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# STUDY OF CORRELATION OF RED CELL DISTRIBUTION WIDTH WITH SEVERITY OF HEART FAILURE

General Medicine

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## ABSTRACT

**Introduction-** RDW is a commonly used parameter to narrow down the diagnoses of anemia. Recently there has been growing attention given to the relationship between RDW and cardiovascular disorders, such as heart failure and coronary artery disease. **Aims and objectives-** this study was conducted with the primary objective to study and compare red cell distribution width between heart failure patients and healthy subjects. **Materials and methods-** In this study 56 cases of heart failure and 56 controls were recruited. The RDW were measured in both groups. The values of RDW were correlated with NYHA grading , ejection fraction and NT-Pro-BNP levels. **Results-** The mean RDW of cases was 15.1±1.3%, while that of controls was 13.8±0.9%. The difference between the two groups was statistically significant (p-value < 0.0001). RDW was elevated in heart failure cases irrespective of etiology. There was a significantly positive correlation between higher RDW and higher grades of heart failure (r=0.7; p=0.0001)and negative correlation between higher RDW and Lower Ejection Fraction(r=-0.37; p=0.005. There was also a highly significant correlation between NT-ProBNP levels and RDW (r=0.59; p value < .00001) and Using a ROC curve, RDW of 14.55% as a cut-off had best sensitivity (71.4%) and specificity (78.6%). **Conclusion-** Being a readily available test, RDW could serve as a reliable and affordable marker for HF patients. RDW could be utilized as an additional marker for the early diagnosis of suspected cases and monitoring their recovery.

## KEYWORDS

## INTRODUCTION

Heart Failure (HF) is the heart's inability to maintain an adequate cardiac output that is insufficient to maintain the body's demands.[1] The reported prevalence of cardiac failure in the adult population from developed countries has been estimated to be around 2%, while in India it is roughly over 1%.[2]

However, the incidence of HF in patients aged 70 years is ≥10% than the rest of the population.[3] This number has been increasing significantly every decade. The etiology of HF is widely variable across different parts of the world and amongst different age groups. It has been observed that up to 50% of cases of HF are HF with reduced ejection fraction (HFrEF). Approximately two-thirds cases of HFrEF have underlying coronary artery disease (CAD). Hypertension and diabetes are the two most significant contributory factors in the pathogenesis of HFrEF. Other factors include alcoholism, cigarette smoking, chemotherapy, viral infections and 'idiopathic' dilated cardiomyopathy.[4]

Another category of HF includes cases having HF with preserved ejection fraction (HFPEF). These patients have diastolic HF. Most cases of HFPEF are obese females. Often such cases are more likely to have raised blood pressure and atrial fibrillation and less likely to have CAD. Although patients having HFPEF often carry a better prognosis than patients with HFREF.[5]

Red cell Distribution Width (RDW) quantitatively grades the degree of the variation of RBCs or anisocytosis. RDW measurement is an affordable investigation as part of the routine hemogram. If the RDW is higher it indicates that the size of individual RBCs in a given blood sample is highly variable. RDW is a commonly used parameter to narrow down the diagnoses of anemia.[6] Recently there has been growing attention given to the relationship between RDW and cardiovascular disorders, such as heart failure and coronary artery disease.[7] Red cell distribution width (RDW) has recently been discovered to be a novel prognostic marker in patients with heart failure. There is still a dearth of data on the role of RDW in prediction the prognosis of diastolic Heart failure.[8]

To date, there is still a paucity of literature on the association between RDW and HF, especially in the Indian subcontinent. Keeping this in mind, this study was conducted with the primary objective to study and compare red cell distribution width between heart failure patients and healthy subjects. Secondary objectives were to establish a correlation of RDW with the severity of heart failure according to NYHA Classification and to correlate the NT-Pro-BNP level with the Severity of Heart failure. The study also did a comparative analysis of RDW and NT-Pro-BNP in HF cases.

