which possibly was related to the carotid artery occlusion caused by great-sized red blood cells (15).

In a population-based cohort study, Soderholm (16) *et al* found that high RDW values increase the risk of ischemic stroke.

In this study delimiting the study population to those who underwent tPA injection resulted in different findings compared with previous publications. It is also showed by Lappegård *et al* that the elevated RDW level cannot predict the risk of stroke-induced mortality after the exclusion of patients with Anemia (17). However, findings of Turcato *et al.* in a similar study indicated that RDW can be used as an independent predictor of the severity of stroke and prognosis in patients with acute ischemic stroke who would undergo anti-thrombotic therapy (18).

Possible mechanisms and implication for future studies

RDW has found to be elevated in conditions of ineffective erythropoiesis and may associate with erythrocyte destruction. It's still not clear whether it can be related to the incidence of stroke, however a population-based study with normal control group is required to answer this question. Based on the present study, RDW didn't predict the severity of stroke and final outcomes in those who underwent tPA injection. This may explain the discrepancies in our finding compared with other studies in the literature. We only included patients with acute ischemic attack and excluded other types of stroke, severe cases with NIHSS >> 22 and those who admitted > 4.5 hour after the symptom onset. Moreover, while other studies have proposed that inflammation as a predisposing factor in ischemia maybe related to elevated RDW levels (12,19), the results of our study did not confirm that mechanism for the association of RDW and ischemia. Further studies are required to resolve this issue.

Limitations

Our study had some limitations that should be considered. The population of our study included some patients with other medical conditions, which may have a confounding impact on findings. It's better to add that with regards to the pathologic nature of ischemic stroke which afflict aged population, the exclusion of such comorbities was impossible. Moreover, only the patients with ischemic stroke who were admitted within sufficient time for tPA injection were included in the study. So, the results cannot be generalized to all forms of stroke patients or with admission severity score. However, the study population in this study were followed prospectively and any possible factor that could affect the outcome measure were considered. Thus, the results could provide sufficient information about the predictive role of RDW in ischemic stroke.

# Declaration

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Authors' contributions

KSh, ZhKh and ES contributed to study design and supervision, YGh, FH and FS contributed to the experimental evaluation, and analysis of data and writing of the manuscript. PM, MP and SM collected the data. All the authors read and approved the final manuscript.

Ethics approval and consent to participate

This study protocol was approved by the Ethical Committee of Tabriz University of Medical Sciences. All the participants were given written informed consent for the participation in this study.

Consent to publish

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Availability of data and material

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

# References

1. Seifar F, Khalili M, Khaledyan H, Amiri Moghadam S, Izadi A, Azimi A, et al. alpha-Lipoic acid, functional fatty acid, as a novel therapeutic alternative for central nervous system diseases: A review. Nutr Neurosci. 2017 Nov;1–11.

2. Dalal PM, Malik S, Bhattacharjee M, Trivedi ND, Vairale J, Bhat P, et al. Population-based stroke survey in Mumbai, India: incidence and 28-day case fatality. Neuroepidemiology. 2008;31(4):254–61.

3. Boysen G. European Cooperative Acute Stroke Study (ECASS): (rt-PA-Thrombolysis in acute stroke) study design and progress report. Eur J Neurol. 1995 Jan;1(3):213–9.

4. Molina CA, Alvarez-Sabin J. Recanalization and reperfusion therapies for acute ischemic stroke. Cerebrovasc Dis. 2009;27 Suppl 1:162–7.

5. Turley KR, Toledo-Pereyra LH, Kothari RU. Molecular mechanisms in the pathogenesis and treatment of acute ischemic stroke. J Invest Surg. 2005;18(4):207–18.

6. DeMers G, Meurer WJ, Shih R, Rosenbaum S, Vilke GM. Tissue plasminogen activator and stroke: review of the literature for the clinician. J Emerg Med. 2012 Dec;43(6):1149–54.

7. Goldberg G. Constraints on predicting functional recovery after stroke: Application of clinical, laboratory, neurophysiologic, and neuroimaging parameters. Top Stroke Rehabil. 1994 Sep;1(3):51–76.

8. Ozkan AK, Yemisci OU, Saracgil Cosar SN, Oztop P, Turhan N. Can high-sensitivity C-reactive protein and ferritin predict functional outcome in acute ischemic stroke? A prospective study. Top Stroke Rehabil. 2013;20(6):528–36.

9. Kara H, Degirmenci S, Bayir A, Ak A, Akinci M, Dogru A, et al. Red cell distribution width and neurological scoring systems in acute stroke patients. Neuropsychiatr Dis Treat. 2015;11:733–9.

10. Bujak K, Wasilewski J, Osadnik T, Jonczyk S, Kolodziejska A, Gierlotka M, et al. The Prognostic Role of Red Blood Cell Distribution Width in Coronary Artery Disease: A Review of the Pathophysiology. Dis Markers. 2015;2015:824624.

11. Vizzardi E, Sciatti E, Bonadei I, Pezzali NL, Lombardi CM, Metra M. Red cell distribution width and chronic heart failure: prognostic role beyond echocardiographic parameters. Monaldi Arch chest Dis = Arch Monaldi per le Mal del torace. 2016 Jun;84(1–2):59.

12. Kaya A, Isik T, Kaya Y, Enginyurt O, Gunaydin ZY, Iscanli MD, et al. Relationship between red cell distribution width and stroke in patients with stable chronic heart failure: a propensity score matching analysis. Clin Appl Thromb Hemost. 2015 Mar;21(2):160–5.

13. Sultana GS, Haque SA, Sultana T, Ahmed AN. Value of red cell distribution width (RDW) and RBC indices in the detection of iron deficiency anemia. Mymensingh Med J. 2013 Apr;22(2):370–6.

14. Vijayashree R, Abirami R, Govindaraju S, Ramesh Rao K. Relevance of Red Cell Distribution Width (RDW) Determination in Stroke: A Case Control Study. Int J Sci Res Publ. 2014;4(11):1–5.

15. Jia H, Li H, Zhang Y, Li C, Hu Y, Xia C. Association between red blood cell distribution width (RDW) and carotid artery atherosclerosis (CAS) in patients with primary ischemic stroke. Arch Gerontol Geriatr. 2015;61(1):72–5.

16. Soderholm M, Borne Y, Hedblad B, Persson M, Engstrom G. Red cell distribution width in relation to incidence of stroke and carotid atherosclerosis: a population-based cohort study. PLoS One. 2015;10(5):e0124957.

17. Lappegard J, Ellingsen TS, Skjelbakken T, Mathiesen EB, Njolstad I, Wilsgaard T, et al. Red cell distribution width is associated with future risk of incident stroke. The Tromso Study. Thromb Haemost. 2016 Jan;115(1):126–34.

18. Turcato G, Cappellari M, Follador L, Dilda A, Bonora A, Zannoni M, et al. Red Blood Cell Distribution Width Is an Independent Predictor of Outcome in Patients Undergoing Thrombolysis for Ischemic Stroke. Semin Thromb Hemost. 2017 Feb;43(1):30–5.

19. Furer A, Finkelstein A, Halkin A, Revivo M, Zuzut M, Berliner S, et al. High red blood cell distribution width and preclinical carotid atherosclerosis. Biomarkers Biochem Indic Expo response, susceptibility to Chem. 2015;20(6–7):376–81.

## Tables And Figure

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