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CLINICAL & BASIC RESEARCH

Haematological and Inflammatory Biomarkers Among Stable COPD and Acute Exacerbations of COPD Patients

Ramya Priya A, *Madhusmita M. Mohapatra, Vinod K. Saka, Rakhee Kar, Sunitha V. Chakkalakkoombil, Mahesh B. Vemuri

abstract: ***Objectives:*** This study aimed to assess the variation in the levels of the neutrophil lymphocyte ratio (NLR) and platelet indices in patients with stable chronic obstructive pulmonary disease (COPD) and acute exacerbation of COPD (AECOPD) patients and its association with GOLD stages. COPD is heterogeneous in nature. AECOPD is diagnosed clinically, which is subjective, and clinical judgement may vary from clinician to clinician. Since chronic inflammation underlies the pathogenesis of COPD, markers of inflammation have generated considerable interest in their potential to be used as biomarkers of COPD. ***Methods:*** This prospective analytical study was carried out at the Department of Pulmonary Medicine, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India, from December 2018 to July 2020. A total of 64 subjects (32 stable COPD, 32 AECOPD) who satisfied the study criteria were included. Blood samples were taken from stable and AECOPD patients and were compared. ***Results:*** It was observed that the NLR, the platelet distribution width, the erythrocyte sedimentation rate (ESR) and the C-reactive protein (CRP) increased in AECOPD patients compared to stable COPD patients (P <0.001). A positive correlation was observed between the neutrophil lymphocyte ratio, the platelet distribution width, the ESR and the CRP (P <0.001). ***Conclusion:*** The NLR and platelet distribution width values increased significantly in AECOPD patients compared to stable COPD patients.

Keywords: Biomarkers; Chronic Obstructive Pulmonary Disease; Acute Exacerbation; India.

Advances in Knowledge

- *Heightened inflammatory response is noted well before the clinical symptoms of acute exacerbation period. Even though acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is a clinical diagnosis according to the definitions provided in the literature, during routine follow-up of COPD patients, when elevated neutrophil lymphocyte ratio (NLR) and platelet distribution width (PDW) is detected, it aids in early detection of acute exacerbation and appropriate intervention.*

Applications to Patient Care

- *Even though AECOPD is a clinical diagnosis based on definitions which may be subject to inter-person variability, this study found that NLR and PDW values increased significantly in AECOPD patients compared to stable COPD patients.*
- *Thus, these biomarkers which could be obtained from routine haemogram can serve as objective evidence in predicting AECOPD and evidence based early intervention could be provided, thereby reducing mortality and improve quality of life in these patients.*

Chronic obstructive pulmonary disease (COPD) is one of the top three leading causes of death worldwide. In 2012, approximately three million people died due to COPD, accounting for 6% of deaths worldwide. COPD is likely to increase in the coming years because of increased prevalence of smoking and smokeless tobacco use, ageing, environmental pollution and other risk factors.[1] 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, the prevalence of COPD increased by 29%. In 2016, out of the total deaths, 8.7% of deaths were attributed to COPD.[2] It is a preventable and treatable disease with considerable systemic and extrapulmonary effects. Frequent exacerbations of COPD have a serious impact not only on the severity and course of disease but also on the quality of life.[3] Therefore, a 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 considerable interest in their potential to be used as biomarkers of COPD. Only a few studies have been done in India to examine the role of these biomarkers in COPD patients.[4] More studies are needed to confirm their association with COPD. It will help in assessing individualised risk stratification,

Department of Pulmonary Medicine, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India
**Corresponding Author's e-mail: drmadhusmita1@gmail.com*

disease severity and better management of COPD. From this perspective, this study aimed to assess the levels of neutrophil lymphocyte ratio, platelet indices and inflammatory biomarkers amongst patients with stable COPD and patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) and the association of haematological markers with GOLD stages.

Methods

This cross-sectional comparative study was conducted in the Department of Pulmonary Medicine, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India, over a period of 18 months from December 2018 to July 2020. Patients who were aged ≥18 years and clinically diagnosed with COPD based on spirometry results were recruited. Stable COPD patients with or without inhaled medications and not on systemic steroids during the last three months were recruited. AECOPD patients who presented with aggravated symptoms to emergency care 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 a prerequisite data collection proforma. History of smoking and biomass smoke exposure was obtained in a face-to-face interview. Patients with smoking history were categorised as never smoker/current smoker/ex-smokers. Details of years of biomass smoke exposure and details of the comorbidities were also noted.

