



## Association Between Red Cell Distribution Width (RDW) And Severity Of Ischemic Stroke

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### Abstract

**Introduction :** Stroke is ranked as the second leading cause of death worldwide, with high morbidity and disability. Red Cell distribution width is a measure of the variation in RBC sizes. Inflammation, important in the development of atherosclerosis, ischemia and ischemic stroke may cause elevated RDW levels by inhibiting red cell maturation. The study was undertaken to determine the RDW in stroke and to assess the association between RDW and severity of ischemic stroke.

**Materials And Methods :** A cross sectional observational study was conducted in 186 patients admitted in Medical wards, Govt. Medical College, Kottayam. Detailed history, clinical examination and investigations including a CT brain and CBC including RDW was done at admission. Patients were categorized into mild, moderate and severe degree of ischemic stroke using NIHSS. The values of RDW was determined in each patient. . The relationship between stroke severity and RDW was assessed using appropriate statistical tests and was compared to the outcome as per modified Rankin Scale on day 5 or at the time of discharge.

**Results:** 186 patients were assessed. Mean value of RDW in minor stroke was 11.7, moderate stroke was 13.76, moderate to severe stroke was 15.63 and severe stroke was 19.66. There was significant correlation between severity of ischemic stroke and higher values of RDW (p<0.001).

**Keywords:** Disability, increased RDW, predictor, stroke, severity

### Introduction

Stroke is an important cause of disability as well as mortality. Ischemic stroke accounts for about 70% of all the cerebrovascular accidents. The ICMR report (2004) <sup>1</sup> claims that stroke accounts for 41% of deaths and 72% of disability adjusted life years (DALY) among non-communicable diseases. The extent of disability and the occurrence of mortality are dependent on the severity of stroke. The neurological impairment in ischemic stroke is assessed by NIHSS and the outcome is predicted by Barthel Index, Rankin scale or Glasgow outcome scale.

Red cell distribution width (RDW) in a standard complete blood count is a measure of the variability in size of circulating erythrocytes and is indicated as the coefficient of variation of the erythrocyte size. It is a marker of anisocytosis and is associated with mortality and cardiovascular events in the general population.

High RDW levels are associated with a poor prognosis in disorders such as acute myocardial infarction, stroke, and peripheral artery disease. RDW is a predictor of mortality in patients who have cardiovascular disease, chronic congestive cardiac insufficiency, acute stroke, or acute cardiac insufficiency. Besides RBC abnormalities, many disorders may be frequently associated with a high

degree of anisocytosis<sup>2</sup>. RDW is associated with both the presence and the complexity of vascular disease.

There is no clear mechanism which can explain the elevated RDW values in acute ischemic stroke. The existing hypothesis includes micro vascular disorders, anemia, inflammation cytokines etc. Inflammation is important in the development of, atherosclerosis, ischemia and ischemic stroke. The inflammatory cytokines may cause elevated RDW levels by inhibiting red cell maturation and enabling the release of new and large reticulocytes to the circulation. High oxidative stress may prolong the survival of red blood cells, increase the premature release of large red blood cells into the peripheral circulation, and cause elevation in RDW. Furthermore, inflammation may contribute to morphologic changes in red blood cells by changing membrane glycoproteins and ion channels. Chronic inflammation, oxidative stress, and neuro-humoral activation may contribute to the development of atherosclerosis, and elevated RDW may be useful as a simple parameter to follow the development of atherosclerosis. As a marker of inflammation, RDW is correlated with other inflammatory markers such as CRP. RDW has been reported as a diagnostic and prognostic marker in cardiovascular and thrombotic disorders and a marker of mortality risk in acute dyspnea, community-acquired pneumonia, and critical intensive care patients. Early detection and intervention in time of these vascular diseases is critical for delaying their progression. RDW as a new predictive marker and an independent risk factor plays a significant role in assessing the severity and progression of cerebrovascular diseases. In recent years, many clinical studies have proved that the alterations of RDW levels may be associated with the incidence and prognosis in many cardiovascular and cerebrovascular disease.