## MATERIALS AND METHODS

This case-control study was conducted at the in-patient department of General Medicine at our tertiary care center over a course of one year after obtaining due approval from the institution's ethical board.

### *Sample size calculation*

The sample size was calculated using 90% power (probability of achieving a significant result at a 5% level), 80% preference rate for Heart failure, and a significance level of 5%. The preference rate for Heart failure with elevated RDW was taken at 80% and a significant level of 5% was kept. This gave a sample size of 50 per group. However, in order to avoid any further dropouts, we increased the sample size to 56.

Inclusion criteria for cases were patients aged 18 years and above with newly diagnosed heart failure as per "European society of cardiology Criteria"[9] or follow-up cases of HF coming in decompensated state.

Patients refusing to give consent, those having anemia, congenital heart disease, chronic obstructive pulmonary disease, chronic kidney or liver disease, and inflammatory bowel disease were excluded.

The study subjects were divided into two groups. Group I included patients with HF after inclusion and exclusion criteria. Group II included healthy volunteers who were selected randomly from the same center.

The detailed demographic and clinical data of the study subjects were recorded in a proforma. Complete hemogram, NT-pro BNP, random blood sugar, liver, and renal function tests, lipid profile, and serum electrolyte levels were recorded. Additionally, 12-lead electrocardiography, chest radiography, and 2-D echography (2D Echo) were done for all patients in group I.

### *2D echocardiography*

2D echo was done using an echocardiography machine with 3 Hz

probe. The parameters were recorded as per the American Society of Echo Cardiography. M-mode echocardiography was used to assess the dimensions of the chambers.

The following parameters were checked: dimensions of various chambers, diastolic dysfunction, ejection fraction (Simpson's method), and regional wall motion abnormality.

The criteria for the diagnosis of HFREF or HFPEF were specified:
1. HFREF: Typical symptoms of HF + typical signs of HF + reduced left ventricular ejection fraction (LVEF).
2. HFPEF: Typical symptoms of HF + typical signs of HF + normal to mildly reduced LVEF without left ventricular dilatation + diastolic dysfunction and/or relevant structural heart disease.[10]

***Statistical Analysis***

Descriptive statistics were performed by calculating the mean and standard deviation for the continuous variables. Categorical variables were presented as absolute numbers and percentages. Continuous variables were compared using the student T-test. Nominal categorical data between the groups were compared using Chi-square goodness-to-fit test.

## RESULTS

The mean age of patients was 60±14.25 , while that of controls was 47.66 ± 20.53. There were 42 male and 14 females among controls and 43 males and 13 females among controls.

Of the 56 heart failure patients , 35 had reduced EF(EF<40%) , 17 had preserved EF ( EF ≥ 50%) and 4 were in midrange EF ( EF 40-49%) . Among the ethology of Heart failure Ischemic heart disease(35patients - 62.5%) stands at first followed by Hypertensive heart disease (11patients,19.64%) , Dilated cardiomyopathy (3 patients, 5.36%) , Rheumatic Heart disease (3 patients, 5.36%) , Myocarditis (2 patients, 3.57% ) ,Alcoholic cardiomyopathy (1 patient, 1.79%) and calcification aortic regurgitation (1 patient, 1.79%). On clinical grading of heart failure patients, 10 patients belong to NYHA grade -4 , 25 patients to grade-3, 17 patients to grade-2 and 4 patients to grade-1.

RDW was studied in 56 cases and an equal number of controls. The mean RDW of cases was 15.1±1.3%, while that of controls was 13.8±0.9%. The difference between the two groups was statistically significant (p-value < 0.0001).

**Table 1**

| | Case(n=56) | Control(n=56) | P-Value |
|---|---|---|---|
| Mean | 15.1 | 13.8 | 0.0001 |
| SD | 1.3 | 0.9 | |

RDW was ≥ 13.6 in 49 out of 56 cases and 33 out of 56 controls . The difference was found statistically significant ( p= 0.0006 ).

