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Original Research Article

# RED CELL DISTRIBUTION WIDTH AS A PROGNOSTIC INDICATOR IN PATIENTS WITH ACUTE HEART FAILURE – AN OBSERVATIONAL STUDY

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## ABSTRACT

**Background:** Heart failure is becoming increasingly prevalent worldwide, especially in emerging nations like India. Newer biomarkers of heart failure, such as Red Cell Distribution Width (RDW), provide valuable insights for heart failure risk assessment and prognosis. RDW measures variability in erythrocyte (red blood cell) size, which indirectly reflects overall cardiovascular health and inflammation. This study assesses the efficacy of RDW as a prognostic indicator of morbidity and mortality among patients with heart failure and compares it with already established.

**Materials and Methods:** This hospital based prospective observational study was carried out from December 2021 to September 2022. A total of 140 patients who presented to the hospital with signs and symptoms of acute heart failure were included.

**Results:** The study included 140 subjects with a mean age of 51.7±16.7 years and a male to female ratio of 1.15:1. Coronary artery disease was the most common cause of heart failure. The mean RDW at admission was 16.7% (SD 2.8%). Subjects were divided into quartiles based on a median RDW of 16.3%, with the 4th quartile having RDW > 18.3%. The mortality rate increased from 8.6% in the 1st RDW quartile to 51.4% in the 4th quartile. High NT PROBNP values (>35000) were found in 45.7% of cases in the 1st RDW quartile and 71.4% in the 4th quartile.

**Conclusion:** Higher RDW values were significantly associated with increased risk of mortality, prolonged hospital stay and correlated with higher NTpro-BNP values. Patients whose RDW decreased during their hospital stay had a better overall prognosis.

**Keywords:** Red cell Distribution Width (RDW), Heart Failure, NTpro BNP, Mortality.

## INTRODUCTION

Heart failure (HF) is a complex clinical syndrome resulting from structural and functional impairment of ventricular filling or ejection of blood1. The global incidence and prevalence rates of heart failure are approaching epidemic proportions in the recent decades. The prevalence of HF in emerging nations like India is uncertain because of the lack of population- based studies.[1]

Apart from standard laboratory testing, the measurement of newer biomarkers has emerged as an important adjunct to the initial and subsequent evaluation of patients with suspected or proven heart failure, in both acute and chronic settings as a part of risk stratification and prognostication.[1] Clinically useful biomarkers of HF should be easily measured with high analytical precision, should reflect important processes involved in HF presence and progression, help in therapeutic decisions and

prognostication. Only the natriuretic peptides have met these requirements till date. [1]

An emerging concept in cardiovascular disease is the role of the erythrocyte as a barometer of overall cardiovascular health. The erythrocytes or red blood corpuscles (RBCs) are non-nuclear corpuscular elements of blood produced in the bone from erythroid precursors. RBCs display a physiological size heterogeneity in adult human blood, which is usually measured in terms of Red Cell Distribution Width (RDW). This value is calculated from the Mean Corpuscular Volume (MCV); thus, cell width is not being measured but cell volume is. The normal range of RDW-CV is 11.5-14.5% but often varies according to the technique used for its assessment by thedifferent commercially available hematological analyzers.[2]

There is convincing evidence that both cell and cytokine-mediated inflammatory pathways actively contribute to development and progression of HF,[3] along with other factors like nutritional deficiencies, chronic disease and advanced age and these are reflected by different degrees of anisocytosis. Increased RDW values truly mirror the degree of anisocytosis, thus can be used for diagnostic, prognostic, and even therapeutic decisions in many acute and chronic conditions, including heart failure. Serial measurement of RDW, and especially the combination of admission value with subsequent changes during in-hospital or follow up visits may be seen as an affordable and efficient tool to help in assessing the prognosis of patients with HF and for reliably predicting the risk of adverse events especially in resource limited settings like India.

**Aims and Objectives**

- To observe the trend of RDW among patients admitted with acute heart failure.
- To assess the efficacy of RDW as a prognostic indicator of morbidity and mortality among patients with heart failure and compare it with already established indicators like NTproBNP.

## MATERIAL AND METHODS

**Study Design:** Prospective observational study.

**Study Period, Place of Study and Duration**

The study was conducted at a tertiary care hospital in South India over a period of nine months from December 2020 to September 2022. Institutional ethical committee clearance was taken for conducting the study.

**Sample Size**

A total of 140 patients were included in the study.

**Inclusion Criteria**

- All adult patients (age > 18yrs) of both sexes with clinical symptoms (dyspnea, fatigue, chest pain, lower limb swelling) and signs (pedal edema, pulmonary crackles, elevated JVP) of heart failure.
- Any evidence of heart failure on 2D Echocardiography.
- Patients willing to give informed consent.