The National Institutes of Health Stroke Scale (NIHSS) is a clinical assessment and research tool that provides reliable information useful for quantifying neurological injuries and predicting stroke outcomes when performed in a consistent manner. The present study is conducted to find the relation between severity of ischemic stroke according to NIHSS and values of RDW.

## Materials And Methods

**Type of study** - Cross sectional observational study

**Duration of the study** - 12 months

**Setting** - Dept of General Medicine, Govt. Medical College, Kottayam

**Study population** - Patients with acute ischemic stroke (CT proven) admitted to the General Medicine Department, Government Medical College, Kottayam.

### Inclusion criteria

1. Patients with ischemic stroke confirmed by CT imaging within 48 hours of presentation
2. Age 18-80

### Exclusion criteria

1. Age less than 18 and more than 80
2. Patients with hemorrhagic stroke
3. Pregnant patients
4. Patients with previous history of stroke
5. Patients with anemia

Sample size was calculated using the formula

$$(Z1 - \alpha/2)^2 * \text{specificity} * (1 - \text{specificity})$$

$$N = (1 - \text{prevalence}) d^2$$

Where  $Z1 - \alpha/2 = 1.96$  @  $\alpha$  error 5% Specificity = 67.5

Prevalence = 0.4%

N = 173

### Research question

Is there any association between Red Cell Distribution Width and severity of ischemic stroke. ?

### Research hypothesis

There is no association between Red Cell Distribution Width and severity of ischemic stroke.

### Study procedure

After permission from SRC, Department of General Medicine and the Institutional Research Board, an informed consent was obtained from the patients/ local guardian enrolled in the study. Detailed history from patients/bystanders were taken and clinical examination was done on patients admitted with acute ischemic stroke. Routine investigations were

done, including CT brains at the time of admission and blood investigations to determine the RDW value. Patients were categorized into mild, moderate and severe degree of ischemic stroke using NIHSS. The values of RDW was determined in each patients using TRANSASIA SYSMEX KX21-3 PART ANALYSER and relationship between stroke severity and RDW was assessed using appropriate statistical tests and was compared to the outcome as per modified Rankin Scale on day 5 or at the time of discharge.

**Statistical analysis**

Analysis was done by entering data in Microsoft Excel and using the SPSS software. For qualitative frequencies were calculated, for quantitative variables, mean and standard deviation were calculated. Association between quantitative variables was analyzed using paired t test. Qualitative assessment was analyzed using chi square test. Other parameters were utilized whenever necessary. Significance level was fixed at p value of p<0.05.

**Red Cell Distribution Width**

The red cell distribution width (RDW) test measures variation in red blood cell size (anisocytosis) or red blood cell volume as a part of a complete blood count (CBC), and it is used along with other RBC indices, especially mean corpuscular volume (MCV), to help determine the causes of anemia. RDW is usually calculated by dividing the standard deviation (SD) of the mean corpuscular volume (MCV) by the MCV and multiplying by 100 to yield a percentage value to be on behalf of the RBC size heterogeneity . Since the methods of measuring the RBC size, the instruments, the experimenters, the laboratory standards, and statistical approaches are dissimilar in different laboratories, there is no universal reference range till now . The normal reference range of RDW most laboratories used was 11–15%.

**National Institutes of Health Stroke Scale (NIHSS)**

The National Institutes of Health Stroke Scale (NIHSS) is a clinical assessment and research tool that provides reliable information that is useful for quantifying neurological injuries and predicting outcomes after stroke when performed in a consistent manner .The NIHSS is typically a component of pre-randomization and post-treatment assessment of clinical trial participants and generally takes less than 10 minutes to complete at the bedside. It provides a reliable, reproducible, and validated measure of stroke severity. This 15 item scale includes assessment of gaze, visual fields, language, and attention functions.

