ISSN 2250-3153

Relevance of Red Cell Distribution Width (RDW) Determination in Stroke: A Case Control Study

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Abstract- BACKGROUND: Stroke is an important cause of disability and death. Recently several studies have claimed that RDW is a good predictor of outcome in stroke. As RDW is a complete blood count (CBC) parameter that is routinely determined in clinical laboratories, these studies important implications in patient management in developing countries. The present study was taken up to find out if RDW can be used as an inexpensive biomarker for stroke. MATERIALS AND METHODS: A case-control study involving 52 test subjects and 54 matched controls was conducted. RDW values were determined in test and control groups, compared and statistically analysed. RESULTS & CONCLUSIONS: Significantly higher mean values for RDW ($p < 0.001$) are observed in stroke patients compared to reference population. RDW values higher than 13.0 are associated with several fold increase in the risk of stroke (odds ratio 4.1; p value <0.006); but, the level of RDW does not show a linear relationship with the severity of stroke. So, RDW values can predict the occurrence of stroke but not its severity.

Index Terms- RDW, Stroke, Biomarker, case control study, predictor of outcome.

I. Introduction

Stroke or the cerebrovascular accident affects well over 20 million people every year globally and kills close to 6 million of them (Dalal, Malik et al. 2008). It is the second most important cause of mortality(Strong, Mathers et al. 2007). Besides, it also causes significant disability with nearly 20% of the survivors requiring institutionalised care(Steinwachs, Collins-Nakai et al. 2000). Due to the limited availability of reliable data on stroke related mortality and morbidity, the situation in India is not entirely clear. But the gravity of the problem can be understood from the ICMR report (2004) which claims that stroke accounts for 41% of deaths and 72% of disability adjusted life years (DALY) among non-communicable diseases(ICMR 2004). The age adjusted annual incidence rate for stroke is 124/100000 in Rural India(Bhattacharya, Saha et al. 2005) and 145 in Urban India(Das, Banerjee et al. 2007).

The neurological impairment associated with stroke is usually assessed by NIH stroke scale (NIHSS) (Brott, Adams et al. 1989, Matt B. Jensen and Patrick Lyden 2006) and the outcome is predicted by using Barthel index, Rankin Scale or Glasgow Outcome Scale (Adams, Davis et al. 1999). Recently, several studies have claimed that red cell distribution width (RDW) is a good independent predictor of outcome in stroke (Ani and Ovbiagele 2009, Kim, Kim et al. 2012, Ramírez-Moreno, Gonzalez-Gomez et al. 2013), having a statistically significant correlation with the NIHSS scores and grading. If these claims are true, then RDW will be a simple inexpensive biomarker for the assessment of the severity of stroke, since RDW is a routine haematological parameter detected easily by most modern automated counters. This will be particularly beneficial for patients of the third world countries, who cannot afford expensive investigations. However, this claim has been disputed by some investigators, who failed to find similar association(Ntaios, Gurer et al. 2012). The present study was taken up to find out if RDW can be used as an independent prognostic biomarker in stroke.

II. Materials and Methods

A case control study was conducted involving 52 study subjects and 54 age and sex matched controls. All the participants were 16 years of age or above, of either sex and were admitted in the medical and the neurology wards of Chettinad Hospitals and Research Institute, Kelambakkam, Tamilnadu, India. All the study subjects had confirmed stroke, with or without co-morbid conditions like hypertension, diabetes, cardiac or renal disease. The control subjects had no history or evidence of cerebrovascular disease.

In the study subjects, the severity of stroke was scored according to NIH stroke scale and was graded into mild, moderate and severe categories (Adams, Davis et al. 1999). From all the subjects, venous blood was collected in K_2EDTA vacutainers for haemoglobin and RDW (CV) estimations using Coulter LH 780 automated haematology analyser.

The statistical analysis was done using SPSS version 21. RDW was used as continuous variable and in quartiles. The participants were also categorised into two groups based on RDW values of ≤ 12.9 and ≥ 13.0 respectively and the odds ratio were determined. For comparing the results in study subjects and the controls, and for assessing the relationship between RDW and the co-morbidities, independent samples t-test was performed. One way ANOVA was performed to find out the relationship between RDW and the severity of the stroke. A 'p' value of 0.05 or less was taken as significant.