**Table 2**

| | RDW > | RDW | Total no.of | P value |
|---|---|---|---|---|
| | 13.6 | <13.6% | subjects | |
| CASES | 49 | 7 | 56 | 0.0006 |
| CONTROLS | 33 | 23 | 56 | |

Analysis of variance revealed patients with higher NYHA grades of heart failure had signicantly higher RDW ( p=0.0001)

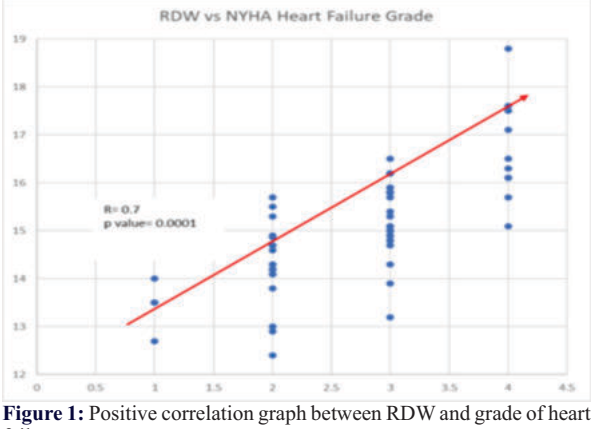


**Figure 1:** Positive correlation graph between RDW and grade of heart failure

**Table 3**

| NYHA GRADE | MEAN RDW | SD |
|---|---|---|
| GRADE 1 | 13.42 | 0.54 |
| GRADE 2 | 14.31 | 0.91 |
| GRADE 3 | 15.29 | 0.77 |
| GRADE 4 | 16.68 | 1.08 |
| ANOVA TEST | | |
| F-ratio=22.76157 | | |
| P-value is < .00001 | | |

On comparing RDW with EF patients with lower EF had significantly higher RDW (p=0.02)

**Table 4: Ejection Fraction Versus Mean RDW**

| EF | MEAN RDW | SD |
|---|---|---|
| <40% | 15.38 | 1.2 |
| 40-49% | 15.30 | 0.91 |
| >50% | 14.37 | 1.19 |
| F-ratio=3.84358 P-value=0.02. | | |

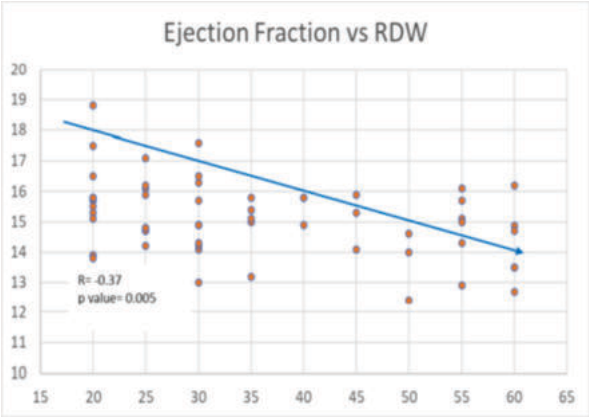


**Figure 2:** Negative correlation graph between RDW and low ejection fraction

The scatter diagram (Figure 2) reveals significant negative correlation between RDW and low EF in cases ( r= -0.37 ; p = 0.005 ).

The mean NT-pro-BNP of patients was 9094.6 ± 7582.3 pg/ml. For the same ejection fraction females had a higher level of NT proBNP in all 3 grades of EF. However the difference was insignificant. There was a highly significant correlation between NT proBNP levels and RDW of heart failure patients as shown in scatter diagram ( r=0.59 ; p=< 0.0001).

