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Original Article

Internal Medicine Section

Role of C-reactive Protein and Mean Platelet Volume in Predicting COPD Severity and its Association with Cardiac Abnormalities among the Southern Indian Population: A Cross-sectional Study

SURESH SAGADEVAN[1], RADHIKA SHARMA[2], ARUNA SHANMUGANATHAN[3], MEENAKSHI NARASIMHAN[4]

ABSTRACT

Introduction: Chronic Obstructive Pulmonary Disease (COPD) is one of the leading causes of disease and mortality worldwide. In individuals with mild-to-moderate COPD, serum C-reactive Protein (CRP) corresponds with disease severity and poor health outcomes. Mean Platelet Volume (MPV) is also linked to an elevated degree of inflammation in the body, as well as the severity and acute exacerbation of COPD.

Aim: To evaluate the relationship between serum CRP levels and MPV and its association with COPD disease severity and the patient's cardiac abnormality.

Materials and Methods: A cross-sectional study was conducted in the Department of Respiratory Medicine, Chettinad Hospital and Research Institute, Chennai, Tamil Nadu, India, between January 2015 and January 2016. Study was carried out among 55 patients who were diagnosed with COPD in accordance with Global Initiative for Chronic Obstructive Lung Disease 2014 (GOLD) and who were within the age range of 40-70 years were included in the investigation. Severity of airflow obstruction was confirmed by Spirometry using True Flow Easy on PC sensor Pulmonary Function Test (PFT) machine with bronchodilator reversibility testing, as per Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines 2014 and abnormality was evaluated by clinical and radiological assessment. A 3 mL of blood was collected into a clot vial and sent for analysis of CRP using an immunoassay system based on antigen-antibody reaction and fluorescence technology and MPV using the impedance count technique. Receiver Operating Characteristic (ROC) curve was used to find out the sensitivity and specificity of MPV and CRP levels with cardiac abnormality. The study was statistically analysed by Pearson's Chi-square test.

Results: Out of total sample, majority (n=25, 45.5%) were between 51-60 years age group and, there were 35 (63.63%) males and 20 (36.37%) females. The mean CRP levels of mild COPD patients were found to be 6.980±0.7328 mg/dL, moderate and severe COPD patients were found to be 7.243±0.5324 mg/dL and 7.550±0.4950 mg/dL, respectively and it was statistically significant (p-value <0.0001). In the present study, the mean CRP levels and mean MPV were found to be significantly higher in patients with cardiac abnormality than the patients without cardiac abnormality (p-value <0.0001).

Conclusion: Finally, it was concluded that systemic inflammation is common in COPD patients and that CRP and MPV are significant COPD biomarkers for assessing disease severity, predicting cardiac abnormalities, and predicting patient prognosis.

Keywords: Biomarkers, Blood platelets, Chronic obstructive pulmonary disease, Electocardiography

INTRODUCTION

Chronic obstructive pulmonary disease is a complicated chronic inflammatory disease of the lungs that involves a number of inflammatory cells and mediators [1]. It is distinguished by cellular inflammation and structural remodeling of small airways, as well as gradual impairment of lung function caused by airway blockage [1,2]. COPD, rather than being an isolated disorder with pathological processes exclusive to the lungs, is a heterogeneous disease with a chronic inflammatory process and systemic symptoms associated to other systemic diseases such as cardiovascular disease, diabetes, metabolic syndrome and osteoporosis [3-5]. To prevent the effects of COPD, the mainstay of treatment is inflammation control. As a result, identifying the inflammatory process and assessing its severity are essential for treatment decisions [6,7]. Many factors, including CRP, Erythrocyte Sedimentation Rate (ESR), MPV, procalcitonin, Vascular Endothelial Growth Factor (VEGF), Tumour Necrosis Factor-alpha (TNF-α), and Interleukin-6 (IL-6) and IL-8 have been determined as inflammatory markers and used for these purposes. A number of these indicators have been used to predict future problems or lung function [8-10].

C-reactive protein is one of the inflammatory indicators that is increasingly being tested in COPD patients. CRP is a common systemic biomarker that measures an individual's total systemic inflammatory load [11]. In persons with mild-to-moderate COPD, serum CRP levels are associated to disease severity and poor health outcomes. CRP is more commonly utilised due to its availability and cheaper cost [12]. In individuals with stable COPD, CRP is also sensitive to changes in the intensity of inflammation, disease exacerbation, or therapy [13]. A number of studies support the idea that platelets have a role in the development and progression of COPD [14,15]. Platelet count, MPV, and Platelet Distribution Width (PDW) are frequently used to measure platelet number and function [14,15].