III. Results

Summary statistics is given in table 1.

Table 1. Summary statistics							
		Group				Mann Whitny U Test	
		Test (n = 52)		Control (n =54)			
		Count	%	Count	%	Z	p value
Sex	Male	35	67.31	36	66.67	-.070	0.944
	Female	17	32.69	18	33.33		
Smoking	Yes	7	13.46	2	3.70	-1.793	0.073
	No	45	86.54	52	96.30		
Alcoholism	Yes	8	15.38	4	7.41	-1.290	0.197
	No	44	84.62	50	92.59		
Diabetes Mellitus	Yes	22	42.31	26	48.15	-.601	0.548
	No	30	57.69	28	51.85		
Hypertension	Yes	21	40.38	18	33.33	-.749	0.454
	No	31	59.62	36	66.67		
Previous CVA*	Yes	6	11.54	0	.00	--	--
	No	46	88.46	0	.00		
CAD**	Yes	5	9.62	5	9.26	-.062	.950
	No	47	90.38	49	90.74		
Anemia	Yes	24	46.15	34	62.96	-1.730	.084
	No	28	53.85	20	37.04		

*CVA=cerebrovascular accident; **CAD=Coronary artery disease

The present case control study was carried out on 52 test subjects and 54 age and sex matched controls. The test group consisted of 35 men and 17 women; and the control group had 36 men and 18 women. The average age of the test group was 60.29 years while the control group averaged 59.74 years. Apart from the absence of past history of cerebrovascular accident in the control group, there were no other significant differences between the groups with regard to co-morbidities. The categories based on severity of stroke are given in table 2.

Majority of the study subjects were having strokes of mild (38.46%) or moderate severity (57.69%). Only two subjects had severe degree of stroke.

Table 2. Grades of Stroke		
	Count	%
Mild	20	38.46
Moderate	30	57.69
Severe	2	3.85

The mean values for RDW along with standard deviation, and the results of independent t-tests in the test and the control groups are given in table 3. RDW values ranged from 11.3 to 24.5 in the test group, and from 11.9 to 16.1 in the control group. Mean for RDW in the test group was 15.12 ±2.87 and in the control group, 13.27±0.79. The difference between the groups was statistically highly significant (p =<0.001) (table 3).

Table 3.								
	Group						Independent Samples t-test	
	Test (n = 52)			Control (n = 54)				
	Range	Mean	SD	Range	Mean	SD	t-value	p value
Age	16 – 85	60.29	15.27	17 – 89	59.74	14.91	0.187	0.852
Hb (g/dl)	6.2 – 18.7	12.71	2.84	9.1 – 18.7	12.58	1.64	0.291	0.771
RDW (%)	11.3 – 24.5	**15.12**	2.87	11.9 – 16.1	**13.27**	0.79	4.485	**<0.001**

Table 4. RDW and severity of stroke											
	Mild (n =20)			Moderate (n = 30)			Severe (n = 2)			One way ANOVA	
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	F	p value
RDW	14.20	2.57	11.3-24.5	15.76	2.95	12.3-22.0	14.75	3.32	12.4-17.1	1.87	0.165
	t value = 1.926; p value = 0.06										

Mean values for RDW varied with the severity of stroke (table 4). In mild form of stroke, the mean value for RDW was 14.2±2.57 and in stroke of moderate severity, it was 15.76±2.95. However, the difference was not statistically significant (p value = 0.06). In severe form of stroke, the value was lower than the mean value in stroke of moderate severity. But the number of cases were very few. When all the participants were categorised into two groups based on RDW values of ≤12.9 and ≥ 13.0 respectively, it was found that the participants in the group with RDW values ≥13.0 were several times more likely to have a stroke than the other group(odds ratio= 4.16; p value 0.006) (table 5).

Table 5. RDW categories and Stroke

Group		RDW Categories		Total
		>= 13.0	**<= 12.9**	
Test	Count	46_a	6_b	52
	Row %	88.46	11.54	100.00
Control	Count	35_a	19_b	54
	Row %	64.81	35.19	100.00
Total	Count	81	25	106
	Row %	76.42	23.58	100.00
Chi Square Value: 8.219; **p value: 0.0041454**				
Odds Ratio: 4.1619048; p Value: 0.0060276				
95% CI for Odds ratio: (1.5042339, 11.5151315)				

The co-morbidities did not affect RDW significantly (table 6).

