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Original Article

Serum CRP levels in healthy controls and stable COPD and its correlation with different stages of COPD in north Indian population

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ABSTRACT: Background: Chronic Obstructive pulmonary disease a systemic inflammatory disease, characterized by airway inflammation and progressive airflow limitation is an increasing cause of morbidity and mortality worldwide including India. C-reactive protein (CRP) is an acute phase reactant secreted by the liver in response to infection, inflammation or tissue damage.
Objectives: The aim of this study was to investigate serum levels of CRP in North Indian population and to study its correlation with disease severity.
Methods: This case control study was conducted on 145 healthy controls and 145 stable COPD patients at a tertiary care hospital in north India. CRP levels were measured in serum by ELISA kits.
Results: The present study showed that mean serum CRP levels was significantly higher in COPD group as compared to control group **(p<0.0001)]** and the levels increased with the increasing severity of the disease.
Conclusion: Our study confirms that C-reactive protein levels were higher in stable COPD patients as compared to controls and their levels increased with the increasing severity of the disease. Measuring CRP levels in combination with other biochemical markers can be helpful in monitoring disease outcome and management of disease.

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a complex disease with multiple components and is characterized by airway inflammation and progressive airflow limitation. It is gradually increasing worldwide including India. Projections from WHO predict that by 2020 this disorder will rank as the fifth most prevalent disease and third most common cause of death [1].

COPD is strongly associated with smoking and not seen in every smoker, but in some individuals, it adverse effects are seen. Long term smoking causes airway inflammation characterized by neutrophil, macrophage and activated T lymphocyte infiltration and by increased CRP and cytokine concentration. The risk of developing COPD becomes higher as smoking duration increases [2]. The indoor air pollution resulting from biomass exposure is also an important risk factor for COPD especially in developing countries. Previous studies demonstrate that many different inflammatory markers appear to be increased in the serum of stable COPD patients [3]. Stable COPD patients have a proinflammatory state with increased circulating levels of many inflammatory cytokines and acute phase reactants [4]. However, the best studied of these markers is the C-reactive protein (CRP), an acute phase reactant secreted by liver in response to infection, inflammation, or tissue damage [5]. Biomarkers in COPD may be useful in aiding diagnosis,

monitoring the disease severity and evaluating the effects of drugs. Man, *et al*., [6] measured CRP levels in individuals with mild to moderate airway obstruction and found that patients in the lowest CRP quartile had the highest risk of all-cause mortality, cancer deaths, and cardiovascular events, and suggested that CRP could be a marker of outcome in COPD. The higher levels of CRP observed in patients with COPD increase even more during exacerbations [7].

Dahl *et al*., [8] found that CRP level was the strong and independent predictor of COPD outcomes represented by hospitalization and death. Modulating AECOPD frequency and severity is an important goal in the management of COPD. Standard and novel anti-inflammatory therapies are under intense investigation to decrease the frequency and severity of AECOPDs progression. There is a lack of readily measurable marker that can correlate with disease severity or outcome. Forced expiratory volume in one second measured by spirometry is the most widely accepted measure of disease severity, but this reflect only one aspect of disease and is not predictive of disease progression. Long term monitoring of declines in FEV 1 has been used to identify the risk factors and gauge the efficacy of putative therapies, but that approach is slow and expensive and using it alone may underestimate the impact of the disease in some patients and overestimate in others. Diagnosis of COPD is confirmed by spirometry, but it depends mainly on the level of effort done by patient and so this may alter the diagnosis in many patients.

Therefore, with this aim the present study was done in North Indian COPD patients to analyze the correlation of CRP with severity as well as other clinical parameters so that there may be other surrogate method along with FEV1 that can help clinicians in better understanding the stage of disease and its proper management using anti-inflammatory therapies and other measures.

MATERIALS AND METHODS

Study Population

This case control study was conducted in the department of respiratory medicine at a tertiary care hospital of North India. The current study comprises 145 stable COPD patients recruited from the outpatient department of respiratory medicine and 145 healthy controls. The study was approved by institutional ethics committee. Healthy controls and patients fulfilling the inclusion and exclusion criteria were recruited only after their written informed consent. Inclusion criteria for patients were age over 35 years, post bronchodilator FEV1/FVC < 0.7, FEV1 change <12% and who has symptoms of persistent cough, sputum production, or dyspnoea, and/or a history of exposure to risk factors for the disease.

