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Hematological and Inflammatory Biomarkers among Stable COPD and Acute Exacerbations of COPD Patients

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Abstract

Objectives: Chronic Obstructive Pulmonary Disease (COPD) is heterogeneous in nature. Acute exacerbation of COPD (AECOPD) is diagnosed clinically which is subjective and clinical judgment may vary from clinician to clinician. Since chronic inflammation underlies the pathogenesis of COPD, markers of inflammation have generated lot of interest for their potential to be used as biomarkers of COPD. This study aimed to assess the variation in levels of neutrophil lymphocyte ratio (NLR) and platelet indices in patients with stable COPD and acute exacerbation of COPD patients and its association with GOLD stages. ***Methods:*** This prospective analytical study was carried out in our tertiary care hospital from December 2018 to July 2020. About 64 subjects (32- stable COPD, 32- AECOPD) who satisfied study criteria were included. Blood sample was taken from stable and AECOPD patients and were compared. ***Results:*** It was observed that Neutrophil Lymphocyte Ratio, Platelet Distribution Width, Erythrocyte Sedimentation Rate and C-Reactive Protein were increased in AECOPD patients when compared with stable COPD patients which was statistically significant with p value of <0.001. A positive correlation was observed between Neutrophil Lymphocyte Ratio, Platelet Distribution Width and Erythrocyte Sedimentation Rate, C-Reactive Protein which was statistically significant with p value of <0.001.

Conclusion: We found that neutrophil lymphocyte ratio and platelet distribution width values increased significantly in AECOPD patients when compared to stable COPD patients.
Keywords: AECOPD; COPD; Neutrophil Lymphocyte Ratio; Platelet Distribution Width.

Advances in Knowledge

- This study was done to assess levels of neutrophil lymphocyte ratio, platelet indices and inflammatory biomarkers among stable chronic obstructive pulmonary disease (COPD) patients and patients with acute exacerbation of chronic obstructive pulmonary disease.
- Since chronic inflammation underlies the pathogenesis of COPD, markers of inflammation have generated lot of interest for their potential to be used as biomarkers of COPD. There are few studies done in India to study the role of these biomarkers in COPD patients.

Application to Patient Care

- The stable COPD patients have low graded inflammation with increased inflammatory protein levels and inflammatory cells. Whereas in exacerbation, systemic inflammation worsens and higher levels of inflammatory proteins and cells and mediators have been demonstrated.
- Heightened inflammatory response is noted well before the clinical symptoms of acute exacerbation period.
- Even though acute exacerbation of COPD is a clinical diagnosis according to the definitions provided in the literature, during routine follow up of COPD patients, when elevated NLR is detected, it aids in early detection of acute exacerbation and appropriate intervention.

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the top three leading cause of death worldwide. In 2012, about 3 million people died due to COPD accounting to 6% death all over the world. Burden of COPD is likely to rise in the coming years because of increased prevalence of smoking and smokeless tobacco use, aging, environmental pollution and other risk factors. COPD is characterised by persistent respiratory symptoms and airflow limitation that results secondary to airway and/or alveolar abnormalities caused mostly by significant

exposure to noxious particles or gases and can be influenced by host factors which include abnormal lung development.[1]

From 1990 to 2016, prevalence of COPD has increased by 29%. In 2016, out of the total deaths, 8.7% of deaths was attributed to COPD.[2] It is a preventable and treatable disease with considerable systemic and extra pulmonary effects. Frequent exacerbations of COPD not only have serious impact on the severity and course of disease but also on the quality of life.[3] Therefore, strategy for prevention, early diagnosis and treatment of COPD exacerbations is essential to better address the disease.

Since chronic inflammation underlies the pathogenesis of COPD, markers of inflammation have generated lot of interest for their potential to be used as biomarkers of COPD. There are few studies done in India to study the role of these biomarkers in COPD patients.More studies are needed to confirm their association with COPD. It will help in assessing individualized risk stratification, disease severity and better management of COPD.[4] Under this perspective, The study aimed to assess levels of neutrophil lymphocyte ratio, platelet indices and inflammatory biomarkers among stable COPD and acute exacerbation of chronic obstructive pulmonary disease (AECOPD) patients and association of haematological markers with GOLD staging.