Patients underwent spirometry by the Jaeger Masterscreen PFT machine (CareFusion Ltd., Basingstoke, UK) in the spirometry laboratory of the Department of Pulmonary Medicine. Patients were given 400 mcg of salbutamol by a metered dose inhaler and spirometry was repeated to get a post-bronchodilator value. Patients with a post-bronchodilator FEV1/FVC ratio <0.7 were included in the study, and those who were suspected to have AECOPD underwent spirometry after stabilisation 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 thorax in full inspiration at a later date when stable, to rule out alternative diagnosis and emphysema extent with Siemens Somatom sensation 64 slice CT (Siemens, Munich, Germany) placed in the Department of Radio-Diagnosis. A 5 mL blood sample was taken from stable COPD patients during their outpatient visit. A blood sample of 5 mL was taken from the patients who presented with AECOPD within one hour of hospital admission or before administration of any treatment, whichever was the earliest. These blood samples were divided into two separate vials. A 2 mL blood sample was collected in ethylene diamine tetra acetate vials and sent to the Department of Pathology for neutrophil-lymphocyte ratio, platelet indices and erythrocyte sedimentation rate (ESR) analysis. The remaining 3 mL sample was collected in plain vials and the serum was separated and stored at –70°C. This centrifuged blood sample was used for estimating C-reactive protein (CRP) values by ELISA. The neutrophil lymphocyte ratio (NLR), platelet indices including the mean platelet volume (MPV), platelet distribution width (PDW), ESR and CRP in both stable and AECOPD patients.

Data were collected and entered in an Excel sheet. Statistical analysis was done using the Statistical Package for the Social Sciences (SPSS), Version 19 (IBM Corporation, Armonk, New York, USA). Due to no normal distribution, the NLR, MPV, PDW, ESR, CRP values were presented as median and inter-quartile range. Continuous variables were expressed as mean and standard deviations. The dependent variables (haematological parameters and inflammatory biomarkers) were compared between stable COPD and AECOPD by a two-tailed t-test. Karl Pearson correlation analysis was used to compare the correlation between the NLR, MPV, and PDW (haematological parameters) and the ESR and CRP values (inflammatory biomarkers). Confounders were analysed using multivariate regression analysis.

In a study done by Sharma *et al*., the mean NLR level was 4.263 ± 1.900 in the stable COPD group and 6.389 ± 3.071 in the AECOPD group.[4] The NLR measurement demonstrated a sensitivity and specificity of 40% and 77.14%, respectively. Assuming a mean difference of 2.1, the sample size was calculated assuming a power of 80% as 32 patients in each group amounted to a total of 64 patients.

This study was approved by the Institutional ethics committee of JIPMER, Puducherry, India. Informed written consent was taken from each patient.

Results

A total of 106 patients were screened during the study period from December 2018 to July 2020, while 18 stable COPD patients and seven AECOPD patients were excluded from the study as they did not fulfil the

Table 1: Demographic details of stable COPD and AECOPD patients included in this study (N = 64)

Variable	Stable COPD patients (n = 32)	AECOPD patients (n = 32)	*P* value
Age in years			
≤55	14 (43.8)	8 (25)	
56–65	12 (37.5)	11 (34.4)	0.119
≥66	6 (18.8)	13 (40.6)	
Gender			
Male	31 (96.9)	23 (71.9)	0.006
Female	1 (3.1)	9 (28.1)	
Occupation			
Labourer	31(96.9)	22 (68.8)	
Housewife	1 (3.1)	9 (28.1)	
Coal mine worker	0	1 (3.1)	
Systemic hypertension	5 (15.6)	1 (3.1)	
Diabetes mellitus and systemic hypertension	1 (3.1)	1 (3.1)	0.012
Thyroid disorder	1 (3.1)	1 (3.1)	
Systemic hypertension and thyroid disorder	0	1 (3.1)	
Unemployed	22 (68.8)	25 (78.1)	
BMI			
Underweight (<18.5)	3 (9.4)	3 (9.4)	
Overweight (25–29.9)	4 (12.5)	6 (18.8)	0.28
Obese (≥30)	12 (37.5)	17 (53.1)	
Normal (18.5–24.9)	13 (40.6)	6 (18.8)	

