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Original Research Paper

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PROGNOSTIC SIGNIFICANCE OF RED CELL DISTRIBUTION WIDTH (RDW) IN STROKE PATIENTS

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ABSTRACT

AIM: To study the prognostic significance of RDW in stroke, comparing it in both ischemic and hemorrhagic stroke.

Materials and methods: Prospective observational study. All patients of Cerebrovascular accidents aged >18 years were included. Exclusion Criteria are Iimmunological disorder, Underlying Malignancy, Pregnancy, or Anemia. CBC, RDW, KFT, PT/INR, aPTT, CRP, ESR, CT scan head was done for each patient.GCS, NIHSS and MRS scores were used which were repeated, along with RDW on D3, D5, D7 to assess the prognosis. The study enrolled 180 patients out which 18 patients were excluded owing to exclusion criteria, out of which 70 patients expired and 92 patients survived. Data so obtained was fed into computer using Microsoft Excel 2013 software and was subjected to statistical analysis.

RESULTS: Mean day 1, day 3, day 5 and day 7 red cell distribution width was 15.61±1.56, 15.22±1.41, 14.87±1.23 and 14.55±1.09% respectively. At all the follow-up intervals, mean RDW values were significantly lower as compared to corresponding baseline (Day 1) values ($p<0.001$).

DISCUSSION: On comparison of RDW values in ischemic and hemorrhagic stroke patients, we found a statistically significant difference on day 1 only when mean values were significantly lower in hemorrhagic as compared to ischemic stroke patients. Rrelatively lower mean RDW values in hemorrhagic as compared to ischemic stroke indicated a possible independent role of both the factors in determination of mortality.

CONCLUSION: RDW can be used as a prognostic marker in patients of stroke, while it held higher value in hemorrhagic stroke patients than ischemic stroke.

KEYWORDS : ischemic stroke, hemorrhagic stroke, red cell distribution width

INTRODUCTION

Stroke is a major global health hazard and is recognized as the second leading cause of death and third major cause of disability globally[1,2].In terms of mortality, it is next only to heart disease. As per reports of American Heart Association (AHA), stroke can be attributed as the cause of death in 11.8% of total global deaths[3] . Each year stroke causes nearly 5.5 million deaths and 116.4 million Disability-Adjusted-Life Years (DALYs)[4] . This trend is largely attributable to an increase in stroke incidence and prevalence as well as stroke-related deaths and disability in low and middle-income countries, reflecting suboptimal preventive strategies[5,6] . Additionally, cerebrovascular disease is the leading cause of disability in adults and each year millions of stroke survivors have to adapt to a life with restrictions in activities of daily living as a consequence of cerebrovascular disease[7]. In India too, Stroke is recognized as one of the leading causes of death and disability. As per a report published in the year 2017, the cumulative incidence of stroke ranged from 105 to 152/100,000 persons per year, and the crude prevalence of stroke ranged from 44.29 to 559/100,000 persons in different parts of the country during the past decade. These values were higher than those of high-income countries[9] . These rates, age standardized to world standard Aims and Objectives 2 population, are similar to or higher than many Western nations[10]. These rates are also much higher than those reported previously from other parts of India[11,12].

Stroke is defined as a clinical syndrome characterized by "rapidly developing clinical symptoms and/or signs; focal and at times global loss of brain function, with symptoms lasting >24 hours or leading to earlier death, and with no apparent cause other than that of vascular origin"[17] . As per estimates from Indian studies, nearly 30-45% of stroke patients remain fully or partially dependent on their caregivers during the first one-year and as many as 7-15.7% remain completely disabled[21]. Speech dysfunction, seizures, depression and cognitive impairment are some of the commonly encountered post-stroke complications[21].

This vascular rupture is accompanied with severe blood loss which is associated with premature release of immature cells into the blood loss as a result of conditions conducive to change the shape of red blood cells vis-à-vis a change in red blood cell distribution width (RDW)[22,23]. Apart from these sophisticated tests and evaluations, some simple evaluations based on assessment of blood counts such as Red cell distribution width (RDW) and platelet volume have traditionally been considered useful in the differential diagnosis of anemia and other coagulation disorders. RDW, which is routinely reported in complete blood counts as a statistical concept, is a measure of the variation in red blood cell volume. Red cell distribution width is a simple statistical assessment of hematological investigations that are carried out as routine assessment and does not have any additional cost burden[24].

