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ORIGINAL ARTICLE

Evaluation of Red Cell Distribution Width and its Correlation with Left Ventricular Ejection Fraction in Heart Failure Patients

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Abstract:

Introduction: Red cell distribution width (RDW) is a coefficient of variation of the distribution of individual RBC volume, as determined by automated blood cell counting instrument. Numerous studies, conducted elsewhere, have demonstrated increased RDW to bea significant prognostic marker in patients with heart failure, both with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF). So, we designed this cross-sectionalstudy, to study the relationship between RDW and left ventricular ejection fraction (LVEF), the most significant echocardiographic parameter of left ventricular systolic function, in patients of heart failure in our region, at a tertiary care centre of North India.

Methods: This study was a cross sectional study conducted on 52 patients of heart failure,who attended medical emergency/outpatient services of Guru Nanak Dev Hospital, Amritsar. RDW was assessed with automated analyzer and LVEF was seen by echocardiography in heart failure patients and their association was studied by Pearson Correlation method.

Results: LVEF and RDW-CV revealed a Pearson Correlation coefficient of -0.861 which was statistically highly significant ($p < 0.001$), which stayed highly significant even after adjusting for other potential confounding factors like diabetes mellitus (DM), dyslipidemia andhypertension (HTN)

Conclusion: Heart failure patients with low LVEF have elevated RDW levels compared with normal LVEF, thus RDW correlated with severity of left ventricular systolic dysfunction.

Keywords: Heart failure, RDW, LVEF

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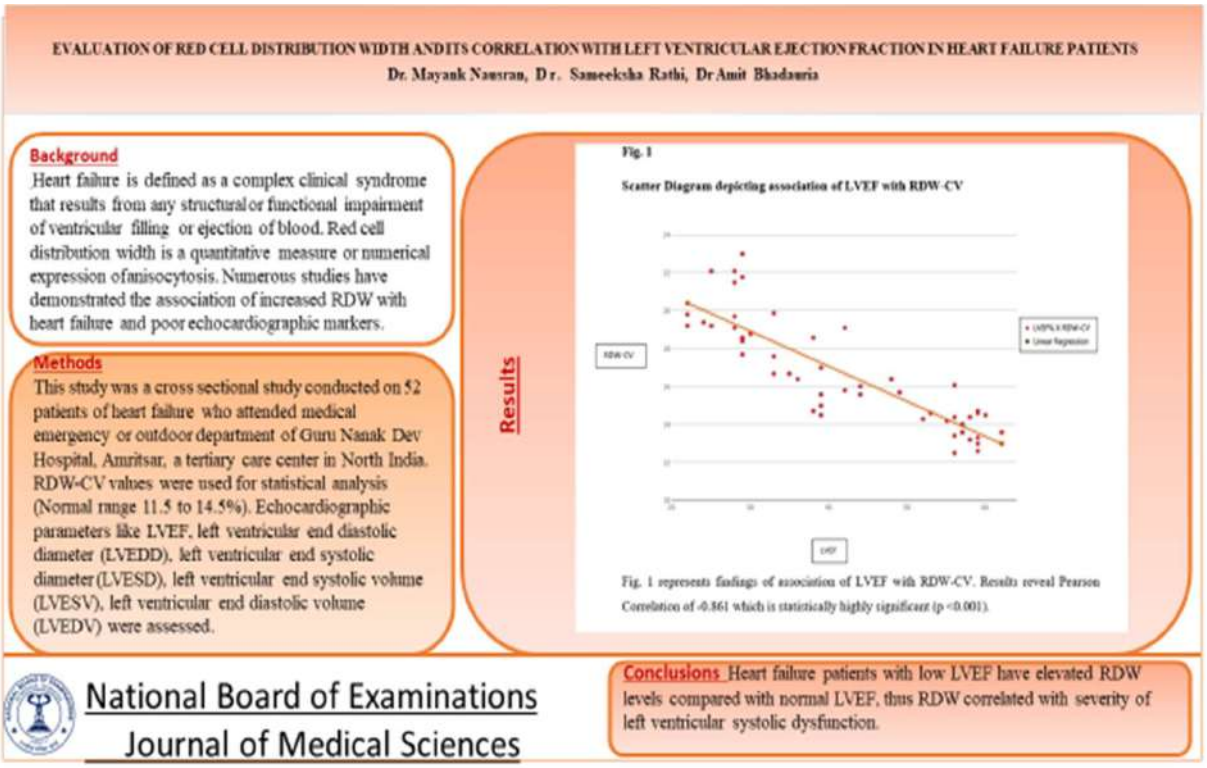
Graphical Abstract



