Red Blood Cell Distribution Width as a prognosticator of Clinical Outcome in Acute Ischemic Stroke

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Abstract

Background: Red cell distribution width (RDW) is a critical parameter that is reported to have a relation with the incidence and prognosis of cerebrovascular strokes. Altered RDW has been shown to predispose to the development of vascular thrombosis which is the underlying cause of cerebrovascular disease. We in the current study tried to evaluate the relationship between RDW values and stroke severity and prognosis.

Methods: N=50 cases of acute ischemic stroke and age and sex-matched controls were included in the study. The patients were analyzed with a detailed history with the profile of stroke, GCS, NIHSS, mRS, including risk factors such as hypertension, Diabetes mellitus, IHD, and vascular risk factors. All the patients were subjected to 12 lead ECGs, 2D Echo, and CT scans. The sample was sent to the Department of Pathology for complete blood analysis including RDW.

Results: the cases were divided into two groups those with RDW ≥14.5 and those with RDW ≤14.5. We found 62% of cases with RDW ≥14.5 and 28% cases with RDW ≤14.5. We found CRP levels, MCV, Modified Rankin Scale mRS, and Stroke size significantly increased in patients with RDW ≥14.5. Analysis of cases based on RDW in both groups the p-values was found to be 0.0122 considered significant. The diagnostic value of RDW levels at the cutoff value of 13.5 found the sensitivity was 76.5% and specificity was 75.8%.

Conclusion: RDW is an important indicator of the prognosis of ischemic stroke. Although the exact mechanisms underlying it has not been fully elucidated, it may be used routinely in laboratories as it is inexpensive, and when combined with GCS, NIHSS, and mRS parameters it could provide information on stroke severity and increased risk of mortality.

Keywords: Red Blood Cell Distribution Width (RDW), Acute Ischemic stroke, Modified Rankin Scale mRS, C reactive protein (CRP).

Introduction

Stroke or cerebrovascular accident is one of the important causes of morbidity and mortality. The World Health Organization defined stroke as a "neurological deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by death within 24 hours" It is a disease that has multifactorial etiology. It results from occlusion or hemorrhage and is considered a leading cause of death across the world. [1-3] The incidence of stroke is increasing in recent years especially in developing countries. In India stroke is increasingly becoming the cause of premature death or disability. It has been largely driven by demographic changes and by the existence of several important modifiable risk factors. The risk rate of stroke across the world in the age above 25 years has increased from 22.8% in 1990 to 22.8% in the year 2016. [4] Early detection and treatment are the keys to a favorable prognosis. [5] The inquest of early

biomarkers for stroke and its prognosis Red cell distribution width (RDW) has been recently found to be an important parameter. RDW measures the size variability of the circulating erythrocytes. Some consider it as an electronic counterpart of peripheral anisocytosis. It represents the coefficient of variations of red blood cells volume percentage. [6] Several studies have pointed out that RDW elevations are seen in diseases which include cardiovascular diseases, thrombosis, and stroke. [7-10] RDW has been found to vary based on the inflammatory status of the individual and it has a profound impact on stroke development. [11] Feng et al., [12] have found an increased incidence of inflammation and oxidative stress which occurs during ischemia could result in elevation of RDW and is often associated with poor prognosis. However, there is no comprehensive investigation of RDW in our group population. If the increased RDW can be used to detect major complications and strengthen treatment and reduce mortality it may have a profound impact on the method of management. Since the RDW determination is rapid and inexpensive and is performed in most of the laboratories it can be monitored with ease. We in the current study tried to evaluate the RDW as the prognosticator of acute stroke in cases reporting to our tertiary care hospital.

Material and Methods
This cross-sectional study was conducted in the Department of General Medicine, Government Medical College, and Hospital, Mahaboobnagar, Telangana. Institutional Ethical committee permission was obtained for the study after following the protocol for human research. Written consent was obtained from the guardian/relative of the patient included in the study.

Inclusion criteria
1. All the cases of acute ischemic stroke
2. Admitted to the hospital within 24 hours of onset
3. Age and sex-matched with associated risk factors to act as controls.