RDW has also been seen to be associated with cryptogenic stroke[25]. The findings of these studies are encouraging and show a possible role of RDW as a prognostic factor in stroke, however, owing to geographical and ethnic differences and difference in nature of outcome events, it has yet to be accepted as a universally accepted prognostic indicator in stroke requiring more evidence to be built from different parts of the world. Unfortunately, most of the previous work on this issue is from western countries and there is lack of evidence

from Asian countries, particularly India. Hence, the present study was planned to evaluate the prognostic significance of red blood cell distribution width (RDW) in stroke patients at a tertiary care centre in North India.

METHODS

STUDY DESIGN: Prospective observational study conducted in SRN Hospital, MLN Medical College, Prayagraj, U.P. India.

STUDY POPULATION:

All patients (both male and female) presenting with Cerebrovascular accidents by suggestive symptoms and confirmed by physical examination and radiological imaging, were selected randomly from medicine emergency IPD of SRN Hospital, MLN Medical College, Prayagraj, Uttar Pradesh , India from January 2019 to March 2020.

INCLUSION CRITERIA:

All patients of Cerebrovascular accidents aged >18 years.

EXCLUSION CRITERIA:

Patients with history of immunological disorder, Underlying Malignancy, Pregnancy, Anemic patients (hemoglobin <11gm/dl)or current use of Iron, folic acid, or vitamin B12 supplements.

162 patients were chosen for the study. After obtaining informed and written consent and fulfilling inclusion and exclusion criteria, demographic characteristics, and other details of the diagnosis of stroke were ascertained. A venous sample was drawn and sent for following investigations- CBC, RDW, KFT, PT/INR, aPTT, CRP and ESR. CT scan head was obtained to assess the nature, size and pattern of stroke. RDW value at the day of admission was correlated with the CT finding in patients with ischemic and haemorrhagic stroke.

Stroke severity was calculated using National Institute of Health Stroke Scale (NIHSS).

The severity of stroke was judged using the following criteria:

Score 1-4	Mild
Score 5-20	Moderate
Score 21-42	Sever

Glasgow coma scale (GCS) and Modified Rankin Scale (mRS) for Neurologic disability were also used to assess the level of consciousness and neurological disability in patients.

All the patients were followed up to day 7 with repeat measures of RDW, NIHSS, GCS and mRS on day 3, 5 and 7. Outcome till-day 7 was noted. In order to assess the pattern of change in RDW and severity of score, a select number of surviving patients (n=38) were again followed up at day 30 with repeat measurement of RDW, NIHSS, GCS and mRS.Data so obtained was fed into computer using Microsoft Excel 2013 software and was subjected to statistical analysis.

RESULTS

The present study enrolled a total of 180 stroke patients. 18 patients were excluded owing to exclusion criteria. Twelve patients were anaemic out of which eight were newly diagnosed anemics and four were on medications for anaemia- iron folic acid, vitamin B12) and three patients had carcinoma- (carcinoma of prostate gland, carcinoma of colon, and the third patient had chronic myeloid leukemia). Three more patients were excluded on the grounds of having an immunological disorder (one patient was a known case of SLE, one patient had rheumatoid arthritis and one patient was a newly diagnosed case of gout). A total of 162 patients who satisfied the inclusion criteria were further included.

Table 1: Baseline Profile of stroke patients enrolled in the study (n=162)

SN	Characteristic	No.	%
1.	Age		
	≤30 Years	3	1.9
	31-40 Years	6	3.7
	41-50 Years	25	15.4
	51-60 Years	33	20.4
	61-70 Years	55	34.0
	71-80 Years	26	16.0
	>80 Years	14	8.6
	Mean Age±SD (Range) in years	63.0±13.6 (22-95)	
2.	Sex		
	Male	88	54.3
	Female	74	44.7
3.	Type		
	Hemorrhagic	60	37.0
	Ischemic	102	63.0
4.	Hematoma size (n=60)		
	<30 cc	29	48.3
	>30 cc	31	51.7
5.	Infarct Pattern/Location (n=102)		
	ACA	11	10.8
	ACA+MCA	3	2.9
	Lacunar	27	26.5
	MCA	47	46.1
	MCA+PCA	2	2.0
	PCA	12	11.8
6.	Laterality		
	Unilateral	133	82.1
	Bilateral	29	17.9
7.	Diabetics (HbA_{1c}>6.5%)	57	35.2
8.	Hypertensives	92	56.8%

