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Dr. Avneesh Prasad
Junior Resident in Medicine, Department of Medicine, NIMS Medical College & Hospital, Jaipur, Rajasthan-303121, India

Dr. Moxit Shah
Junior Resident in Medicine, Department of Medicine, NIMS Medical College & Hospital, Jaipur, Rajasthan-303121, India

Dr. Shruti Behal
Junior Resident in Medicine, Department of Medicine, NIMS Medical College & Hospital, Jaipur, Rajasthan-303121, India

Dr. Mihir Rathod
Junior Resident in Medicine, Department of Medicine, NIMS Medical College & Hospital, Jaipur, Rajasthan-303121, India

Dr. Manju Pandey
Assistant Professor, Department of Medicine, NIMS Medical College & Hospital, Jaipur, Rajasthan-303121, India

Correspondence:
Dr. Avneesh Prasad
Senior Resident in Medicine, Department of Medicine, NIMS Medical College & Hospital, Jaipur, Rajasthan-303121, India

Prognostic significance of C-Reactive protein and its correlation with predictors of outcome in stable and unstable patients of COPD

Avneesh Prasad, Moxit Shah, Shruti Behal, Mihir Rathod, Manju Pandey*

Abstract

Aim- The aim of the study was to find out value of CRP in COPD patients and its correlation with the predictors of outcome. **Method-** We studied 100 COPD patients (80 stable and 20 unstable) with spirometry, body mass index, MMRDC dyspnoea scale, 6-minute walk distance and BODE index. The CRP values were measured in these patients and compared with 50 sex and age matched controls. CRP was subjected to evaluation for any correlation with the predictors of outcomes in COPD patients. **Results-** Serum CRP levels were significantly higher in COPD patients than in healthy subjects (Mean 13.55+10.83 vs.2.07+ 0.82 mg/lit, p<0.001). CRP levels were significantly higher in unstable than stable patients (mean 33.78+7.74 mg/lit vs. 8.50+1.81 mg/lit, p<0.001). Severity of dyspnoea as measured by MMRC dyspnoea scale was significantly higher in unstable patients than in stable patients (mean 3.60+0.5 vs. 1.84+0.86, p<0.001). The exercise capacity of the patients as measured by 6 MWD was significantly lower in unstable patients than in stable patients (mean 180.5+53.26m vs. 219.58+67m, p=0.017). The BODE index was found to be significantly higher among unstable patients than stable patients (mean 7.30+1.66 vs. 4.94+1.94, p<0.001). A significant negative correlation was found between CRP and FEV1 (r=-0.284, p=0.004) and FEV1/FVC (r=-0.305, p=0.002). CRP levels were independent of FVC (r=-0.162, p=0.107). A significant positive correlation was found between CRP and severity of dyspnoea according to MMRC dyspnoea scale (r=0.638, p<0.001). The CRP levels negatively correlated with the exercise capacity of the patient (6MWD) which was statistically significant (r= -0.364, p<0.001). A significant positive correlation was found between CRP with BODE index (r=0.780, p<0.001) and BODE stage (r=0.726, p<0.001). **Conclusion-** We conclude that systemic inflammation is present in COPD patients and CRP is important biomarker in COPD in means of reflecting severity of disease and prognosis of patients.

Keywords: COPD, CRP, BODE index, 6 minute walk distance, BMI, Spirometry.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the leading respiratory disease in terms of prevalence and socioeconomic impact worldwide [1]. COPD is projected to be the third leading cause of death in the world by the year 2020 [2]. COPD, a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases [3]. COPD was thought to cause only pulmonary abnormality, but recent studies have demonstrated the presence of systemic and extra pulmonary effects [4].

Although COPD primarily affects the lungs, it is associated with important systemic consequences which include malnutrition with a low body mass index (BMI) and impaired peripheral muscle function [5]. Although the origin of systemic inflammation present in COPD remains poorly understood and correlations in the regulation of inflammation in the pulmonary and systemic compartments are not well-documented yet, it is clearly established that some inflammatory markers are raised in systemic circulation [6]. Blood markers, such as Interleukin-6, C - reactive protein (CRP) and fibrinogen have attracted interest during recent years [7]. One of the inflammatory markers which are increasingly evaluated in COPD patients is CRP [8].