Exclusion criteria
1. Patients with post-trauma stroke
2. Brain tumors or CNS infections
3. With a history of recent MI
4. History of immunological disorders
5. All types of anemic cases

The patients were analyzed with a detailed history with the profile of stroke, including risk factors such as hypertension, Diabetes mellitus, IHD, and vascular risk factors. All the patients were subjected to 12 lead ECGs, 2D Echo, and CT scans. A 5 ml of venous sample was obtained from the patients (within 24 hours of stroke onset) in a vacutainer with EDTA as an anticoagulant. The sample was sent to the Department of Pathology for complete blood analysis including RDW. In the Pathology lab, the sample was analyzed with an automated blood cell counter (SYSMEX K1000 Kobe Japan). RDW is calculated by dividing the standard deviation of the RBC volume by MCV multiplied by 100 to give the value in percentage. It is expressed as the percentage coefficient of variation normal range is from 11.6 – 14.6%. The severity of stroke was assessed by the National Institutes of Health Stroke Scale (NIHSS) score which as grades as mild with scores < 8, Moderate scores 9-15, and severe > 16. [13] The severity of neurological impairment was graded as mild (CNS, 8.5–10), moderate (CNS, 2.5–8), or severe (CNS, 0–2). The functional outcomes were measured by using a modified Rankin scale (mRS) with good outcomes defined by scores of ≤ 2 and poor outcomes if the scores are > 2. [13] The collected data was uploaded on an MS Excel spreadsheet and analyzed by SPSS version 21 on windows format. Quantitative data were expressed as mean and standard deviations. Qualitative data was represented by frequencies and percentages. Chi-square test was used to

calculate the difference between qualitative variables p values of (<0.05) was considered significant.

Results

In the present study, n=50 cases of ischemic stroke patients and age and sex-matched n=50 controls were taken. In the ischemic stroke patients, 70% were male and 30% were females similarly in the control group 76% were male and 24% were females. The mean age of cases in the study group was 60.5 ± 2.5 years and in the controls group, the mean age was 58.5 ± 3.5 years. All the risk factors were analyzed between the cases and the control group given in table 1. Of all the risk factors Atrial fibrillation was found to be significantly higher prevalence in cases as compared to controls p values were 0.02 hence significant. The mean GCS score of the patients at the time of admission was 10.25 ± 3.5 and the mean NISS score at admission was 17.35 ± 4.2 and the mean stroke size was 11.4 ± 2.5 cms.

Table 1: Demographic profile of the cases in the study

Variable	Ischemic stroke (n=50)		Controls (n=50)		P-value
	Frequency	Percentage	Frequency	Percentage	
Male	35	70	38	76	0.125
Female	15	30	12	24	0.332
Risk Factors					
Hypertension	35	70	20	40	0.412
Diabetes Mellitus	22	44	12	24	0.122
Dyslipidemia	26	52	15	30	0.06
Smoking	5	10	6	12	0.221
Atrial Fibrillation	10	20	3	6	0.02*
Previous stroke	11	22	0	0	0.0

significant

All the inflammatory and hematological parameters were compared between the cases and the control groups as depicted in table 2. Of all the parameters CRP was found to be significantly increased in the ischemic stroke patients and Red cell distribution width was also significantly increased in the stroke patients as compared to the control group.

Table 2: Comparison of hematological profile

Variable	Ischemic Stroke	Control group	P values
CRP mg/L	29.9 ± 3.34	11.25 ± 1.5	0.022*
Hb gm/dl	14.5 ± 1.5	13.9 ± 1.8	0.785
WBC x 10^3/mm³	8.15 ± 3.6	7.66 ± 4.2	0.36
Platelets x 10^5/mm³	2.2 ± 0.5	2.6 ± 0.66	0.41
RDW %	15.66 ± 1.9	13.4 ± 1.22	0.010*
MCV fl	82.33 ± 2.5	81.2 ± 3.6	0.54

significant

Out of n=50 cases based on the RDW, we divided the cases into two groups those with RDW ≥14.5 and those with RDW ≤14.5. We found 62% of cases with RDW ≥14.5 and 28% cases with RDW ≤14.5. Among all the parameters mentioned in table 3. We found CRP levels, MCV, Modified Rankin Scale mRS, and Stroke size significantly increased in patients with RDW ≥14.5. Analysis of cases based on RDW in both groups the p-values was found to be 0.0122

considered significant. The diagnostic value of RDW levels at the cutoff value of 13.5 found the sensitivity was 76.5% and specificity was 75.8%. Univariate and multivariate logistical regression analysis revealed that despite adjustment of other risk factors RDW remains an important independent factor for poor functional outcomes following Acute Ischemic Stroke.

Table 3: comparison of parameters based on the Red cell width distribution

Variable	RDW ≥14.5 (n=31)	RDW ≤14.5 (n=19)	P values
	Mean ± SD	Mean ± SD	
CRP mg/L	32.6 ± 5.5	21.9 ± 6.4	0.036*
Hb gm/dl	13.22 ± 2.9	14.8 ± 3.3	0.561
WBC x 10^3/mm^3	8.81 ± 2.3	9.77 ± 4.6	0.157
MCV fl	80.22 ± 6.5	84.69 ± 3.7	0.045*
GCS	10.88 ± 2.3	10.96 ± 3.3	0.781
NIHSS	18.66 ± 4.5	15.47 ± 2.6	0.219
mRs	4.5 ± 1.44	3.72 ± 1.2	0.029*
Stroke size cms	14.5 ± 3.7	12.22 ± 2.41	0.017*