The outcomes of studies examining the relationship between these parameters in COPD patients were inconsistent [15,16]. Previous research indicates that elevated MPV to an enhanced inflammatory state in the body, as well as the severity and acute exacerbation of COPD [16,17]. A study also discovered that patients with

COPD had right ventricular hypertrophy, right atrial enlargement, marked clockwise rotation with poor R-wave progression, Right Bundle Branch Block (RBBB), an S1S2S3 pattern, a QS pattern in leads III and Augmented vector foot (AVf), low voltage in the limb leads, Right Axis Deviation (RAD), Left Axis Deviation (LAD), sinus tachycardia, premature atrial complexes [18]. Determining whether the severity of the disease and cardiac abnormalities of COPD was associated with changes in CRP level and MPV independently or in combination will help clinicians to take appropriate decision in treatment. Considering the above factors, CRP levels and MPV in patients with COPD were evaluated in this study and the relationship between serum CRP levels, MPV and its association with the disease severity and also with cardiac abnormalities was also assessed.

MATERIALS AND METHODS

The present cross-sectional study was carried out in the Department of Respiratory Medicine, Chettinad Hospital and Research Institute, Chennai, Tamil Nadu, India, between January 2015 and January 2016. The study was approved from the Institutional Research Ethical Committee of Chettinad Hospital and Research Institute, Kelambakkam (ethical approval: Reg. No: IHC/01/23Jan2015/Desp. No.013/27.02.2015). In compliance with the regulations of the Institutional Research Ethical Committee, patients visiting the Respiratory Medicine outpatient and inpatient clinics were recruited after providing written consent with information in their native understandable language.

The research included 55 stable individuals with COPD. The study comprised participants diagnosed in accordance with GOLD 2014 [19] and aged 40-70 years.

Inclusion criteria: Stable patients with COPD, diagnosed in line with GOLD 2014 and in the age group of 40-70 years were included in the study.

Exclusion criteria: Acute exacerbations of COPD, patients with obstructive airway diseases other than COPD and patients those who were not willing to participate were excluded from the study.

Sample size calculation: According to the pilot study the prevalence of stable COPD cases in the present study centre was 63.8%. The sample size was calculated using the following formula.

$$n=\frac{Z_{1-\alpha/2}{}^2 P Q}{L^2}$$

Where, n:Sample size; Z:Probability; P:Expected proportion; Q:100-P; L:Allowable error; 1-α/2:Desired confidence level. Single proportion: Allowable error; Expected proportion-63.8; Allowable error (%)- 20; Desired confidence level (1-alpha)-95%. The minimum sample size required to conduct the study was 55.

Study Procedure

A detailed clinical history and a complete physical examination were performed on patients who were chosen for this study. Spirometry utilising True Flow Easy on PC sensor PFT machine with bronchodilator reversibility testing (as per GOLD Guidelines 2014) validated the diagnosis of COPD and the degree of airflow restriction [19]. Cardiac abnormality was evaluated using clinical and radiological assessment. Then 3 mL of blood is drawn in a clot vial and sent for estimation of MPV was done by the impedance count method and CRP was done by Immunoassay system based on antigen-antibody reaction and fluorescence technology.

Electrocardiography (ECG) was performed on all patients using a PHILIPS equipment. A 12-lead ECG was conducted, using three bipolar limb leads, three unipolar limb leads, and six unipolar pericardial leads. Various ECG parameters were observed, including rate, right axis deviation (>+110 degree axis), P-pulmonale (Peaked P-wave >2.5 mm), QRS Complex, T-wave abnormality, Right Ventricle Hypertrophy (RVH), and Right Bundle Branch Block (RBBB).

STATISTICAL ANALYSIS

Based on clinical history and examination, imaging study (Chest X-ray), PFT, MPV and CRP values and patient data were analysed using Statistical Package for the Social Sciences software (SPSS) version 17.0 (MEDCALF). The quantitative variables have been described as Mean+SD or Frequency analysis with numbers and percentage. ROC curve was used to find out the sensitivity and specificity of MPV and CRP levels with cardiac abnormality. The study was statistically analysed by Pearson Chi-square test. With observed value of p-value <0.05 was considered to be statistically significant.