Table 2: Distribution of cases according to Severity of Stroke (NIHSS), GCS, mRS

SN	Severity	NIHSS Score range	No.	%
1.	Mild	<5 (1-4)	-	-
2.	Moderate	5-20	48	29.6
3.	Severe	>20 (21-42)	114	70.4
Mean NIHSS ±SD (Range)			25.52±6.98 (11-39)	
Mean GCS ±SD (Range)			9.16±1.86 (3-13)	
Mean mRS±SD (Range)			4.17±0.80 (2-5)	

At admission, majority (70.4%) of patients had NIHSS scores >20, thus indicating the severity of stroke as severe while remaining 48 (29.6%) had scores in 5-20 range, indicating the severity as moderate. None of the patients had scores <5 (mild stroke).

NIHSS scores ranged from 11 to 39 with a mean of 25.52±6.98. GCS scores ranged from 3 to 13 with a mean of 9.16±1.86 while mRS scores ranged from 2 to 5 with a mean of 4.17±0.80.

Table 3: Clinical Course of RDW, NIHSS, mRS and GCS

Time interval	Number of Cases	Corresponding baseline value*		Follow-up value		Statistical significance (Paired 't'-test)	
		Mean	SD	Mean	SD	't'	'p'
Red Cell Distribution Width (RDW)							
Day 1	162	15.61	1.56			-	-
Day 3	151	15.52	1.42	15.22	1.41	4.03	<0.001
Day 5	124	15.42	1.51	14.87	1.23	6.28	<0.001
Day 7	96	15.27	1.35	14.55	1.09	6.86	<0.001
NIHSS							
Day 1	162	29.78	6.02	-	-	-	-
Day 3	151	24.75	6.56	24.81	7.09	0.51	0.611
Day 5	124	23.54	5.88	23.42	7.05	0.59	0.555
Day 7	96	21.84	4.57	21.07	7.21	4.84	<0.001

GCS							
Day 1	162	9.16	1.86	-	-	-	-
Day 3	151	9.33	1.78	9.39	2.20	-0.68	0.501
Day 5	124	9.62	1.61	9.94	2.29	-2.55	0.012
Day 7	92	9.95	1.44	10.89	1.61	-9.19	<0.001
mRS							
Day 1	162	4.17	0.80	-	-	-	-
Day 3	151	4.11	0.80	4.03	0.86	2.61	0.010
Day 5	124	4.02	0.75	3.85	0.83	4.32	<0.001
Day 7	95	3.84	0.66	3.54	0.73	5.87	<0.001

*Corresponding baseline values imply mean day 1 values of the surviving patients

Mean day 1, day 3, day 5 and day 7 red cell distribution width was 15.61±1.56, 15.22±1.41, 14.87±1.23 and 14.55±1.09% respectively. At all the follow-up intervals, mean RDW values were significantly lower as compared to corresponding baseline (Day 1) values ($p<0.001$) (Table 3).

Table 4: Distribution of cases according to outcome

SN	Characteristic	No.	%
1.	Outcome in terms of death		
	Yes (Non-Survivors)	70	43.2
	No (Survivors)	92	56.8
2.	Outcome in terms of duration of hospital stay (days)		
	Mean±SD (Range)	7.07±3.14 (1-18)	
	Median	7	

A total of 70 (43.2%) patients died during the observation period (Table 4; Fig. 5.1).Duration of hospital stay ranged from 1 to 18 days with a mean of 7.07±3.14 days. Median duration of hospital stay was 7 days (Table 4; Fig. 5.2).

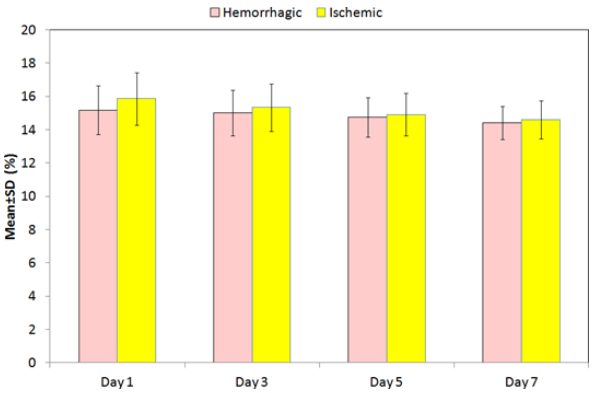

Fig. Comparison of RDW profile at different intervals between Hemorrhagic and Ischemic Stroke patients