**Table 5- NT-Pro-BNP Level According To Ejection Fraction**

| EF | NT-Pro BNP levels (pg/ml) | | | | P VALUE |
|---|---|---|---|---|---|
| | MALES | | FEMALES | | |
| | Mean | SD | Mean | SD | |
| <40% | 11067.86 | 8586.26 | 14022.14 | 6802.32 | 0.41 |
| 40-49% | 7071 | 2857.33 | 10932 | 0 | 0.26 |
| ≥50% | 4063.73 | 2573.02 | 4280.50 | 2151.69 | 0.66 |
| Total | 9880.5 | 6751.69 | 8832.64 | 7898.52 | 0.65 |

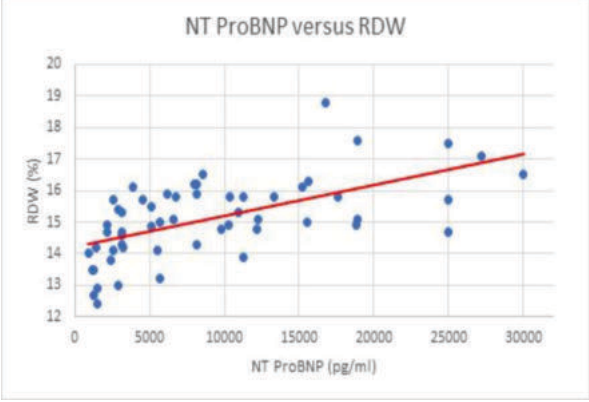


**Figure 3:** Positive correlation graph between RDW and NT proBNP

At RDW Cut off of 13.6 , sensitivity, specificity , PPV and NPV were 87.5% , 41%, 59%, 76% respectively. Using a ROC curve maximum sensitivity of 71.4% and specificity of 78.6% was achieved with an RDW cut-off of 14.55% in our study. ROC curve also revealed the AUC (area under the curve) of 0.807 (figure 3). In simpler terms, RDW ≥14.55 could correctly predict HF in 80.7% time.

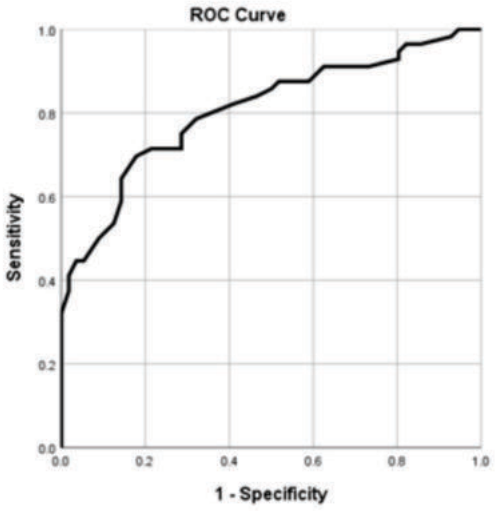


**Figure 4: -** ROC curve of the sensitivity and specificity of high RDW in predicting HF

## DISCUSSION

Recent evidence has found that RDW values are emerging as a novel predictor for disease activity in various inflammatory conditions like diabetes, cardiovascular diseases, infections, and malignancies.[11] In fact, a high RDW value is now being considered to be an independent and strong risk factor for predicting disease-associated mortality in the population.[12,13]

Even though it is yet to be determined with conclusive evidence whether high RDW is a potential risk factor or merely an epiphenomenon, the literature on its role as a reliable marker is increasing.

Of late, RDW has emerged as a promising marker for diagnosing and predicting the prognosis of heart failure patients.[14,15] The various causes of RDW elevation in heart failure patients include inflammation, suboptimal erythropoiesis, nutritional deficiencies, renal function impairment, and activation of the neurohormonal axis.[14]

The age of patients in our study ranged from 21 to 87 years, with a mean of 60.69 ± 14.25 years in cases and 47.66 ± 20.53 in controls. Although heart failure may involve patients from any age group, the most common causes in older age groups are hypertension and ischemic heart disease. In younger patients, however, common causes are valvular heart disease and non-ischemic cardiomyopathy. In our study, the mean age of cases and controls was fairly comparable. These findings are similar to a study conducted by Atac Celik et al.[8] for determining the profile of diastolic heart failure patients. They included 71 patients with a mean age of 57±7 years along with 50 controls having a mean age of 56±7 years. Similar findings were also reported by Rudresh et al.[7]