COPD = chronic obstructive pulmonary disease; AECOPD = acute exacerbation of COPD; BMI = body mass index.

inclusion criteria. There was no statistically significant difference in the age groups amongst stable COPD and AECOPD patients (P = 0.119). There was male gender predilection in both stable and AECOPD patient groups. The majority of patients in both stable COPD and AECOPD groups were agricultural labourers [Table 1]. The majority of the patients with AECOPD were obese while the majority of stable COPD patients had a normal body mass index [Table 1]. Baseline characteristics such as gender, occupation, smoking index and biomass smoke exposure were analysed by multivariate analysis and were found to have no significant impact on the outcome of COPD with exacerbation status.

Table 2: Distribution of haematological and inflammatory biomarkers among stable COPD patients and AECOPD patients

Haematological parameters	Median (IQR)		*P* value
	Stable COPD patients	AECOPD patients	
Mean neutrophil lymphocyte ratio	2.14 (1.71–2.78)	11.2 (5.86–15.28)	<0.001
Mean platelet volume in fl	9.40 (7.80–9.13)	13.657 (7.78–8.62)	0.189
Mean platelet distribution width	8.60 (8.78–9.83)	8.35 (12.55–14.9)	<0.001
Erythrocyte sedimentation rate in mm/hr	27 (14.75–38)	54 (48.75–59)	<0.001
C-reactive protein in mg/dL	5.95 (4.40–8.98)	22.3 (19–24.30)	<0.001

IQR = interquartile range; COPD = chronic obstructive pulmonary disease; AECOPD = acute exacerbation of COPD.

The mean FEV1 value was 44 ± 14.61 for stable COPD patients and 37.37 ± 14.72 for AECOPD patients. The mean FEV1/FVC value was 51.38 ± 11.04 for stable COPD patients and 51.35 ± 9.69 for AECOPD patients. The majority of stable COPD patients were ≤55 years of age with a mean age of 58.02 ± 8.07, while the majority of AECOPD patients were ≥65 years with a mean age of 62.56 ± 10.03. The median (interquartile range) for the NLR was 2.14 (1.71–2.78) in stable COPD patients and 11.2 (5.86–15.28) in AECOPD patients. The median (interquartile range) for the MPV was 9.40 (7.80–9.13) in stable COPD patients and 13.657 (7.78–8.62) in AECOPD patients. The median (interquartile range) for the PDW was 8.60 (8.78–9.83) in stable COPD patients and 8.35 (12.55–14.9) in AECOPD patients [Table 2].

A statistically significant difference was noted for the NLR and the PDW (P <0.001) between stable COPD patients and AECOPD patients. A statistically significant difference was found for the ESR and the CRP (P <0.001) between stable COPD patients and AECOPD [Table 2].

The area under the receiver operating characteristic analysis obtained for the NLR was 0.986 (98%) with a 95% confidence interval (CI). The sensitivity and the specificity of the NLR for predicting AECOPD was noted as 94% for both, with the cut-off

Table 3: Correlation of haematological parameters (neutrophil lymphocyte ratio, mean platelet volume, platelet distribution width) with GOLD stages of COPD (N = 64)

Haematological parameters	Mean ± SD (range)				F value	*P* value
	GOLD stage I (n = 1)	GOLD stage II (n = 15)	GOLD stage III (n = 29)	GOLD stage IV (n= 19)		
Neutrophil lymphocyte ratio	5.70	3.60 ± 3.42 (1.32–12.19)	7.36 ± 6.40 (1.02–23.65)	8.43 ± 6.80 (1.47–20.73)	1.996	0.124
Mean platelet volume	8.30	8.53 ± 0.91 (7.20–10.60)	8.31 ± 0.62 (7.40–9.60)	8.37 ± 0.72 (7.10–9.40)	0.295	0.829
Platelet distribution width	13.40	10.94 ± 1.96 (8.60–14.90)	11.58 ± 2.60 (8.20–15.90)	11.97 ± 2.52 (8.50–15.80)	0.692	0.561

SD = standard deviation.