C-reactive protein is an acute phase protein synthesized predominantly by the hepatocytes in response to

tissue damage or inflammation. It reflects the total systemic burden of inflammation of individuals and has been shown to be increased in COPD in stable condition [9] and during exacerbations [10]. However, the patients with COPD have systemic manifestations that are not reflected by FEV1. Cardiovascular, mental and musculoskeletal co morbidities, as well as elevated markers of systemic inflammation can frequently be found in patients with COPD and have an impact on mortality in this population [11]. Hence, a multidimensional grading system that assessed the respiratory and systemic expressions of COPD was designed to predict outcome in these patients [12].

In this study, the role of C-reactive protein in COPD, its level and correlation with lung function (forced expiratory volume in 1 second (FEV1) and its association with predictors of outcome (Body Mass Index, Dyspnoea according to MMRC dyspnoea scale, 6-minute walk distance, BODE index) of disease will be analyzed in stable and unstable patients.

MATERIAL AND METHODS

The study was conducted in National Institute of Medical Sciences, Jaipur from July 2014 to September 2015. The study was conducted on 100 subjects, patients admitted in wards and ICU under Department of Medicine, NIMS Medical College &Hospital, Jaipur and 50 controls who were normal age/sex matched during the study period.

The cases included male and female patients aged more than 40 years, patients who had dyspnoea, chronic cough and sputum production, patients exposed to risk factors like tobacco use(current or ex smoker) and occupational exposure to dust and chemicals, patients having baseline post bronchodilator FEV1 of <80% predicted and FEV1/FVC of <=0.7 after inhaling 400µg of salbutamol and patients presenting in acute exacerbation (Patients complaining of acute change of symptoms that is beyond normal day to day variation).

The exclusion criteria were prior history or presence of asthma, tuberculosis and bronchiectasis, acute coronary syndromes, myocardial infarction within past 6 months, congestive heart failure, collagen vascular disease/autoimmune disease, pulmonary embolism, malignancy, renal insufficiency, liver cirrhosis, use of statins and hormone replacement therapy in the past, active infection, recent trauma, surgery, blood transfusion in the 4 weeks prior to study start, radiation exposure, ventilator dependency, cerebrovascular or peripheral arterial disease and history of exacerbation within 1 month.

A detailed history and physical examination was carried out for every subject who entered in the study as per a pre-designed proforma. Body mass index or BMI was calculated as: BMI= Weight(kg)/ Height ^{2}(m^2). 6-Minute walk Distance was calculated by measuring the distance that a patient can quickly walk on a flat, hard surface in a period of six minutes (as per American Thoracic Society Guidelines). It was carried out in a 50m corridor in the hospital. Period of rest if taken any was also included in the six minute test period. For degree of airflow obstruction, all patients had to undergo physiologic evaluation that included measurement of the forced expiratory volume in 1 second (FEV1) and a forced vital capacity (FVC) using RMS Spirometer (Helios_v3.1.80) on the day of enrolment into the study and 20 minutes following the administration of salbutamol nebulisation. Modified Medical Research Council Dyspnoea Scale was used to assess the severity of dyspnoea in COPD patients. BODE Index is a composite marker of disease severity taking into consideration the systemic nature of COPD. The BODE index was calculated for each patient using the body mass index(B), the threshold value of FEV1(O), the score on the Modified Medical Research Council (MMRC) dyspnoea scale (D) and the distance walked in 6 minutes (E). Blood samples were obtained when the patients were at rest, after 4 hours of fasting before any other test was performed to find out the C-reactive protein levels in serum by Latex agglutination (CRP turbilatex) using kit number TK1107001.