In our study out of the 56 cases, 75% were male and 25% were females. Heart failure involved males more frequently than females. This is similar to what most other studies have reported. Felker et al.also reported a male preponderance with 68.3% men with HF compared to only 31.7% women.[16] Even the Framingham heart study reported men to have a significantly higher incidence of HF than women across all ages with the age-standardized sex ratio of 1.67.[17] Although Rudresh et al.reported a female preponderance.[7] These differences in the gender distribution could be attributed to the difference in the pattern of hospital admissions across different centers.

In our study, IHD was the most common etiology of HF followed by hypertensive heart disease, DCMP, RHD, myocarditis, alcoholic cardiomyopathy, and calcified valve aortic regurgitation. Similar results have also been reported by Rudresh et al., Felker et al., and Yahya Al-Najjar et al.[7,16,18] In the Indian subcontinent the leading causes of HF are coronary artery disease, hypertension, diabetes, and valvular heart diseases. Additionally, rheumatic heart disease is also a common etiology of HF.[10] We reported 5.36% of such cases.

A handful of studies have found that RDW is an independent predictor of the mortality and morbidity associated with HF. In our study cases with both systolic and diastolic dysfunction had elevated red cell distribution width. RDW is measured using an impedance analyzer. as part of the routine complete blood count. The following formula is used for calculating, RDW= standard deviation of RBC volume/mean RBC volume x 100. Normally, RDW ranges from 11.5% to 14.5%.[19] The calculated cut-off of RDW for predicting HF in Celik et al.'s study was 13.6.[8] A similar observation was also made by Rudresh et al.[7] However, in our study, a cut-off of 14.5% had the best sensitivity and specificity for predicting the risk of HF.

Often the value of RDW is used for the classification of anemia. RDW values can differentiate iron deficiency anemia from folate deficiency anemia.[20] It has already been established that higher values of RDW are independently related to increases cardiovascular events and mortality in patients having a previous history of strokes and myocardial infarcts.

NT-Pro BNP is one of the most important independent risk factors for the diagnosis and prognosis of HF.[21] We also found a highly significant positive correlation between NT-ProBNP and RDW. NT-Pro BNP is an expensive investigation. RDW could serve as its cheaper supportive investigation at resource-poor centres.

Although the pathomechanics underlying this elevation in RDW is still elusive, it has been postulated that impaired bone marrow functioning and increased RBC destruction are the two most important causes in patients with HF. Since inflammation is an established pathological event in HF, this could also be a contributory factor for the RBC destruction in HF. Inflammatory cytokines released during the initiation of the HF cascade can directly impact bone marrow activity. These cytokines also hold a prognostic significance in HF. In their study, Atac Celik et al.hypothesized that the elevation of RDW in HF could also be a result of increased neurohormonal activity, raised filling pressure, and renal function.[8] Although, the literature on these pathophysiological events is still sparse. Our study attempts to evaluate RDW in various grades of heart failure patients and correlate with NT proBNP and the study also suggest new RDW cut off of 14.55% as an optimum level for predicting heart failure.

### Study Limitation

Our study had a few limitations like small sample size and the absence of analysis of analysis of serum ferritin and erythropoietin level. Serum ferritin is a marker of iron storage. It is reduced in iron deficiency state and correlates with elevation of RDW. Erythropoietin is an independent prognostic marker for HF. It is still unclear whether RDW values could be influenced by the fluctuation in the level of erythropoietin.

## CONCLUSION

In conclusion, being a readily available test, RDW could serve as a reliable marker for HF patients. Since this parameter is already reported alongside the complete hemogram, the investigation incurs no extra cost. We found RDW to be a good marker with an impressive prognostic value, which is statistically as good as that of the relatively expensive NT-pro BNP. RDW could be utilized as an additional marker for the early diagnosis of suspected cases and monitoring their recovery.

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