Patients were excluded if they had a history of TB, asthma, active cancer, diabetes, ischemic heart disease, chronic kidney disease, liver failure etc. The control group consisted of apparently healthy volunteers who were either relatives of patients or other visitors coming in the department or in the hospital and have normal spirometry. Non-smokers as well as participants with smoking history were also included in the control group.

At the enrolment visit all patients underwent detailed history, clinical evaluation (by a specialized Respiratory Physician), Chest x-ray, spirometry and venous blood sampling. The demographic information was ascertained from self-reported responses to the pre-designed questionnaire that includes demographic details, smoking history/pack years, respiratory symptoms, and risk factors for COPD, health status and limitation of activity etc.

The diagnosis of COPD was confirmed by spirometry according to GOLD criteria: FEV1/FVC < 0.7 and reversibility to inhaled bronchodilator in FEV1 <12% or <200ml after administration of 200 µg salbutamol (2 puffs) using a pressurized metered dose inhaler with a spacer. The clinical severity of COPD was determined as per the criteria defined in the Global Initiative for Chronic Obstructive Lung Disease guidelines based on the Post-Bronchodilator FEV1 values [9].

Subjects were classified as current smokers, ex-smokers and non-smokers, according to self-reported smoking history. The participants were categorized as smokers if they were currently smoking, non-smokers if they have never smoked during their life time and ex-smokers were who have quit smoking 1 year back. Occupational as well as biomass exposure was also reported based on the patient statement. The Body mass index (BMI) was calculated by dividing the body weight in kilograms by the height in meters square (kg/m2). Dyspnoea was assessed by Modified Medical Research Council scale (mMRC). BODE index score [10] was also evaluated in all patients.

Venous Blood samples (5ml) were collected from all patients and healthy controls and centrifuge to analyze levels of C-reactive protein in serum. The obtained serum was kept at -80°C until the time of the analysis. CRP level was assessed in serum by Elisa method according to manufacturer protocol.

Statistical analysis

Graph pad PRISM version 6.01 was used for analysis of data. Values have been represented in mean ± SD (in case of continuous variable) and expressed as number and percentages (in case of categorical variables). Analysis of variance (ANOVA) was used for comparison of continuous data. Pearson's correlation was used for determining correlation of CRP levels with other parameters. p value <0.05 was considered statistically significant in all analysis.

RESULTS

In this study, 145 healthy controls and 145 COPD patients representing all stages of disease severity as defined by GOLD were recruited. The baseline characteristics of the study groups are shown in **Table 1.** Age of patients ranged from 35 to 75 years. Mean age of patients was 57.41 ± 9.88 and that of healthy controls was 55.49 ± 10.65 years respectively. Statistically, there was no significant difference between groups with respect to age (p=0.113). In both the groups, majority of patients were males. Proportions of males were slightly higher in cases (83.4%) as compared to that in controls (73.7%) while females were 16.5 % in COPD group and 26.2% in controls.

In our study, BMI of COPD patients was lower as compared to that of controls (20.37±4.21 Vs 24.34±4.25) and this difference was significant statistically (p<0.001). Regarding socioeconomic status of COPD patients in this study 35.6% were having low socioeconomic status while 39.3% and 24.1% belong to middle and high socioeconomic status.

Table 1: Socio demographic profile and clinical characteristics of COPD patients and healthy controls

