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A Study on Association Between Selected Inflammatory Markers with Disease Severity of Chronic Obstructive Pulmonary Disease

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ABSTRACT

Background: COPD is also a common inflammatory disease of the respiratory tract and the lung tissues and its prevalence is going to increase throughout the world.Several studies have shown that COPD patients have higher levels of inflammatory markers in blood.**Aim:** This hospital-based cross-sectional study try to the study has the scope to find any correlation between levels of inflammatory markers with the disease severity.**Material and methods**: A total of 150 patients with a diagnosis of COPD aged minimum 50 years who attended Medical College were selected as case and 150 subjects having no COPD or any other chronic diseases nor taking any supplementation as age and sex-matched control by systematic random sampling after informed consent. Then according to GOLD stages the cases are divided into 4 stages. Thereafter, all of the patients and healthy persons were subjected to the estimation of serum Interleukin -6 (IL-6), D-Dimer, Lactate dehydrogenase (LDH), C-Reactive Protein (CRP), ferritin, and Procalcitonin (PCT). **Results:** The result showed that among all inflammatory markers only IL6 and CRP are well correlated with disease severity but after multiple regression analysis it is found that the CRP concentration was not well correlation with other inflammatory markers in different severity. **Conclusion:** Compared to other inflammatory markers, we found that only serum IL6 concentration was significantly associated with COPD severity.

Keywords*: Association, Chronic Obstructive Pulmonary Diseases, inflammatory markers, disease severity.*

INTRODUCTION

Chronic Obstructive Pulmonary Diseases (COPD) is characterized by airflow obstruction that is not fully reversible and usually progressive in the long term.[1] It is in the top five leading causes of deaths in the world and is associated with a significant health and economic burden through hospital admission and absenteeism form work.[2,3]

Patients with COPD have impaired functional status.[1-3] Quality of life and exercise tolerance provide comprehensive information about the patient and there is evidence that frequency of exacerbation is associated with health status impairment.[4] The degree of breathlessness using the Medical Research Council (MRC) dyspnoea scale has been identified as a stronger predictor of 5-year mortality than the forced expiratory volume in one second (FEV1)[5] and measures of health status and exercise tolerance are strongly associated with mortality.[6] However, severity of COPD is most often assessed using measures of lung function, usually FEV1, although functional status in COPD bears little or no relationship with FEV1.[7] In the primary care management of COPD, assessment of exercise tolerance and health status may prove unrealistic, thereby highlighting a need for simple biomarkers of severity.

COPD is also a common inflammatory disease of the respiratory tract and the lung tissues and its prevalence is going to increase throughout the world. The disease is characterized by a chronic inflammatory response of the airways and lungs

to noxious gas and particles along with progressive and irreversible airflow limitation but is a preventable and treatable condition. Pulmonary inflammation results in the entry of immune cells, both in the airway wall and lumen, as well as the alveoli and pulmonary vessels that lead to release of cytokines.

Several studies have shown that COPD patients have higher levels of inflammatory markers in blood, notably C-reactive protein (CRP), fibrinogen, and the inflammatory cytokines interleukin (IL)-6 and IL-8 but no existing literature could be found that have seen the correlation between levels of inflammatory markers with the disease severity.

So, the study has the scope to find any correlation between levels of inflammatory markers with the disease severity.

MATERIAL AND METHODS

Study area

The present case-control, retrospective, cross-sectional study was conducted in the Department of Biochemistry with the collaboration of Department of Respiratory Medicine of Medical College, Kolkata, West Bengal, India

Sample size calculation –

Sample size for this observational study has been determined by the Cochran's formulation [8]

$n = z^2pq/d^2$

[z = confidence level (95%) = 1.96
p = proportion of factor of interest
(Prevalence of COPD= 7.4 %)[9]
q = 1-p
d = Absolute precision (5%)

$n = 1.96X1.96X0.074X(1-0.074)/0.05X0.05 = 105.29$

Considering 10% as non-responder, the final minimum sample size would be = 105.29 + 105.29/10 = 116
Sample size was calculated at 95% confidence interval, with a power of 80%. [10]