Methods

This cross-sectional comparative study was conducted in department of pulmonary medicine of a tertiary care centre for a period of 18 months from December 2018 to July 2020.Patients aged ≥ 18 years with clinical and spirometry based diagnosis of COPD were recruited. Stable COPD patients with or without inhaled medications and not on systemic steroid during the last 3 months were recruited. AECOPD patients having aggravation of symptoms reported to emergency were also recruited. Patients who were diagnosed and proven cases of asthma, pneumonia, sepsis, pulmonary embolism and with obstructive sleep apnoea were excluded from the study. Patients with autoimmune diseases, haematological malignancies and solid tumours were also excluded as they were potential confounders. Demographic and clinical details of the patients were noted in prerequisite data collection proforma. History of smoking and biomass fuel exposure was obtained in a face-to-face interview. Patients with smoking history were categorized as never smoker/current smoker/ex-smokers. Details of years of biomass fuel exposure and details of the co-morbidities were also noted. Patients underwent

spirometry by JAEGER MASTER SCREEN PFT machine in spirometry laboratory placed in pulmonary medicine department. Patients were given 400mcg of salbutamol by metered dose inhaler and spirometry was repeated to get post bronchodilator value. Patients with post-bronchodilator FEV1/FVC ratio < 0.7 was included in the study and who were suspected to have AECOPD underwent spirometry after stabilization following a period of six weeks if possible and were included if their post bronchodilator FEV1/FVC < 0.7. Eligible COPD patients meeting the inclusion criteria were subjected to chest X-Ray PA view and high resolution computed tomography (HRCT) thorax in full inspiration at a later date when stable to rule out alternative diagnosis and emphysema extent with PHILIPS 6 slice CT placed in the department of radio diagnosis. Blood sample of 5ml was taken from stable COPD patients during their outpatient visit. Patients who presented with AECOPD, blood sample of 5 ml was taken within 1 hour of hospital admission or before administration of any treatment whichever was the earliest. These blood samples were divided into two separate vials. A vial with 2ml of blood was sent in ethylene diamine tetra acetate (EDTA) vials to department of pathology for neutrophil-lymphocyte ratio, platelet indices and erythrocyte sedimentation rate (ESR). The remaining 3 ml sample was taken in plain vials and serum was separated and kept at -70°c. This centrifuged blood sample was used for estimating C- reactive protein (CRP) values by ELISA. Neutrophil lymphocyte ratio (NLR), platelet indices including mean platelet volume (MPV), platelet distribution width (PDW), ESR, CRP in both stable and AECOPD patients were noted down.

Data was collected and spread in excel sheet. Statistical analysis was done using SPSS version 19.[4] Due to not normal distribution, NLR, MPV, PDW, ESR, CRP values were presented as median and inter-quartile range. Continuous variables were expressed as mean and standard deviation. The dependent variables (haematological parameters and inflammatory biomarkers) were compared between stable COPD and AECOPD by two-tailed t test. Karl Pearson correlation analysis was used to compare the correlation between NLR, MPV, PDW (haematological parameters) with ESR and CRP (inflammatory biomarkers). Confounders were analysed using multivariate regression analysis.

In a study done by Sharma *et al*, mean NLR levels in stable COPD group was 4.263±1.900 and in AECOPD group was 6.389±3.071.[5] NLR measurement demonstrated a sensitivity and specificity of 40%and 77.14%. Assuming a mean difference of 2.1, sample size was

calculated assuming a power of 80% as 32 patients in each group amounting to a total of 64 patients.

Results

A total of 106 patients were screened during the study period from December 2018 to July 2020. Eighteen stable COPD patients and 7 AECOPD patients were excluded from the study as they did not fulfill the inclusion criteria. There was no statistically significant difference in the age groups among stable COPD and AECOPD patients with a p value of 0.119. There was male gender predilection in both stable AECOPD patients group. Majority of patients belonging to both stable COPD and AECOPD groups were agricultural labourers. Majority of patients with AECOPD were obese while majority of stable COPD had normal body mass index. Baseline characteristics like gender, occupation, smoking index and biomass fuel exposure were analysed with multivariate analysis and were found to have no significant impact on the outcome of COPD with exacerbation status.