The continuous variables were expressed as means± standard deviation (SD) and categorical variables were expressed as absolute numbers and percentages. For comparison of the groups, unpaired t-test was applied. Chi square (χ^2) test was used for categorical variables. Pearson's correlation coefficient was used to find correlation between serum CRP and other variables. A p value <0.05 was considered statistically significant. Data obtained was analyzed statistically by SPSS software.

RESULT

A total of 100 patients of COPD which were further subdivided into 80 as stable and 20 as unstable patients aged more than 40 years (mean 62.06±8.72) were recruited in the study as cases. Also recruited in the study were 50 healthy subjects from the general population of similar age (mean60.14±14.08) and location. Among the patients with COPD, most of the patients were in GOLD stage 2 and 3. 41% and 43% of the patient s belonged to GOLD stage 2 and 3, respectively. 16% of the patients belonged to GOLD stage 4.

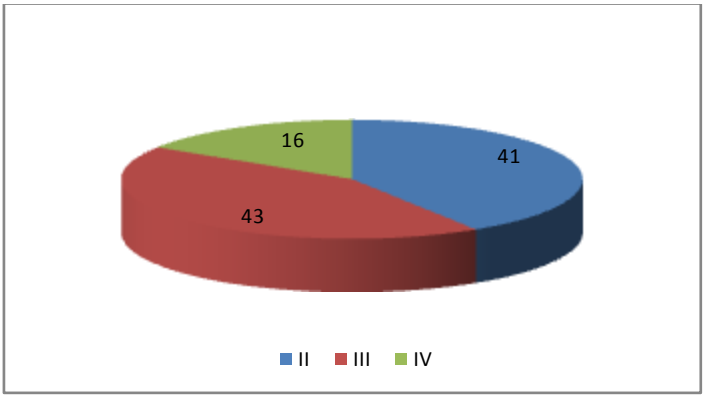

Figure 1: Distribution of cases according to GOLD stage

Among the patients with COPD, 11% had BODE score 0-2 (Stage 1), 24% had BODE score 3-4 (Stage 2), 48% had BODE score 5-7 (Stage 3) and 17% had BODE score 8-10 (Stage 4). Most of the COPD patients had a normal BMI (88%), 8% were under weight and 4% were overweight. Among the control group, 70% had a normal BMI while 12% were underweight, 10 % were overweight and 8% were obese.

Serum CRP levels were significantly higher in COPD patients than in healthy subjects (Mean 13.55±10.83 vs.2.07± 0.82 mg/lit, p<0.001). Serum CRP was elevated in 95 (95%) of the cases but in none (0%)of the controls.

Among the cases (stable and unstable patients), serum CRP levels were significantly higher in unstable than stable patients (mean 33.78±7.74 mg/lit vs. 8.50±1.81 mg/lit, p<0.001). Severity of dyspnoea as measured by MMRC dyspnoea scale was significantly higher in unstable patients than in stable patients (mean 3.60±0.5 vs. 1.84±0.86, p<0.001). The exercise capacity of the patients as measured by 6MWD was significantly lower in unstable patients than in stable patients (mean 180.5±53.26m vs. 219.58±67m, p=0.017). The BODE index was found to be significantly higher among unstable patients than stable patients (mean 7.30±1.66 vs. 4.94±1.94, p<0.001). Parameters such as BMI, FEV1, FVC and FEV1/FCV were found statistically insignificant among stable and unstable patients.