Discussion

Stroke is the common cause of morbidity and death in India, and it is the second most common cause of death worldwide. [14] Red cell distribution width is a marker of anisocytosis and is commonly measured by automated cell counters. It is also used for the diagnosis of anemia. [15] Various studies have found that Red cell distribution width can be a useful marker for stroke, pulmonary arterial hypertension, heart failure, pulmonary embolism in predicting mortality and morbidity. [16, 17] The current study aimed to evaluate the role of RDW as a predictor of stroke outcome in acute ischemic stroke. In this study, a comparison of RDW values in patients with those having values less than 14.5 and more than 14.6 increased the stroke risks and had poorer outcomes (table 3). Some studies have revealed that cryptogenic stroke with RDW >14% was an independent predictor of the risk of cryptogenic stroke and the risk increased to 2.5 times in patients with RDW >14%. [18] The exact mechanism of association of RDW levels and stroke has not been fully elucidated. It appears that inflammatory factors and oxidative stress are two important determinants of cerebral infarction. [19] Ramirez M et al., [20] in a case-control study with n=224 patients with stroke with equal age and sex-matched controls found RDW as a powerful indicator of stroke. Jia et al., [21] found RDW values were significantly higher in n=392 ischemic stroke patients. Studies have shown that RDW may reflect the state of inflammation which further leads to impaired erythrocyte maturation and decreased the life span of RBC. [22] Inflammatory mediators such as IL-6, TNF-α, CRP, and ESR were associated with RDW independent confounding factors as part of the inflammatory process. [23] In this study, the comparison of normal RDW and those with increased RDW (table 3) found CRP and MCV were significantly higher in those with higher RDW. Our findings agreed with the findings of Lippe et al., [24] in their study found a higher RDW was associated with higher inflammatory parameters such as CRP. Studies have revealed that RDW value is also influenced by demographic factors such as age, gender, and race. [24, 25] It has been found that normally gradual increase in RDW parameter with the increase in age in normal healthy controls. [26] Although the relationship of gender with RDW is controversial. Studies have found a slightly higher RDW value in females as compared to males. [24, 27] Other studies have proposed that no significant gender-based differences in RDW values are noted. [28, 29] Going

with the fact that gender differences are insignificant we have not compared the RDW parameter differences based on gender. In this study, we evaluated the stroke severity with a bedside scoring system that included GCS, mRS, and NIHSS. Of these with values with RDW distribution indicated the modified Rankin Scale mRS was significantly higher in patients with higher RDW. Kara et al., [30] in n=128 cases with acute ischemic stroke and symptoms of less than 24 hours on comparison with RDW found significantly higher RDW predict in increased bedside scoring systems in agreement with the results of the current study. Kim et al., [18] have reported that a higher magnitude of RDW predicted higher mortality rates and worsening of functional outcomes of ischemic stroke. These studies indicated that RDW can be used as a biomarker for assessing the severity of stroke and prognosis of patients with acute ischemic stroke.

Conclusion

Based on the observations of this study we conclude that RDW is an important indicator of the prognosis of ischemic stroke. Although the exact mechanisms underlying it has not been fully elucidated it may be used routinely in laboratories as it is inexpensive and when combined with GCS, NIHSS, and mRS parameters it could provide information on stroke severity and increased risk of mortality.

References

1. O'Donnell MJ, Chin SL, Rangarajan S, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. Lancet 2016; 388:761–75.
2. Harris R, Nelson LA, Muller C, et al. Stroke in American Indians and Alaska Natives: a systematic review. AM J Public Health 2015; 105: e16–e26.
3. Patra J, Taylor B, Irving H, et al. Alcohol consumption and the risk of morbidity and mortality for different stroke types - A systematic review and meta-analysis. BMC Public health 2010; 10:258.
4. Behnke S. Time is brain: Time management in acute stroke treatment. Radiology 2019; 59:590–95.
5. Jensen MB, Chacon MR, Sattin JA, et al. Potential biomarkers for the diagnosis of stroke. Expert Rev Cardiovasc Ther 2009; 7:389–93.
6. Sadaka F, O'Brien J and Prakash S. Red cell distribution width and outcome in patients with septic shock. J Intensive Care Med 2013; 28(5):307-13.
7. Felker GM, Allen LA, Pocock SJ, Shaw LK, McMurray JJ, Pfeffer MA, et al. Red cell distribution width as a novel prognostic marker in heart failure: data from the CHARM Program and the Duke Databank. J Am Coll Cardiol 2007; 50:40–47.
8. Montagnana M, Cervellin G, Meschi T, Lippi G. The role of red blood cell distribution width in cardiovascular and thrombotic disorders. Clin Chem Lab Med 2011; 50:635–41.
9. Tonelli M, Sacks F, Arnold M, Moye L, Davis B, Pfeffer M, et al. Relation between red blood cell distribution width and cardiovascular event rate in people with coronary disease. Circulation 2008; 117:163–68.
10. Tonelli M, Wiebe N, James MT, Naugler C, Manns BJ, Klarenbach SW, et al. Red cell distribution width associations with clinical outcomes: a population-based cohort study. PLoS ONE. (2019) 14:e0212374.
11. Song Si-Ying, Hua Chang, Dornbors David, Kang Rui-jun, et al. Baseline Red Blood Cell Distribution Width as a Predictor of Stroke Occurrence and Outcome: A Comprehensive Meta-Analysis of 31 Studies. Frontiers in Neurology 2019; 10:1237.
12. Feng G-H, Li HP, Li Q-L, Fu Y, Huang R-B, Soderholm M, et al. Red blood cell distribution width and ischaemic stroke. Stroke Vasc Neurol. 2017;2(3):172–75.

