Section: Neurology

Original Research Article

PROGNOSTIC SIGNIFICANCE OF RED CELL DISTRIBUTION WIDTH AND NEUTROPHIL-TO-LYMPHOCYTE RATIO IN ACUTE ISCHEMIC STROKE

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ABSTRACT

Background: Stroke is the second leading cause of death worldwide. Inflammatory response plays an important role in pathophysiology of acute ischemic stroke (AIS) as ischemic brain induces the release of various inflammatory markers. Both Red blood cell distribution width(RDW) and Neutrophil-to-Lymphocyte Ratio(NLR) are inexpensive measures that are routinely available in clinical laboratories. According to previous studies, RDW and NLR have role in predicting severity of stroke which may have implications in patient management in developing countries like India. Our study was done to find out the role of RDW and NLR as prognostic biomarkers for stroke. **Objectives:** To evaluate the association between RDW and NLR with Modified Rankin Scale (MRS), Glasgow Coma Scale (GCS) and National Institute of Health Stroke Scale (NIHSS) scores in patients with acute ischemic stroke. **Design, Materials and Methods:** This is a Prospective observational study including 50 patients of AIS of ≥18 years age admitted within 48 hours of symptom onset in the Department of Neurology, GMC Machilipatnam. On admission, NIHSS and GCS scores were calculated and testing for RDW and NLR was done. MRS scoring was done at the time of discharge or death and after 1 month followup. Using Pearsons correlation coefficient, Student t test and ANOVA, the association of RDW and NLR with various scores was evaluated. **Result:** In our study, mean age group is 61.16 years including 58 males and 42 females. Patients with NIHSS ≤4 were 46%, 5-15 were 29%, 16-20 were 15% and 10% had ≥21. 53% patients had MRS ≤2, 47% had MRS >2. Hypertension and diabetes mellitus has no influence over different NIHSS scores, RDW and NLR values in our study($p>0.05$). Mean RDW in this study was 15.43, 36% patients had RDW <14 and 64% had >14. Mean NLR in this study was 3.5, 52% patients had RDW <14 and 48% had >3. The association between RDW and NLR with NIHSS, MRS and GCS suggests highly significant correlation between RDW and NLR value with these scores in prognostication of stroke. **Conclusion:** Our study highlights the prognostic value of readily available inexpensive biomarker RDW in Acute ischemic stroke patients and it's correlation with various scores in assessing the severity. Higher values of RDW on admission is a predictor of severity and poor prognosis of ischemic stroke.

INTRODUCTION

Stroke is the second leading cause of death worldwide. The word "stroke" was likely first introduced into medicine in 1689 by William Cole in A Physico-Medical Essay Concerning the Late Frequencies of Apoplexies.[1] Stroke is classically defined as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no

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apparent cause other than that of vascular origin.[2]". Transient ischemic attacks are episodes of temporary and focal dysfunction of vascular origin, which are variable in duration, commonly lasting from 2 to 15 minutes, but occasionally lasting as long as a day (24 hours) with no persistent neurological deficit.[3]

The 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 India during the past decade.[4] Inflammatory response plays an important role in pathophysiology of acute ischemic stroke (AIS). Ischemic brain induces the release of proinflammatory cytokines and recruitment of immune cells which lead to secondary progression of brain lesion and consequent excessive production of reactive oxygen species.[5]

Biomarkers like S100 calcium binding protein B, IL-6, glial fibrillary acidic protein, brain natriuretic peptide, and matrix metalloproteinase-9 are routinely available in hospital laboratories in the time frame needed to make acute care decisions but may be a focus of clinical research.[6] Some of the easily available biomarkers including red blood cell distribution width (RDW), Neutrophil to-lymphocyte ratio (NLR), hsCRP and Lp-PLA2 are associated with severe neurologic impairment, larger infarct size and poor prognosis.[7]