Mean FEV1 value for stable COPD patients was 44 ± 14.61 and for AECOPD patients was 37.37 ± 14.72. Mean FEV1/FVC value for stable COPD patients was 51.38 ± 11.04 and for AECOPD patients was 51.35 ± 9.69. In our study, majority of stable COPD patients belonged to ≤ 55years of age with mean age of 58.02 ± 8.07 and majority of AECOPD patients were of ≥ 65 years age group with a mean age of 62.56 ± 10.03.In our study, median ± interquartile range for NLR in stable COPD patients was (2.14 ± 0.97) and in AECOPD patients was (11.2 ± 9.42). Median ± interquartile range for MPV in stable COPD patients was (9.40 ± 1.05) and in AECOPD patients was (13.657 ± 2.35). Median ± interquartile range for PDW in stable COPD patients was (8.60 ± 1.33) and in AECOPD patients was (8.35 ± 0.85).

Statistically significant difference was noted for NLR and platelet distribution width ($p < 0.001$) between stable COPD patients and AECOPD patients.. Statistically significant difference for ESR and CRP ($p < 0.001$) was found between stable COPD patients and AECOPD.

Area under Receiver Operating Characteristic analysis obtained for NLR was 0.986 (98%) with 95% confidence interval. It was noted that sensitivity and specificity of NLR for predicting AECOPD were 94%and 94% respectively for the cut-off value of 3.79. The PDW had an AUC of is 0.99 (99%) with 95% confidence interval and the sensitivity and specificity was 93.8% and 93.7 % respectively for the cut-off value of 11.55. Area under Receiver

Operating Characteristic analysis obtained for CRP was 0.988 (98%). It was noted that sensitivity and specificity of CRP were 97% and 97%, respectively, for the cut-off value of 14.15.

There was a positive correlation between NLR and Erythrocyte Sedimentation Rate with correlation coefficient value of 0.489 ($p< 0.001$) and a positive correlation with C-Reactive Protein with correlation coefficient value of 0.721 ($p < 0.001$). A positive correlation between PDW and Erythrocyte Sedimentation Rate with correlation coefficient value of 0.518 ($p< 0.001$) and C - reactive protein with correlation coefficient value of 0.754 ($p < 0.001$) was observed. Pearson correlation analysis and scatter plot showed negative correlation which was not statistically significant between MPV and ESR (r - 0.146, P value of 0.251), between MPV and CRP (r -0.181 , P value of 0.151).[9]
The haematological markers like NLR, Mean Platelet Volume And Platelet distribution width did not show any statistically significant difference in all the GOLD stages of COPD and regression coefficient was not significant.

Discussion

During acute exacerbation of COPD, systemic inflammation worsens and higher levels of inflammatory proteins, cells and mediators are secreted. These forms the basis for development of neutrophil lymphocyte ratio as a marker to predict increased systemic inflammation during the period of acute exacerbation.[6] A total of 64 patients were recruited of which 32 were stable COPD patients and 32 were AECOPD patients. Socio demographic data, haematological and inflammatory biomarkers between the stable COPD patients and AECOPD patients were compared and analyzed. In our study, it was observed that mean neutrophil lymphocyte ratio among stable COPD patients was 2.32 ± 8.4 and among AECOPD patients was 11.22 ± 5.88 which was statistically significant($p<0.001$). Ercan Kurtipek *et al*. did a cross sectional study on 94 male patients over 40 years.[7] They observed that NLR among stable COPD patients was 2.75 ± 1.11 and among AECOPD patients was 7.99±5.72. They proposed that mean NLR levels were higher in AECOPD patients when compared to patients with stable COPD patients and the observation was statistically significant. Their findings were similar to our results. From the systematic review, in AECOPD, NLR cut-off value of 3.34 with a median AUC of 0.86 would help in diagnosis with sensitivity of 80% and specificity of 86%.[8] In our study, it was found that AUC obtained for NLR was 0.986 (98%) with 95% confidence interval. It was noted that sensitivity of NLR

was 94%and specificity of 94% for the cut-off value of 3.79. It means that value of NLR ≥ 3.79 has 94% chance of predicting exacerbation in COPD patients.