**Exclusion Criteria**

- Patients with severe anemia - Hb- <7gm%.
- Patients with history of recurrent blood transfusions or blood transfusion in the recent past or present hospital stay.
- Patients with known connective tissue disorders.
- Patients with malignancies or on chemotherapy.
- Patients with established ESRD on maintenance hemodialysis.
- Patients with primary or secondary bone marrow disorders.
- Patients with RVD on ART.
- Patients with any evidence of ongoing hemolysis.
- Duration of present hospital stay for less than 2 days.

**Study Methods**

**Data Collection**

- After obtaining prior informed consent, relevant information about the patients was collected regarding their demographic characteristics, clinical history, and examination findings.
- The RDW is calculated as follows: RDW = (standard deviation of MCV ÷ mean MCV) × 100. In the presence of morphologic anisocytosis, RDW (normally 11–14%) increases to 15– 18%.
- The coefficient of variation (RDW-CV) of erythrocyte volumes [i.e., (RDW-SD)/ (MCV)*100] were analysed using fully automated Beckman analyser.
- The RDW CV values at admission (RDW-CV1), after 48hrs of admission (RDW-CV2) and at discharge (RDW-CV3) were noted.
- Additionally, the NT Pro BNP values were also collected.

**Data Analysis**

- Data was coded and recorded in the MS Excel spreadsheet program. SPSS v23 (IBM Corp.) was used for data analysis.
- Descriptive statistics were elaborated in the form of means/standard deviations and medians/IQRs for continuous variables, and frequencies and percentages for categorical variables. Data was presented in a graphical manner wherever appropriate for data visualization using histograms, bar graphs and pie charts.
- Chi-squared test was used for group comparisons for categorical data. In case the expected frequency in the contingency tables was found to be <5 for >25% of the cells, Fisher's Exact test was used instead.

## RESULTS

In the present study a total of 140 patients who presented to the hospital with acute heart failure were included.

**DEMOGRAPHIC CHARACTERISTICS OF STUDY SUBJECTS**

Majority of the study sample, 56 (40.0%) belonged to 41-60 years (middle age). 48 cases (34.3%) belonged to the >60 years (elderly) age group followed by 36 cases (25.7%) in the 18-40 age group.

Out of the 140 subjects, males were 75 (53.6%) and females were 65 (46.4%).

Among 140 cases, most common etiology leading to acute heart failure was ischemic cardiomyopathy which was seen in 40 cases (28.6%) followed by myocarditis (19.3%), hypertensive heart failure and dilated cardiomyopathy in 17.9% each, Acute Coronary Syndrome with heart failure (7.9%), postpartum cardiomyopathy (5%) and alcoholic cardiomyopathy (3.6%) respectively. [Table 1]

Out of 140 cases, 47.1% improved while 24.3% were not improving/worsening. 40 cases (28.6%) died in the study sample.

**DIVISION OF RDW VALUES INTO QUARTILES**

RDW values were divided based on the median into four equal quartiles for further analysis as shown below:

<14.325%-Normal

14.325-16.3%-High

16.3-18.25%-Moderately high

>18.25%-Very high

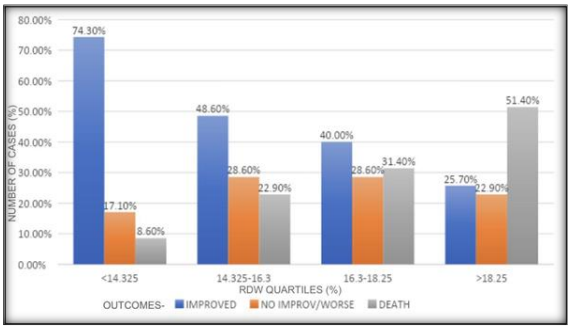


**Figure 1: Correlation Between Rdw Values (Quartiles) And Outcome of the Study Population**

Among the total cases, 51.4% cases in 4th RDW quartile died and it was observed that proportion of cases who died was progressively increasing as we go from 1st to 4th RDW quartile from 8.6% to 51.4% respectively. On performing a chi square test, this difference was found to be statistically significant (P value <0.05).

