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Comparative Study of Systemic Inflammatory Markers in Clinical Phenotypes of Chronic Obstructive Pulmonary Disease

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Background: Chronic Obstructive Pulmonary Disease (COPD) is an inflammatory pulmonary disorder with systemic inflammatory manifestations. This study aims to identify the profile of systemic inflammatory markers in the different phenotypes of COPD to help predict the disease and identify suitable treatment options.

Materials and Methods: A prospective observational study was conducted on 92 patients with COPD admitted to Victoria Hospital, Bangalore between August 2021 to December 2021. Levels of C-reactive protein (CRP), Serum Creatinine, Erythrocyte Sedimentation Rate (ESR), Absolute Lymphocyte Count (ALC), Absolute Eosinophil Count (AEC), and Lactate Dehydrogenase (LDH) were measured within 48 hours of presentation.

Results: Significantly higher levels of CRP were found in frequent exacerbator emphysema and chronic bronchitis phenotypes (p=0.001). The frequent exacerbator emphysema phenotype had significantly higher levels of LDH (p=0.001) and serum creatinine (p=0.001). Not surprisingly, absolute eosinophil counts were significantly raised in the overlap COPD-Asthma phenotype (p=0.001).

Conclusion: Raised serum CRP levels in the frequent exacerbator phenotypes of emphysema and chronic bronchitis suggest a possible inflammatory response to an infective etiology. Raised LDH levels in frequent exacerbator emphysema phenotype could signify underlying lung parenchymal destruction. Systemic inflammation and oxidative stress can lead to skeletal muscle injury and atrophy in COPD patients. This may explain the raised serum creatinine levels in frequent exacerbator emphysema phenotype. Eosinophilia seen in Overlap COPD-Asthma phenotype is suggestive of type 2 inflammation of the airways with better response to steroids.

Keywords: Inflammatory Markers; Chronic Obstructive Pulmonary Disease (COPD); Clinical Phenotypes

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) had a global prevalence of 11.7% in 2010 (1). It is now one of the top three causes of death worldwide and 90% of these deaths occurred in low- and middle-income countries (LMIC) (2). After diagnosis, the 10-year survival rate is 50% with more than one-third of patients dying due to respiratory insufficiency (3). The prevalence of COPD has been studied extensively by Indian investigators over the last 5 decades. The COPD prevalence varied from 3% to 8%

among Indian males and approximately 2.5% to 4.5% among Indian females (4).

COPD is defined as a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases and influenced by host factors including abnormal lung development (5). It is an inflammatory pulmonary disorder with systemic inflammatory manifestations. Chronic inflammation causes structural changes, narrowing of the small airways, and destruction of the lung parenchyma (emphysema) that leads to the loss of alveolar attachments to the small airways and decreases lung elastic recoil (5).

COPD phenotype is defined as a single or combination of disease attributes that describe differences between individuals with COPD and relate to clinically meaningful outcomes (symptoms, exacerbations, response to treatment, speed of progression of the disease or death) (6). COPD exacerbations are defined as acute events characterized by a worsening of the patient's respiratory symptoms (baseline dyspnea, cough, and/or sputum production) that is beyond normal day-to-day variation and leads to a change in medication periods of acute worsening of respiratory symptoms (5).

Spanish guidelines for the treatment of COPD [Gui´a Espan˜ ola de la EPOC (GesEPOC)] have proposed four different phenotypes as follows:

1) **Frequent exacerbator with predominant chronic bronchitis**: When COPD exacerbator frequently presents with chronic bronchitis, defined as the presence of productive cough or expectoration for >3 months per year and >2 consecutive years (7).

2) **Frequent exacerbator with predominant emphysema**: When the frequent exacerbator does not present with chronic cough and sputum production and the typical clinical and radiological signs of emphysema can be identified, this establishes the exacerbator with an emphysema phenotype (7).

3) Infrequent exacerbator with either chronic bronchitis or emphysema: It is defined as any patient experiencing less than two exacerbations per year with either chronic bronchitis or emphysema (8).

4) **Overlap COPD-asthma:** They are those with a history of asthma before the age of 40 years, the demonstration of eosinophilic inflammation in sputum or increased peripheral eosinophilia, and enhanced reversibility in airflow obstruction after the bronchodilator test. Due to the poor reproducibility of bronchodilator response, a marked response (>400 mL in FEV1) or at least two positive bronchodilator tests are required (9).

It has been suggested that systemic inflammation may explain part of the heterogeneity of COPD phenotypes, such as loss of lean body mass and the higher prevalence of comorbid disorders (10). The response to treatment is dependent on the type of inflammation involved. It is therefore important to consider the clinical phenotypes and their systemic inflammatory profile using a few commonly performed cost-effective tests to help prognosticate the disease and tailor suitable treatment options.

Unlike the GOLD guidelines which utilize the degree of airflow obstruction and symptoms to distinguish patients and find a suitable treatment, this study suggests the use of clinical phenotypes as a means to suggest suitable treatment and prognosticate the disease.

