



## Original Research Article

### **Relationship between Red cell Distribution Width and Left Ventricular Dysfunction- Case Control Study**

Authors

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#### **Introduction**

Heart failure is the end stage for all heart diseases. Because of longevity of life and modern diagnostic equipments and advanced management, disease burden due to heart failure keeps on increasing. In developing countries like India, infectious disease like Rheumatic valvular heart disease still contributing much of this disease burden. Because of the westernisation trend non-infectious causes like metabolic disease started increasing in the last decade<sup>1</sup>.

For a proper and methodical algorithmic approach in the management of heart failure, we need a simple but effective prognostic model. This model should contain all the variables which are easily available, cheaper and prognostically significant. They have to predict the outcome in an easily explained way, so that we can discuss with the patients and relatives about the prognosis and the need for further advanced interventions.

Over a period of decade, various attempts have been made for this simple but effective model, which includes variables like BNP, NT-pro BNP, C Reactive protein, high sensitivity CRP, Interleukin-6, ESR, and echocardiographic parameters<sup>2</sup>. But, nothing fits into the category of

'ideal'. Variables like BNP has helped much in the diagnosis and prognosis determination of heart failure cases<sup>8</sup>. However, their added benefits in guiding therapy remain unknown. Other caveat in using these variables is, these markers are not unique for heart failure alone and these can also be elevated in other clinical conditions. Therefore, natriuretic peptides are not always sufficient.

Recently, elevated red cell distribution width (RDW) has been identified and proposed as a statistically significant prognostic marker in heart failure<sup>4</sup>. Red cell distribution width is a measure of the variability in size of circulating red blood cells and is expressed as the coefficient of variation or in standard deviation format. As many of the basic hematology autoanalysers can produce RDW as one of many parameters, this can be used in the prognostic model of heart failure.

As RDW is a hematological parameter routinely obtained as a part of CBC, the association between RDW and mortality might provide a valid reason to introduce this easy and inexpensive RDW in algorithms for cardiovascular risk prediction and management strategies. Thus explore the possibility of RDW to

serve as a reference indicator for clinicians to provide relevant information in stratifying high risk patients.

### Aims and Objectives

- To study the correlation between RDW and NYHA classification of heart failure
- To analyse the relationship between RDW and the severity of heart failure
- To analyse the relationship between RDW and the prognosis of Cardiac failure.

### Methodology

This case control study was conducted in Mahathma Gandhi memorial Government hospital, Trichy and was carried out from August 2016 to July 2017. All patients admitted in the medical ward were taken up for the study.

Operational definition– **Case:** Heart failure patients due to various etiologies who meet the following inclusion criteria and not presenting the following exclusion criteria will be selected.

**Inclusion criteria:** Cases of heart failure as per Framingham criteria, >15 years of age of varied etiologies like Rheumatic heart disease, Ischemic heart disease, Hypertensive heart disease, Cardiomyopathy, Corpulmonale

**Exclusion Criteria:** < 15 years, Chronic liver disease, Renal failure with serum creatinine > 2mg%

**Control:** Individuals between 20 – 60 years of age without any known history of heart and liver disease, who are all admitted for illnesses other than heart disease and also without anemia.

Sample size was calculated with the help of statistician and it came around 182 cases and 50 controls.

Study groups thus identified were instructed about the nature of the study. Willing participants were taken up after getting a written informed consent from them.

For all patients admitted with clinical picture of HF, a detailed history, general examination and systemic examination were made. All patients were subjected to Blood investigations like CBC

including RDW, urea, creatinine estimation and LFT including serum Bilirubin, AST, ALT and Serum protein estimation. RDW in coefficient variation format, haemoglobin in gram per decilitre, and mean corpuscular volume were determined using the XE-2100 model auto analyser in the hematology laboratory. RDW was measured as a part of complete blood count in EDTA whole blood through flow cytometry. Radiological investigations like CXR, USG abdomen, and 2D Echocardiography with Doppler study done within 24 hours of admission and blood tests. ECHO was done by the cardiologist. Controls were selected as per the selection criteria and they were also subjected to the same modalities of examination and investigations.