RDW is a measure of the variation of red blood cell volume. Apart from anemia, RDW level can be used as diagnostic and prognostic marker in disorders such as acute myocardial infarction, stroke, and peripheral artery disease. The pathogenesis of acute CVA in the presence of high RDW are (a) Activation of Renin Angiotensin System and increase risk of ischemic stroke by increasing BP. (b) High RDW may stimulate systemic inflammation and release proinflammatory cytokines which is responsible for vascular endothelial changes. (c) It also increases incidence of carotid intimal medial thickness.[8]

Neutrophils and lymphocytes play important roles in mediating the response to cerebrovascular disease. Total Leukocyte count is an independent predictor of stroke severity, greater degree of disability, and 30-day mortality in patients with AIS. Recently, NLR which is a simple marker that can be easily calculated from the differential WBC count has been newly reported to be an indicator of overall systemic inflammatory status in the Asian population.[10] It has been thought as a better predictive factor than total WBC count or neutrophil count in cardiovascular disease.[9,10]

Given the immense burden that stroke exerts, there becomes the need to develop more precise estimates of a stroke survivors prognosis and it remains a very important goal. Also identification of predictors of mortality is very vital so that we can institute many prompt therapeutic measures to improve outcome. In recent studies, RDW and NLR was shown to correlate with prognosis in patients with AIS. There were only few previous Indian studies on correlation and prognostic significance of these biomarkers in stroke patients. Our study was planned to highlight the importance of these easily available biomarkers on correlation and prognostic significance in AIS patients.

Objectives

1. To evaluate the association between RDW and the GCS and NIHSS scores in patients with acute ischemic stroke.
2. To evaluate the relationship of NLR with stroke severity and functional outcome in patients with AIS.

MATERIALS AND METHODS

This study was conducted in department of Neurology, GMC, Machilipatnam from Feb to June 2025 over a period of one year after getting clearance from ethical committee. Subjects included were adult patients admitted in Neurology Ward. All patients were included after written informed consent. A total of 100 patients were recruited for this study with clinical and imaging findings consistent with acute ischemic stroke.

On admission, patients were assessed by physical examination, neurological examination and scoring with the GCS and NIHSS scores. The severity of stroke was graded as mild (NIHSS ≤8), moderate (NIHSS 9–15) or moderate to severe (NIHSS 16-20), severe (NIHSS >21). The severity of impaired level of consciousness if present was rated as mild (GCS 15), moderate (GCS 8–14), or severe (GCS ≤7). MRS score ≤2 is taken as good prognostic factor and >3 is taken as poor prognostic factor due to functional independence.

Immediately after assessment, patients were sent for imaging studies (CT/MRI Brain), ECG and routine blood investigations including RDW and NLR. RDW value of > 14% and NLR of > 3 was taken as the upper limit as these values are associated with poor prognosis in acute ischemic stroke patients based on previous studies. The primary functional outcome was measured using the modified Rankin Scale (MRS) at the time of discharge and after 1 month follow up. An unfavorable functional outcome was defined as MRS of 3-6 points.

Inclusion Criteria

- Patients 18 yrs or older
- Symptoms ≤ 48 hours and were diagnosed with acute ischemic stroke based on the history, physical examination, computed tomography (CT) scan / diffusion-weighted magnetic resonance imaging scan.

Exclusion Criteria

- Those diagnosed with infection within 1 week before stroke onset or within 72 hours after admission
- CT diagnosis of cerebral hemorrhage, subdural hematoma, intracerebral mass, or cerebrovascular damage secondary to trauma

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- Patients with hematologic disorders, presence of hemoglobinopathy, coronary heart disease, or a history of cancer
- Use of steroids or immunosuppressants
- Past history of stroke
- Patients who are thrombolysed

