Original Article

Evaluation of Red Cell Distribution Width as a Screening Marker for Right Ventricular Dysfunction in Stable COPD Patients

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Abstract

Objective. Right ventricular (RV) dysfunction is a commonly overlooked; but prognostically important complication of chronic obstructive pulmonary disease (COPD). Red cell distribution width (RDW) is a potential blood parameter that may have a role in the detection of RV dysfunction. The present study was conducted to evaluate the role of RDW as a screening marker for RV dysfunction in COPD.

Methods. A total of 80 consecutive stable COPD patients were enrolled. After initial spirometry, patients were screened for RV dysfunction using RDW measurement. Thereafter, two-dimensional (2D) transthoracic echocardiography (2D-TTE) was performed to confirm the RV dysfunction by measuring tricuspid annular plane systolic excursion (TAPSE) and RV lateral wall tissue doppler systolic velocity (S velocity). Sensitivity, specificity and positive and negative predictive values of RDW was calculated using 2D-TTE as the reference standard.

Results. The study cohort of COPD patients mainly comprised of middle-aged males (mean age: 57.1+9.3 years; M:F=6:1). Out of 80 patients, 26 (32.5%) had RDW above the cut-off value of 14%. On comparing them with the 10 patients (12.5%), diagnosed on 2D-TTE, RDW showed a sensitivity and specificity of 90% and 75%, respectively in detecting RV dysfunction. On multivariate logistic regression analysis, RDW was the only independent parameter predicting RV dysfunction (OR: 4.04; 95% CI: 1.5-10.5; p= 0.004) in COPD patients.

Conclusion. Red cell distribution width is a sensitive screening marker of RV dysfunction that may be incorporated in the in diagnostic algorithm of COPD patients. **[Indian J Chest Dis Allied Sci 2020;62:9-12]**

Key words: Red cell distribution width, Chronic obstructive pulmonary disease, TAPSE, S velocity, Right ventricular dysfunction

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive airway disease with an estimated 2.2 crore patients in India in 2016.[1] Apart from the lung involvement, different extra-pulmonary manifestations, notably, cardiovascular disease affects the quality of life and contributes to 20% to 25% of all deaths in these patients.[2]

Right ventricular (RV) dysfunction secondary to COPD is one of the most common cardiac complications of COPD. It can present either in early phase with increased RV end-diastolic volume but preserved RV stroke volume or in the later stage with decreased stroke volume (termed as RV failure). Currently, transthoracic echocardiography is the standard diagnostic investigation to evaluate RV dysfunction that has shown a sensitivity and specificity of 83% and 72%, respectively.[3] However, its yield is often affected by the poor acoustic window that makes the right heart evaluation a difficult task in COPD patients. Moreover, poor accessibility and lack of expertise in performing echo are the other limiting factors in a resource-limited country, like India.

Red cell distribution width (RDW) is a routine, cost-effective haematological parameter obtained from a standard complete blood count. It represents variability in the size and/or volume of circulating erythrocytes (also known as anisocytosis). A variety of underlying abnormalities, such as oxidative stress, inflammation, hypoxia, poor nutritional status and dyslipidaemia occurring in different conditions cause dysregulation of erythrocyte homeostasis leading to the increased red cell membrane deformability and raised RDW.[4] The marker has been evaluated as a prognostic tool in different clinical settings, like left ventricular dysfunction,[5] pulmonary hypertension,[6] obstructive sleep apnoea,[7] lung cancer[8] interstitial lung diseases[9] and critically ill patients.[10]

With similar mechanisms contributing to pathogenesis of COPD and heart failure, it was hypothesised that raised RDW could also be associated with RV dysfunction seen in COPD patients. In a recent study by Sincer *et al*[11], RDW was found to be an independent marker of RV dysfunction in COPD patients with a sensitivity and specificity of 70% and 93.1%, respectively. In view of paucity of data on

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this marker in COPD from India, the present study was conducted to evaluate RDW as a marker of RV dysfunction in the stable COPD patients.