### Statistical Methods

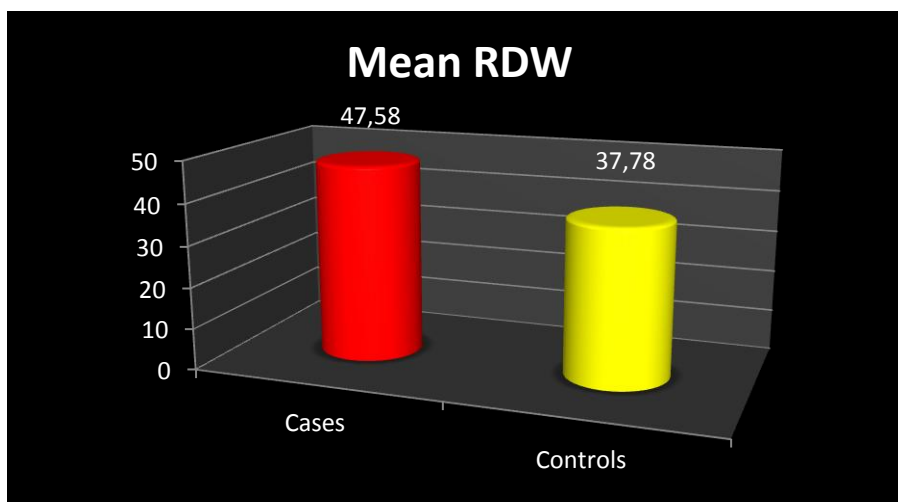
One-way analysis of variance (ANOVA) inter-group comparison was used to examine the association between RDW and heart failure. Data was analysed using simple descriptive statistics. Two-sided tests were used and a P-value of less than 0.05 was considered as statistically significant in all the considered variables.

### Results

In this case control study 182 cases and 50 controls were taken up for the study. Among the cases, males 120(65.9%) and females 62(34.1%) and among the controls, males 33(66%) and 17(33%) were females. Majority of cases had coronary heart disease 124(68%) followed by valvular heart disease 23(12.3%). Under the study with respect to NYHA II, III & IV came around 41, 98 & 43 respectively. Most common cause for cardiac failure among our hospitalised patients is Coronary heart disease. Rheumatic heart disease still contributes around 10% of the total heart failure admissions. The risk for developing heart failure increases with age. Male sex is an independant risk factor for heart failure. Smokers have high chance of developing heart failure due to coronary heart disease. High blood pressure is a significant risk factor for heart failure. NYHA functional classification essentially enumerates the

underlying progression of heart failure and is still the best method for prognostic purpose. Average LVEF among NYHA II staging is 46.9, for NYHA III 36.1. For NYHA IV staging heart failure LVEF is 24.37. RDW-CV values rises significantly in heart failure patients compared to normal persons and this rise is not associated with the Hb level. RDW-CV values rises dynamically

along with worsening of heart failure. Its rise is in concordance with the worsening of heart failure staging estimated by NYHA classification. RDW between LVEF are significantly negatively correlated. As an simple and easily available investigation, Red cell distribution width can be considered as a prognostic marker in heart failure.



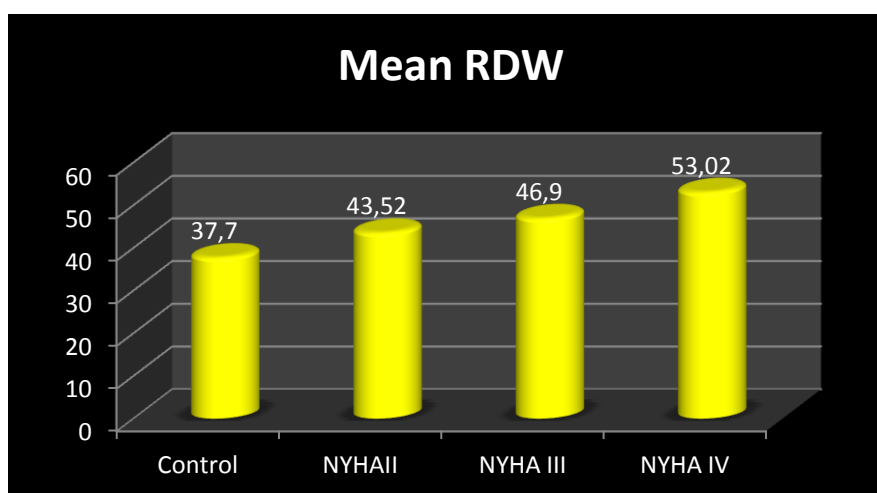
**LVEF:**

Average LVEF among the controls was 62.42. LVEF diminishes progressively in NYHA II, III and IV groups viz., 46.9, 36.1, 24.37 respectively. Our values correlates well with the LVEF values given by Simon D.R.Thakray et al in 2002 for NYHA II, III and IV functional staging viz, 45, 35 and 22. So, LVEF linearly correlates with NYHA staging in heart failure.