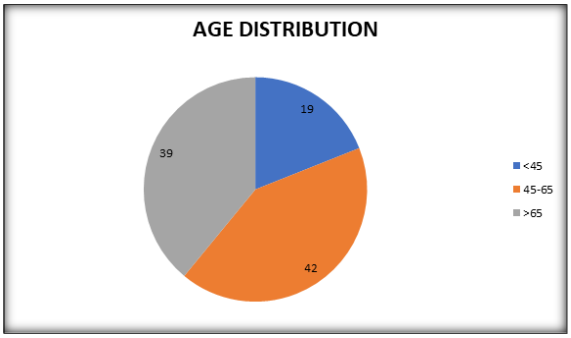
Statistical Analysis

The results are analyzed using SPSS software version 20. Association between variables were analyzed using chi-square test for categorical variables and student t test for numerical variables. Analysis of Variance (ANOVA) was done for multigroup comparisons. Pearson's correlation coefficient was used to assess the association of RDW and NLR with prognosis of stroke patients. The primary association expected was high RDW and high NLR with severity of stroke. Hence both were compared with the outcome of stroke at discharge and at 1 month follow up. Statistical significance is assumed with a p value of less than 0.05.

RESULTS

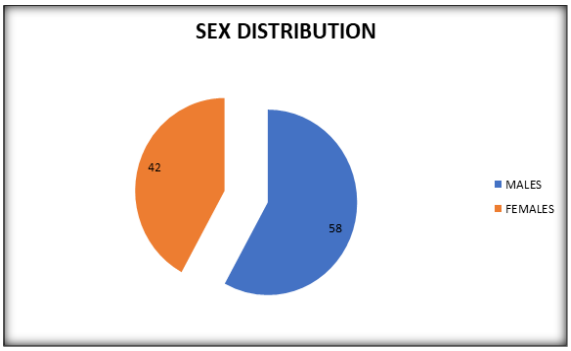
Age Distribution

In our study, mean age group is 61.16 years. About 19 % of patients are
below age 45, 42% of patients are between ages 46-65, 39% of patients are >65 years of age.

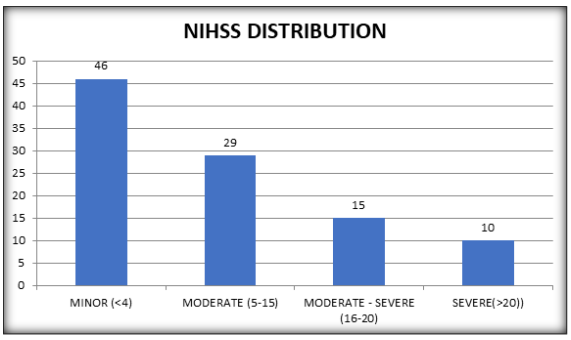


Sex Distribution

In our study, about 58% are male and about 42% are about female.



NIHSS Distribution



MRS Distribution (On admission)

In our study, about 26% belong to MRS 1, 21% belong to MRS 2, 16% - MRS 3, 14% to MRS 4, 11% to MRS 5 and 12% of patients belong to MRS 6.
MRS of ≤2 is seen in 47% and >2 in 53% of patients.

MRS Distribution (after one month)

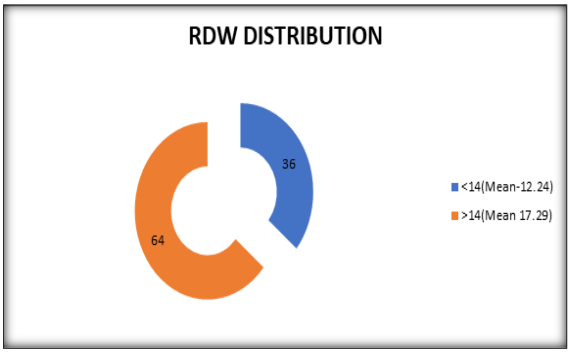
About 25% belong to MRS 0, 29% belong to MRS 1, 13% belong to MRS 2, 10% - MRS 3, 8% to MRS 4, 3% to MRS 5 and 12% of patients belong to MRS 6.
MRS of ≤2 is seen in 67% and >2 in 33% of patients.

Hypertension, Diabetes Mellitus and Stroke

In our study, we analysed the hypertension and diabetes mellitus with different NIHSS score and p value obtained was insignificant. This shows hypertension and diabetes mellitus has no influence over different NIHSS score in our study.

RDW Distribution

In this study, about 64% patients have high RDW (> 14), rest have normal RDW.