Introduction

Heart failure is defined as a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood [1]. It can also be defined as a pathophysiological state in which an abnormality in cardiac function (structural or functional) results in the failure of the heart to pump blood under normal cardiac pressures at a rate that isneeded to meet the metabolic demands of the body and if does so, it does it at high cardiac filling pressures [2].

Red cell distribution width is a quantitative measure or numerical expression ofanisocytosis. It is a coefficient of variation of the distribution of individual RBC volume, as determined by automated blood cell counting instrument. High red cell distribution width valuemirrors a large range in red cell size. It can be measured as either RDW-CV (Red cell distribution width–coefficient of variation) or RDW-SD (Red cell distribution width–standard deviation). RDW-CV is calculated from formula (standard deviation of RBC volume/mean corpuscular volume)*100. It varies normally from 11.5 –14.5%. RDW-SD is regarded as widthof the distribution

curve calculated arithmetically which is measured at the 20% frequency level. It is direct measure of calculating RDW.

RDW can be increased in a variety of conditions e.g. inflammation, ageing, oxidative stress, nutritional deficiencies, renal insufficiency. Numerous studies have demonstrated the association of increased RDW with heart failure and poor echocardiographic markers. It has been shown to be a poor prognostic marker, associated independently with increased rates of cardiovascular and all-cause mortality, hospitalization for acute decompensation or worsened left ventricular function, length of hospital stay, in patients with acute and chronic heart failure (HF). It is also a significant and independent predictor of developing heart failure in patients who currently do not have any signs or symptoms of heart failure.

This study was designed to assess the relationship between RDW and LVEF, the most significant echocardiographic parameter of left ventricular systolic function, in patients with HFpEF and HFrEF in our region, presenting at a tertiary care centre of North India.

Methods

This study was a cross sectional study conducted on 52 patients of heart failure (already diagnosed and newly diagnosed), who attended medical emergency or outdoor department of Guru Nanak Dev Hospital, Amritsar, a tertiary care centre in North India. The study was conducted after approval from institutional ethics committee, and informed consent was taken from patients to be enrolled in study. Our study conforms to widely accepted ethical principles guiding human research (such as the Declaration of Helsinki). The patients either newly diagnosed or already diagnosed cases of heart failure (HFrEF and HFpEF), who were 18 yearsand above, were included in the study. Patients who refused to give consent, had liver disease,renal disease, or anemia with Hb of <12 g/dl, and those with history of blood transfusion within past 3 months or haematological malignancy, were excluded from the study. All eligible patients were subjected to a detailed history taking and clinical examination, including assessment of signs and symptoms of heart failure, the NYHA classification of heart failure, risk factors such as smoking (smoking index >100), alcoholism (>14 units/week), hypertension, diabetes, dyslipidemia, coronary artery disease, and current and pastmedications. Biochemical investigations including HbA1c, fasting and post-prandial plasma glucose, oral glucose tolerance test (if required), liver function tests, fasting lipid profile, renal function tests were performed on all patients. Complete hemogram was performed in an automated cell counter Erba Mannheim H360. Hemoglobin, MCV, Hematocrit, RDW-CV and RDW-SD, amongst other parameters, were determined. Only RDW-CV values were used for statistical analysis. Normal range of RDW-CV was taken to be 11.5 to 14.5%. M-mode echocardiography was performed on these patients and echocardiographic parameters like LVEF, left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter(LVESD), left ventricular end systolic volume (LVESV), left ventricular end diastolic volume(LVEDV) were assessed.