Table 5: Comparison of predictive value of Baseline RDW at pre-determined cut-off value (For Mortality as outcome)

Baseline RDW	Outcome		Total
	Expired	Survived	
≥14.5	63 (TP)	61 (FP)	124
<14.5	7 (FN)	31 (TN)	38
Total	70	92	162

Sensitivity	Specificity	PPV	NPV	Accuracy
TP / Total Expired	TN / Total Survived	TP / TP+FP	TN/ FN+TN	TP+TN/ Grand Total
63/70	31/92	63/124	31/38	94/162
90%	33.7%	50.8%	81.6%	58.0%

On evaluating the predictive efficacy of pre-determined laboratory value of RDW at a cut-off >14.5% for prediction of mortality in study population, there were 63 true positive, 61 false positive, 7 false negative and 31 true negative cases. Correspondingly, the sensitivity, specificity, positive predictive, negative predictive and accuracy values were 90%, 33.7%, 50.8%, 81.6% and 58% respectively (Table 5).

On overall evaluation, statistically significant differences in mean RDW of those with hospital stay >7 days and <7 days were seen for day 3 and day 5 evaluations only. At both these intervals, mean value was significantly lower in patients with longer stay (>7 days) as compared to those with shorter stay (<7 days). At day 1 and day 7, though mean value was lower in patients with prolonged stay as compared to those with shorter stay yet this difference was not significant statistically ($p>0.05$).

Among non-survivors, no significant difference in mean RDW of those with prolonged and shorter stay at any of the observation periods

DISCUSSION

Physiological changes in various parameters such as blood pressure, body temperature, blood glucose, and blood oxygen saturation take place following stroke70. Incidentally, these physiological changes have an impact on hematological parameters, especially, Red Blood Cell Distribution Width (RDW) too. A number of previously conducted studies have shown that RDW values of stroke patients are elevated as compared to controls. This study have also indicated that RDW also correlates with the severity of stroke and can also play a role in differentiation of types of stroke and their outcome prediction. Most of the evidence in this connection stems from western countries and there are only few studies from Indian subcontinent addressing this correlation. Hence, the present study was planned to assess the prognostic significance of red blood cell distribution width in stroke patients at a tertiary care centre in North India. In this study, a total of 162 stroke patients (60 hemorrhagic, 102 ischemic) were enrolled in the study. At admission, red distribution width values ranged from 12 to 21.4% with a mean of 15.60±1.56%. Mean RDW in stroke patients have been recorded in 14.48% to 15.12% range in different studies.

In the present study, majority (70.4%) of patients had severe stroke while remaining 48 (29.6%) had moderate stroke. Mean RDW values of moderate and severe grade patients were 14.64±1.39 and 16.01±1.45% respectively, thus showing a significant association between RDW and severity of stroke. In present study, a total of 70 (43.2%) patients died upto 7 days of hospital stay. We did not make such a distinction, and as such hemoglobin levels of none of the patients were <11.1g/dl, thus showing that anemia as such was not a problem in our study, despite this the mortality rate in present study was higher, which could be owing to a dominance of severe grade stroke patients in our study.

In present study, there were 60 (37.0%) patients of hemorrhagic stroke and 102 (63.0%) patients of ischaemic stroke. As such hemorrhagic stroke is associated with a higher mortality rate as compared to ischaemic stroke71 . In the present study we also found mortality rate to be significantly higher in hemorrhagic stroke (65%) as compared to ischemic stroke (30.4%). A higher proportion of hemorrhagic stroke patients in a series could thus affect the mortality rate too as observed in the present study. In the present study, among other factors hypertension, lower mean GCS and higher mRS and NIHSS were also associated with mortality. As such GCS, mRS and NIHSS are the predictors of severity of stroke and related disability and their association with mortality is undisputed and well-explained.

In present study, the sequential assessment of RDW values showed a variable picture for ischemic and hemorrhagic stroke patients. On comparison of RDW values in ischemic and hemorrhagic stroke patients, we found a statistically

significant difference on day 1 only when mean values were significantly lower in hemorrhagic as compared to ischemic stroke patients. Interestingly, while both hemorrhagic stroke and RDW emerged as significant predictors of mortality, relatively lower mean RDW values in hemorrhagic as compared to ischemic stroke indicated a possible independent role of both the factors in determination of mortality.