Pearson correlation analysis and scatter plot showed positive correlation between NLR and ESR (r 0.714, P < 0.000), between NLR and CRP (r 0.609, P < 0.000).[9]

Observed elevated levels of Willebrand factor, D-dimer, and prothrombin fragment- 1, 2 which are surrogate markers for inflammation, endothelial damage and clotting activation respectively from various studies led to the concept that COPD exacerbation is associated with systemic inflammation and is a prothrombotic state.[10] In our study, it was observed that mean platelet volume among stable COPD patients was 8.50± 0.84 and among AECOPD was 8.27 ± 0.56 which was not statistically significant (p- 0.189). Dentener *et al.* in 2001 proposed the idea that increased production of proinflammatory cytokines and acute phase reactants during AECOPD interfere with megakaryopoiesis thereby reducing the size of platelets in the bone marrow which is then released into the blood circulation.[10] Thus explains the fall in MPV in AECOPD when compared to stable COPD patients.

Pearson correlation analysis and scatter plot showed negative correlation which was not statistically significant between MPV and ESR (r - 0.146, P value of 0.251), between MPV and CRP (r -0.181 , P value of 0.151).[9]

The most widely used application of PDW is to provide information on the viability of platelets which is to be transfused.[12] Increase in PDW indicate that abnormally large and small platelets are in circulation. Steiropoulos *et al.* reported no significance difference in PDW amongst different stages of COPD.[13] In our study, we observed that mean PDW was 9.48 ± 0.94 for stable COPD patients and 13.67 ± 1.43 for AECOPD patients. Statistically significant difference was observed for PDW (p < 0.001) between stable COPD patients and AECOPD patients.

Günay E *et al*. did retrospective study on 319 subjects with 269 COPD patients (178 stable COPD patients, 91 AECOPD patients) and 50 were age and sex matched control group.[14] They assessed the levels of NLR, MPV, PDW, RDW, CRP among three groups (control, stable COPD and COPD with acute exacerbation patients). They also assessed the levels of these parameters among GOLD stages of COPD. They observed that PDW levels were

similar in all 3 groups. So, further correlation of levels of PDW with CRP was not done.Our study observed lower PDW values in stable and AECOPD patients. Variability could be due to the presence or absence of underlying co-morbid conditions which was not noted in the study by Günay E *et al*.[14] In the meta-analysis by Ma *et al.*, levels of MPV were compared pair wise among control group, stable COPD group, AECOPD group.[15] Also, correlations between MPV level and levels of systemic inflammatory biomarkers such as high sensitivity C-reactive protein (hs-CRP), C-reactive protein (CRP), white blood cells (WBC), neutrophils were also compared. They concluded that levels of MPV cannot be used to discriminate between patients with stable COPD group, AECOPD group, and control group. The study could not find significant correlation between MPV levels and other inflammatory biomarkers. The proposed hypothesis for this was MPV can be affected by multiple risk factors like diabetes, hypertension, dyslipidemia, smoking.[15] It was observed from our results that mean value for MPV for stable COPD patients was 8.50 ± 0.84 and for AECOPD patients was 8.27 ± 0.56. The difference of MPV value between stable COPD patients and AECOPD patients was not statistically significant (p= 0.189). Ulasli *et al*. did a study on 47 patients with COPD and on 40 healthy subjects.[16] In their study they observed that the mean MPV levels for control, stable and acute exacerbation group was 9.3 ±0.8 fl, 9.3 ±1.4 and 8.6 ±1.0 fl. They suggested that MPV can be used as a negative acute phase reactant in AECOPD.[16] Our study is also in agreement that MPV falls during acute exacerbation.