Selection of subjects and study design

A total of 120 patients with a diagnosis of COPD aged minimum 50 years who attended Medical College were selected as case and 120 subjects having no COPD or any other chronic diseases nor taking any supplementation as age and sex-matched control by systematic random sampling after informed consent had been received from the concerned ethics committee [Memo No. MC/KOL/IEC/NON-SPON/1949/05/2023] between May 2023 and December 2024. All patients were examined and structured interview was performed. In short, such as respiratory symptoms including cough with phlegm and dyspnea were reported through self-completed questionnaire.[11] Information about smoking habits, comorbidities, medication use and excerbations was gathered. All subjects with suspicious or diagnosis of autoimmune diseases, asthma or cancer in the last 5 years was excluded from the study. Subject with acute exacerbation, common comorbidities including cardiovascular diseases and diabetes were excluded. A smoking history of ≥10 pack-years and a FEV1/FVC ratio < 0.7 and FEV1 < 80% predicted were criteria for inclusion.[11] Then all cases were subdivided into 4 groups based on GOLD.

Exacerbation identification -

Every 3 months patients were reviewed in the outpatient clinic and their dietary cards collected. Previously accepted criteria of exacerbations are as follows - [12-15]

Major Criteria: increase in dyspnoea, sputum purulence or sputum volume,

Minor criteria: increase in nasal discharge, wheeze, sore throat, cough or fever.

Symptom pattern persists for minimum two consecutive days, either two or more major symptoms or one major with any one of the minor symptoms was considered as exacerbation of COPD. Then annual exacerbation rate of each patient was calculated by dividing the number of exacerbations by the number of days they participated in the study, and multiplying by 365 and classify the exacerbators in two, frequent and infrequent exacerbators. Frequent exacerbators are those who are having ≥2 exacerbations treated with antibiotics and/or oral steroids and/or hospitalization the last 12 months and infrequent exacerbator are having <2 exacerbations.

Pulmonary function tests

Pulmonary function was measured both pre-and post-inhalation of 0.4 mg salbutamol, on a spirometer (HELIOS 401) by trained study staff. As the FEV1 is the most reproducible lung function test parameter therefore is best adopted to assessment of large group of people. Presence of COPD was defined by a post-bronchodilator FEV1/FVC ratio <0.7 and severity of disease was staged by FEV1 expressed as percentage of Forced Vital Capacity (FVC), predicted according to the latest GOLD (Global Initiative for Obstructive Lung Disease) classification.[16]

Anthropometric measurements

Weight and height measurements were obtained, using the Rosscraft Tom Kit Anthropometric Instrument Set, Canada [17]. BMI was calculated as the weight in kilograms divided by the square of height in meters. Body mass index (BMI) was calculated as the weight (kg) divided by the square of height (m^2), and was categorized as underweight (BMI < 18.5), normal (BMI 18.5–24.99), overweight (BMI 25.0–29.99), and obese (BMI 30.0 or more) according to the current World Health Organization (WHO) classification.

Collection of samples

Peripheral venous blood was drawn under aseptic precautions from all participants and the samples were divided into two aliquots. The first one was collected in Ethylene Diamine Tetra Acetic acid (EDTA) tubes for obtaining the hematology auto-analyzer (Pentra 80. manufactured by the ABX-Horiba group, Minami-Ku Kyoto Japan). On the same day, the second part of the blood samples was collected and allowed to clot for 30 min at room temperature and then centrifuged at 2400×g for 10 min to separate serum. This serum is used for the determination of serum concentration of IL-6, D-Dimer, LDH, CRP, and ferritin. All serum samples were stored at (-70^{0}C) and kept under these conditions until chemical analysis was performed. All parameter assays should be done as soon as possible.