**Modified Rankin Scale (mRS)**

The seven-level, modified Rankin Scale (mRS) has several major strengths: it covers the entire range of functional outcomes from no symptoms to death, its categories are intuitive and easily grasped by both clinicians and patients, its concurrent validity is demonstrated by strong correlation with measures of stroke pathology (for example, infarct volumes) and agreement with other stroke scales,<sup>4</sup> and its use has demarcated effective and ineffective acute stroke therapies in trials with appropriately powered sample sizes.<sup>(40)</sup> The modified Rankin scale (mRS) is a measure of global disability that is commonly used as a functional outcome for stroke studies<sup>(9)</sup>. The mRS was designed to assess post stroke recovery levels.<sup>(41)</sup>

**Results And Observations**

186 patients who were diagnosed with acute ischemic stroke were assessed with NIHSS score, m RS and their RDW was estimated.

The maximum number of patients were in the category of 61-70 years. Mean age was 61.93 years. In this study, out of 186 patients, 90(48.4%) were males and 96 (51.6%) were females.

**Table 1- Age distribution of study population.**

Age	Number (Percentage)
≤40years	0

41-50years	15 (8.1%)
51-60 years	64 (34.4%)
61-70 years	84 (45.2%)
71-80 years	23 (12.4%)

**Table 2 - Gender distribution of the study population**

Sex	Number (Percentage)
Male	90 (48.4 %)
Female	96 (51.6 %)

Out of 186 patients, 22 (11.8%) had minor stroke, 64 (34.4%) had moderate stroke, 51 (27.4%) had moderate to severe stroke and 49 (26.3%) had severe stroke.

**Table 3- Severity of stroke using NIHSS in study population**

NIHSS severity score	Number (Percentage)
Minor stroke	22 (11.8 %)
Moderate stroke	64 (34.4 %)
Moderate to severe stroke	51 (27.4 %)
Severe stroke	49 (26.3 %)

**Table 4 – NIHSS Mean/ Median in the study population**

NIHSS	Value
Mean	16.73±8.9
Median	16 (11-21)

Mean score of NIHSS was 16.73.

According to MRS scale, the maximum number of patients were in the category of moderate disability with 30.6%.

**Table 5- Disability categorization based on MRS scoring system**

Modified Rankin Scale	Number (Percentage)
<b>No significant disability</b>	24 (12.9 %)
<b>Slight disability</b>	32 (17.2 %)
<b>Moderate disability</b>	57 (30.6 %)
<b>Moderately severe disability</b>	53 (28.5 %)
<b>Severe disability</b>	9 (4.8 %)
<b>Death</b>	11 (5.9 %)

The mean value of RDW in the study population was 15.59 and the median was 14.6.

**Table 6- Value of RDW (mean and median) of the study population**

RDW score	Value
<b>Mean</b>	15.59±3.7
<b>Median</b>	14.6 (12.4-18)

The mean value of RDW in category of minor stroke was 11.7, that of moderate stroke was 13.76, that of moderate to severe stroke was 15.63 and that of severe stroke was 19.66. There was significant correlation between severity of ischemic stroke and higher values of RDW (p<0.001).

**Table 7- Association of RDW with stroke severity**

	Stroke severity				P value
	Minor (N=22)	Moderate (N=64)	Moderate to Severe (N= 51)	Severe (N=59)	

Mean	11.7±0.81	13.76±1.89	15.63±2.45	19.66±3.63	< 0.001*
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There was significant correlation between the severity of stroke and the final outcome of patients, the p value being <0.001.

**Table 8- Association between the stroke severity using NIHSS and MRS outcome scale**

mRS outcome ->	Number (Percentage)						
	No disability	Slight disability	Moderate disability	Moderately severe disability	Severe disability	Death	
<b>Mild</b>	20(90.9)	2(9.1)	0	0	0	0	< 0.001*
<b>Moderate</b>	4(6.3)	28(43.8)	32(50)	0	0	0	
<b>Moderately severe</b>	0	2(3.9)	20(39.2)	26(51)	2(3.9)	1(2)	
<b>Severe</b>	0	0	5(10.2)	27(55.1)	7(14.3)	10(20.4)	

The mean RDW value for MRS category with no disability was 11.83, that of slight disability was 13.75, moderate disability was 14.7, that of moderate to severe disability was 16.98 and that of severe disability was 20.66. The mean RDW value of patients who expired was 22.83. Higher the stroke disability, higher was the RDW values which was statistically significant at p value < 0.001.