Association between Hypertension and stroke

NIHSS	HTN	N	Mean NIHSS	P value
MINOR	YES	28	2.5	0.11
	NO	18	2.17	
MODERATE	YES	22	8.72	0.058
	NO	7	10.83	

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MODERATE-SEVERE	YES	9	18.22	0.195
	NO	6	17.5	
SEVERE	YES	5	22.6	0.24
	NO	5	21.8	

Association between Diabetes and Stroke

NIHSS	DM	N	Mean NIHSS	P value
MINOR	YES	7	2.57	0.268
	NO	39	2.35	
MODERATE	YES	3	6.33	0.03
	NO	26	9.53	
MODERATE-SEVERE	YES	5	17.8	0.41
	NO	10	18	
SEVERE	YES	1	21	
	NO	9	22.3	

NLR DISTRIBUTION

In this study, about 48% patients have high NLR (> 3), rest have normal NLR.

NLR	N	MEAN
≤3	52	2.28
>3	48	4.83
TOTAL	100	

Patient with Hypertension, Diabetes and High RDW

In our study, we analysed the hypertension and diabetes mellitus with RDW value and p value obtained was insignificant. This shows hypertension and diabetes mellitus has no influence over RDW score in our study

Patient with Hypertension and High RDW (>14)

	HTN	N	Mean	p value
RDW	Yes	41	17.3	0.43
	No	10	17.5	

Patient with Diabetic and High RDW (>14)

	DM	N	Mean	P value
RDW	Yes	10	17.8	0.244
	No	54	17.1	

Patient with Hypertension, Diabetes and High NLR

In our study, we analysed the hypertension and diabetes mellitus with NLR value and p value obtained was insignificant. This shows hypertension and diabetes mellitus has no influence over NLR score in our study.

Patient with Hypertension and High NLR (>3)

	HTN	N	Mean	P value
NLR	Yes	31	4.99	0.146
	No	17	4.52	

Patient with Diabetic and High NLR (>3)

	DM	N	Mean	P value
NLR	Yes	9	4.2	0.20
	No	39	4.7	

COMPARISON OF RDW and NLR FOR NIHSS CLASSIFICATION

In our study, p value between RDW, NLR and NIHSS is < 0.05 which is highly significant. This shows that there is significant difference in each score. Similarly, there is significant difference between moderate and minor stage, in moderate severe and minor and severe and minor.

COMPARISON OF HIGH RDW FOR NIHSS CLASSIFICATION

	NIHSS	N	Mean	SD	F value	P value
RDW	Minor	46	13.01	1.78	46.08746	< .00001
	MODERATE	29	15.82	2.48		
	MODERATE -SEVERE	15	19.19	2.62		
	SEVERE	10	19.78	2.62		

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COMPARISON OF HIGH NLR FOR NIHSS CLASSIFICATION

	NIHSS	N	Mean	F value	P value
NLR	Mild	46	2.55	15.09199	< .00001
	MODERATE	29	3.90		
	MODERATE -SEVERE	15	4..82		
	SEVERE	10	4.74		

COMPARISON OF RDW and NLR according to MRS on discharge

P<0.05

In our study, p value between RDW and NLR and MRS < 0.05 which is highly significant. This shows that there is significant difference in each score.

COMPARISON OF HIGH RDW according to MRS on discharge

	MRS	N	Mean	F value	P value
RDW	1	26	12.8	27.99987	< .00001
	2	21	13.36		
	3	15	14.87		
	4	14	17		
	5	12	18.8		
	6	12	19.9		

COMPARISON OF HIGH NLR according to MRS on discharge

	MRS	N	Mean	F value	P value
NLR	**1**	**26**	**2.62**	**17.35951**	**< .00001**
	2	**21**	**2.51**		
	3	**15**	**3.68**		
	4	**14**	**3.2**		
	5	**12**	**5**		
	6	**12**	**5.78**		

COMPARISON OF RDW and NLR according to MRS after 1 month

P<0.05

In our study, p value between RDW and NLR and MRS < 0.05 which is highly significant. This shows that there is significant difference in each score.