Statistical analysis was done with SPSS software ver. 26.0 and Epi Info 7.2.5.0. Difference of means in RDW-CV in different NYHA classes was tested with ANOVA. Correlation between RDW-CV and LVEF was assessed with Pearson Correlation Coefficient. Linear regression analysis was done to evaluate the potential

confounding effect of other variable that could have affected RDW-CV.

Results

Table 1 shows the baseline characteristics of the patients enrolled for the study. Mean age of the patients included in the study was 51.5 ± 15.47 years. Most of the patients were male (71.2%, n=37). Ischemic heart disease was the most common etiology of heart failure (59.6%, n=31). A majority of the patients were in NYHA class 3 (65.4%, n=34). Mean LVEF in these patients was 42 ± 12.9%. In the hematological markers, mean haemoglobin was 13.5 ± 4.04 g/dl, the mean MCV was 89.6 ± 5.23 fL, and the mean RDW-CV value was 16.7 ± 2.78%.

The RDW-CV values showed a statistically significant increase from NYHA class 2 to 4 (p value <0.001) (Table 2). On subgroup analysis, there was significant increase in RDW-CV from NYHA class 2 to 3, 3 to 4 and 2 to 4 (results not shown).

There was a highly significant statistical negative correlation between RDW-CV and LVEF (r = -0.861, p value <0.001) (Fig. 1).

On analysis of correlations of various other variables that could potentially affect RDW-CV, we found that presence of diabetes mellitus and dyslipidemia significantly increased RDW-CV (p values <0.001 and 0.002 respectively) and presence of hypertension also increased RDW- CV but marginally failed to achieve the level of statistical significance (p value 0.055). There was no statistically significant correlation between RDW-CV and age, gender, smoking, alcohol consumption and patient's Hb levels. So we performed a multiple linear regression analysis with RDW-CV as outcome variable and LVEF, DM, dyslipidemia and HTN as independent variables (Table 3). On conducting multiple linear regression analysis, we found that LVEF was strongly negatively correlated with RDW-CV, even after adjusting for other variables that affected RDW-CV in single linear regression analyses. In fact, the effect of DM, dyslipidemia and HTN became non-significant in this model, with a much greater than 10% change from individual correlation coefficients, suggesting that the effect of these variables onRDW-CV is due to LVEF itself.

Table 1. Baseline Characteristics

Characteristic	Value
Age (Mean ± SD)	51.5 ± 15.47
Sex (% (n)) Males Females	71.2 (37) 28.8 (15)
Risk Factors for heart failure (% (n)) Diabetes Mellitus HypertensionDyslipidemiaSmoking Significant Alcohol intakePrior CAD Prior hospitalization for heart failure	36.5 (19) 40.4 (21) 32.7 (17) 17.3 (9) 42.3 (22) 19.2 (10) 21.1 (11)
Underlying Etiology of heart failure (% (n)) Ischemic heart disease Rheumatic heart diseaseCalcific AS/AR Alcoholic Cardiomyopathy DCM – unknown cause Peripartum Cardiomyopathy Right Ventricular Dysfunction CHD with Eisenmenger's Complex	59.6 (31) 9.5 (5) 3.9 (2) 3.9 (2) 5.8 (3) 1.9 (1) 3.9 (2) 1.9 (1)
Myocarditis Cor pulmonale	1.9 (1) 7.7 (4)
NYHA Class (% (n)) Class 1 Class 2 Class 3 Class 4	0 15.4 (8) 65.4 (34) 19.2 (10)
LVEF (Mean ± SD)	42 ± 12.9
RDW-CV (%) (Mean ± SD)	16.7 ± 2.78
Hemoglobin (g/dl) (Mean ± SD)	13.5 ± 4.04
MCV (fL) (Mean ± SD)	89.6 ± 5.23

Table 1 shows the baseline characteristics of the patients enrolled for the study. Abbreviations:SD – Standard Deviation, CAD – Coronary Artery Disease, AS – Aortic Stenosis, AR – AorticRegurgitation, DCM – Dilated Cardiomyopathy, CHD – Congenital Heart Disease, NYHA – New York Heart Association, LVEF – Left Ventricular Ejection Fraction, RDW-CV – Red Cell Distribution Width - Coefficient of Variation, MCV – Mean Corpuscular Volume