MATERIALS AND METHODS

A prospective observational study was conducted on patients with COPD admitted to Victoria Hospital, Bangalore between August 2021 to December 2021. This study was approved by the ethics committee of Bangalore Medical College and Research Institute issued with approval number BMCRI/PS/224/2021-22.

The sample size of 92 patients was obtained based on a similar study done by Gracia-Rio et al. (11), the levels of CRP were taken at 0.477 ± 14.68 %.

Using the formula $\eta = Z_{\alpha}^2 * \sigma^2 / d^2$

Where, n = sample size

Z_{α}= Standard table value for 95% confidence interval (CI)

σ = mean SD values of CRP = 14.68%

d = estimated precision = 3

After obtaining written informed consent, a total of 92 patients were enrolled in the study. All patients above the age of 18 years, diagnosed cases of COPD with previous spirometric records of postbronchodilator Forced Expiratory Volume in 1 second (FEV_1)/ Forced Vital Capacity (FVC) < 0.7 presenting with exacerbation to the hospital and requiring admission were included in the study. Patients with Chronic Kidney Disease, Ischemic Heart Disease, Chronic Liver Disease, Active Tuberculosis, and other systemic inflammatory diseases were excluded from the study. The levels of C-reactive protein (CRP), Serum Creatinine, Erythrocyte Sedimentation Rate (ESR), Absolute Lymphocyte Count (ALC), Absolute Eosinophil Count (AEC), and Lactate Dehydrogenase (LDH) were measured within 48 hours of hospital admission.

SPSS (Statistical Package for Social Sciences) version 20. (IBM SPASS statistics) was used to perform the statistical analysis. Descriptive statistics of the explanatory and outcome variables were calculated by median and interquartile range (IQR) for quantitative variables (Based on normalcy test- Shapiro Wilk test), frequency, and proportions for qualitative variables. Inferential statistics like the Chi-square test were applied for qualitative variables. The Kruskal-Wallis test was applied to compare the lab and clinical parameters among the groups with the post hoc Mann-Whitney test for inter-group comparison. The level of significance was set at 5%.

RESULTS

In our study, a total of 92 patients were included among which, 4 phenotypes were identified: 17 patients were frequent exacerbators of chronic bronchitis phenotype (Group 1), 39 patients belonged to frequent exacerbator emphysema phenotype (Group 2), 30 patients were infrequent exacerbators of either chronic bronchitis and emphysema phenotype (Group 3), and 6 patients belonged to overlap COPD-asthma phenotype (Group 4). Out of the 92 patients, 69 were males (75%) and 23 were females (25%). The age distribution shows the majority i.e., 58.8% of the 40–50-year-olds belonged to Group 1 (n=10), followed by 23.3% who belong to Group 3 (n=7). The majority i.e., 48.7% of the 61 to 70-year-olds belonged to Group 2 (n=19) followed by 43.4% (n=13) who belonged to Group 3.

Table 1 shows a comparison of the measured lab parameters between the 4 groups using the ANOVA test. The median value of AEC was 666 (cells/mm^3), when compared to the other phenotypes, this value was significantly higher (p=0.001). The value of ESR did not significantly differ among the groups. The median value of CRP was significantly higher being 37.2 and 38.2 (mg/L) among Group 1 and Group 2 when compared to the 3.2 and 2.7 (mg/L) among Group 3 and Group 4 (p=0.001). The mean value of Serum creatinine was significantly higher among Group 2 i.e., 1.2 (mg/dL) in comparison with the rest of the groups (p=0.001). The mean value of LDH among Group 2 is significantly higher in comparison with the rest of the groups (p=0.001).

Intergroup comparison using the Mann-Whitney U test was performed. Group 1 and Group 2 showed significant differences in their distributions comparing AEC levels, serum creatinine, and LDH levels (U=130.5, p=0.001; U=10.00, p=0.001; U=0.00, p=0.001). Group 1 and Group 3 showed significant differences in their distributions comparing AEC levels and CRP levels (U=125.5, p=0.004; U=0.00, p=0.001). Group 1 and Group 4 showed significant differences in their distributions comparing AEC levels and CRP levels (U=0.00, p=0.001; U=0.00, p=0.001).

Group 2 and Group 3 showed significant differences in their distributions comparing CRP levels, serum creatinine, and LDH levels (U=0.00, p=0.001; U=31.5, p=0.001; U=0.00, p=0.001).

Group 2 and Group 4 showed significant differences in their distributions comparing AEC levels, CRP levels, Serum creatinine, and LDH levels (U=0.00, p=0.001; U=0.00, p=0.001; U=3.00, p=0.001; U=0.00, p=0.001).

Group 3 and Group 4 showed significant differences in their distributions comparing AEC levels (U=0.00, p=0.001)(Table 2).