RESULTS

The present study included 55 patients of COPD patients who were attending the tertiary care hospitals, Outpatient Department (OPD) and Inpatient Department (IPD) of Department of Respiratory Medicine. Among study group, 25 (45.5%) subjects between 51-60 years were observed more in number and male gender were predominant (n=35, 63.63%) than female gender (n=20, 36.37%). Regarding occupation 36.36% were homemakers, 30.91% were farmers. In this study, the severity of COPD on the basis of GOLD guidelines, 10 (18.18%) patients were stage-I (mild), 17 (30.91%) were stage-II (moderate) and 28 (50.91%) were stage-III (severe). There were no patients in GOLD stage IV {Forced Expiratory Volume (FEV1) less than 30% of predicted}. In this study, cardiac abnormalities were observed in 28 (50.9%) cases [Table/Fig-1].

Variables	Frequency (n)	Percentage (%)
Age group (years)		
40 to 50	16	29%
51 to 60	25	45.5%
61 to 70	14	25.5%
Gender		
Male	35	63.63%
Female	20	36.37%
Occupation status		
Homemaker	20	36.36%
Farmer	17	30.91%
Labour	13	23.64%
IT profession	5	9.09%
Smoking status (n=37)		
Non smoker	7	12.73%
<20 pack year	13	23.64%
>20 pack year	35	63.63%
Severity staging (GOLD 2017 guidelines)		
Mild	10	18.18%
Moderate	17	30.91%
Severe	28	50.91%
Very severe	0	0
Cardiac abnormalities		
Yes	28	50.9%
No	27	49.1%

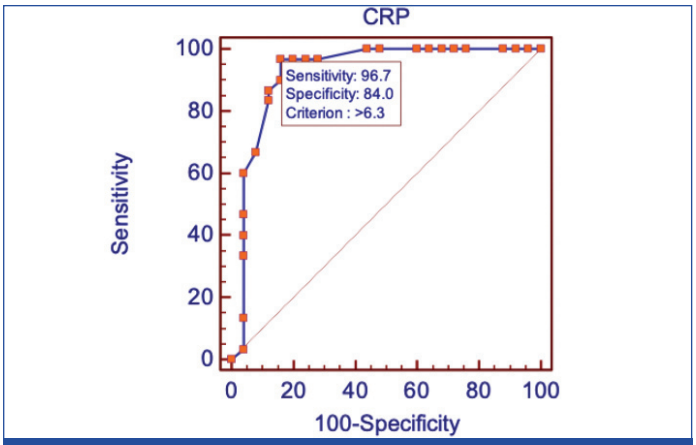
[Table/Fig-1]: Distribution of patient's demographics and clinical features.

In this study, mean CRP levels of patients with cardiac abnormality were found to be 7.22±0.5616 mg/dL and patients without cardiac abnormality were found to be 5.612 ±0.9015 mg/dL. The observed distribution was statistically significant (p-value <0.0001). CRP levels of >6.3 mg/dL were significantly observed with cardiac abnormality with 96.7% sensitivity and 84.0% specificity. The mean CRP levels of mild COPD patients were found to be 6.980±0.7328 mg/dL, moderate and severe COPD patients were found to be 7.243±0.5324 mg/dL and 7.550±0.4950 mg/dL, respectively and it was statistically significant (p-value <0.0001) [Table/Fig-2,3]. In the present study,

mean MPV levels of patients with cardiac abnormality were found to be 9.180±0.1769 fL and patients without cardiac abnormality were found to be 8.588±0.5167 fL. The observed distribution was statistically significant (p-value <0.0001) and cardiac abnormalities is predicted by MPV levels in the threshold >9.1 with 73.3% sensitivity and 100% specificity with a 95% confidence interval of 0.0878 to 0.997. The observed data was statistically significant with p-value of (p-value <0.0001). The mean MPV levels of mild COPD patients were found to be 9.100 fL, moderate and severe COPD patients were found to be 9.178 and 9.400 fL, respectively and it was statistically significant (p-value <0.0001) [Table/Fig-4,5].

Category	Type	CRP level mean±SD (mg/dL)	p-value
Cardiac abnormalities	Yes (n=28)	7.22±0.5616	**<0.0001**
	No (n=27)	5.612±0.9015	
COPD severity	Mild	6.980±0.7328	**<0.0001**
	Moderate	7.243±0.5324	
	Severe	7.550±0.4950	