The differences in trends of RDW in ischemic and hemorrhagic stroke patients had an impact on the outcome too, we found that in ischemic stroke patients, mean Day 1, 3 and 5 RDW levels of survivors were significantly lower as compared to that of non-survivors, however, day 7 RDW levels of survivors and Review of Literature 81 non-survivors did not show a significant difference whereas in hemorrhagic stroke patients, mean RDW levels of survivors were significantly lower as compared to that of non-survivors on all the assessment times (Day 1, 3, 5 and 7). However, these differences in their predictive ability were for sequential assessments only. As such in present study, baseline higher RDW was significantly associated with mortality in both ischemic as well as hemorrhagic strokes. In fact, ours is the first study evaluating role of sequential assessments in outcome prediction. Moreover, the separate role of RDW in ischemic and hemorrhagic stroke types has also not been assessed extensively. In present study, we assessed the prognostic value of RDW in terms of mortality for a fixed cut-off of >14.5% and a study-specific cut-off value derived through receiver-operator characteristic curve analysis. The predictive value of RDW at a pre-determined cut-off of >14.5% for in-hospital mortality in terms of sensitivity, specificity, positive predictive value and negative predictive value was found to be 90%, 33.7%, 50.8% and 81.6% respectively. This cut-off had an accuracy of only 58%. On the other hand, the study-specific derived cut-off value was much higher at >15.85% and had a sensitivity, specificity, positive predictive value and negative predictive value of 67.1%, 64.1%, 58.8% and 72% only. Thus compared to pre-determined cut-off value, the specificity was much higher (33.7% vs 64.1%) but at the cost of loss of sensitivity (60% vs 67.1%). In both the scenarios, RDW seemed to have a limited prognostic efficacy for prediction of mortality. The findings of present study were interesting, provided some useful information, and indicated a possible role of RDW as a prognostic marker for mortality, but also indicated that the mortality in stroke patient is dependent on a multiple factors and RDW has a limited independent role. Further studies on a larger sample size with longer duration of follow-up to include more outcome Review of Literature 83 measures and a multivariate analysis plan might help in understanding the prognostic role of RDW in stroke in a better way.

CONCLUSION

Mortality rate was significantly higher in hemorrhagic (39/60; 65.0%) as compared to ischemic stroke (31/102; 30.4%). Hypertension, lower mean GCS and higher mRS and NIHSS were associated with mortality.Among ischemic stroke patients, MCA involvement was significantly associated with an increased mortality. On comparing the mean RDW values at day 1, day 3, day 5 and day 7 between non-survivors and survivors, RDW values were significantly higher in non-survivors as compared to that in survivors. Statistically significant differences in RDW levels of ischemic and hemorrhagic stroke patients were observed on day 1 only.

On assessment in ischemic stroke patients, mean Day 1, 3 and 5 RDW levels of survivors were significantly lower as compared to that of non-survivors, however, day 7 RDW levels of survivors and non-survivors did not show a significant difference. On assessment of hemorrhagic stroke patients, mean RDW levels of survivors were significantly lower as compared to that of non-survivors on all the assessment times (Day 1, 3, 5 and 7).

Duration of hospital stay >7 days was significantly associated with ischemic stroke, higher mean GCS and lower mean mRS and NIHSS values. Day 1 RDW values did not show a significant association with duration of hospital stay on overall analysis. However, mean RDW values of survivors having hospital stay >7 days were significantly higher as compared to their counterparts having hospital stay $\leq$7 days. On evaluating the correlation of different study parameters with RDW, we could found significant correlation of day 1 RDW with Triglyeride, GCS, mRS and NIHSS only. The correlation of TG and RDW was weak positive and significant. Correlation of RDW with GCS was mild negative and significant whereas correlation of RDW with mRS and NIHSS was mild positive and significant.

Correlation of RDW with different severity scores (GCS, mRS and NIHSS) at different time intervals was significant statistically at all the time intervals. RDW showed a mild negative and significant correlation with GCS at day 1, day 5 and day 7 whereas with mRS and NIHSS, there was a mild positive and significant correlation on all the occasions.

At all the time intervals (day 1, 3, 5 and 7), mean RDW of those with moderate stroke was significantly lower as compared to that of patients with severe stroke.

RDW could be a useful parameter in stroke patients. It was well correlated with the severity and type of stroke and also showed a significant association with outcome. As far as prognostic values of RDW were concerned, they seemed to hold more value in hemorrhagic stroke patients as compared to ischemic stroke patients in present study. Further studies to corroborate the findings of present study are recommended.

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