Material and Methods

A prospective, observational study was conducted in the Department of Pulmonary Medicine, Government Medical College and Hospital, Chandigarh, between November 2015 and September 2017. All stable COPD patients presenting to the pulmonary outpatient department (OPD) during the study period were consecutively enrolled. Based on an estimated prevalence of 52% of RV dysfunction in COPD with an expected sensitivity of 80% of RDW in detecting RV dysfunction, a sample size of 80 COPD patients was required for RDW screening at 5% level of significance and 80% power.[11,12] Subjects with anemia, recent blood transfusion (within past 3 months), recent lower respiratory tract infection (in last 6 weeks), recent systemic infection, altered liver function tests, altered renal function test, left ventricular systolic dysfunction, obstructive sleep apnoea, lung cancer and overt RV failure were excluded. Informed consent was taken from all the participants. The study was approved by the Institutional Ethics Committee.

The demographic and clinical data was collected from all patients. Thereafter, spirometry was performed as per American Thoracic Society (ATS) guidelines[13] using a spirometer (Spiro analyser, RMS Helios-401, India)). Staging of COPD was done using post-bronchodilator forced expiratory volume in one second (FEV_1%) predicted value as per recent Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.[14] All patients were subjected to complete blood count including measurement of RDW. The test was done using three-part automated haematology cell counter (Sysmex blood analyzer KX-21, Japan). The normal vale of RDW for the equipment was 11.6-14%.[15,16]

Two-dimensional (2D) transthoracic echocardiography (2D-TTE) was conducted on all patients using latest generation high-end 2D echocardiography (Philips EPIQ 7 ultrasound system; Phillips Medical System, Bothell, WA, USA) machine. The cardiologist performing the echocardiography was blinded about the patient's RDW values. Images were obtained in the parasternal long and short axis, apical long axis, apical four chamber and subcostal views as per standard protocol. RV function was assessed by tricuspid annular plane systolic excursion (TAPSE) using M mode and RV lateral wall tissue doppler systolic velocity (S velocity) using tissue doppler imaging (TDI).

Right ventricular dysfunction was defined by TAPSE <16 mm and/or S velocity <10 cm/sec, as per standard guidelines.[17] TAPSE represents the distance of systolic excursion of the RV annular plane towards the apex. It is obtained using an M-mode cursor passed through the tricuspid lateral annulus in a four-chamber view and measuring the amount of longitudinal displacement of the annulus at peak-systole. After obtaining the values, test performance of RDW was evaluated using echocardiographic diagnosis of RV dysfunction as reference standard.

Statistical Analysis

Quantitative data was expressed as mean ± standard deviation (SD) and qualitative data was expressed as percentage or proportions. A Chi-square test and Fisher's exact test was performed to examine the relationship between RDW and RV dysfunction. Sensitivity, specificity, positive predictive value and negative predictive value of RDW in detecting RV dysfunction were also calculated. Multivariate logistic regression analysis was performed with forward inclusion approach to evaluate independent factors predicting RV dysfunction. All statistical calculations were done using computer program statistical package for the Social Sciences (IBM SPSS Statistics 21.0; Armonk, NY, USA). A P-value of <0.05 was considered significant.

Results

The study cohort comprised of middle-aged and elderly patients (mean age 57.1±9.3 years). Males outnumbered the females in the ratio of 6:1. Majority of them were smokers (n=75) with a mean pack years of 26.5±12.9. Out of a total 80 patients, 45 (56.2%) were in severe or very severe stage of the disease. There was a statistically significant difference in spirometry values (FEV_1, FVC [forced vital capacity] and FEV_1/FVC) between patients with and without RV dysfunction (P<0.001). Patients with RV dysfunction had higher haemoglobin than those without RV dysfunction (Table 1).