COMPARISON OF HIGH RDW according to MRS after 1 month

	MRS	N	Mean	F value	P value
RDW	**0**	**25**	**13.04**	**17.51491**	**< .00001**
	1	**29**	**13.67**		
	2	**13**	**15.54**		
	3	**10**	**16.24**		
	4	**8**	**19.96**		
	5	**3**	**18.86**		
	6	**12**	**19.9**		

COMPARISON OF HIGH NLR according to MRS after 1 month

	MRS	N	Mean	F value	P value
NLR	**0**	**25**	**2.53**	**9.28218**	**< .00001**
	1	**29**	**2.85**		
	2	**13**	**3.20**		
	3	**10**	**3.63**		
	4	**8**	**5.08**		
	5	**3**	**5.43**		
	6	**12**	**5.78**		

COMPARISON OF RDW and NLR according to GCS SCORE

P<0.05

In our study, p value between RDW and NLR and GCS SCORE < 0.05 which is highly significant. This shows that there is significant difference in each score.

COMPARISON OF HIGH RDW FOR GCS SCORE

	GCS	N	Mean	F value	P value
RDW	**MILD**	**37**	**15**	**247.32**	**< .00001**
	MODERATE	**44**	**11.20**		
	SEVERE	**19**	**6.73**		

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COMPARISON OF HIGH NLR FOR GCS SCORE

	GCS	N	Mean	F value	P value
NLR	MILD(>15)	37	2.67	23.32137	< .00001
	MODERATE(9-14)	44	3.41		
	SEVERE(≤ 8)	19	5.33		

Pearson Correlation Coefficient

RDW with NIHSS

The value of R is: 0.7923, p < .05

This is a strong positive correlation, which means that high X variable scores go with high Y variable scores (and vice versa).

This shows that lower levels associated with lower NIHSS score and vice versa .

RDW with MRS (on discharge)

The value of R is 0.763, p < .05

This shows that lower levels associated with lower MRS score and vice versa .

RDW with MRS (after 4 weeks)

The value of R is 0.7471, p < .05

This shows that lower levels associated with lower MRS score and vice versa.

RDW with GCS

The value of R is -0.7368, p < .05

This is a moderate negative correlation, which means there is a tendency for high X variable scores to go with low Y variable scores (and vice versa)

This shows that lower levels associated with higher GCS score and vice versa .

NLR with NIHSS

The value of R is 0.5488, p < .05

This shows that lower levels associated with lower NIHSS score and vice versa .

NLR with MRS(on discharge)

The value of R is 0.6339, p < .05

This shows that lower levels associated with lower MRS score and vice versa.

NLR with MRS(after 4 weeks)

The value of R is 0.6749, p < .05

This shows that lower levels associated with lower MRS score and vice versa.

NLR with GCS

The value of R is -0.5902, p < .05

This shows that lower levels associated with higher GCS score and vice versa .

NIHSS with AND MODIFIED RANKING SCALE (on discharge)

The value of R is 0.9016, p < .05

p value between MRS and NIHSS is < 0.05 which is highly significant.

This shows that lower MRS is associated lower stages and higher MRS score having higher NIHSS score with poor prognosis in acute ischemic stroke.

NIHSS with MODIFIED RANKING SCALE(after 4 weeks)

The value of R is 0.8554, p < .05

p value between MRS and NIHSS is < 0.05 which is highly significant.

This shows that lower MRS is associated lower stages and higher MRS score having higher NIHSS score with poor prognosis in acute ischemic stroke.

NIHSS with GCS

The value of R is -0.7787, p < .05

This is a strong negative correlation,

This shows that higher GCS is associated lower stages and lower GCS score having higher NIHSS score with poor prognosis in acute ischemic stroke.

