Original Article

Relationship of red cell distribution width-coefficient of variance with the severity of systolic dysfunction in patients of heart failure with reduced ejection fraction

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ABSTRACT

Background: *Red blood cells distribution width (RDW)-coefficient of variance (RDW-CV) is a measure of red blood cell width variation, reported as part of a standard complete blood count. Although it is usually measured as a routine test, actually its values have been only used in the differential diagnosis of anemia and its high values indicate the presence of anisocytosis. It has been demonstrated that RDW could be considered as an independent additional marker of cardiovascular events in patients with heart failure with reduced ejection fraction. However, the role of RDW in patients with heart failure is less known. This study was designed to evaluate the relationship between RDW-CV and severity of systolic dysfunction in patients with heart failure with reduced ejection fraction (HFrEF).*

Methods*: This cross-sectional study was carried out at the Department of Cardiology, Sir Salimullah Medical College and Mitford Hospital, Dhaka, Bangladesh from April 2019 to March 2020. This study included 100 consecutive patients with dyspnea, fatigue and fluid retention suggestive of heart failure. Participating subjects were subjected to a detailed history taking, complete physical examination, New York Heart Association (NYHA) class, 12-lead electrocardiogram (ECG) and routine laboratory investigations including RDW-CV calculate from complete blood count were performed. Left ventricular ejection fraction (LVEF) was measured by echocardiography.*

Results*: The study showed statistically significant negative correlation between RDW-CV and LVEF (r = -0.498, p value<0.001).*

Conclusion*: In the study showed that elevated RDW was associated with decreased ejection fraction assessed by echocardiography in patients of HFrEF. Therefore, increased RDW could be used as an additional marker for identifying severity of left ventricular dysfunction.*

Key words: *red blood cells distribution width-coefficient of variance, heart failure, ejection fraction.*

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INTRODUCTION

As a complex clinical syndrome, heart failure (HF) is characterized by certain symptoms and signs such as dyspnea and fatigue, impaired exercise tolerance, fluid retention, pulmonary and/or splanchnic congestion, peripheral edema, elevated jugular venous pressure and pulmonary crackles.[1] These are principally due to structural and/or functional cardiac abnormalities, which result in an impaired cardiac output and/or elevated intracardiac pressures.[1,2] The classification of the different types of HF is based on left ventricle ejection fraction (LVEF) as follows: (1) HF with preserved LVEF (HFpEF), i.e., patients with normal LVEF (≥50%); (2) HF with reduced EF (HFrEF), i.e., patients with reduced LVEF (< 40%); (3) HF with midrange EF (HFmrEF), i.e., patients with an LVEF in the range of 40%-49%.[1]

The etiology of HF is varied, including a wide range of pathologies both cardiovascular and non-cardiovascular. The prevalence of HF in developed countries is considered to be around 1%-2% of the adult general population.[3] The incidence increases with age, up to ≥10% among people > 70 years of age. In recent years, studies have reported a strong independent association between red blood cells distribution width (RDW) and prognosis in cardiopulmonary disorders such as coronary artery disease (CAD)[4], acute myocardial infarction (AMI)[5], acute HF[6] and chronic HF[7] and pulmonary embolism.[8] Convincing evidence has accumulated that both cell and cytokine-mediated inflammatory pathways actively contribute to development and progression of HF.[9] As regards oxidative stress, an excess production of reactive oxygen species (ROS) has been associated with both adverse cardiac remodeling[10] and deranged hematopoiesis, ultimately leading to anisocytosis. This study aimed to evaluate the relationship between RDW-coefficient of variance (RDW-CV) and severity of left ventricular systolic dysfunction in patients with HFrEF.

METHODS

This cross-sectional study was carried out at the Department of Cardiology, Sir Salimullah Medical College Mitford Hospital (SSMC and MH), Dhaka, Bangladesh from April 2019 to March 2020. A total of 100 adult (age >18 years) patients with HFrEF as per inclusion criteria who were admitted in the cardiology department were selected for the study by using convenient sampling technique. The study population were divided into two groups on the basis of cut off value of RDW[15], **Group 1:** HFrEF with RDW < 13.6; **Group 2**: HFrEF with RDW ≥ 13.6.