**NYHA staging:**

Total cases under NYHA II was 41. Mean RDW among this group was 43.52 without considering

age and sex. For males which comprises 21patients average RDW was 42.27 and for 20 females enrolled in this group mean RDW was 44.84. 98 patients were in the NYHA III staging. Among them 72 were males and 26 females. Mean RDW among male NYHA III patients were 46.67 and for females 47.52. The joined mean RDW among this group was 46.9. Among 43 NYHA class IV patients, mean RDW was 53.2. Out of this male contributes 27 and remaining are females. For Males the value stood as 52.05 and for females 54.66



In 50 controls enrolled in the study , mean RDW was 37.78 and this value is significantly lower compared to all cases or comparing with NYHA I stage as per statistical analysis with the ‘p’ value of <0.001. In the male controls mean RDW value was 37.23 and when this value is compared with the mean RDW among cases i.e. 46.65 it showed positive prediction of significant heart failure with the RDW cut off above 45. Even comparing the control value with the individual NYHA groups in failure cases, that also showed ‘p’ value of <0.001 and this was very much significant statistically. Among 17 female controls enrolled in our study

the mean RDW was 38.85 and when compared this value with female group’s value of 49.00 , ‘p’ value was < 0.001 when analysed on chi square test. While splitting the female groups as per NYHA staging also shows the mean RDW values progresses dynamically from control group to progressive NYHA groups. This RDW values correlate very well with NYHA staging.

In the NYHA staging as mentioned before, the LVEF diminishes progressively from NYHA I to IV. Like that RDW-CV values also raises dynamically in parallel to the worsening heart failure stages.

**RDW-cv between Cases and Controls:**

	RDW-cv			P value
	Max	Min	Average	
Heart Failure Cases	65.6	38.2	47.58	< 0.001
Control	41.1	34.2	37.78	

**Group Statistics**

Groups	N	Mean	Std. Deviation	Std. Error Mean
RDWCV Heart failure Patients	182	47.588	4.6744	.3465
normal	50	37.784	1.5648	.2213

**Multiple Comparisons**

Dependent Variable tested: RDWCV

(I) NYHA	(J) NYHA	Mean Difference (I-J)	Std. Error	Significance	95%age Confidence Interval	
					Lower Bound	Upper Bound
2.00	3.00	-3.3752	6.1159	.023	-18.472	11.721
	4.00	-19.8801*	7.1775		-37.597	-2.163
3.00	2.00	3.3752	6.1159	.859	-11.721	18.472
	4.00	-16.5049*	6.0148		-31.352	-1.658
4.00	2.00	19.8801*	7.1775	.023	2.163	37.597
	3.00	16.5049*	6.0148		1.658	31.352

\*. Considered significant at the .05 level.

**ANOVA**

RDWCV

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	10387.333	2	5193.666	4.803	.009
Within Groups	193541.4	179	1081.237		
Total	203928.8	181			

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means				
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference
RDWCV	Equal variances assumed	30.278	.000	14.588	230	.000	9.8045	.6721
	Equal variances not assumed			23.848	222.204	.000	9.8045	.4111