MRS(on discharge) with GCS

The value of R is -0.8729, p < .05

This is a strong negative correlation

DISCUSSION

Stroke is an important cause of permanent disability and death worldwide and is responsible for 63,98,000 disability adjusted life years. In India alone, more than 1.5 million new cases are seen yearly.[11] Ischemic stroke accounts for about 80% of all strokes, which is caused by occlusion of blood supply to brain. The extent of disability depends on the severity of stroke which is assessed by NIHSS, which has been shown to be a reliable predictor of outcome. Recent alternatives to NIHSS in the prediction of stroke severity are RDW and NLR which are the main focus of discussion in our study. We also studied the effect of other factors like hypertension, diabetes and smoking on severity of stroke. We found no statistically significant effect of these factors on stroke severity and prognosis ($p<0.05$). So these factors may increase the risk of stroke but do not influence the severity independently.

After an acute ischemic insult, imbalance between oxidants and antioxidants will cause oxidative damage to nucleic acids, proteins and lipids affecting the red blood cells by causing membrane damage, increased fragility, reduced maturation and elevation of RDW. This oxidative is also associated with cerebral ischemia and reperfusion injury.[12] NLR was an independent predictor for recurrent ischemic stroke in patients with AIS. After cerebral ischemia WBCs increase significantly from admission to 3 months after stroke as a marker of systemic inflammation. At first Neutrophils accumulate within hours and play an active role in extension of infarction. This increased total WBC and neutrophil counts were found to be associated with more severe stroke at admission.[13] After 3-6 days post stroke lymphocytes are elevated much later than neutrophils. In cardiovascular disease, lymphocytes have proven prognostic value.[14] But their role in the pathogenesis of ischemic stroke is still controversial. Based on prior evidence, lymphocytes have an important role in healing and repair of damage caused by inflammation. It was shown that lower lymphocyte counts are associated with poor neurological functional outcome in stroke patients. This also highlights the fact that anti-inflammatory

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therapy by inhibiting neutrophils may emerge potential treatment option for AIS.[15]

In a study done by Kara H et al in 2015, stroke patients had significantly higher median RDW than control subjects. The median RDW values were significantly elevated in patients who had more severe rather than milder strokes (rated with GCS and NIHSS scoring systems).[16] Likewise in 2015, Kaya A et al prospectively included 153 patients of chronic heart failure and followed them for one year. An RDW of 15.2% measured on admission had 87% sensitivity and 74% specificity in predicting stroke in patients with HF and concluded that RDW may be important hematological indices for stroke in patients with HF.[17] In our study there was statistically significant difference in RDW value between different NIHSS groups ($p<0.05$). Also we evaluated the correlation of RDW with GCS on admission, MRS on discharge and 1 month follow up period by Pearson's co-efficient which was found to be significant. Past studies by Turcato G et al in 2016, Ramírez-Moreno et al in 2013 in 224 patients also had shown clear association of high RDW value in prognostication of stroke patients..[18,19]

In a metaanalysis done by Lakani I et al in 2017, NLR is a significant predictor of incident ischemic stroke, hemorrhagic stroke and adverse outcomes following stroke.[20] In 2016, Jie Xue et al did a study in 280 patients of AIS and found that NLR was associated with an increased risk of stroke severity on admission.[21] In our study, we found significant difference in NLR value between different grades of NIHSS and GCS scores (p value<0.05) with mild grades showing lower values and severe grades showing higher values. On calculation of pearsons's co-efficient, positive correlation was found between NLR value with NIHSS, MRS score on admission and 1 month followup. Negative correlation was found between NLR and GCS scores. NLR also predicts length of stay and acute hospital cost, mortality and recurrence in patients with acute ischemic stroke.[22] Our study findings were similar to findings in other previous studies done by Sen Qun et al in 2017 in 143 patients and Tokgoz S et al. in 2013 in 255 patients.[23,24]

CONCLUSION

Our study highlights the prognostic value of readily available inexpensive biomarkers RDW and NLR in Acute ischemic stroke patients and it's correlation with various scores in assessing the severity. Higher values of RDW and NLR on admission predicts the severity and poor prognosis of ischemic stroke and can act as an indirect marker of socioeconomic burden of stroke.

Limitations

1. One of the limitation is sample size which is less and this study should be tested in large number of patients.
2. We did not test the effect of RDW and NLR on each other.
3. Role of these variables in different etiological subtypes of stroke was not studied.
4. Extended follow up of patients was not possible due to time constraint.

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