Patients with HFpEF (LVEF ≥50%), HFmrEF(40-49%), hematologic disorders, active infection, inflammatory diseases, severe liver disease, chronic kidney disease, patients receiving glucocorticoids, malignancy and/or neoplastic metastasis in the bone marrow, cyanotic congenital heart diseases, bleeding disorders, recent blood transfusions, pregnancy, severe anemia (Hb%<7 gm/dl) and unwilling to participate in the study were excluded. The study protocol was approved by the Ethical Review Committee of SSMC& MH. Informed consent was taken from each participant. Informed consent was taken from each patient. Particulars of the patient, relevant history was taken and detailed clinical examination findings were recorded in predesigned data collection sheet. Approximately 10 ml of blood was drawn from patient for biochemical and hematological test including complete blood count (CBC). Of the 10 ml of the blood, about 3 ml of blood was collected in thylenediamine tetraacetic acid (EDTA) vial for CBC. Blood sample was then put in on automated hematology analyzer (Penta Dx, Horiba) in our hospital laboratory. RDW was measured automatically from the machine and the data was collected from the CBC report. Echocardiography was done by VIVID E95 echocardiographic machine of GE corporation. EF was measured by modified Simpson's methods as per recommendation by the American Society of Echocardiography (ASE). A patient who had LVEF < 40% was included as study subject and study populations were divided into two groups on the basis of cut off value of RDW. Group 1: HFrEF having (RDW <13.6) and Group 2: HFrEF having (RDW ≥13.6).[15]

Data were processed and analyzed manually and using Statistical Package for Social Sciences (SPSS) Version 25.0. Quantitative data was expressed as mean and standard deviation and comparison was done by "student t" test. Qualitative data was expressed as frequency and percentage and comparison was carried out by Chi-square (χ^2) test. Correlation between RDW and EF was assessed by Pearson's correlation test. A probability (p) value of <0.05 was considered as significant.

RESULTS

Total 100 consecutive patients with HFrEF were included and divided into two groups: **Group 1:** HFrEF with RDW < 13.6 (n=30); **Group 2**: HFrEF with RDW ≥13.6 (n=70). Age and gender distribution is shown in Table I. Other base-line characteristics, clinical features and risk/co-morbidities are are shown in Table II, III and IV respectively.

Table I. Comparison of the study patients according to age and gender (N=100)

Variables	Group I (n= 30)		Group II (n= 70)		p value
	No.	%	No.	%	
Age in years					
<30	0	0.0	2	2.9	
30 – 39	1	3.3	4	5.7	
40 – 49	2	6.7	6	8.6	
50 – 59	18	60.0	25	35.7	
≥ 60	9	30.0	33	47.1	
Mean ± SD(Range)	56.23±6.69(34-67)		56.44±11.29(19-85)		0.925^{ns}
Gender					
Male	22	73.3	46	65.7	0.454^{ns}
Female	8	26.7	24	34.3	

Group I- HFrEF patients with RDW-CV <13.6
Group II-HFrEF patients with RDW-CV ≥13.6

Table II. Baseline clinical characteristics and laboratory findings in two groups (N=100)

Variables	Group I (n= 30)	Group II (n= 70)	p value
NYHA class			
Class III	24(80.0%)	15(21.4%)	<0.001^{s}
Class IV	6(20.0%)	55(78.6%)	
SBP (mm Hg)	118.17±15.62	115.07±12.95	0.306^{ns}
DBP (mm Hg)	74.00±10.94	72.14±8.75	0.370^{ns}
Hb (%)	11.27±1.63	11.28±1.36	0.982^{ns}
Fasting blood glucose (mmol/L)	5.64±1.04	5.78±1.06	0.548^{ns}
Serum creatinine (mg/dl)	1.03±0.25	1.08±0.30	0.468^{ns}
Total cholesterol (mg/dl)	173.70±17.06	180.89±17.81	0.064^{ns}
High density lipoprotein (mg/dl)	44.87±9.37	41.61±8.38	0.089^{ns}
Low density lipoprotein (mg/dl)	140.90±20.77	131.20±20.40	0.033^{s}
Triglyceride (mg/dl)	120.07±22.46	107.13±24.60	0.015^{s}

Table III. Distribution of study subjects by clinical manifestation (N=100)

Clinical Feature	Group I (n= 30)		Group II (n= 70)		p value
	Number	%	Number	%	
Breathlessness	27	90.0	67	94.3	0.592^{ns}
Fatigue	26	86.7	65	92.9	0.322^{ns}
Orthopnea	28	93.3	62	88.6	0.467^{ns}
Peroxysmal nocturnal dyspnoea	20	66.7	49	70.0	0.741^{ns}
Edema	22	73	52	74	0.921^{ns}

Among the clinical parameters, a greater number of patients were symptomatic in group II than in group I.