Parameters assay

Serum PCT was determined by an immunoluminometric assay (Sphere Light B.R.A.H.M.S PCT; Wako Diagnostics, Tokyo, Japan). The normal range of PCT is 0.5 ng/ml and the lower limit of detection is 0.1 ng/ml. At a concentration between 0.1 and 0.3 ng/ml, an intra-assay CV of less than or equal to 7% and an inter-assay CV of less than or equal to 10%, and at concentrations greater than 0.3 ng/ml the intra-assay CV is less than or equal to 3% and the inter-assay CV is less than or equal to 6%. For estimation of serum interleukin-6, Electrochemiluminescence immunoassay technique and (Cobas) instrument are used in patients and the control group using a kit performed by Roche company (Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim. 2020). The assay has a claimed measuring range of 1.5−5000 pg/ml, a limit of quantitation (LOQ) of 2.5 pg/mL, an inter-assay precision (CV) of 17.4 % (at 1.82 pg/ml) and 2.0 % (at 4461 pg/ml). Determination of serum D-dimer and C-reactive protein Serum concentrations of D-Dimer and CRP were evaluated using a specific automated protein analyzer (PA120) provided by (Shenzhen Genius Electronics Co., Ltd. China 2019). Serum samples for each of the patients and healthy persons were applied to the instrument then the concentrations of D-dimer and CRP are calculated automatically. EDTA blood samples from both patients and the control group are applied to a hematology autoanalyzer (Pentra 80 manufactured by ABX-Horiba group, Minami-Ku Kyoto Japan) to estimate total counts of white blood cells (WBCs) and neutrophils. Samples are processed by the instrument then total WBCs and neutrophils are calculated automatically. LDH was determined based on the principle of the enzymatic coupling reaction. LDH catalyzes the conversion of pyruvate and NADH to lactate and NAD^+. Oxidation of NADH was monitored by reflectance spectrophotometry, which is used to measure the LDH activity. The ferritin was measured using the principle of immunoturbidimetry. Agglutination formed due to the reaction between latex-bound ferritin antibodies and the antigen in the sample to form an antigen/antibody complex was measured turbidometrically

Statistical analysis

Data were entered using Microsoft Excel 2007.Then the data for biochemical analysis was subjected to standard statistical analysis such as Student's t test using the Statistical Package for Social Science (SPSS) 27 software. For all tests 'p' value was considered to be significant if it was less than 0.05 at a confidence level of 95 %. Correlations were evaluated with normal and Pearson correlation tests. The values are expressed as mean ± SD.

RESULT

The characteristics and their comparison among different groups of study population – Chi-square test

Table 1: The characteristics and their comparison among different groups of study population – Chi-square test t test

Characteristics	Control (n = 120)	Cases (n =120)		
		Stage I (Mild illness)	Stage II (Moderate illness)	Stage III& IV (Severe illness)
Number of participants	120	64	34	22
Age (years)	62.96 ± 10.32	63.46 ± 9.29	63.12 ± 10.28	62.46 ± 11.02
Sex				
Male	48 (58)	33 (51.6)	18 (52.9)	12 (54.4)
Female	52 (62)	31 (48.4)	17 (47.1**)**	10 (45.6)
Demographic data				
Urban background	54	30 (46.8)	11 (44)	11 (50)
Rural background	66	34 (53.2)	14 (56)	11 (50)
BMI (Kg/m^2)	23.8±2.8	23.4±2.6	22.7 ± 2.2	22.3 ± 1.9

Data are expressed as numbers (group percentages in parentheses) for categorical variables and mean values ± SD for continuous variables

Comparison of serum levels of IL-6, ferritin, LDH, CRP and PCT in COPD patients and control group – Unpaired t test

Table 2: The differences in the serum levels of IL-6, ferritin, LDH, CRP and D-Dimer in COPD patients and control group

Parameters	Case	Control	p value
IL6 (pg/ml)	22.31± 7.02	4.65± 1.05	0.003
Ferritin (µg/ml)	348.86± 53.43	69.54 ± 19.23	0.018
CRP (mg/ml)	85.44 ± 33.21	3.19 ± 2.25	0.002
LDH (IU/L) at 37^0C	357.56±97.85	155.87 ±38.08	0.031
PCT (ng/ml)	9.84± 0.98	0.19 ± 0.04	0.011

Serum concentration of IL-6, ferritin, LDH, CRP, and PCT in COPD patients according to the disease severity of COPD

The mean of IL-6, ferritin, LDH, CRP and PCT are increased with disease severity. But the D-Dimer level was found to decrease with disease severity of COPD [Table 3].

Table 3:Differences in the levels of IL-6, ferritin, LDH, CRP and PCT in COPD patients according to the severity of infection

Parameters	Mild illness (Mean ± SD)	Moderate illness (Mean ± SD)	Severe illness (Mean ± SD)
IL6 (pg/ml)	9.29±0.17	19.46 ± 0.34	36.22 ±12.93
Ferritin (µg/ml)	287.75 ± 87.39	316.92 ± 111.24	338.60±174.17
CRP (mg/ml)	42.64±22.53	74.88 ± 43.82	129.98±68.54
LDH (IU/L) at 37^0C	349.80±83.18	389.47 ± 59.39	429.52±85.19
D-Dimer (µg/ml)	0.51±0.79	0.76 ± 0.31	0.82 ±0.30
PCT (ng/mL)	08.69 ± 1.05	10.22 ± 1.06	12.92 ± 0.12

Pairwise multiple comparison of different inflammatory markers within the case group - the post hoc ANOVA analysis with Bonferroni correction

Pairwise multiple comparisons in the post hoc ANOVA analysis with Bonferroni correction within the case group was performed and it became evident that increase of IL6, ferritin, LDH, D-Dimer and CRP concentration was significantly increased compared to control as shown in Table 2 but only IL6 and CRP are well correlated with disease severity.