13. Muchada M, Rubiera M, Rodriguez-Luna D, Pagola J, Flores A, Kallas J, Sanjuan E, et al. Baseline National Institutes of Health stroke scale-adjusted time window for intravenous tissue-type plasminogen activator in acute ischemic stroke. Stroke. 2014; 45(4):1059-63.

14. Go AS, Mozaffarian D, Roger VL, et al. Executive Summary: Heart Disease and Stroke Statistics—2014 Update: A Report from the American Heart Association. Circulation 2014; 127(1): 143-52.

15. Ntaios G, Chatzinikolaou A. Red cell distribution width in iron deficiency anemia and beta-thalassemia minor. Am J Clin Pathol 2008; 130: 313.

16. Zalawadiya SK, Veeranna V, Panaich SS, et al. Red cell distribution width and risk of peripheral artery disease: analysis of National Health and Nutrition Examination Survey 1999-2004. Vasc Med 2012; 17 (3) :155-63.

17. Ani C, Ovbiagele B. Elevated red blood cell distribution width predicts mortality in persons with known stroke. J Neurol Sci 2009; 277 (1-2) :103-08.

18. Kim J, Kim YD, Song TJ, et al. Red blood cell distribution width is associated with poor clinical outcome in acute cerebral infarction. Thromb Haemost 2012; 108:349–56.

19. Di Napoli Mario, Slevin Mark, Popa-Wagner Aurel, et al. Monomeric C-reactive protein and cerebral hemorrhage: from bench to bedside. Front Immunol 2018; 9:1921.

20. Ramírez-Moreno JM, Gonzalez-Gomez M, Ollero-Ortiz A, et al. Relation between red blood cell distribution width and ischemic stroke: A case-control study. Int J Stroke 2013; 8(6): E36.

21. Jia H, Li H, Zhang Y, et al. Association between red blood cell distribution width (RDW) and carotid artery atherosclerosis (CAS) in patients with primary ischemic stroke. Arch Gerontol Geriatr 2015; 61:72-75.

22. Chen PC, Sung FC, Chien KL, et al. Red blood cell distribution width and risk of cardiovascular events and mortality in a community cohort in Taiwan. Am J Epidemiol 2010; 171:214–20.

23. Forhecz Z, Gombos T, Borgulya G, et al. Red cell distribution width in heart failure: prediction of clinical events and relationship with markers of ineffective erythropoiesis, inflammation, renal function, and nutritional state. Am Heart J 2009; 158:659–66.

24. Lippi G, Targher G, Montagnana M, et al. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. Arch Pathol Lab Med 2009; 133:628–32.

25. Kaya A, Isik T, Kaya Y, *et al*. Relationship between red cell distribution width and stroke in patients with stable chronic Heart failure. Clinical and Applied Thrombosis/Hemostasis 2015; 21:160–65.

26. Salvagno GL, Sanchis-Gomar F, Picanza A, Lippi G. Red blood cell distribution width: a simple parameter with multiple clinical applications. Crit Rev Clin Lab Sci 2015; 52:86–105.

27. Alis R, Fuster O, Rivera L, Romagnoli M, Vaya A. Influence of age and gender on red blood cell distribution width. Clin Chem Lab Med. (2015) 53:e25–28.

28. Hoffmann JJ, Nabbe KC, Van Den Broek NM. Effect of age and gender on reference intervals of red blood cell distribution width (RDW) and mean red cell volume (MCV). Clinical Chem Lab Med. 2015; 53:2015–19

29. Qiao R, Yang S, Yao B, Wang H, Zhang J, Shang H. Complete blood count reference intervals and age- and sex-related trends of North China Han population. Clin Chem Lab Med. 2014; 52:1025–32.

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