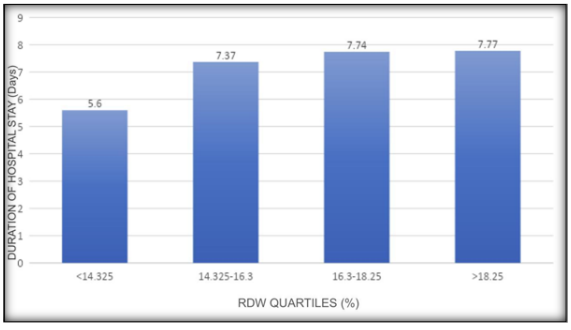


**Figure 2: ?**

As shown in the above table, mean duration of hospital stay was observed to be gradually increasing from 1st RDW quartile to 4th RDW quartile. On performing ANOVA test, this difference was found to be statistically significant (P value <0.05).

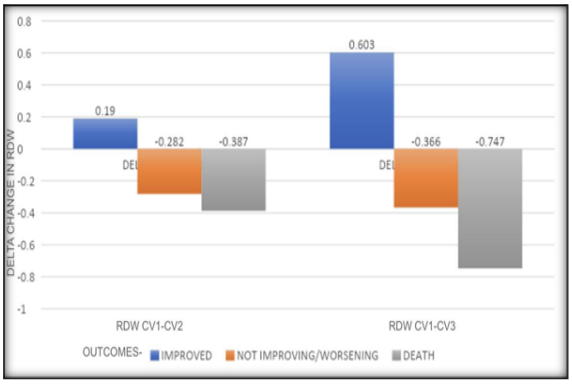


**Figure 3: Correlation Between the Delta Change in RDW [At Admission (CV1), at 48hrs (CV2) and at Discharge (CV-3)] and Outcome**

As shown in the figure the admission RDW (RDW-CV1) value was higher as compared to the RDW values after 48hrs (RDW-CV2) and at discharge (RDW-CV3) in cases that improved, thus the delta change in RDW showed a positive trend. However, the RDW values progressively increased and delta change in RDW was more negative in the cases that died. This difference was found to be statistically significant (P value <0.05).

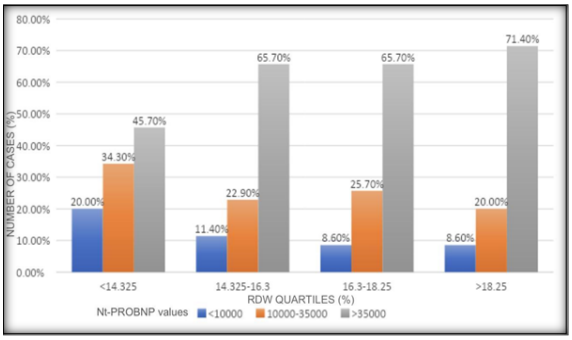


**Figure 4: Correlation Between RDW Values (Quartiles) and Nt- PRO BNP of The Study Population**

As shown in the above figure 45.7% cases in 1st RDW quartile had high NT PROBNP values of >35000 and in 4th RDW quartile their proportion was 71.4%. However, this difference was not found to be statistically significant (P value >0.05).

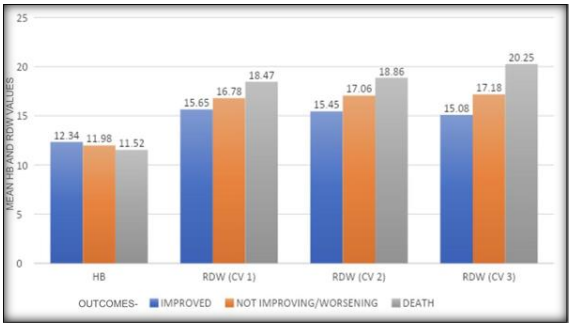


**Figure 5: Correlation Between Hemoglobin, RDW Values at All 3 Intervals and Outcome**

When hemoglobin was compared with outcome, mean values were in a decreasing trend with respect to poor

outcome (from 12.348 to 11.523). However this difference was not found to be statistically significant (P value>0.05). When RDW was compared with the outcomes, there was an increasing trend in RDW values with respect to poor outcome and it was found to be statistically significant (p<0.05).

**Table 1: Etiology of Heart Failure**

| ETIOLOGY | Frequency | Percent |
|---|---|---|
| MYOCARDITIS | 27 | 19.3 |
| ISCHEMIC CARDIOMYOPATHY | 40 | 28.6 |
| HYPERTENSIVE HEART FAILURE | 25 | 17.9 |
| ALCOHOLIC CARDIOMYOPATHY | 5 | 3.6 |
| DILATED CARDIOMYOPATHY | 25 | 17.9 |
| ACUTE CORONARY SYNDROME WITH HEART FAILURE | 11 | 7.9 |
| POSTPARTUM CARDIOMYOPATHY | 7 | 5.0 |
| Total | 140 | 100.0 |