Table 4:ANOVA with Bonferroni correction showing multiple comparisons of different inflammatory markers in different severity of COPD patients with significance of difference

Dependent variable	Factor (I)	Factor (J)	Mean difference (I-J)	Significance at 95% CI
IL6 (pg/ml)	1	2	-4.08	0.031*
		3	-14.25	0.003*
		4	-31.01	<0.001*
	2	1	4.08	0.031*
		3	-10.17	0.012*
		4	-26.93	<0.001*
	3	1	14.25	0.003*
		2	10.17	0.012*
		4	-16.76	<0.001*
	4	1	31.01	<0.001*
		2	26.93	<0.001*
		3	16.76	<0.001*
Ferritin (µg/ml)	1	2	-214.19	<0.001*
		3	-243.36	<0.001*
		4	-265.04	<0.001*
	2	1	214.19	<0.001*
		3	-29.17	0.161
		4	-50.85	0.092

	3	1 2 4	325.04 50.85 -21.68	<0.001* 0.061 0.094
	4	1 2 3	265.04 50.85 21.68	<0.001* 0.061 0.094
CRP (mg/ml)	1	2 3 4	-40.47 -72.71 -127.81	0.011* <0.001* <0.001*
	2	1 3 4	40.47 -36.24 -87.34	0.011* 0.036* <0.001*
	3	1 2 4	72.71 36.24 -55.1	<0.001* 0.036* 0.015*
	4	1 2 3	127.81 87.34 55.1	<0.001* <0.001* 0.015*
LDH (IU/L) at 37^0C	1	2 3 4	-218.36 -258.03 -298.08	<0.001* <0.001* <0.001*
	2	1 3 4	218.36 -39.67 -79.72	<0.001* 0.126 0.086
	3	1 2 4	258.03 39.67 -40.05	<0.001* 0.126 0.098
	4	1 2 3	298.08 79.72 40.05	<0.001* 0.086 0.098
PCT (ng/ml)	1	2 3 4	-8.5 -10.03 -12.73	<0.001* <0.001* <0.001*
	2	1 3 4	8.5 -1.53 -4.23	<0.001* 0.214 0.079
	3	1 2 4	10.03 1.53 -2.7	<0.001* 0.214 0.104
	4	1 2 3	12.73 4.23 2.7	<0.001* 0.079 0.104

*p value significant ($p < 0.05$) at 95% Confidence interval (CI); 1 = Baseline activity, 2 = stage I severity, 3 =Stage II, 4 = Stage III& IV

Correlation of CRP with other inflammatory markers - By multiple regression analysis

Among all inflammatory markers only IL6 and CRP are well correlated with disease severity as shown in Table 4 but after multiple regression analysis it is found that the CRP concentration was not well correlation with other inflammatory markers in different severity of COPD as shown in Table 5.

Table 5. Multiple linear regression analysis showing significance of dependence of the CRP (mg/ml) on other inflammatory markers in different stages of COPD patients

Dependent factor	**Predictor factors**	**Mild illness**			**Moderate illness**			**Severe illness**		
		Standardized beta coefficients	t	Significance	Standardized beta coefficients	t	Significance	Standardized beta coefficients	t	Significance
CRP (mg/ml)	**IL6 (pg/ml)**	0.066	0.716	0.104	0.118	0.343	0.448	0.910	0.179	0.016

	Ferritin (µg/ml)	5.76	3.39	0.62	4.10	0.23	2.51	5.23	0.43	1.25
	LDH activity (IU/L) at 37^0C	4.72	0.01	0.749	3.65	0.053	0.552	0.003	0.822	0.056
	PCT (ng/ml)	1.034	0.485	0.577	1.171	0.374	0.758	0.819	0.497	0.308