Table 1. Comparison of the lab parameters among the groups

	Groups	N	Minimum	Maximum	Median	IQR	P value
ALC	Group 1	17	959	2515	1578	448	0.41
	Group 2	39	620	3517	1685	703	
	Group 3	30	904	3102	1673.5	531	
	Group 4	6	888	2256	1582.5	944	
AEC	Group 1	17	197	320	262	58	0.001*
	Group 2	39	112	360	220	60	
	Group 3	30	77	333	219.5	65	
	Group 4	6	452	666	654	194	
ESR	Group 1	17	18	34	24	11	0.17
	Group 2	39	21	38	25	10	
	Group 3	30	18	36	23	12	
	Group 4	6	22	36	29	13	
CRP	Group 1	17	23.00	51.00	37.2	12.05	0.001*
	Group 2	39	21.80	56.00	38.2	9.5	
	Group 3	30	1.50	5.70	3.2	0.85	
	Group 4	6	2.30	5.00	2.7	2.03	
S. Creatinine	Group 1	17	0.40	0.90	0.78	0.23	0.001*
	Group 2	39	0.75	1.40	1.21	0.14	
	Group 3	30	0.30	1.20	0.76	0.28	
	Group 4	6	0.60	0.90	0.73	0.23	
LDH	Group 1	17	106	214	123	26	0.001*
	Group 2	39	340	486	380	63	
	Group 3	30	103	217	118	26	
	Group 4	6	112	184	120.5	36	

Table 2. Intergroup comparison using the Mann-Whitney test

		AEC	ESR	CRP	S. Creatinine	LDH
Group 1 V/s Group 2	U value	130.5	246.5	330.5	10.00	0.00
	p-value	0.001*	0.1	0.986	0.001*	0.001*
Group 1 V/s Group 3	U value	125.5	248.0	0.00	244.0	248
	p-value	0.004*	0.9	0.001*	0.806	0.87
Group 1 V/s Group 4	U value	0.00	29.5	0.00	49.5	41.5
	p-value	0.001*	0.1	0.001*	0.915	0.505
Group 2 V/s Group 3	U value	553.0	458.0	0.00	31.5	0.00
	p-value	0.698	0.1	0.001*	0.001*	0.001*
Group 2 V/s Group 4	U value	0.00	96.5	0.00	3.00	0.00
	p-value	0.001*	0.5	0.001*	0.001*	0.001*
Group 3 V/s Group 4	U value	0.00	54.0	85.5	83.5	69.0
	p-value	0.001*	0.1	0.84	0.78	0.37

*p value set significant at 0.05/4=0.025

DISCUSSION

COPD patients have a pro-inflammatory state, with increased circulating levels of many inflammatory cytokines and acute-phase reactants. C-reactive protein (CRP) is one of the common test parameters used in clinical practice to assess, diagnose, and prognose inflammation. CRP is the first acute-phase reactant to be described and is a sensitive systemic marker for inflammation and tissue damage (12). A randomized trial found a marked reduction in antibiotic prescriptions without impaired outcomes in UK primary care outpatients with acute exacerbation of COPD in

whom antibiotic prescriptions were guided by point-of-care CRP testing (13). Gracia-Rio et al. compared 324 COPD patients and 110 reference subjects. After adjusting for gender, age, BMI, and tobacco consumption, COPD patients showed higher levels of CRP ($p = 0.049$) (11). Our study showed increased serum CRP levels in the frequent exacerbator phenotypes of emphysema and chronic bronchitis suggesting a possible inflammatory response to an infective etiology. LDH is an enzyme found in almost all the body's tissues including those in the blood, heart, kidneys, brain, and lungs. When these tissues are damaged, they release LDH into the bloodstream or other body fluids. Our study showed elevated LDH levels in frequent exacerbator emphysema phenotype which could be a result of underlying lung parenchymal destruction. However, the elevation of this enzyme is highly non-specific, and very few studies have been done demonstrating its elevated levels in exacerbations of COPD.

Skeletal muscle groups show oxidative stress, signs of damage, and epigenetic changes in patients with COPD. Fiber atrophy, increased number of inflammatory cells, altered regenerative capacity, signs of apoptosis and autophagy, and an imbalance between protein synthesis and breakdown are features of the limb muscles of COPD patients with reduced body weight. Skeletal muscle injury and atrophy in COPD patients can explain raised serum creatinine in frequent exacerbator emphysema phenotype. Eosinophilia seen in Overlap COPD-Asthma phenotype is suggestive of type 2 inflammation of the airways with better response to steroids. Most studies have found that regular treatment with inhaled corticosteroids alone does not modify the long-term decline of FEV1 or mortality in patients with COPD (14). However, in moderate COPD, fluticasone furoate alone or in combination with vilanterol was associated with a slower decline in FEV1 compared with placebo or vilanterol alone by an average of 9 ml/year (15). This study aims to understand the profile of systemic inflammation in the different phenotypes of COPD to help predict the disease and tailor suitable treatment options.

The study was performed using non-specific markers of inflammation and other indirect biomarkers which forms a limitation of this study. The biomarkers were tested in the periods of acute exacerbation. The effect of pharmacotherapy given to the patients was not considered. Further studies need to be done to understand the levels of biomarkers even in stable COPD patients.

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Conflict of interest

No conflict of interest.

Ethical approval

This study was approved by the ethics committee of Bangalore Medical College and Research Institute issued with approval number BMCRI/PS/224/2021-22.

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