36 (87.8%) patients had CRP>6 mg/lit. belonged to GOLD stage 2 and 5 (12.2%) patients had CRP<6 mg/lit. 43(100%) patients had CRP >6 mg/lit belonged to GOLD stage 3. 16(100%) patients had CRP>6mg/lit belonged to GOLD stage 4. Pearsons's correlation coefficient showed that CRP levels significantly correlated with GOLD stage(r=0.529, p<0.001). A significant negative correlation was found between CRP and FEV1 (r=-0.284, p=0.004) and FEV1/FVC (r=-0.305, p=0.002). CRP levels were independent of FVC (r=-0.162, p=0.107). A significant positive correlation was found between CRP and severity of dyspnoea according to MMRC dyspnoea scale(r=0.638, p<0.001). The CRP levels negatively correlated with the exercise capacity of the patient (6MWD) which was statistically significant (r= -0.364, p<0.001). A significant positive correlation was found between CRP with BODE index (r=0.780, p<0.001) and BODE stage (r=0.726, p<0.001). As shown in the following table, 6(54.55%) patients had CRP>6 mg/lit belonged to BODE stage 1 while 5(45.45%) of the patients had CRP<6 mg/lit. 24(100%) patients had CRP> 6mg/lit belonged to BODE stage 2. 48(100%) patients had CRP> 6 mg/lit belonged to BODE stage 3. 17(100%) patients had CRP>6 mg/lit belonged to BODE stage 4.

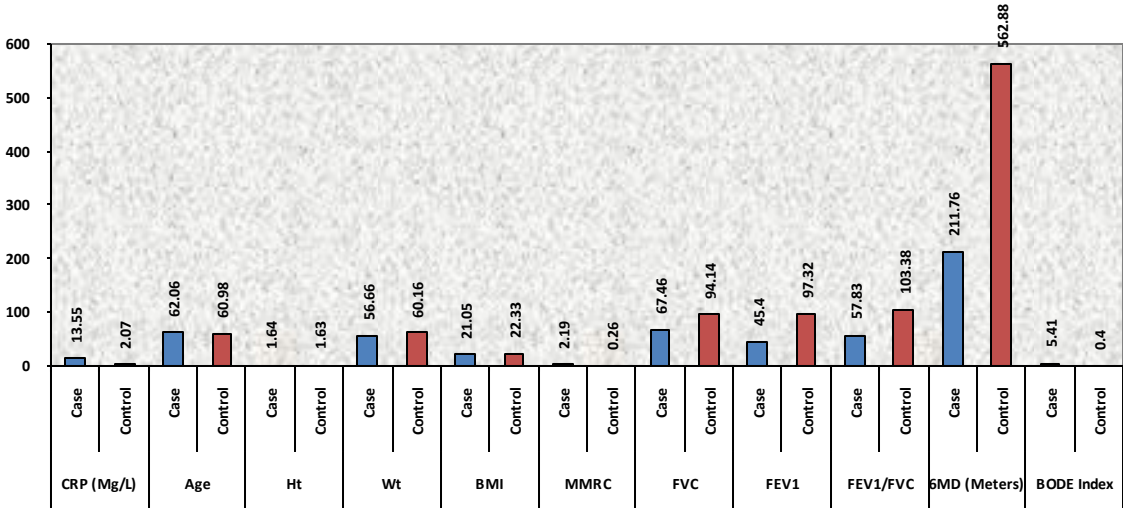

Figure 2: Clinical and physiological characteristics of case and control group

DISCUSSION

In the present study 100 COPD patients (80 stable and 20 unstable) and 50 age/sex matched controls were studied and analysed on the basis of clinical history, CRP levels, BMI, Obstructive capacity, MMRC dyspnoea scale, exercise capacity and BODE index to assess their functional status and predict their outcome. In our study, serum CRP levels were found to be higher in stable COPD patients (13.55±10.83 vs. 2.07±0.82 mg/lit, p<0001) than in well matched healthy control subjects that was statistically highly significant. This finding is in accord with studies conducted by Abolhassan Halvani *et al*[13], Broekhuizen *et al*[14], Biljana Lazovic *et al.* [15] and Deng *et al*[16] who concluded that COPD itself can increase the serum CRP which is a major factor causing extrapulmonary complications and it may be used as a long term predictor of future outcomes. In our study CRP was found to be higher in Unstable COPD patients (those presenting in acute exacerbation of COPD) than in stable patients (33.78+7.74 vs. 8.50+1.81 mg/lit, p<0.001) that was statistically highly significant. Our work duplicates with the finding of Daiana Stolz *et al* who assessed circulating levels of CRP in patients presenting with acute exacerbation on COPD (p = 0.003) [17].