Table 1. Baseline demographic and clinical parameters of COPD patients

Parameters	RV Dysfunction Present (n=7)	RV Dysfunction Absent (n=73)	P value
Mean age (years)	54.4±10.8	57.7±10.8	0.5
Male gender (n)	6	62	1
Pack years of smoking	23.5±6.9	26.8±13.4	0.53
Chullah exposure (n)	1	12	1
FEV_1% predicted	24±4.1	51.1±13.3	<0.001
FVC% predicted	46.1±9.3	69.7±15.8	<0.001
FEV_1/FVC	50.4±6.3	56.7±8.8	0.07
GOLD Stage			
Mild	0	1	<0.001
Moderate	0	34	
Severe	0	34	
Very severe	7	4	
Haemoglobin(g/dL)	15.3±.12	13.3±1.3	<0.001
RDW	20.2±1.4	13.3±2.6	<0.001

Definition of abbreviations: COPD=Chronic obstructive pulmonary diseases; RV=Right ventricular; FEV_1=Forced expiratory volume in one second; FVC=Forced vital capacity; RDW=Red cell distribution width; GOLD=Global Initiative for Chronic Obstructive Lung Disease

Red cell distribution width

The mean RDW of all patients was 13.9+3.2% (range 9-22). There was a strong negative correlation between RDW and spirometry parameters (for FEV_1% r=–0.94; p<0.001 and for FVC, r=–0.77, p=<0.001). Twenty-six (32.5%) patients had RDW values above the normal cut-off of 14%. There was no significant difference in age (P=0.21) and gender (P=0.94) between the patients with or without high RDW values.

Echocardiography findings

All patients with left ventricular ejection fraction (LVEF) in normal range were enrolled at baseline. The baseline echocardiography findings of the COPD cohort are shown in table 2. The mean TAPSE score and S velocity were 18.2±2.2 mm and 11.4±1.1 cm/sec, respectively. Out of 80 patients, 10 (12.5%) had TAPSE and/or S velocity below the normal value and were labelled as having RV dysfunction. On a continuous scale, both TAPSE and S velocity had a strong correlation with post bronchodilator FEV_1% predicted (r=+0.79, P=<0.001 and r=+0.54, P=<0.001, respectively). The difference also remained statistically significant on comparing them as per GOLD stages.

Table 2. Echocardiographic findings in COPD patients

Parameter	Value (mean+SD)
TAPSE (mm)	18.23±2.24
S velocity(cm/s)	11.45±1.15
RV dimension	
RV base(mm)	29.91±6.32
RV mid(mm)	27.98±4.74
RV length(mm)	59.21±8.48
RA dimension	
RA area(cm^2)	8.81±2.82
RA length(mm)	35.1±6.84
RA diameter(mm)	29.77±4.52

Definitions of abbreviations: COPD=Chronic obstructive pulmonary diseases; SD=Standard deviation; TAPSE=Tricuspid annular plane systolic excursion; S=Velocity: RV=Lateral wall tissue Doppler systolic velocity; RV=Right ventricular; RA=Right atrial

Performance parameters of RDW

On Chi-square analysis, the high RDW (>14%) was significantly associated with RV dysfunction (X^2=17.22; P=<0.001) (Table 3). The sensitivity, specificity and positive and negative predictive values of RDW in detecting RV dysfunction was 0.90 (95% confidence interval [CI] 0.56–0.99), 0.75 (95% CI: 0.70–0.77), 0.34 (95% CI: 0.21–0.38) and 0.98 (95% CI: 0.92–0.99), respectively.

On univariate regression analysis, haemoglobin, FEV_1%, FVC% and RDW had statistically significant association with RV dysfunction. However, on multivariate analysis, RDW remained the only independent factor associated with RV dysfunction (Odds ratio [OR] =4.04, 95% CI1.5–10.4, P=0.004) (Table 4). The association also remained significant after adjusting for stages of COPD (OR=3.86, 95% CI 1.4–10.6, P=0.009).

