

PREDICTION OF PULMONARY HYPERTENSION IN COPD PATIENTS BASED ON RED CELL DISTRIBUTION WIDTH, MEAN PLATELET VOLUME, PLATELET DISTRIBUTION WIDTH

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Abstract

Background: Pulmonary hypertension (PH) increases morbidity and death in chronic obstructive pulmonary disease (COPD) patients. Early detection of pulmonary hypertension results in aggressive treatment, which improves quality of life. Platelet activation is key in its pathogenesis, and mean platelet volume (MPV) is regarded as a reliable indicator of platelet activation. The aim of this work is to assess the ability of RDW, MPV and PDW in predicting PH secondary to COPD as well as its severity. **Materials and Methods:** A total of 150 blood samples of clinically suspected COPD patients from Govt. tertiary care hospital Theni, Tamil Nadu were collected from March 2020 to March 2021. Clinical information such as demographics, comorbidities, CBC, echocardiography, pulmonary function, and the findings of ultrasound scans, imaging examinations, and laboratory tests were collected. **Result:** The prevalence of PH was high (86.6%), with the majority of patients having a mild degree (60%). There were 130 (86.6%) smokers and 90 (60%) alcoholics among the 150 cases. The prevalence of stage 1 and stage 4 is higher in Government Medical College, Theni, according to this study. The average mPAP of the 150 cases was 41.973 ± 10.846 . The average PAPs value of 150 patients was 53.86 15.04. The mean TAPSE of 150 patients was 11.907, and RA was dilated in 46 individuals, indicating severe pulmonary hypertension. Tricuspid regurgitation was observed in 42 individuals with pulmonary hypertension, with a mean total count of 3037.8 and a mean platelet count of 2.175 lakh. **Conclusion:** Platelet activation occurs in COPD-related pulmonary hypertension, and RDW indicates inflammation in these individuals. Platelet indices differ between COPD with pulmonary hypertension and COPD without pulmonary hypertension. RDW, MPV and PDW is significantly increased in COPD patients with PH and thus may be a useful biomarker for PH secondary to COPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an irreversible airway inflammation that causes persistent airflow restriction. It is also linked to a slew of secondary repercussions, depending on the severity of the condition and the frequency with which the inflammatory process occurs.^[1,2] Regardless of the etiology, pulmonary hypertension (PH) is described as a chronic persistent rise of pulmonary artery pressure and pulmonary vascular resistance, which leads to right side heart failure.^[3]

The WHO divided PH into four types, with COPD-related PH falling under category 3.^[4] Over 80% of these deaths occurred in low- and middle-income countries. COPD affects the airway and/or the lung parenchyma and is characterized by airflow obstruction that is not totally reversible.^[5] COPD includes various processes such as emphysema, chronic bronchitis and the missed phenotype COPD-asthma. One of the most common complications of COPD is mild- moderate pulmonary hypertension and is thought to be due to combined effects of hypoxia, inflammation and loss of capillaries in

severe emphysema. If pulmonary hypertension is left untreated, the disease carries a high mortality rate, with the most common cause of death being decompensated right heart failure.^[6] RDW (red blood cell distribution width) is a measure used to assess the variability of circulating erythrocyte volume. An higher RDW suggests defective erythropoiesis, increased red blood cell death, or a shorter red blood cell lifespan.^[7] RDW is closely related to the prognosis of various disorders. In pulmonary hypertension, there is persistent vasoconstriction due to pulmonary vascular remodeling which lead to platelet activation and the markers for platelet activation which are readily available in all centers are Mean platelet volume (MPV) and Platelet distribution width (PDW).^[8,9] Furthermore, platelet activation may lead to further increase in pulmonary vasculature. Since there is airway limitation accompanied by chronic inflammation, increase in red cell distribution width (RDW) is seen due to oxidative stress.^[10] Mean platelet volume is one of the platelet indicators that represent its activity; it is a simple and easy technique to anticipate platelet dysfunction, either from excess production and tiny size formation or from insufficient production and large size.^[11,12] The goal of this study is to employ red cell and platelet indices as surrogate markers for pulmonary hypertension in COPD patients and to see how they correlate with the severity of both COPD and pulmonary hypertension.