It was observed that there was a positive correlation between PDW and ESR with correlation coefficient value of 0.518 ($p<0.001$). Also, positive correlation was observed between PDW and CRP with correlation coefficient value of 0.721 ($p < 0.001$). It was observed from the current study that there was a positive correlation between NLR and ESR with correlation coefficient value of 0.489 ($p<0.001$). Also, positive correlation was observed between NLR and ESR with correlation coefficient value of 0.754 ($p < 0.001$). To our knowledge, correlation between MPV levels and ESR has not been studied previously. We found that Mean Platelet volume has negative correlation between ESR which was not statistically significant (p value- 0.251) and also negative correlation was observed between MPV and CRP which was not statistically significant (p value- 0.151).Wang *et al.* did study on 70 patients with AECOPD with age, sex matched controls.[17] They compared levels of MPV, CRP, WBC and fibrinogen between stable COPD patients and in patients with AECOPD. They shared their observation that during acute exacerbation, levels of MPV were lower and CRP values were higher. Thus, a statistically significant negative correlation was found

between MPV and CRP during the acute event ($p<0.001$).[17] Though negative correlation between MPV and CRP was observed in our results, it was not statistically significant. Estimated sample size could not be attained due to pandemic and trends of haematological parameters could not be analysed.

Conclusion

In our study, we assessed the utility of parameters like neutrophil lymphocyte ratio and platelet indices (mean platelet volume, platelet distribution width) in stable COPD and AECOPD patients. We found that neutrophil lymphocyte ratio and platelet distribution width values increased significantly in COPD patients with acute exacerbation when compared to stable COPD patients. Thus, these biomarkers which could be obtained from routine hemogram can be used for predicting acute exacerbation in COPD patients.

Authors' Contribution

RPA, MMM, VKS, RK and SVC conceptualized and designed the study. All authors collected the data. RPA, VKS, RK, SVC and MBV analysed and interpreted the data. MMM drafted the manuscript. All authors approved the final version of the manuscript.

Conflict of Interest

The authors declare no conflicts of interest.

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345 **Table 1:** Demographic details.

Variables	**Categories**	**Stable COPD patients N = 32**	**AECOPD patients N= 32**	**P value**
Age	≤ 55 years	14(43.8)	8(25)	0.119
	56-65 years	12(37.5)	11(34.4)	
	≥65 years	6(18.8)	13(40.6)	
Gender	Male	31(96.9)	23(71.9)	0.006
	Female	1(3.1)	9(28.1)	
Occupation	Laborer	31(96.9)	22(68.8)	0.012
	House wife	1(3.1)	9(28.1)	
	Coal mine worker	0	1(3.1)	
	Systemic Hypertension	5(15.6)	1(3.1)	
	Diabetes Mellitus& systemic hypertension	1(3.1)	1(3.1)	
	Thyroid disorder	1(3.1)	1(3.1)	
	Systemic	0	1(3.1)	
	hypertension and Thyroid disorder			
	None	22(68.8)	25(78.1)	
BMI	Underweight (<18.5)	3(9.4)	3(9.4)	3.841
	Overweight (25-29.9)	4(12.5)	6(18.8)	
	Obese (≥ 30)	12(37.5)	17(53.1)	
	Normal (18.5-24.9)	13(40.6)	6(18.8)	