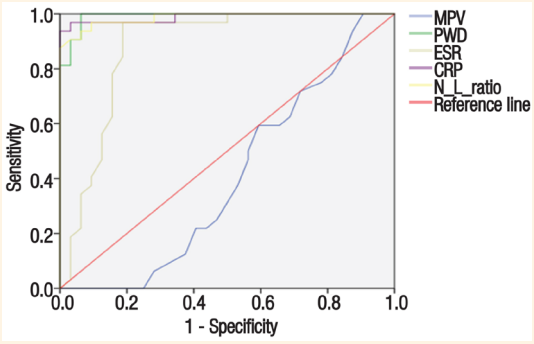

Figure 1: Receiver operating characteristic analysis to evaluate the performance of haematological parameters (neutrophil lymphocyte ratio, mean platelet volume, platelet distribution width) and inflammatory biomarkers (erythrocyte sedimentation rate, C-reactive protein).

MPV = mean platelet volume; PDW = platelet distribution width; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; N_L_ratio = neutrophil lymphocyte ratio.

value of 3.79. The PDW had an area under the curve (AUC) of 0.99 (99%) with a 95% CI and the sensitivity and specificity were 93.8% and 93.7%, respectively, with the cut-off value of 11.55. The area under the Receiver Operating Characteristic analysis obtained for the CRP was 0.988 (98%). The sensitivity and specificity of the CRP was 97% for both, with the cut-off value of 14.15 [Figure 1].

A positive correlation was observed between the NLR and the ESR, with a correlation coefficient value of 0.489 (P <0.001) and between the NLR and the CRP with a correlation coefficient value of 0.721 (P <0.001). In addition, the PDW and the ESR displayed positive correlation with a correlation coefficient value of 0.518 (P <0.001) and the same was observed between PDW and CRP, with a correlation coefficient value of 0.754 (P <0.001). Pearson correlation analysis and scatter plot showed a negative correlation between the MPV and ESR (r = 0.146; P = 0.251), as well as between the MPV and CRP (r = 0.181; P = 0.151), which were not statistically significant.[6]

The haematological markers such as the NLR, the MPV and the PDW did not show any statistically significant difference in all the GOLD stages of COPD and the regression coefficient was not significant [Table 3].

Discussion

During AECOPD, systemic inflammation worsens and higher levels of inflammatory proteins, cells and mediators are secreted. These form the basis of the development of the NLR 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. Sociodemographic data and haematological and inflammatory biomarkers between the stable COPD patients and AECOPD patients were compared and analysed. The mean NLR was observed at 2.32 ± 8.4 among stable COPD patients and at 11.22 ± 5.88 among AECOPD patients, which was statistically significant (P <0.001). Kurtipek *et al*. did a cross-sectional study on 94 male patients over 40 years.[7] They observed that the NLR was 2.75 ± 1.11 among stable COPD patients and 7.99 ± 5.72 among AECOPD patients. They proposed that the mean NLR levels were significantly higher in AECOPD patients compared to patients with stable COPD. Their findings were similar to the results of this study. From a systematic review, in AECOPD patients, the NLR cut-off value of 3.34 with a median AUC of 0.86 would help in the diagnosis with a sensitivity of 80% and a specificity of 86%.[8] In the current study, it was found that AUC obtained for the NLR was 0.986 (98%) with a 95% confidence interval. For the NLR, both the sensitivity and specificity were 94%, with the cut-off value of 3.79. This means that values of the NLR ≥3.79 has a 94% chance of predicting exacerbation in COPD patients.

In another study, Pearson correlation analysis and scatter plot showed a positive correlation between the NLR and the ESR (r = 0.714; *P* <0.001) and between the NLR and the CRP (r = 0.609; *P* <0.001).[9]

The elevated levels of Willebrand factor, D-dimer and prothrombin fragment-1, 2, which are surrogate markers for inflammation, endothelial damage and clotting activation, respectively, observed in various studies led to the concept that COPD exacerbation is associated with systemic inflammation and is a prothrombotic state.[10] In the current study, the MPV was observed to be 8.50 ± 0.84 among stable COPD patients and 8.27 ± 0.56 among patients with AECOPD, which was not statistically significant (*P* = 0.189). In 2001, Dentener *et al*. proposed the idea that increased production of proinflammatory cytokines and acute phase reactants during AECOPD interferes with megakaryopoiesis, thereby reducing the size of platelets in the bone marrow, which is then released into the blood circulation.[11] This explains the fall in the MPV in AECOPD when compared with stable COPD patients.