Table 3. Chi-square analysis of RDW with RV dysfunction

Screening Test	RV Dysfunction		Chi-square value (χ^2) (P value)
	Present	Absent	
RDW >14%	9	17	17.2 (Pearson) p<0.001
RDW ≤14%	1	53	

Definitions of abbreviations: RDW=Red cell distribution width; RV=Right ventricular

Table 4. Association of RV dysfunction with different independent variables using logistic regression analysis

Variables	Univariate Analysis		Multivariate Logistic Analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	0.98 (0.91-1.06)	0.7		
Female	1.5 (0.27-8.1)	0.60		
Pack years	0.98 (0.92-1.04)	0.54		
RDW	4.73 (1.5-13.4)	0.004	4.04 (1.5-10.5)	0.004
FVC	0.85 (0.76-0.94)	0.001		
FEV_1<50%	9.01 (1.08-76.9)	0.04		
Hemoglobin	6.3 (0.2- 13.1)	0.074		

Definitions of abbreviations: RV=Right ventricular; OR=Odds ratio; CI=Confidence interval; RDW=Red cell distribution width; FVC=Forced vital capacity; FEV_1=Forced expiratory volume in one second

Discussion

The study evaluated efficacy of a simple and cost-effective blood marker, RDW, in detecting RV dysfunction in stable COPD patients. Justifying the hypothetical surmise, high RDW was found to be a sensitive screening marker of RV dysfunction that retained significant association with it even after adjusting for the disease stage.

In the present study, levels of RDW had a strong negative correlation with TAPSE and S velocity. These two echo parameters are surrogate markers of RV function. RDW showed a sensitivity and specificity of 90% and 75%, respectively, in detecting RV dysfunction. The results of the present study are better than a study by Sincer *et al*[11] in which RDW, at the cut-off value of 17.7%, had a sensitivity and specificity of 70% and 93.1%, respectively. The study by Sincer *et al*[11] included a matched control group and a higher RDW cut-off value that might be the reason for the difference in the results. However, a small sample size was also a limiting factor in their study as compared to the present study. The present study was comparable with another case-controlled study of 175 COPD patients observing a high RDW as an independent predictor of

cardiovascular disease and RV dysfunction on multivariate analysis.[18]

In a retrospective study, Tertemiz *et al*[19] showed a significant negative correlation between RDW and severity of COPD (FEV_1% predicted) (r=–0.29; P<0.001).[19] They concluded that RDW may be used as a biomarker to evaluate the severity of the disease. In concordance with the results, the present study also achieved a strong association between the two parameters (r=–0.94; P<0.001). Patients with high RDW (>14%) had a low mean FEV_1% predicted of 32.3±6.5% in comparison to 57.1±10.3% in those with normal RDW (p<0.001). Interestingly, TAPSE and S velocity, the markers of RV dysfunction, also correlated with the severity of COPD in the study (P<0.001). However, on multivariate analysis, RDW remained the only significant variable predicting RV dysfunction even after adjusting for COPD stage (OR=4.04, 95% CI 1.5L–10.4, P=0.004).

To the best of our knowledge, the present study is the first Indian study to document the role of RDW in screening COPD patients for RV dysfunction. A reasonable sample size with stringent exclusion of confounding factors increased the authenticity of the results. The results have a strong clinical implication in the management of COPD, especially in resource-poor countries, like India. On the one hand, RDW level above the cut-off value may predict RV dysfunction (thus, directing for echocardiographic confirmation), whereas a normal RDW value can avoid further diagnostic work-up, especially in patients with low clinical suspicion.

Our study also had few limitations. The low prevalence of RV dysfunction (12.5% of the patients on 2D–TTE) might have affected the results. It was likely due to exclusion of patients with overt RV failure in the study who ideally do not require screening prior to 2D-echo. This helped us to evaluate the exclusive role of RDW in detecting patients with early RV dysfunction who often remain undetected due to lack of suspicion. Absence of control group also might have affected the validity of the results. However, rigorous measures to exclude patients with confounding factors might have offset this confounding factor. Previous research has also shown an association of RDW with poor survival in COPD patients.[19,20] However, due to cross-sectional study design, we could not evaluate the longitudinal effects of serial RDW values on survival in these patients.

Conclusions

Being a simple, cost-effective and readily accessible test, RDW seems to be promising marker for evaluation of RV dysfunction in COPD patients. However, the results should be interpreted cautiously in the presence of the confounding factors which are often present during the course of the disease. Further large scale longitudinal studies with a control arm are needed to further validate the role of RDW in the evaluation of RV dysfunction in COPD patients.

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