PARAMETERS	COPD group (Mean ± S.D) (n=145)	Controls group (Mean ± S.D (n=145)	p value
Demographic parameters			
Age (years)	57.41±9.88	55.49±10.65	0.113
M/F ratio (%)	83:17	74:26	0.044
Height (cm)	159.37±7.61	160.86± 8.66	0.121
Weight (kg)	51.54±10.76	63.02±12.08	**<0.0001**
BMI (kg/m^2)	20.37±4.21	24.34±4.25	**<0.0001**
Spirometry parameters			
Post FVC (l)	2.11±0.67	3.10 ± 0.72	**<0.0001**
Post FEV1/FVC (%)	56.73 ± 9.10	97.29 ±12.32	**<0.0001**
Post FEV 1 (l)	1.22 ± 0.43	2.60 ± 0.62	**<0.0001**
Post FEV1 (%) Pred	47.40 ± 15.78	92.12 ± 8.35	**<0.0001**
Biochemical parameter			
CRP(mg/l)	5.68 ±3.02	1.81 ± 0.95	**<0.0001**
Pack years	17.87±16.2	13.9 ± 7.7	**0.03**

Results are expressed as mean ± SD or percentages depending on the distribution. Abbreviations: COPD: Chronic obstructive pulmonary disease; CRP: C-reactive protein; FVC = forced vital capacity; FEV1= forced expiratory volume in 1 second; BMI; Body mass index. There were 52 smokers (35.8 %), 39 non-smokers (26.8%) and 54 ex-smokers (37.2%) in the COPD group. Among non-smokers, 25 patients were having history of exposure to biomass also. In control group, there were 56 smokers (38.6%), 53 non-smokers (36.5%) and 36 ex-smokers (24.8%). The mean pack years were (17.87 ± 16.2) in the COPD group than compared to control (13.9 ± 7.7).

Spirometric values such as mean FEV1% predicted, FVC and FEV1/FVC ratio as mentioned in Table 1, were significantly lower in COPD patients when compared to Control group (p <0.0001). According to GOLD criteria, COPD patients were grouped into four stages based on their severity. There were 4 patients (2.7%) having mild COPD (stage1), 59 patients (40.6%) have moderate COPD (stage2), 62 patients (42.7%) have severe COPD (stage 3) while 20 patients (13.7%) were having very severe COPD (**Table 2**).

Table 2: Baseline Characteristics of COPD patients and CRP levels grouped based on severity according to GOLD Stages

PARAMETERS	Mild (Stage 1) (n=4)	Moderate (Stage 2) (n=59)	Severe (Stage 3) (n=62)	Very severe (Stage 4) (n=20)	p value
Age	69 ± 3.55	58.64 ± 10.9	57.01 ± 9.00	52.85 ± 8.00	0.01
BMI	22.29 ± 3.29	20.81 + 3.84	20.16 ± 4.65	19.39 ± 3.92	0.443
FEV1post (L)	1.82 ± 0.09	1.41 ± 0.30	1.06 ± 0.23	0.65 ± 0.13	**<0.0001**
FEV1%pred (post)	88.75 ± 9.56	60.5 ± 7.54	40.41 ± 5.15	24.2 ± 3.45	**<0.0001**
FVC post(L)	2.89 ± 0.08	2.48 ± 0.55	1.88 ± 0.54	1.42 ± 0.35	**<0.0001**
FEV1/FVC (post)	63 ± 3.36	60.15 ± 7.10	56.08 ± 8.91	47.53 ± 8.52	**<0.0001**
CRP (mg/l)	2.7 ± 0.7	4.4 ± 1.1	6.01±2.55	9.04 ± 5.01	**<0.0001**
mMRC	1.25 ± 0.5	1.7 ± 0.61	2.18 ± 0.83	2.4 ± 0.94	**<0.0001**
BODE Index	1.5 ± 0.57	2.82±1.11	4.1±1.27	4.7±1.62	**<0.0001**

The distribution of smokers, non-smokers and ex-smokers have been given in Table 3. The higher no of all the three were present in stage 2 (moderate COPD) and stage 3(severe COPD). The mean values of pack years were higher in severe and very severe COPD patients (stage 3 and 4). Mean BMI also decreases progressively as the severity of COPD increases based on Gold stage.

Mean value of serum CRP levels were significantly higher in the COPD patients as compared to healthy controls (5.68±3.02 Vs 1.81±0.95, P<0.0001). In our study we also found higher levels of mean CRP in smokers and ex-smokers compared to non-smokers but the difference between groups was not statistically significant. As the severity of COPD increases the levels of CRP also increases and was highest in very severe COPD patients (Fig. 1).