**Table 2: Outcomes of The Study Population**

| OUTCOME | Frequency | Percent |
|---|---|---|
| IMPROVED | 66 | 47.1 |
| NOT IMPROVING/WORSENING | 34 | 24.3 |
| DEATH | 40 | 28.6 |
| Total | 140 | 100.0 |

**Table 3: Correlation Between RDW Values and Mean Duration of Hospital Stay of the Study Population**

| RDW quartiles | N | Mean duration of hospital stay | Std. Deviation | P VALUE |
|---|---|---|---|---|
| <14.325 | 35 | 5.60 | 1.897 | .016 |
| 14.325-16.3 | 35 | 7.37 | 3.789 | |
| 16.3-18.25 | 35 | 7.74 | 3.230 | |
| >18.25 | 35 | 7.77 | 3.631 | |
| Total | 140 | 7.12 | 3.312 | |

## DISCUSSION

In the present study a total of 140 patients who presented to a tertiary care hospital in South India with signs and symptoms of acute heart failure were included.

The mean age of the study population was 51.7+/-16.7 years. Among the 140 subjects involved, majority of them, 56 (40.0%) were middle aged, belonging to the 41-60 years age group, whereas around 48(34.3%) of them were elderly who belonged to the >60 years age group and 36 (25.7%) were in the 18-40 years age group.

These findings were in line with the ones from the AFAR (Acute Failure Registry Study) study on the epidemiology of acute heart failure by Sandeep Seth et al at AIIMS, New Delhi and PGIMER, Chandigarh in 2015 where the mean age was 53.5+/-

17.7 years4. In the Trivandrum Heart Failure registry study by Sevadasanpillai which assessed the clinical presentation, management and 90-day mortality outcomes in 1205 patients with heart failure, the mean age was 61.2+/-13.7 years with around 57% of the subjects belonging to <65 years age group.[5]

The mean age in Indian studies on heart failure was clearly lower than Western cohorts such as EuroHeart Failure (EURO-HF) Study where the mean age was 71 years.[6] This supports the emerging concept that cardiovascular disease affects patients in India at a younger age than their Western counterparts.

In our study 53.6% (75) of the 140 subjects were males and 46.4% (65) were females with a male to female ratio of 1.15:1 showing a slight male preponderance. These findings were similar to a study done by Trinath Kumar Mishra et al in 2018 on the prevalence and short term prognosis of heart failure; the male to female ratio was 1.9:1 with males being affected more significantly.[7]

In this study, the most common etiology of acute heart failure was ischemic cardiomyopathy seen in 28.6% of the cases followed by myocarditis 19.3%, hypertensive heart failure and dilated cardiomyopathy in 17.9% each. Acute Coronary Syndrome presenting with heart failure accounted for 7.9%, postpartum cardiomyopathy (5%) and alcoholic cardiomyopathy (3.6%).

More than 70% of participants in Trivandrum Heart Failure registry study on the in hospital and three year outcomes of heart failure patients in south India, presented with heart failure due to ischemic heart disease.[8]In Asia and the Middle East, ADHERE-AP reported 50% of 10,171 participants,[9] and Gulf CARE reported 47% of 4,539 participants had a history of coronary artery disease,[10] respectively.

The outcome of the 140 patients admitted with acute heart failure was assessed, of which 47.1% showed clinical improvement and were discharged. Around 28.6% of the study subjects died and the remaining 24.3% either worsened or showed no significant improvement. The in-hospital mortality rate of acute heart failure patients from 2008 to 2012 in India as per a meta-analysis on the heart failure care in middle and low income countries done by Thomas Callender et al, was 8%, whereas in Europe and the USA, it was 7.7% and 9.3 respectively.[11] The overall hospital mortality of 12.7% was noted in the data from the AHEAD heart failure registry in the Czech Republic.[12]Data from ADHERE,[13] OPTIMIZE-HF,[14]EURO-HF6 demonstrate an overall in-hospital mortality rate of 4–7%.

Therefore, country-level, environmental, healthcare infrastructure, and accessibility factors should be addressed if the differences in outcomes of heart failure in India were to be further explained especially when in comparison to the west.

With respect to the outcome, 51.4% of the study subjects with RDW >18.2% at admission died and it was observed that proportion of cases who died increased significantly from 1st to 4th RDW quartile from a meager 8.6% in the first quartile to 51.4% in the fourth. Around 74.3% and 48.6% of the subjects with normal and mild increase in RDW respectively had improved and were subsequently discharged.In this study the duration of hospital stay was observed to be significantly increasing from 1st RDW quartile to 4th quartile, with a mean duration of 5.6+/-1.8 days for those with normal RDW to 7.7+/-3.6 days for those with >18.2% RDW values at admission.