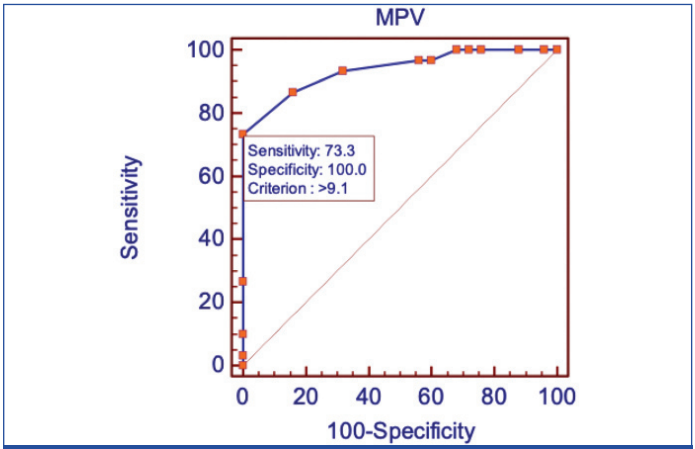
[Table/Fig-2]: Association of cardiac abnormalities and Chronic Obstructive Pulmonary Disease (COPD) severity with C-reactive Protein (CRP) level.
The p-value in bold font indicates statistically significant values



[Table/Fig-3]: Correlation of cardiac abnormality with mean C-reactive Protein (CRP) levels.
Area under the ROC curve (AUC)-0.924667; Standard error-0.0434;
95% Confidence interval-0.840 to 1.000; Significance level P (Area=0.5) <0.0001

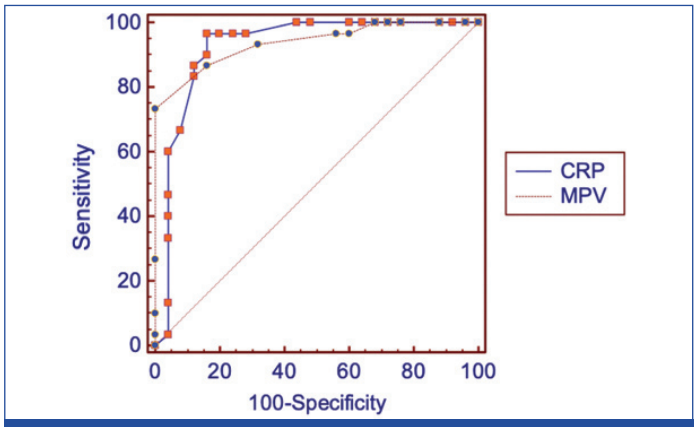
Category	Type	MPV mean±SD (fL)	p-value
Cardiac abnormalities	Yes (n=28)	9.180±0.1769	**<0.0001**
	No (n=27)	8.588±0.5167	
COPD severity	Mild	9.10±0.1581	**<0.0001**
	Moderate	9.178±0.1734	
	Severe	9.400±0.1414	

[Table/Fig-4]: Association of cardiac abnormalities and Chronic Obstructive Pulmonary Disease (COPD) severity with MPV.



[Table/Fig-5]: Correlation of cardiac abnormality with mean MPV levels.
Area under the ROC curve (AUC)-0.937333; Standard error-0.0303; 95% Confidence interval- 0.878 to 0.997; Significance level (Area=0.5) p-value <0.0001

The comparison of ROC between CRP and MPV showed that the difference between area was 0.0127, very negligible and Area Under the Curve (AUC) for CRP was 0.925 whereas for MPV was 0.937 which was almost perfect in prediction. Thus, authors interpret that both CRP and MPV can predict cardiac abnormality [Table/Fig-6,7].



[Table/Fig-6]: Correlation of cardiac abnormality with mean MPV and mean C-reactive Protein (CRP) levels in ROC curve.

Parameters	AUC	95% CI[b]
CRP	0.925	0.840 to 1.000
MPV	0.937	0.878 to 0.997
CRP ~ MPV		
Difference between areas		0.0127
Standard error		0.0462
95% Confidence interval		-0.0780 to 0.103
z statistic		0.274
p-value		0.7841

[Table/Fig-7]: Comparison of ROC curves with mean C-reactive Protein (CRP) and MPV levels Area under the ROC curve (AUC).

DISCUSSION

The CRP and MPV levels were higher in stable COPD patients independent of COPD stage or cardiac problems, according to the present study's primary results. With the growing recognition that COPD is a complex disease involving multiple organs and clearly established low-grade systemic inflammation, biomarkers have become a more important focus of interest in clarifying the pathogenesis and progression of the disease as well as designing new therapeutic targets for the disease [20]. Elevated blood CRP levels in COPD patients indicated low grade chronic systemic inflammation in the early 2000s [21]. Then, in 2006, de Torres JP et al., reported a link between CRP levels and significant prognostic clinical factors in patients with stable COPD [22].

In this study, the mean CRP levels of patients with cardiac abnormality were found to be significantly higher than the patients without cardiac abnormality. Authors also observed cardiac abnormalities is predicted by CRP levels in the threshold >6.3 with 96.7% sensitivity and 84.0% specificity and mean CRP levels of severes COPD patients was significantly higher than mild and moderate category. Pinto-Plata VM et al., found no significant relationship between the degree of illness and serum CRP levels, but de Torres JP et al., found that serum CRP level rose considerably with disease aggravation [22,23].