Table 3: Characteristics of COPD patients and their CRP levels according to smoking status

Parameters	Smoker(n=39)	Non-smoker(n=39)	Ex-smoker(n=54)	P value
Age	55.2 ± 11.2	58.5 ± 9.5	58.7 ± 7.4	0.13
BMI	19.7 ± 3.59	21.7 ± 5.6	20.0 ± 3.3	0.06
Post FVC	2.3 ± 0.7	1.84 ± 0.65	2.13 ± 0.61	**0.005**
FEV1%pred(post)	48.38 ± 14.0	49.35 ± 16.08	44.68 ± 16.05	0.28
FEV1/FVC Post	55.8 ± 8.32	60.2 ± 8.5	54.9 ± 9.53	**0.01**
CRP	6.14 ± 4.06	5.16 ± 2.15	5.69 ± 2.29	0.31
Pack years	20.33 ± 17.91	-	15.50 ± 14.13	**0.001**

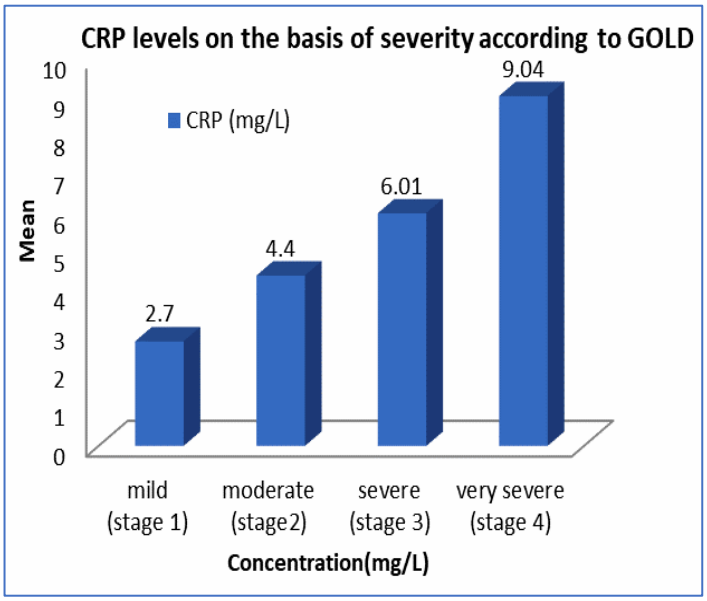

Figure 1: C-reactive protein levels based on severity according to GOLD

Breathlessness was the main symptom present in all COPD patients (100%) while (94%) patients gave a history of also having cough and expectoration as the other symptoms. Health status and quality of life of COPD patients was also assessed by mMRC Dyspnoea scale grading, and BODE Index score. As the severity of COPD increases, according to Gold stages the mean value of Bode index score and mMRC also increases. (Table-2) CRP levels showed a significant negative correlation with FEV1 % pred and FVC which denotes that increase in its levels in serum of COPD patients is correlated with severity of airway obstruction while it showed a positive correlation with mMRC and BODE index score (**Table 4**).

Table 4: Correlation of C- reactive protein with Spirometry and other parameters of COPD patients

Parameters	'r'	p-value
Age	-0.118	0.154
BMI	-0.040	0.625
FVC(l)	-0.350	**<0.0001**
FEV1%Pred	-0.474	**< 0.0001**
FEV1/FVC	-0.222	**0.007**
mMRC	0.271	**< 0.0001**
BODE	0.504	**< 0.0001**

DISCUSSION

Systemic inflammation in COPD patients has been associated with increased neutrophil, macrophage, T-lymphocytes and high concentrations of inflammatory mediators in peripheral blood such as C-reactive protein (CRP) and other cytokines (IL-6, IL-8 and TNF-α etc) [4,11-15]. Higher levels of CRP and cytokines in COPD patients have also been associated with mortality and among them CRP is one of the most important systemic inflammatory biomarker [8]. The present case-control study showed that mean serum CRP levels were significantly higher in the COPD group as compared to control group ($p<0.0001$) which was consistent with many previous studies [4, 14, 16, 17, 21]. Study by Pinto Plata *et al*., showed a significantly higher level of CRP in COPD patients (50.03±1.51 mg/l) in comparison to smoking (2.02±1.04 mg/l) and non-smoking control groups (2.24±1.04 mg/l) ($p < 0.001$). Serum CRP level more than 3mg/l was associated with increased risk of hospitalization and death in follow up study of COPD patients [8]. Higher CRP and IL-6 levels in COPD patients in comparison to control group was also seen in the study conducted by Tanni *et al*., [19] while in another study on 4800 individuals with mild to moderate COPD, serum CRP levels were found to be a significant predictor of all-cause mortality [4]. However, Silva *et al*., [18] have excluded smokers in their study and did not find significant differences in CRP levels when compared to control.