These results were in concordance with the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity program (CHARM) study, in which cardiovascular death or heart failure hospitalization and mortality were significantly increased with patients with RDW more than 14.7%.[15]A study on the relation between RDW and cardiovascular event rate in patients with coronary artery disease done by Marcello Tonelli et al, conclusion, concluded that a graded independent relation exists between higher levels of RDW and the risk of heart failure, cardiovascular events, and all-cause death in people with prior myocardial infarction but no evidence of heart failure at baseline.[16]

Among the 140 subjects included in this study, 45.7% of them in the 1st RDW quartile had high NT-proBNP values of >35,000pg/ml and in the 4th RDW quartile their proportion was 71.4%. Though there was a progressive increase in the NT-proBNP values as we go from 1st to 4th quartiles,this difference was not found to be statistically significant (P value >0.05) probably because of the wide range scale used to measure NT-proBNP as compared to the narrow range of values of RDW.

A study on the prognostic significance of RDW alone and in combination with NT-proBNP in patients with heart failure, by Lin Laing MB et al, found significantly high NT-proBNP values in patients with high RDW values and concluded that the combination of RDW and NT- proBNP improves the prognostic value in patients with heart failure.[17]

In this study RDW significantly correlated with poorer outcomes irrespective of the anemia status of the patient. Similarly, in 2014, Núñez et al who studied the RDW trend and anemia in patients with acute heart failure also stated that the baseline RDW value was found to be independently associated with all- cause mortality both in anemic and nonanemic patients.[18]

The prognostic value of RDW in acute HF was initially reported in a Spanish study by Pascual-Figal et al, in which RDW was found to be a strong and independent marker of all-cause mortality regardless of anemia status demonstrating that RDW may be used as an early predictor of adverse outcomes in non-anemic HF patients.[19]

In patients who improved, the initial RDW (RDW-CV1) was higher compared to the RDW values at 48 hours (RDW-CV2) and at discharge (RDW-CV3), showing a positive delta change in RDW. Conversely, in patients who died, RDW values continuously increased, resulting in a more negative delta change in RDW. This difference was statistically significant ($P < 0.05$).

Uemura et al, studied 229 Japanese patients hospitalized for acute decompensated HF, who had their RDW measured at admission and at hospital discharge and followed up. Although an increased baseline value of RDW at admission was slightly but non-significantly associated with all-cause mortality, patients exhibiting a positive change (i.e., an increase) of RDW between admission and discharge had a 19% higher risk of all-cause mortality.[20]

In a study done by J.B Muhlestein et al, increased initial RDW on hospitalization and delta RDW during hospitalization were both associated with longer duration of hospital stay during acute heart failure exacerbation and with greater risk for rehospitalization within 30 days. Also, the combination of elevated RDW and delta RDW was associated with a greater risk of mortality than either elevated in isolation.[21]

## CONCLUSION

The present study validates the strength of RDW in predicting extended hospitalization, early mortality and poor prognosis in patients admitted with acute heart failure. Being readily available in most of the hemogram analyzers, it may be a valuable tool in identifying which patients would benefit from a higher level of care or more focused care during hospitalization, or from closer follow-up as an outpatient. During hospital stay, a rising trend of RDW suggests a poorer clinical course, adverse intra-hospital outcomes and is also a predictor of post-discharge morbidity and mortality. Also, the combination of RDW and NT-proBNP together improves their efficacy as a prognostic marker in patients with heart failure. RDW can also be used as an independent predictor of adverse outcomes in both anemic and non-anemic heart failure patients. RDW may represent an integrative measure of multiple pathologic processes in heart failure explaining its association with clinical outcomes and its efficacy as a prognostic marker. This highlights the importance of future studies to determine the role of RDW assessment in clinical decision making in the management of patients with acute and chronic heart failure.

**Limitations**

- RDW is a calculated numeric value derived from other measurements, not directly detected. Therefore, its role in disease may be mediated by other factors, with RDW reflecting the combined effect of these factors.
- Being machine calibrated, the standard error may differ from lab to lab leading to falsely high or low values, thereby misguiding its interpretation in most settings.
- As this is a single-centre study with consecutive patient enrolment from both in- and outpatient departments, the results may be influenced by background bias due to patient heterogeneity and the small sample size may limit its generalizability to a larger population.
- Though many previous studies highlighted the use of RDW as a indicator of recurrent hospitalisations and all-cause mortality during follow-up of chronic heart failure patients, the subset of population included in the present study could not be followed up.

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