In our study, CRP is inversely correlated with FEV1(r= -0.284,p=0.004) that was statistically significant which is in accord with study conducted by SJ Wu, P Chen *et al*[18], Andrea Corsonello *et al.* [19] and Yihua Lin[20] who also found negative correlation of CRP with FEV1. Study by Rakesh Kumar and P Nigam [21] concluded that correlation of CRP with FEV1 was negative in cases presenting as acute exacerbation. Thus, the damage of lung function in COPD patients is associated with the increase of CRP level. Interestingly, in our study, CRP is inversely correlated with BMI (r= -0.119, p=0.237) that was statistically insignificant. This contrasts with the study by Tung-Wei Kao *et al.* [22], L.Khaodhiar *et al*[23] and Timpson NJ *et al.* [24] who concluded that higher BMIs as well as central obesity are independently associated with higher levels of CRP. A study by Marie Cathrin Breyer *et al*[25], who found that obese COPD patients were 3.3 times more likely (p=0.002) to have highly elevated CRP levels compared to normal weight COPD patients. But study by Reshu Agarwal *et al.* [26] showed significant negative correlation of CRP with BMI (p<0.0001) that is in compliance with our study. As COPD is a systemic inflammatory disease, there is a pro-inflammatory state [27] in the body with elevated level of CRP, TNFα receptors and soluble adhesion molecules, all of which lead to weight loss. In addition, diaphragmatic muscle weakness, reduced lung function and loss of skeletal mass also lead to weight loss and reduction in BMI [28].

We observed that CRP positively correlated with MMRC dyspnoea scale (r=0.638, p<0.001) which is consistent with the study conducted by Rachel Garrod *et al.* [29], who concluded that inflammation increased with MMRC grade and was significantly correlated with CRP (p=0.002). A study by Judith Garcia-Aymerich *et al* [30] on COPD patients, who presented with acute exacerbation, concluded that physical activity was associated with reduced levels of CRP. In our study, CRP is inversely correlated with 6- minute walk distance(r= -0.364, p<0.001) that was found to be statistically highly significant. Our study duplicates the work of Broekhuizen *et al*[14], Reshu Agarwal *et al.* [26] and Rakesh Kumar & P Nigam [21] who also found that CRP increases in those with poor exercise capacity. Regarding the outcome of disease based on BODE stage, the mean serum CRP levels were found to be significantly increased in severe cases. It was also found to be significantly increased in patients presenting with acute exacerbation of COPD. De Torres and co workers [31] indicated that serum CRP level significantly increased with the aggravation of disease and correlation was found with BODE index (r=0.17, p=0.050). A cross-sectional study performed by Henrik Watz *et al*[32] states that higher values of CRP are associated with reduced physical activity in patients with COPD. Rakesh Kumar and P Nigam showed that there was a significant

correlation of CRP with BODE index (r=0.4, p=0.0001) in patients who presented with acute exacerbation of COPD[21]. Therefore, although we expect the inflammatory process to be worse and inflammatory markers to be increased by increasing the severity of disease, more studies are required in this regard.

CONCLUSION

Finally, we conclude that systemic inflammation is present in COPD patients and CRP is important biomarker in COPD in means of reflecting severity of disease and prognosis of patients. Patients presenting with acute exacerbation of COPD (unstable patients) had intense inflammatory response as measured by high concentration of CRP than those of stable COPD patients and had a much poorer prognosis as measured by the markers of severity.

Higher levels of systemic inflammation are associated with low reversibility suggesting inflammation driven airflow limitation as measured by FEV1. It is also associated with decrease in the functional capacity of the patient as measured by 6MWD as well as severity of dyspnoea as measured by MMRC dyspnoea scale. Thus, high level of systemic inflammation as measured by serum CRP is positively correlated with multi dimensional index (BODE index) which reflects the severity of the disease and can predict future outcome and prognosis of the patient.

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