Health status and quality of life was assessed by mMRC dyspnoea scale and BODE Index score. We found a negative correlation of C-reactive protein with FEV1% pred (r= - 0.35; $p<0.0001$) and FVC (l) (r=-0.47; $p<0.0001$) while significant positive correlation with other parameters. The main finding of our study was that as the severity of COPD increases according to GOLD stage the levels of CRP also increases and was highest in very severe patients (stage 4). An association between levels of CRP and severity of COPD was also observed in the study by Mannnio *et al*., [20].

The present study in concordance with previous studies [22] suggest that COPD is independently associated with low grade systemic inflammation than that in healthy subjects and this inflammatory activity increases as severity of disease increases. We found the mean age to be lowest in very severe and severe patients (gold 3, 4) in comparison to stage 1 and 2 patients in this study. We also found stage 4 patients having lowest BMI. Low BMI also relates to the severity of COPD such as mMRC and Bode index score.

The low BMI has also been considered as predictors of mortality by Yang *et al*., [23]. Previous studies [17] also found *CRP* levels in stable COPD patients was associated with 6MWD, FEV1, FVC as well as BODE index. So, we suggest that these parameters should also be considered in taking decision to document severity of the disease as well as proper treatment and management

Current smokers in the COPD group presented higher serum levels of C-reactive protein compared to non-smokers and ex-smokers (Table 3) in our study but the difference was not statistically significant and this difference in CRP levels were not seen in smokers, ex-smokers or non-smokers of control group which was inconsistent with other studies [8, 14]. COPD patients having a history of biomass exposure also have higher CRP levels compared to control. Therefore, we think that smoking does have a role in promoting the inflammatory process in COPD patients, but it might not be the leading cause of increased inflammatory markers such as CRP because the higher levels were seen only in smokers with COPD and not in control smokers.

So, we suggest that it might be due to genetic differences or some other factors. The strength of our study was that we had taken healthy controls and stable COPD patients without any co morbidities which can induce systemic inflammation. Our study had a few limitations as there were less no of patients moreover, we measured CRP level in COPD patients only at baseline, so we were not able to evaluate the effects on health outcomes by measuring CRP levels again but despite these limitations the results of the present study emphasize the relationship between COPD and C - reactive protein. Recent meta-analysis by G. Leuzzi *et al*., [24] also indicate that baseline high CRP level is significantly associated with higher late mortality in patients with COPD.

COPD is a multicomponent disease which affects the psychological and physiological conditions and social life of patients. Our study confirms that C-reactive protein levels are increased in stable chronic obstructive pulmonary disease. The forced expiratory volume in 1second (FEV1) has been used to grade physiologically the severity of air flow limitation in COPD patient but using it as a sole indicator does not fully reflect the severity of disease in every patient as spirometry test depend on effort of patient.

Therefore, we would like to conclude that measuring levels of systemic inflammatory markers like CRP in combination with other biochemical markers and disease specific scoring tools such as Bode index, mMRC can be helpful in monitoring disease outcome in COPD patients and in proper assessments, treatment and management of disease. The increase in CRP levels with the progression of the disease as seen reflects the severity of the disease and so measuring CRP levels at baseline and after anti-inflammatory therapy will also prove beneficial for proper management of the disease. We suggest that further larger cohort studies on inflammatory markers may provide the basis for future effective treatment for this global burden. Intervention with anti-inflammatory therapy, lifestyle changes and smoking cessation may also provide additional benefit in disease management of COPD in Indian population.

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