MATERIALS AND METHODS

Study Design and Population

This Cross sectional study was carried out Patients admitted in Government Medical College Hospital, Theni from March 2020 to March 2021. Patients were explained about the study in their own language. Patients willing to participate are included into the study after getting consent for the study.

Inclusion Criteria

Emphysematous chest on chest X-ray, Poor progression of 'R' waves, Bilateral wheeze on auscultation, All COPD patients confirmed on the basis of spirometry with FEV1/FVC<0.7.

Exclusion Criteria

All other causes of Pulmonary hypertension, History of hematological disorder or malignancies, abnormal hematocrit and/ or abnormal WBC count, Patients on antiplatelet or anticoagulant drugs in the past 15 days were excluded, Increased thrombotic events like malignancies, thyroid disorder, embolism, HIV infection, Pregnant women, Patients unwilling to cooperate.

Study Sample and Data Collection

150 patients were included in the study. Patients who are diagnosed with COPD admitted in our hospital are taken into the study. Patients are evaluated for symptoms and signs suggestive of pulmonary hypertension with echocardiogram. All patients were subjected through Detailed history, Clinical and

Systemic Examination, Investigations such as Spirometry, Complete Blood count (4ml of blood was collected in EDTA tube and measured using automated analyzer – Total count, Platelet count, MPV, PDW, RDW- SD were specifically recorded.

Pulmonary function tests

Spirometric pulmonary functions were measured in triple readings using the Spirometry system, and the highest value was chosen. Spirometric pulmonary functions were done using spirometric system in triple readings records and the highest value is selected. The report is mentioned under two headings: FeV1/FVC ratio and FEV1 percent of normal. COPD is diagnosed when the Post bronchodilator FEV1/FVC ratio is <0.7. Patients were divided into 4 groups according to the severity of COPD based on FEV1 percent of normal: Stage1 (mild), Stage 2 (mild to moderate), Stage 3 (moderate to severe) and Stage 4 (Severe).

Echocardiography

Trans-thoracic echocardiography was performed on all recruited patients utilizing an Ultrasound system with a 2.5 MHz transducer. The simplified Bernoulli equation ($4*TRV^2$) was used to determine the pressure gradient over the tricuspid valve, which was then added to the right aerial pressure (RAP) to compute the Pulmonary Artery Systolic Pressure (PASP), which is equal to RVSP. If the RVSP was greater than 30 mmHg, the patients appeared to have PH. Patients were classified as mild (30-50 mmHg), moderate (50-70 mmHg), or severe (>70 mmHg) if their PASP was greater than 30 mmHg.

Assessments of tricuspid regurgitate jet velocity and calculating mPAP and PAPS: If TRV is more than 2.9m/sec is diagnostic of pulmonary hypertension along with other signs of pulmonary hypertension. Assessment of TAPSE: <16 mm is diagnostic of pulmonary hypertension. Assessment of dimension of RA: At the end-Systole, RA area >18cm² is diagnostic of pulmonary hypertension. Assessment of RV dysfunction: Presence of TR indicates RV dysfunction.

CHEST XRAY was done to look for Hyperinflated lung, Tubular heart, prominent pulmonary vasculature. ECG was done to look for Right axis deviation, Right atrial enlargement, Right ventricular hypertrophy, Right bundle branch block.

Biochemical measurement

Venous samples were collected from the participants in the morning between 9.00 and 10.00 am after an overnight fast of at least 8 hours. Venous blood samples were collected into K2 EDTA (15%) in vacutainer and invert 8 times. CBC was measured within 1-2 hours of blood sampling using automated analyzer called Stromatoyser-WH.

Statistical Analysis

For statistical analysis, the software SPSS 19.0 (IBM Corp, Armonk, NY) was utilized. The normality of distribution was determined using the Kolmogorov-Smirnov test. Continuous variables were normally distributed and represented as mean standard deviation (SD). Categorical variables were

represented as a percentage or as a number (n). The independent-samples t-test was used to examine continuous data, and the chi-square test was used to assess categorical data. The Pearson correlation approach was used to examine the correlations between the RDW and the parametric variables. The independent risk variables of PH secondary to COPD were identified using logistic regression analysis. $P < 0.05$ was considered significant for all two-sided tests.