Table IV. Distribution of study subjects by risk factors/co-morbidity (N=100)

Risk Factors	Group I (n= 30)		Group II (n= 70)		p value
	Number	%	Number	%	
Ischemic heart disease	14	46.7	50	71.4	0.018[s]
Hypertension	7	23.3	21	30.0	0.496 [ns]
Diabetes mellitus	8	26.7	31	44.3	0.098 [ns]
Dilated cardiomyopathy	6	20.0	17	24.3	0.641 [ns]
Dyslipidemia	12	40.0	60	85.7	<0.001[s]

Sixty three patients had EF <30%, more in Group II (Table V). There was moderate (r = -0.498) negative correlation between RDW-CV and LVEF which was statistically significant (p value<0.001) (Figure 1).

Table V. Distribution of the RDW according to left ventricular ejection fraction (N=100)

LVEF%	RDW				p value
	Group I (n= 30)		Group II (n= 70)		
	Number	%	Number	%	
39% – 30%	19	63.3	18	25.7	<0.001[s]
<30%	11	36.7	52	74.3	
Total	30	100	70	100	

Group I- HFrEF patients with RDW-CV <13.6

Group II-HFrEF patients with RDW-CV e”13.6

S=significant, NS= Not significant

p value reached from unpaired t-test and Chi-square test

LVEF= Left ventricular ejection fraction. LVEF < 30% was considered as severe dysfunction.

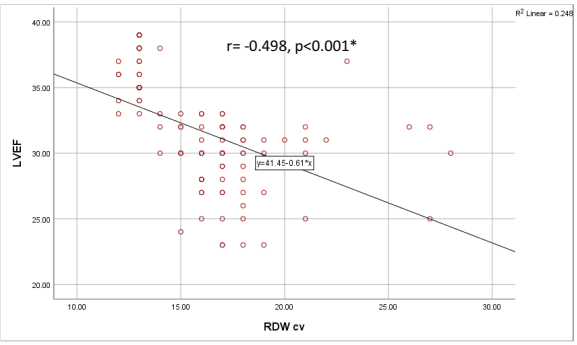

Figure 1. Scatter diagram showing the correlation of RDW-CV with LVEF

DISCUSSION

The normal range for RDW-CV is between 11.5 and 14.5%.[12] In the study conducted by Celik et al.[11], the cut off for the RDW-CV for predicting heart failure was found to be as 13.6. A total of 100 patients of HF were studied. The study patients were categorized into 2 groups on the basis of red cell distribution width - coefficient of variance (RDW-CV): Group I- HFrEF patients with low RDW-CV <13.6; Group II- HFrEF patients with high RDW-CV ≥13.6. Recently, RDW-CV has been shown to be a novel marker for predicting outcomes in the heart failure population.[13] The cause of elevated RDW-CV in heart failure patients has been attributed to inflammation, ineffective erythropoiesis, malnutrition, impaired renal function and neurohormonal activation. Many researchers have demonstrated the role of RDW-CV in patients with heart failure.

According to Al-Najjar et al.[14] RDW-CV has an independent prognostic power in these patients. They analyzed a cohort of patients with he art failure, comparing RDW-CV with NT proBNP, and they suggested that the two factors can be considered similar in predicting cardiovascular events. Moreover, the role

of RDW-CV as a predictor of mortality in patients with heart failure was investigated. [15] In patients with acute heart failure higher RDW-CV levels at discharge were associated with worse long-term outcome regardless of hemoglobin levels and anemia status. A role in the prognosis was established also for patients with diastolic heart failure in a study on the relationship between RDW and NT-proBNP[11] the role of RDW-CV in patients with heart failure has not been investigated in our country.