DISCUSSION

Chronic obstructive pulmonary disease (COPD) is characterized by chronic lung inflammation that results in progressive and irreversible airflow obstruction with periodic acute episodes of worsening, exacerbations. The airflow obstruction arises from a combination of emphysema and chronic bronchitis. It is predicted to be the third leading cause of death worldwide by 2020 and is a major cause of disability-adjusted life years (DALY) along with a lifetime risk of up to 25%. The inflammation in COPD is also systemic and this contributes to important comorbidities. The chronic inflammatory process in COPD involves both innate and adaptive immunity and is most pronounced in the bronchial walls of the small airways. The inflammatory process in COPD does have marked heterogeneity. It results in both emphysema with parenchymal involvement and chronic bronchitis, which predominantly affects the small airways. A characteristic feature of COPD is the presence of acute exacerbations, which are typically associated with increased inflammation. Important causes of exacerbations include infections (bacterial, viral and combined viral/bacteria) and environmental factors. Exacerbations of COPD are strongly associated with mortality, hospitalization and decline in functional status.

The disease has a role of pathophysiology of any inflammation that is reflected by serum IL6, C reactive protein (CRP), procalcitonin (PCT), and hyperferritinemia. Concentrations of inflammatory markers such as CRP, IL6 and tumour necrosis factor (TNF-α) are higher in COPD patients compared with healthy individuals [22,23] and CRP is an independent prognostic variable for heart disease. But no existing literature could be found that have seen the correlation between levels of inflammatory markers with the disease severity. Moreover, for the patients who develop these life threatening conditions, timely identification and intervention is necessary to reduce mortality and hospital stay. Circulatory biomarkers which depict inflammation can be used to assess the disease severity and a possible predictor of progression of disease. So, the purpose of this study was to see if any inflammatory marker can be used as a prognostic marker of disease severity and mortality in COPD patients.

Our result has demonstrated serum IL-6 levels were significantly higher in individuals with COPD when compared with controls.[24] Serum levels of IL-6 were more likely to increase during exacerbations of COPD. IL6 induces foam cell formation, the release of further inflammatory cytokines, and chemotaxis. [24] In COPD, the lungs are persistently exposed to irritants like cigarette smoke, air pollution, and occupational dust.

Zhang, J. et al. in their study explored the relationship between serum IL-6 levels and systemic inflammation in COPD patients and had found that elevated IL-6 levels were associated with increased systemic inflammation and greater disease severity. The study suggests that IL-6 could be a useful marker for assessing systemic inflammation in COPD patients.[25] Singh, S., et al. (2015) investigated the role of IL-6 as a biomarker for disease severity and exacerbation frequency in COPD patients. The results showed a positive correlation between IL-6 levels and COPD severity, as well as the frequency of exacerbations. The study concluded that IL-6 could be a potential biomarker for monitoring COPD progression. [26] Prudente, R., Ferrari (2021) in International Journal of Chronic Obstructive Pulmonary Disease, gives positive evidence of involvement of Il-6 in COPD evolving over 9 years.[27] supporting our study. Hussein et al. (2022) showed Serum interleukin-6 in chronic obstructive pulmonary disease patients and its relation to severity and acute exacerbation.

The present study is also found that the activity of LDH is increased significantly in these patients. Other studies also suggest the similar finding.[28,29] The relationship between serum LDH levels and COPD severity underscores the potential utility of LDH as a biomarker for disease monitoring. Elevated LDH levels may reflect ongoing lung tissue damage and inflammation, providing clinicians with insights into disease progression and the risk of exacerbations. Since LDH is a non specific marker it can act as an adjuvant marker along other inflammatory markers. In our study LDH (IU/L) at 37^0C in cases was estimated to be significantly high than in controls Research on the association between LDH levels and chronic obstructive pulmonary disease (COPD by Maltais F, Simard AA, et al) has produced mixed results. Some studies suggest a relationship between elevated LDH levels and COPD severity, while others indicate a more pronounced or non-significant association.