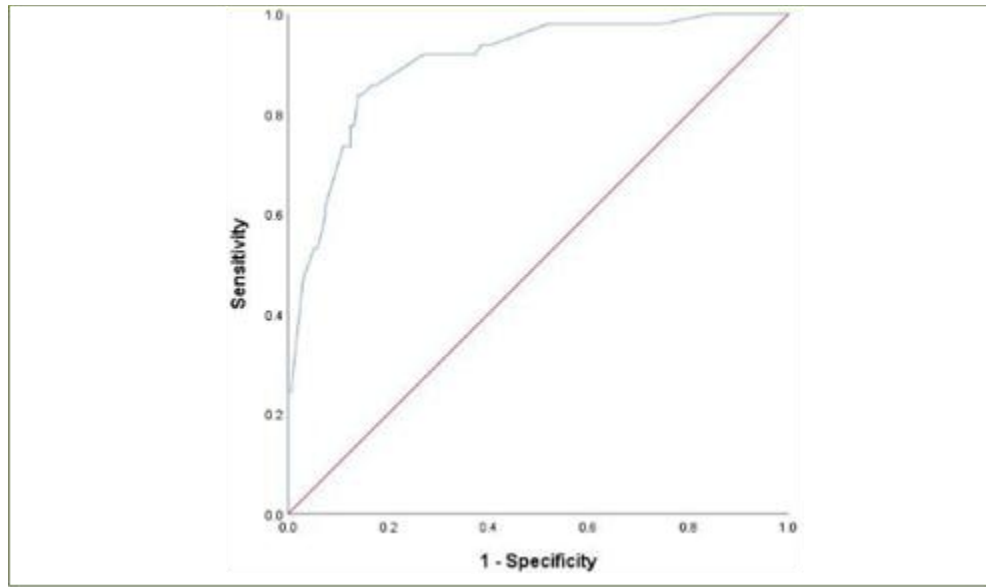
**Table 9- Association of RDW with mRS**

Variable	MRS						
	No disability (N=24)	Slight disability (N=32)	Moderate disability (N=57)	Moderately severe disability (N=53)	Severe disability (N=9)	Death (N=11)	
RDW score-%							

Mean	11.83±0.88	13.75±2.2	14.7±2.18	16.98±2.89	20.66±3.2	22.83±4.2	< 0.001*
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**Predicting Specificity And Sensitivity Of Rdw In Ischemic Stroke**

**Fig 1- ROC curve of RDW for predicting severe stroke**



The area under the receiver operating characteristic curve was 0.904 (95% confidence interval, 0.855– 0.953). Separation of stroke patients was optimal with RDW 16.3 (sensitivity 85.7%; specificity, 83.2%)

**Table 10- Area under the curve**

Area	P value	95% Confidence Interval	
		Lower Bound	Upper Bound
0.904	< 0.001*	0.855	0.953

**Table 11- Cut-off score of RDW for predicting severe stroke**

RDW	Sensitivity	Specificity
16.8	0.837	0.861

16.5	0.837	0.854
16.3	0.857	0.832

**Table 17- Association of RDW with mRS**

Variable	MRS						
	No disability (N=24)	Slight disability (N=32)	Moderate disability (N=57)	Moderately severe disability (N=53)	Severe disability (N=9)	Death (N=11)	
RDW score-%							
Mean	11.83±0.88	13.75±2.2	14.7±2.18	16.98±2.89	20.66±3.2	22.83±4.2	< 0.001*

**Table 18 - Area under the curve**

Area	P value	95% Confidence Interval	
		Lower Bound	Upper Bound
<b>0.904</b>	< 0.001*	0.855	0.953

**Table 19- Cut-off score of RDW for predicting severe stroke**

RDW	Sensitivity	Specificity
<b>16.8</b>	0.837	0.861
<b>16.5</b>	0.837	0.854
<b>16.3</b>	0.857	0.832



## Discussion

The study was conducted in 186 patients admitted with acute ischemic stroke admitted to Government Medical College, Kottayam. The objective was to determine the RDW values in patients admitted with acute ischemic stroke and to assess its correlation between severities of ischemic stroke using NIHSS.