In this study we evaluated the value of monitoring RDW and its correlation with ejection fraction. Our study had been conducted over 100 patients diagnosed as HFrEF. patients had been enrolled in our study as per inclusion criteria and HF diagnosis and managed according to standard guidelines of HF and correlation between RDW and ejection fraction was done. Our patients had mean age Group-I 56.23±6.69 & Group-II 56.44±11.29 years, male patients were 68 (68%) and female patients were 32 (32%). our patients had the following presentations: ischemic heart disease 65 patients (65%), Hypertension 25 patients (25%), and dilated cardiomyopathies 22 patients (22%). We investigated the diagnostic impact of RDW in heart failure patients and correlate it with echocardiographic findings especially ejection fraction.

Our study revealed a significant negative correlation between RDW and ejection fraction ($p<0.001$ and $r = -0.498$) this come in context with Wang et al.[16] who studied patients with acute coronary syndrome for cardiac mortality and events (heart failure and recurrent infarction within one month) and found that in patients with higher levels of RDW there is lower levels of left ventricular ejection fraction ($p<0.001$). Also, we agreed with Osadnik et al.[17] who studied patients with stable coronary disease who underwent PCI and found that with higher RDW values there is lower ejection fraction ($p <0.0001$). Also, this come in context with Felker et al.[7] who studied patients from the North American CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) program with symptomatic heart failure there were strong correlation between ejection fraction and RDW ($p<0.0001$). Also, our study agreed with Zorlu et al.[8] who found that ejection fraction correlated significantly with RDW ($p<0.017$). But our study disagreed with Pascul-Figal et al.[15] who correlate between RDW and left ventricular ejection fraction (LVEF) and left ventricular diastolic function in acute heart failure patients and found no significant correlation but this difference may be due to different type of patients. The strong correlation between RDW and ejection fraction suggest RDW as a cheap rapid noninvasive prognostic marker that affect patient outcome.

In our study RDW shows insignificant correlation with hemoglobin level ($r= -0.064$ and $p =0.70$). This comes in context with Uysal et al.[18] who investigated the relation between RDW and STEMI in young patients and found no significant correlation between RDW & hemoglobin ($p=0.5$) and with Sarýkaya et al.[19] who studied the relation between atrial fibrillation incidence in hypertensive patient and RDW and found that correlation RDW and hemoglobin ($p <0.3$). Our study discordant with Felker et al.[7] who found that correlation between RDW & hemoglobin significant ($p<0.001$) this may be due to different type of patients as we excluded anemic patients in our study but they did not. Our study shows insignificant correlation between RDW and diabetes ($p =0.098$). This agreed with Osadnik et al.[17] who found RDW and diabetes correlation to be insignificant ($p=0.2$).

Our study shows significant correlation between RDW and dyslipidemia ($p<0.001$). This disagreed with Uysal et al.[18] showed insignificant correlation between hyperlipidemia ($p=0.50$). Our study shows insignificant correlation between RDW and hypertension ($p=0.496$). This disagreed with Wang et al.[16] who found that there is significant correlation between RDW and hypertension ($p <0.001$). Our study shows significant correlation between RDW and history of ischemic heart disease ($p=0.018$). This agreed with Cetin et al.[20] who found during his study for RDW and its association with coronary atherosclerosis in patient with stable angina that there is significant correlation between RDW and history of ischemic heart disease ($p<0.005$). Finally, our study finding suggests a very good relationship between red cell distribution width-coefficient of variance and severity of systolic dysfunction in patients with HFrEF.

Conclusion

This study showed that increased RDW is associated with decreased ejection fraction assessed by echocardiography in patients of HFrEF. Therefore,

increased RDW could be used as an additional marker for identifying severity of left ventricular dysfunction. The study documents showed inverse relationship between RDW and LVEF. As because of RDW is a simple test, it may be recommended as assessment of severity of left ventricular systolic dysfunction in heart failure patients where reliable echo facilities are not available. However large-scale study is recommended.

Authors' contribution: MBA planned the research, collected data, analyzed data and drafted manuscript. MMI critically revised the manuscript. MIH, AR, ZR collected data. MU and MAKA supervised the work. All authors read and approved the final manuscript for submission.

Conflicts of interest: Nothing to declare.

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