Table 2. Comparison of RDW-CV according to NYHA Functional Class

NYHA Functional Class	RDW-CV (Mean ± S.D.)	p-value
1	-	<0.001
2	13.30±0.66	
3	16.40±2.02	
4	20.40±1.67	

Table 2 tabulates the findings of comparison of RDW-CV values according to NYHA Functional Class, obtained from Analysis of Variance (ANOVA) test. Results show statistically highly significant difference between RDW-CV values in all NYHA Functional Class ($p<0.001$).

Table 3. Multiple linear regression analysis for potential confounding factors

Variable	Coefficient	P-value
DM	0.665	0.144
Dyslipidemia	0.481	0.328
HTN	0.305	0.491
LVEF (%)	-0.166	<0.001

Table 3 shows the results of multiple linear regression analysis for potential confounding factors in addition to LVEF, that individually showed correlation with RDW-CV in single linear regression analyses (namely DM, dyslipidemia and hypertension). The results show thatthe negative correlation between LVEF and RDW-CV remains to be highly significant even after adjusting for these variables and the effects of the other variables became non-significantwhich suggests that their individual correlations can be explained by LVEF alone.

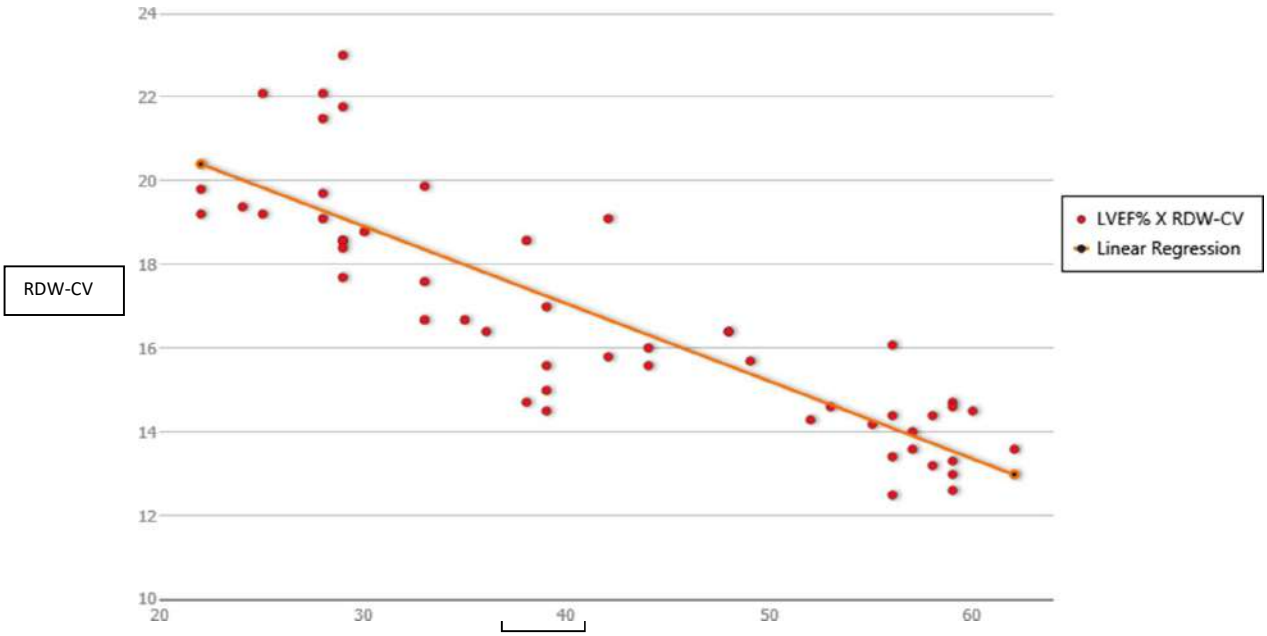


Figure 1. Scatter Diagram depicting association of LVEF with RDW-CV

Figure 1 represents findings of association of LVEF with RDW-CV. Results reveal Pearson Correlation of -0.861 which is statistically highly significant ($p < 0.001$).