Increased levels of inflammatory markers are related with COPD exacerbation owing to airway obstruction and/or severe infection [24]. The degree of inflammation is related to the severity of the condition. Serum CRP has been discovered to be highly sensitive to change in response to COPD exacerbation, hence assessing it provides further evidence in identifying COPD exacerbation [25,26]. Bircan A et al., found that elevated CRP levels in COPD patients predicted acute exacerbation with sensitivity of 72.5% and

specificity of 100% [27]. As a result, serum CRP levels can be used to predict the state of pulmonary function volumes such as FEV1 or other lung function indices. CRP was adversely linked with FEV1 in stable COPD, however in most studies, CRP was preferred and a stronger predictor of FEV1. Higher CRP levels are associated with a decrease in these amounts [28,29].

In the present study, mean MPV levels of patients with cardiac abnormality were found to be higher than the patients without cardiac abnormality (p-value <0.0001) and the MPV levels predicts cardiac abnormality in the criterion >9.1 which has 73.3% sensitivity and 100% specificity with 95% confidence interval is 0.0878 to 0.997 (p-value <0.0001). The mean MPV levels of severe COPD patients were found to be 9.400 which was higher than mild and moderate categories (p-value <0.0001). Platelet activation has been seen in COPD patients [30]. The processes driving platelet activation are unknown, however hypoxia and chronic inflammation have been shown to activate platelets. MPV and PDW is a marker of platelet activation [30].

In several chronic conditions, MPV and PDW have been demonstrated to indicate inflammatory load. When compared to healthy controls, patients with COPD had significantly higher platelet counts and lower MPV, according to Biljak VR et al., [31]. MPV levels were considerably higher in hypoxic patients with COPD compared to non hypoxic participants and controls, according to Onder I et al., and Bansal R et al., [32,33]. Patients with more severe COPD had higher MPV levels, according to Kalemci S et al., [34]. According to research, inflammation in COPD is associated with platelet activation, as seen by higher MPV [32-34]. According to several research, MPV reduces in individuals with inflammatory illnesses such as COPD, even during severe exacerbations [31,35]. Both Biljak VR et al., and Ulasli SS et al., observed that MPV exhibited no change across COPD severity stages [31,36]. Only Cui H et al., discovered a negative connection between MPV and percentage predicted FEV1, implying that larger MPV indicates more severe blockage, although they used a considerably smaller sample size of very elderly male patients [37].

Mean platelet volume levels in the study may differ due to pre-analytical circumstances and the analysis itself. Age, gender, race, ethnicity, lifestyle and genetic background, venepuncture method, anticoagulant used, type of sample, and many other factors, as well as the analysis itself employing a variety of methodologies, may all have an effect on MPV values [32]. Furthermore, inter-individual variability in illness response should be addressed as a factor that influences not just MPV [30]. We found the comparison of ROC between CRP and MPV shows that the difference between area is 0.0127, very negligible and AUC for CRP is 0.925 whereas for MPV is 0.937 which is almost perfect in prediction. According to statistical analysis either CRP or MPV may be used to predict the cardiac abnormality in COPD.

Limitation(s)

The limitation of the present study was no follow-up, therefore prognosis of CRP and MVP were not studied.

CONCLUSION(S)

Finally, the study indicated that COPD patients had systemic inflammation and that CRP, MPV is a useful biomarker in COPD for predicting disease severity and patient prognosis. Cardiac co-morbidities in COPD have a significant association with inflammatory markers and the severity of the disease. As a consequence, the use of inflammatory markers might help anticipate the emergence of cardiac co-morbidities, allowing for improved COPD treatment options. Further large-scale, well-designed studies are needed to further investigate the relationship between CRP and MPV in diagnosis of COPD.

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PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Respiratory Medicine, Chettinad Hospital and Research Institute, Chennai, Tamil Nadu, India.
2. Assistant Professor, Department of Respiratory Medicine, Ayyan Institute of Medical Science, Moinabad, Hyderabad, India.
3. Professor, Department of Respiratory Medicine, Karpaga Vinayaga Institute of Medical Science, Chengelpet, Tamil Nadu, India.
4. Professor and Head, Department of Respiratory Medicine, Chettinad Hospital and Research Institute, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Suresh Sagadevan,
2/3 Lattur Mathura, Angamampattu, Vittilapuram Village,
Kalpakkam-603102, Chennai, Tamil Nadu, India.
E-mail: sagadevansuresh@gmail.com

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