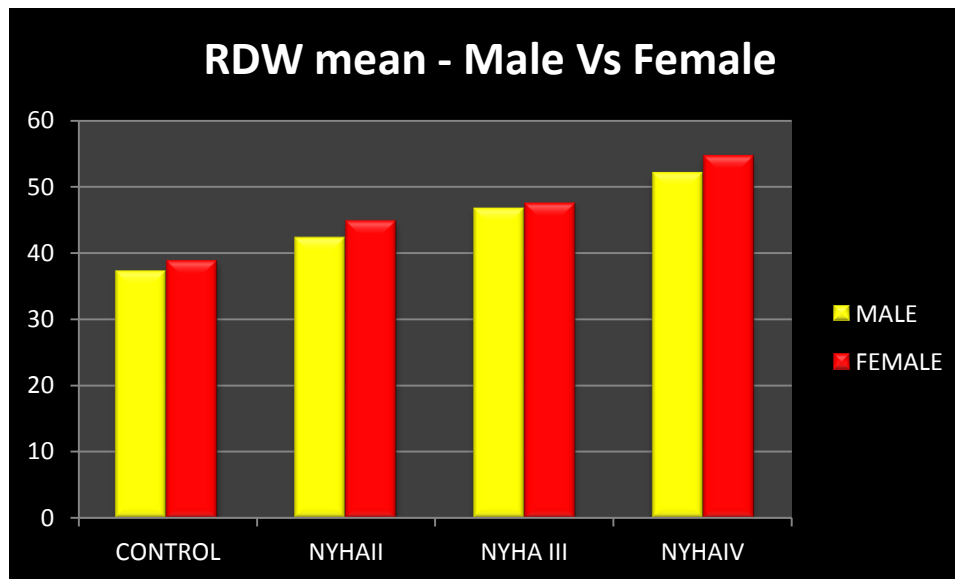
Multiple Comparisons

Dependent Variable: RDWCV

Scheffe

(I) NYHA	(J) NYHA	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
2.00	3.00	-3.3752*	.6156	.001	-4.895	-1.856
	4.00	-9.4988*	.7225	.001	-11.282	-7.715
3.00	2.00	3.3752*	.6156	.001	1.856	4.895
	4.00	-6.1235*	.6055	.001	-7.618	-4.629
4.00	2.00	9.4988*	.7225	.001	7.715	11.282
	3.00	6.1235*	.6055	.001	4.629	7.618

\*. The mean difference is significant at the .05 level.



LVEF by ECHO:

NYHA	No of Cases	LVEF in %age		
		Max	Min	Average
II	41	60	39	46.9
III	98	60	22	36.61
IV	43	49	18	24.37
Control	50	68	56	62.42

**Cases vs controls**

	Frequency	LVEF (%)		RDW-cv	
		Range	Mean	Range	Mean
Control	50	56-68	62.42	34.2-41.1	37.7
NYHA II	41	39-60	46.9	38.2-46.5	43.52
NYHA III	98	22-60	36.61	42.4-62.5	46.9
NYHA IV	43	18-49	24.37	45.6-65.6	53.02

	Frequency	RDW-cv			LVEF(%)		
		Max	Min	Average	Max	Min	average
control	50	41.1	34.2	37.7	68	56	62.42
cases	182	65.6	38.2	47.85	60	18	36.04

**Discussion**

About 232 persons were enrolled in the present study. Out of these 182 persons were grouped as heart failure 'cases' and 50 persons were designated as 'controls' as per the selection criteria. All were subjected to clinical and laboratory examination as per proforma. The results are as follows.

**Age:**

Out of 182 heart failure cases studied 153 were >40 years of age. This contributes 84% of total cases. Most of the patients in the study were between 40-60 years of age. Increasing age is a risk factor for heart failure and this study correlates well with the study done by William B Cannel, published in AHA in 1991.

The mean RDW among <40 years group was 48.9 and for >40 years group 50.3. The minimal difference between this group may be due to high number of heart failure cases among this . Age is not a confounding factor for RDW rise among heart failure cases.

**Sex:**

Out of 182 heart failure cases 120 cases are male and contributes 65% of total case load. Male sex is an independant risk factor for heart failure. This results correlates well with the NHANES 1<sup>3</sup> survey report of 2001.

**Etiology:**

Most common etiology among the heart failure patients is Coronary artery disease (68%). Rheumatic valvular heart disease contributes around 12.5% of heart failure cases. In contrast to the western scenario, where reports pointing CAD and Hypertension as a cause for heart failure in

80% cases, in our study Rheumatic valvular heart disease still contributes to the development of heart failure in 12.5% cases.

There is not much difference in the values of RDW in CAD, Corpulmonale or valvular heart diseases and averages around 47.05- 48.1. But in DCM cases the mean RDW value is 50.77 and this produces significant 'p' value of <0.05. But, majority of this DCM patients are belonging to NYHA III or NYHA IV category. This is the reason for high RDW value among DCM patients.