Discussion

In our study patients more than 18 years of age were taken. Youngest patient enrolled in study was 20 years of age and the eldest one is 78 years of age. Majority of participants belonged to the age group of 40-49 and 60 to 69 years which added up to 23.1% each followedby 19.2% individuals of age group between 50-59 years. This age group is most prone to risk factors of heart failure like HTN/ DM/ Myocardial Ischaemia. Therefore this can be a reason why most of the patients admitted were of this age group. These values were further validatedin a study by Van Craenenbrock EM[3] where most of the patients were of age 50-70 years and study by Bozorgi et al. [4] where most patients were of age between 50-75 years.

In our study of all the individuals involved of various age groups, male participants added up to 71.2% which was more than double of female counterparts which were 28.8%. This may be due to males being more prone to cardiovascular diseases than females. Also intake of alcohol and smoking is more common in males than females. Above values are positively correlated with that in study by Bozorgi A et al[4] where 74.3% were males and Kawasoe et al. [5] 69% were men.

In our study most of the patients which presented in hospital for treatment were of NYHA class 3 which involved 65.4% patients. It was followed by NYHA class 4 which constituted 19.4%. In study by OH et al. [6] NYHA 3 plus 4 combined constitutes 83%. This could be because of the fact that it is a tertiary care centre and most of the patients present in late stages of the disease.

These patients had mean RDW-CV value of 16.7 which is well above the higher normallimit. Mean left ventricular ejection fraction in these patients was 42% which

depicts that even patients of preserved ejection fraction were in significant proportion. In study by Ferreira et al. [7] mean RDW-CV values were 15.4 $\pm$ 2.7 and ejection fraction values between 43.8 $\pm$ 11.1.

Results of this study reveal a statistically highly significant negative correlation between left ventricular ejection fraction and RDW-CV. This correlation becomes stronger as the patients progress from NYHA 2 to NYHA 4 classes of heart failure. This negative correlation stayed highly significant even after adjustment of other potential confounding factors like DM, dyslipidemia and HTN and the effect of these conditions, as seen in individual analyses disappeared after adjustment for LVEF. This suggests that LVEF affects RDW-CV, independent of other potential confounding factors. RDW is a useful prognostic marker not only for heart failure but also for atherosclerotic diseases, such as coronary artery disease or carotid artery disease [4]. In study by Bozorgi et al. [5] pearson correlation analysis demonstrated a significant ($p<0.001$) but weak negative correlation ($r=-0.268$) between RDW and LVEF. Instudy by Senthong V et al[8] high RDW values were significantly associated ($p = 0.04$) with LVEF < 40% in heart failure patients. In study by Ferreira et al. [7] RDW is associated with LVEF having p value less than 0.05 which is highly significant.

The study is not without limitations. The first limitation is the small sample size. The results of this study need to be established in larger studies. Secondly, this is a cross-sectionalstudy. Clear association of increased RDW with poor prognosis in patients with heart failure can be established by long term prospective survival studies. Thirdly, since 83% of the patients enrolled in the study had a NYHA class 3 or 4 heart failure, the results of this study may be more relevant to the patients with severe heart failure and not relevant much to the patients with lesser severity of heart failure. Nevertheless, despite all these limitations, our study has shown a highly significant negative association between RDW and LVEF, which is inconcurrence with the data from earlier studies.

Conclusion

RDW levels are increased amongst patients with heart failure patients. Heart failure patients with low left ventricular ejection fraction have elevated RDW levels compared with normal left ventricular ejection fraction, independent of presence of other potential confounding factors. RDW correlates with severity of left ventricular systolic dysfunction. Thus it can be used as a simple parameter that can help in assessing the severity of the heart failure. This becomes especially relevant in resource-poor settings where access to echocardiography may not be immediately available.

Conflicts of interest

The authors declares that they do not have conflict of interest.

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