The mean age of study was  $61.93 \pm 7.6$ . The number of males were 90 (48.4%) and number of females were 96 (51.6). More strokes occur in women than men, due to the longer lifespan of women compared to men.

In the present study, ischemic stroke patients were categorized according to NIHSS scale. 11.8 % of the study population had minor strokes, 34.4% of patients moderate strokes, 27.4% moderate to severe and 26.3% patients had severe strokes. RDW values were compared with severity and outcome of the ischemic stroke. Stroke severity was categorized according to the NIHSS scale and compared to the RDW values. The mean RDW in the minor stroke category was  $11.7 \pm 0.81$ ,  $13.76 \pm 1.89$  in the moderate stroke category,  $15.63 \pm 2.45$  in the moderate to severe category and  $19.66 \pm 3.63$  in the severe category of stroke.

Comparison of RDW and severity of ischemic stroke as per NIHSS criteria in the current study showed the p value for the relationship between RDW and severity of ischemic stroke was  $< 0.001$  which is highly significant. In the current study, p value between MRS and NIHSS, that is the severity of stroke and the outcome was  $< 0.001$  which is highly significant. This shows that lower mRS is associated with lower NIHSS scores and higher mRS score with higher NIHSS score and a poor prognosis. In acute ischemic stroke as indicated by higher scores of NIHSS and mRS and higher levels of RDW are associated with poor outcome. In a study by Bhaskar *et al*, moderate positive correlation was observed between NIHSS score at admission and mRS scores at 90 days ( $r = 0.47$ ;  $P < 0.001$ ). Severe (OR = 16,

95% CI = [7.6, 35],  $P \leq 0.0001$ ) and moderate (OR = 4.8; 95% CI = [2.13, 10.7];  $P \leq 0.0001$ ) strokes were significantly associated with 90 day mortality.<sup>(45)</sup>

The area under the receiver operating characteristic curve was 0.760 (95% confidence interval, 0.855–0.953). Separation of stroke patients was optimal with RDW 16.3 (sensitivity 85.7%; specificity, 83.2%)

Kara *et al*. compared the RDW values in acute ischemic stroke patients in clusters with different severity scores and found RDW to be a predictive measure of stroke severity. The authors also reported a significant correlation between RDW and other parameters, such as NIHSS and Glasgow coma score (GCS), and found RDW with a cutoff point of 14.<sup>(46)</sup>

A significant association has also been reported between NIHSS score and RDW value on ED admission by Gianni Turcato *et al*. who reported that both the values of RDW (14.0% versus 13.6%;  $p < 0.001$ ) and the NIHSS score (12 versus 4;  $p < 0.001$ ) at admission, were found to be significantly increased in patients of acute ischemic stroke with unfavorable outcome compared to those with favorable outcomes. Turcato *et al*. studied 316 ischemic stroke patients undergoing thrombolytic therapy, and observed an over 6-fold higher mortality and 1.8-fold lower stroke recovery in patients with RDW values above the local cut-off.<sup>(24)</sup>

In summary, the present study showed that RDW, a widely used and inexpensive test, is potentially an important parameter for prediction of stroke severity and may predict prognosis. We used NIHSS to determine stroke severity and observed that increased stroke severity was associated with higher RDW. Therefore, RDW may be considered a strong predictor for stroke severity.

## Conclusions

1. Patients with acute ischemic stroke had a higher value of RDW.

2. RDW has statistically significant correlation with the severity of acute ischemic stroke.
3. RDW value has statistical significance in predicting the outcome of ischemic stroke according to mRS.

### Limitations

The fluctuations in RDW and variations in RDW with time could not be considered as the RDW was measured only once (during admission).

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