Table 6. RDW and co-morbidities

		RDW		t value	p Value
		Mean	SD		
Gender	male	14.02	2.19	-1.027	0.307
	female	14.50	2.42		
Smoking	yes	14.68	1.21	.685	0.495
	no	14.13	2.34		
Alcoholism	yes	14.52	2.30	.543	0.588
	no	14.14	2.28		
Diabetes Mellitus	yes	13.75	1.56	-1.811	0.073
	no	14.54	2.69		
hypertension	yes	14.02	2.05		0.577
	no	14.27	2.40		
Previous CVA*	yes	15.23	3.32	.099	0.921
	no	15.11	2.84		
CAD**	yes	14.87	2.67	1.009	0.315
	no	14.11	2.23		
Anaemia	yes	14.36	2.66	.906	0.367
	no	13.96	1.68		

*CVA=cerebrovascular accident; **CAD=Coronary artery disease

IV. Discussion

Worldwide, stroke is an important cause of permanent disability and death. In India alone, more than 1.5 million new cases are recorded each year with 28-day mortality of 29.8% (Pandian and Sudhan 2013, Taylor and Suresh Kumar 2012). Besides, it is responsible for 6,398,000 disability adjusted life years. The extent of disability and the occurrence of mortality following a stroke are dependent on the severity of stroke. At present, the severity of the stroke is assessed by NIH stroke scale (NIHSS), which has been shown to be a reliable predictor of outcome (Adams, Davis et al. 1999, Matt B. Jensen and Patrick Lyden 2006). Recently, several studies have tried to find a simpler alternative to NIHSS. Some of these studies have focussed on RDW, as it has already been shown to be a prognostic biomarker in a variety of serious human ailments including cardiovascular disease (Chen, Sung et al. 2010, Aung, Dworakowski et al. 2013, Olivares Jara, Santas Olmeda et al. 2013, Yao, Sun et al. 2014), pulmonary ailments (Grant, Kudalkar et al. 2003, Nathan, Reffett et al. 2013) and diabetes(Malandrino, Wu et al. 2012). Another attractive feature about RDW is that it is a routine parameter that is inexpensively determined along with complete blood count by automated haematology counters. Ani and Ovbiagele (2009) in an analysis of data collected from 480 individuals over a period of six years from 1988 to 1994 concluded that elevated RDW was associated with the occurrence of stroke and it strongly predicted all-cause mortality in persons afflicted with stroke. They also found out that those subjects who had RDW values higher than 13.9% had

two fold increased risk of death compared to the reference group(Ani and Ovbiagele 2009). Ramírez-Moreno and others (2013) in a case control study involving 224 stroke patients and an equal number of matched controls found that RDW was a powerful predictor of stroke. In addition, they observed that higher values of RDW was associated with increased risk of stroke suggesting a level response gradient(Ramírez-Moreno, Gonzalez-Gomez et al. 2013).

The present study is a case-control study involving 52 stroke patients and 54 age and sex matched controls. We found that the mean RDW values in the test subjects were significantly higher than the mean values in the control group ($p < 0.001$). We also noted that RDW values higher than 13.0 increased the risk of stroke several folds (odds ratio 4.1; p value 0.006). Although there was difference in the mean values of RDW between mild and moderately severe forms of stroke, it was not statistically significant. From our observations, it appears that severity of stroke does not show a linear relationship with RDW values. So, higher RDW values, while increasing the risk of stroke, may not be associated with more severe forms of stroke. This is in agreement with the observations of Ntaios and others (2012), who after analysing the data from 1504 patients, concluded that RDW did not predict severity or functional outcome(Ntaios, Gurer et al. 2012).

In conclusion, the following observations can be made: significantly higher mean values for RDW ($p < 0.001$) are observed in stroke patients compared to reference population; RDW values higher than 13.0 are associated with several fold increase in the risk of stroke (odds ratio 4.1; p value <0.006); but, the level of RDW does not show a linear relationship with severity of stroke. So, RDW values can predict the occurrence of stroke but not its severity.

ACKNOWLEDGEMENT

Authors acknowledge the Indian Council for Medical Research for partial funding and the management of CHRI for providing the necessary facilities

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