In a previous study, Pearson correlation analysis and scatter plot showed a negative correlation between the MPV and the ESR (r = 0.146; *P* = 0.251) and between the MPV and the CRP (r = 0.181; *P* = 0.151), which was not statistically significant.[8]

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

Günay *et al*. conducted a retrospective study on 319 subjects with 269 COPD patients (178 stable COPD patients, 91 AECOPD patients) and 50 age- and sex-matched control groups.[14] They assessed the levels of NLR, MPV, PDW, RDW and CRP among three groups (control, stable COPD and AECOPD patients). They also assessed the levels of these parameters during the GOLD stages of COPD. They observed that the PDW levels were similar in all three groups. Therefore, further correlation of the levels of the PDW with the CRP was not done. Lower PDW values in stable and AECOPD patients were observed in the current study. The variability could be due to the presence or absence of underlying comorbid conditions, which was not noted in the study by Günay *et al*.[14] In a meta-analysis by Ma *et al*., the levels of the MPV were compared pair-wise among the control group, the stable COPD group and the AECOPD group.[15] In addition, correlations between the MPV level and the levels of systemic inflammatory biomarkers such as high-sensitivity CRP, CRP, white blood cells (WBC) and neutrophils were also compared. They concluded that the levels of the MPV cannot be used to discriminate between patients with stable COPD group, AECOPD group and control group. The study could not find a significant correlation between the MPV levels and other inflammatory biomarkers. The proposed hypothesis for this was that the MPV can be affected by multiple risk factors such as diabetes, hypertension, dyslipidaemia and smoking.[15] It was observed from the results of this study that the mean value for the MPV was 8.50 ± 0.84 for stable COPD patients and 8.27 ± 0.56 for AECOPD patients. The difference in the 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 40 healthy subjects.[16] In their study, they observed that the mean MPV levels for control, stable and acute exacerbation groups were 9.3 ± 0.8 fl, 9.3 ± 1.4 fl and 8.6 ± 1.0 fl, respectively. They suggested that the MPV can be used as a negative acute phase reactant in AECOPD.[16] This study is also in agreement that the MPV decreases during acute exacerbation.

It was observed that there was a positive correlation between the PDW and the ESR with a correlation coefficient value of 0.518 (*P* <0.001). Likewise, a positive correlation was observed between the PDW and the CRP with a correlation coefficient value of 0.754 (*P* <0.001). It was observed in the current study that there was a positive correlation between the NLR and the ESR with a correlation coefficient value of 0.489 (*P* <0.001). Similarly, a positive correlation was observed between the NLR and the CRP with a correlation coefficient value of 0.721 (*P* <0.001). To the best of the authors' knowledge, the correlation between the MPV levels and the ESR has not been studied previously. It was found in this study that there is a negative correlation between the MPV and the ESR, which was not statistically significant (*P* = 0.251), as well as a negative correlation between the MPV and the CRP, which also was not statistically significant (*P* = 0.151). Wang *et al*. conducted a study on 70 patients with AECOPD with age- and sex-matched controls.[17] They compared the levels of MPV, CRP, WBC and fibrinogen between stable COPD patients and AECOPD patients; during acute exacerbation, levels of the MPV were lower and the CRP values were higher. A statistically significant negative correlation was found between the MPV and the CRP during the

acute event (P <0.001).[18] Though a negative correlation between the MPV and the CRP was observed in the results of the current study, it was not statistically significant (P = 0.189). The estimated sample size could not be attained due to the pandemic and the trends of haematological parameters could not be analysed.

Conclusion

The utility of parameters such as the NLR and platelet indices (mean platelet volume, platelet distribution width) in stable COPD and AECOPD patients was assessed. It was found that the NLR and the PDW values increased significantly in AECOPD patients compared to stable COPD patients. Thus, these biomarkers that can be obtained from a routine haemogram can be used for predicting AECOPD in patients.

AUTHORS' CONTRIBUTION

RPA, MMM, VKS, RK and SVC conceptualised 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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