The ferritin level of present study in COPD patients is significantly increased than healthy persons. Ferritin is supposed to be a cellular means of storing iron, yet serum ferritin levels are widely measured as indicator of iron status.. Ferritin is

an acute phase reactant and is potentially higher in any infective or inflammatory process. A study by Dr. GaliShabaris et al. on serum ferritin levels in COPD patients and its correlation with severity and grading of COPD assessed serum ferritin levels in COPD patients and found that 24% exhibited elevated ferritin concentrations. The highest levels were observed in patients classified under the Global Initiative for COPD (GOLD) stage IV, with 34.62% of these individuals displaying increased ferritin. A significant positive correlation was identified between serum ferritin levels and COPD severity, suggesting that hyperferritinemia may be linked to disease progression.[30] This finding corroborates our study findings, Ferritin (ug/ml) 348.86± 53.43 in cases in comparison to 69.54 ± 19.23 in controls (p value significant). However the study by Zhang WZ, Oromendia C, Kikkers SA et al, stated Bronchoalveolar Lavage Fluid (BALF) iron and ferritin were higher in participants with COPD and in smokers without COPD when compared to non-smoker control participants but did not correlate with systemic iron markers.[31]

Likewise, the serum level of CRP was also elevated significantly in patients when compared with the healthy group. High levels of inflammatory markers like circulating CRP have been linked to a higher risk of cardiovascular disease, hospitalization, and death in COPD. Small increases in serum CRP levels are associated with both disease activity and future risk of hospitalization and death from COPD.[32] Milacić N, Milacić B, et al. in their study found that patients with COPD had significantly higher CRP levels compared to healthy controls, suggesting that elevated CRP is associated with increased systemic inflammation in COPD patients. The authors concluded that CRP could serve as a useful biomarker for assessing inflammation and monitoring disease progression in COPD.[33] This study supports our study findings that CRP (mg/ml) in case is significantly higher than controls. In another study also Gan WQ, Man SF, et al identified 14 studies and found that CRP levels were significantly higher in individuals with COPD compared to control subjects. The standardized mean difference in CRP levels was 0.53 units (95% confidence interval: 0.34 to 0.72). This suggests a notable association between elevated CRP levels and COPD.[34]. Also the study by de Torres et al. demonstrated that higher CRP levels in stable COPD patients were inversely correlated with arterial oxygen tension and six-minute walk distance, both indicators of disease severity. These findings suggest that CRP can serve as a valuable biomarker for assessing disease severity and prognosis in COPD patient. [35]

Another inflammatory marker procalcitonin level is significantly increased in the patient. Procalcitonin (PCT) is a biomarker with significant clinical utility in managing COPD, particularly in the context of acute exacerbations. It is primarily used to differentiate bacterial infections from other causes of inflammation, thereby guiding antibiotic therapy. [36] Elevated PCT levels in COPD exacerbations have been linked to increased severity, prolonged hospitalization, and higher mortality rates. Serial PCT measurements may assist in monitoring disease progression and treatment response. Our study showed PCT (ng/ml) in cases were significantly raised 9.84± 0.98 as compared to controls 0.19 ± 0.04 (p value <0.05).

Bafadhel M, et al. in their study compared the usefulness of PCT and C-reactive protein (CRP) as biomarkers in patients with pneumonia or exacerbations of asthma or COPD. The results indicated that both PCT and CRP levels could independently distinguish pneumonia from asthma exacerbations, suggesting their potential utility in guiding antibiotic therapy and reducing overuse in hospitalized patients with acute respiratory illnesses corroborating with our study,[37] Daubin C, et al. compared the efficacy of a PCT-guided antibiotic protocol with standard antibiotic therapy in severe Acute Exacerbation of COPD (AECOPD) cases admitted to the intensive care unit (ICU). The findings suggested that the PCT-guided approach was effective in managing antibiotic therapy in this patient population. [38]

Further, the markers which were found significantly higher in cases than controls were estimated and compared in various stages in COPD. The mean of IL-6, ferritin, LDH, CRP and PCT are increased with disease severity.

Then Pairwise multiple comparison in the post hoc ANOVA analysis with Bonferroni correction within the case group was performed and it became evident that increase of IL6, ferritin, LDH, and CRP concentration was significantly increased compared to control but only IL6 and CRP are well correlated with disease severity.

In spite of every sincere effort the study has several lacunae. The sample size was small. Time was a constraint as the study needs to be followed up for a longer duration and more subjects. The study has been done in a single centre. Bronchodilator, steroid therapy and antibiotic therapy were not taken into consideration. It was possible to measure the biochemical variables of COPD on only one occasion but it is necessary to estimate the markers on serial occasion to establish the relationship in between them with increasing severity. It is the hospital based study, so hospital bias cannot be ruled out.

CONCLUSION

So, it is clear that among all inflammatory markers only IL6 and CRP are well correlated with disease severity but after multiple regression analysis it is found that the CRP concentration was not well correlation with other inflammatory markers in different severity of COPD.

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Conflicts of interest
There are no conflicts of interest.

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