RESULTS

In our study 150 patients were enrolled, out of them 63 cases belong to the age group of >60 years of age. In this study, male incidence is more than the female. 120 (80%) patients were identified as COPD with pulmonary hypertension. Majority of cases were moderate – severe pulmonary hypertension among COPD patients. 75 (50%) patients were known case of diabetes on regular follow-up. Out of 150 cases,

130 (86.6%) were smokers and 90 (60%) were alcoholic. In this study, prevalence of stage 1 and stage 4 is higher in Government Medical College, Theni. The mean mPAP of 150 cases were 41.973 ± 10.846 . Mean PAPs value of 150 patients were 53.86 ± 15.04 . Mean TAPSE of 150 patients were 11.907, RA was dilated in 46 patients which indicates severity of pulmonary hypertension. Tricuspid regurgitation is seen in 42 patients presenting with pulmonary hypertension, Mean total count was 3037.8 and Mean platelet count was 2.175 lakh.

MPV in COPD patients with PH was significantly higher than those. Moreover, a significant statistical rising of MPV with increased severity of PH, $P < 0.001$ [Table 1]. COPD (Stages) and PDW Mean was significantly higher than those. Moreover, a significant statistical rising of PDW with increased severity of PH, $P < 0.001$ [Table 2]. COPD (Stages) and RDW Mean was significantly higher than those. Moreover, a significant statistical rising of RDW with increased severity of PH, $P < 0.001$ [Table 3].

Table 1: Pulmonary hypertension (severity) vs MPV

PHTN (Severity)	MPV Mean	SD	P value
No (30)	7.456	0.982	<0.001
Mild(40)	7.952	1.079	
Moderate(40)	10.755	0.468	
Severe(40)	10.952	0.47	

Table 2: COPD (stages) vs PDW

COPD(Stages)	PDW Mean	SD	P value
1(40)	11.404	0.918	<0.001
2(32)	13.289	1.726	
3(37)	15.29	0.534	
4(41)	15.997	0.848	

Table 3: COPD (stages) vs RDW

COPD(Stages)	RDW Mean	SD	P value
1(40)	36.404	4.37	<0.001
2(32)	44.556	4.736	
3(37)	48.063	3.102	
4(41)	50.797	1.667	

DISCUSSION

This study looked at the link between RDW, MPV and PDW and PH caused by COPD. Because of the increased prevalence of COPD, PH associated with COPD was one of the most common causes of PH2. The 5-year survival rate in COPD patients with beginning mPAP >25 mmHg was only 36%, compared to 62% in those with initial mPAP 25 mmHg.^[13] The current study found that 86.6% of COPD patients had PH, with mild PH accounting for 60%, moderate PH accounting for 20%, and severe PH accounting for 20%. This is consistent with the findings of Maula et al,^[14] and Ali,^[15] who found that the prevalence of PH was 65.4% and 60%, respectively, in their studies, which closely matched the findings of Chaouat et al,^[16] and Chatila et al.^[17] Gajanan and Pophale,^[18] also agreed on the prevalence of mild, moderate, and severe PH being 23%, 18%, and 12%, respectively. Naeije, on the

other hand, had a lower prevalence of less than 10%.^[19]

The prevalence of PH in COPD varied from study to study, ranging from 18%,^[20] to up to 91%,^[21] however, most studies were based on pulmonary hemodynamic assessments performed in those referred for surgical procedures, so the prevalence cannot be generalized to the entire COPD population.^[22]

The current study looked at the MPV and its correlation with COPD severity grades, as well as its correlation with PH presence. It was discovered that increasing the severity of COPD increased the MPV significantly ($P \leq 0.001$) [Table 1], and that patients with PH had a significant statistical elevation compared to those without. When comparing the PDW level in each PH degree, the severe PH group had a significant statistical elevation, $P \leq 0.001$ [Table 2]. That correlation between RDW was

present regardless of COPD severity ($P \leq 0.001$) [Table 3].