**Risk Factors****A) Smoking**

Among the smokers, most are suffering from coronary heart disease and corpulmonale. RDW-CV values are high in smokers ( $47.3 \pm 6.8$ ) . But there were no significant difference compared to non smokers group ( $47.6 \pm 7.5$  p: 0.08). By using pearson correlation test , higher number of cases with high RDW were smokers ( 65% smokers p < 0.05 ). So, smoking as a confounding factor is ruled out. Our study correlates well with the study done by parlak et al in Turkey in 2012.

**B) Blood Pressure**

68% of heart failure patients are hypertensive. This value is highly significant risk factor for heart failure development 'p' value <0.005

**Hemoglobin**

Average Hemoglobin among the 'cases' were 12.71 g%, in 'control' group 12.77 g%. Even though anemia is considered as a precipitating and risk factor for heart failure, because of selection bias there is no significant reduction in haemoglobin levels in patients. So, anemia as a

confounding factor is ruled out for the elevation of RDW in heart failure patients.

RDW:

The mean RDW among case were 47.58 and among control group 37.78. Among the NYHA classification in the heart failure group the mean RDW value for NYHA II is 43.52, For NYHA III 46.9 and For NYHA IV 53.20. The value among these control and case groups and among the NYHA groups is statistically significant ( $p$  value  $< 0.0001$ ). RDW rise in heart failure shows linear correlation with the progression of heart failure.

Among the males, control group have the mean RDW of 37.23 and case group have 46.65 and this value is statistically significant. Among females, control group have the mean RDW of 38.85 and case group have 49.00. The slight rise in the RDW values in females in both the group correlates with the higher levels of estrogen. Normal value of RDW-CV for Male ranges from 35.1-43.9 and For females 36.4-46.3 and our study confirms this higher value in females.

### **Mechanism of RDW Rise in Heart Failure**

RDW is used to evaluate variance in the size and form of red cells. RDW is a coefficient of variation of MCV, therefore higher RDW values reflect greater heterogeneity in MCV (anisocytosis). This heterogeneity in MCV is usually caused by variation in the maturation and degradation rate among the erythrocyte group. Recent researches clearly pointed out the prognostic importance of RDW rise among heart failure patients and regarded as a prognostic marker. But the mechanisms underlying the association between RDW and severity of LV dysfunction and its role in predicting mortality in heart failure remains elusive to all the researchers in all these years. Although exact physiologic mechanism is unknown, systemic factors that alter erythrocyte homeostasis such as inflammation and oxidative stress has been proposed as the potential mechanisms behind this rise of RDW among heart failure cases.

### **Inflammatory Theory<sup>5</sup>**

Role of inflammatory mediators in the pathogenesis of heart failure have been proved beyond doubt. Recent study has shown positive correlation between RDW and the inflammatory markers among the heart failure patients, which was independent of other confounding variables like old age, sex, ferritin or other blood indices. This inflammatory mechanism affects the RDW by three mechanisms.

- 1) Inflammatory mediators inhibiting the erythrocyte production and diminishes the responsiveness of bone marrow to erythropoietin.
- 2) All the inflammatory mediators which are in elevated levels in heart failure, shorten the survival period of erythrocytes.
- 3) Inflammatory mediators impairs iron metabolism.

### **Oxidative Stress Theory**

Heart failure is associated with higher oxidative stress. Oxidative stress causes increase in anisocytosis by disrupting erythropoiesis and to alter blood cell membrane abnormality and red blood cell circulation half life, ultimately leading to increased RDW<sup>6</sup>.

### **Limitations of this Study**

As this study was performed in a cross section format, we did not observe the RDW values dynamically over a period of time. So, it is very hard to get the nature of elevation in RDW values among the heart failure patients whether the values progressed in a same stepwise manner like left ventricle dysfunction or not.

We did not investigate further about the causes of elevated RDW values like serum ferritin, serum iron estimation, TIBC or serum folate and cobalamin estimation. These may play as a confounding factor in RDW estimation.

Because RDW values are easily attainable by means of routine CBC investigation, and it is highly reproducible in a given patient, it may serve as an important biomarker in determining the prognosis of heart failure.

**Conflict of interest:** Nil

**Financial Support :** Nil

**Ethical Committee clearance:** Obtained

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