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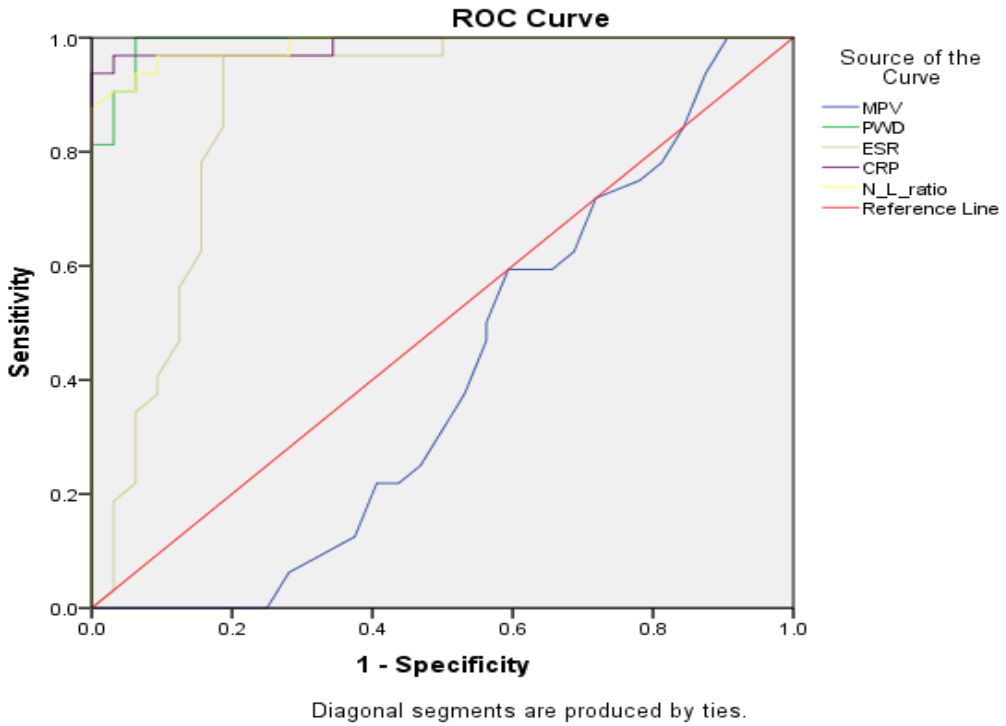
Table 2: Distribution of haematological and inflammatory biomarkers among stable COPD patients and COPD with acute exacerbation patients.

S.NO	Haematological parameter	Stable COPD patients (Median ± IQR)	AECOPD patients (Median± IQR)	P value
1.	**Mean Neutrophil Lymphocyte Ratio**	(2.14 ± 0.97)	(11.24 ± 9.42)	**<0.001**
2.	**Mean Platelet Volume** (fl)	(8.60 ± 1.33)	(8.35 ± 0.85)	0.189
3.	**Mean Platelet Distribution Width**	(9.40 ± 1.05)	(13.65 ± 2.35)	**<0.001**
1.	**Erythrocyte Sedimentation Rate(mm/hr)**	(27 ± 23.25)	(54 ± 10.25)	**<0.001**
2.	**C-Reactive Protein(mg/dl)**	(5.95 ± 4.58)	(22.3 ± 5.3)	**<0.001**

Table 3: Correlation of haematological parameters (neutrophil lymphocyte ratio, Mean Platelet Volume, Platelet distribution width) with GOLD stages of COPD.

Haematological parameter	GOLD Stage(I) (N=1)	GOLD Stage (II) (N=15) Range Mean±SD	GOLD Stage (III) (N=29) Range Mean±SD	GOLD Stage (IV) (N=19) Range Mean±SD	F Value	P value
Neutrophil lymphocyte ratio	5.70	1.32-12.19 3.60 ± 3.42	1.02-23.65 7.36 ± 6.40	1.47-20.73 8.43 ± 6.80	**1.996**	**0.124**
Mean Platelet Volume	8.30	7.20-10.60 8.53 ± 0.91	7.40-9.60 8.31 ± 0.62	7.10-9.40 8.37 ± 0.72	**0.295**	**0.829**
Platelet Distribution Width	13.40	8.60-14.90 10.94± 1.96	8.20-15.90 11.58 ± 2.60	8.50-15.80 11.97 ± 2.52	**0.692**	**0.561**



Area Under the Curve

Test Result Variable(s)	Area
MPV	.403
PDW	.991
ESR	.878
CRP	.988
N_L_ratio	.986

Figure 1: Receiver Operating Characteristic analysis to evaluate the performance of haematological parameters (Neutrophil Lymphocyte Ratio, Mean platelet Volume, Platelet Distribution Width) and inflammatory biomarkers (Erythrocyte Sedimentation Rate, C-Reactive Protein).