In our study, 29 of the 150 patients enrolled were under the age of 18. The most common age of presentation was over 60 years old. Males had a higher prevalence of COPD. Out of 150 patients, 140 were men, the majority of whom smoked. 9 people were overweight. The BMI of 67 of the patients was normal. There were 64 pre-obese patients. Diabetes was discovered in 75 cases, with 5 patients suffering from COPD without pulmonary hypertension. There were 130 smokers and 20 nonsmokers, with 10 female patients and the remaining 10 male patients. According to GOLD criteria based on spirometry, the Government Medical College, Theni had a higher prevalence of COPD stage 1 and stage 4 diseases. An echocardiogram revealed 120 cases of pulmonary hypertension. There was a higher prevalence of moderate to severe pulmonary hypertension among COPD patients in Government Medical College, Theni, out of 120 cases of pulmonary hypertension. 29 cases have mPAPs greater than 50, 34 cases have PAPs greater than 70, 117 cases have TAPSE = 11, 12. In 46 of the cases, the RA was dilated. There is no decreased EF in any of the cases, implying that COPD with pulmonary hypertension is a condition with normal cardiac output but RV dysfunction. TR valvular lesions were found in 42 of the cases. In seven of those cases, there was pericardial effusion. All cases of pulmonary hypertension in this comparison study had an increase in RDW, PDW, and MPV. The pulmonary hypertension group had significantly higher MPV, PDW, and RDW-SD values than the non-pulmonary hypertension group ($P \leq 0.01$). Elevated MPV and PDW were linked to an increase in the severity of pulmonary hypertension, with a statistically significant $P \leq 0.01$. RDW levels in COPD patients were found to be positively related to the severity of pulmonary hypertension.

Many studies summarized platelet dysfunction in COPD patients, including platelet activation, increased aggregation, and platelet volume in pulmonary vessels, which could lead to PH and pulmonary thrombosis.^[23,24] As a result, Alessandri et al discovered pulmonary thrombosis in approximately 25% of COPD patients on autopsy.^[25] Furthermore, Bansal et al discovered a significantly higher MPV in COPD patients, which may contribute to increased pulmonary thrombosis and hypertension.^[26]

In this study, we also looked at MPV, PDW, and RDW-SD and their associations with COPD stage. With increasing severity of COPD, there was a significant increase in MPV, PDW, and RDW-SD ($P \leq 0.001$). This was discovered due to increased erythropoiesis and platelet activation caused by COPD inflammation, and as the stages of COPD progress, the inflammatory process becomes activated with an increase in cytokine release. The severity of PHTN was associated with an increase in MPV ($P \leq 0.001$), with an MPV of 10.952 ± 0.47 found in severe pulmonary hypertension. In severe

pulmonary hypertension, the PDW was 10.04 ± 0.849 . Severe pulmonary hypertension was found to have an RDW-SD of 50.752 ± 1.662 . D'Alto et al enrolled 161 patients who were referred for a suspicion of pulmonary hypertension and were evaluated prospectively by a Doppler echocardiography performed by dedicated cardiologists within 1 hour of an indicated right heart catheterization.^[27] These researchers used a Bland and Altman analysis to determine the accuracy (which was good) and precision (which was acceptable, but only for population studies) of Doppler echocardiography prediction of invasively measured pulmonary vascular pressures and flow. They concluded that there were no significant differences in mean pulmonary artery pressure MPV, PDW, and RDW-SD and other measured variables between echocardiographic and catheterization measurements. As a result, the echocardiographic measurements were highly accurate when compared to catheterization measurements taken as a gold standard.

CONCLUSION

Pulmonary hypertension is caused by structural changes in the pulmonary vascular bed, which have a variety of pathophysiological mechanisms. Pulmonary hypertension in COPD is caused primarily by chronic hypoxia, hypercapnia, and acidosis, which results in pulmonary vascular remodeling. Platelet activation occurs in COPD-related pulmonary hypertension, and RDW reflects inflammation in these patients. Platelet indices differ between COPD with pulmonary hypertension and COPD without pulmonary hypertension. This study found a significant increase in platelet indices and red cell distribution width in COPD patients, but long-term patient follow-up is required to stage degrees of pulmonary hypertension based on RDW, MPV, and PDW. RDW, MPV, and PDW could be a biomarker for the diagnosis of PH in COPD patients.

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