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# Study of Prognostic Association of C-Reactive Protein (A Biomarker) with Clinically Important Predictors of Outcome in Stable and Unstable COPD Patients.

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## ABSTRACT

**Background:** COPD is characterized by persistent airflow limitation that is progressive and is associated with enhanced chronic inflammatory response in the airways to noxious particles or gases. It has both systemic and pulmonary effects. Since COPD deaths estimated to increase by 30% in next 10 years, cost of treatment will be a heavy burden on global economy. The costs are proportional to pulmonary and extra pulmonary components of the disease. **Methods:** In this study, we examined 100 patients of COPD, out of which 80 were stable and 20 were unstable. **Results:** CRP levels were found to be increased in cases more than in controls (13.55±10.83 vs. 2.07±0.82 mg/lit, p<0.001), the levels being higher in unstable patients than in stable patients (33.78+7.74 vs. 8.50+1.81 mg/lit, p<0.001). We also submitted the patients to MMRC dyspnoea scale and found that CRP is positively correlated with MMRC dyspnoea scale (r=0.638, p<0.001) and was inversely correlated with 6- minute walk distance (r= -0.364, p<0.001). There was a significant positive correlation of CRP with BODE index (r=0.780, p<0.001). **Conclusion:** The study is valuable in detecting the severity of COPD cases both in stable and unstable conditions and to forecast the future morbidity and mortality outcome of such cases.

***Keywords:*** COPD, C-Reactive Protein, Pulmonary Disease.

## INTRODUCTION

India with a population of nearly 125 crores harbours millions of COPD patients due to increased percentage of persons habitual to smoking beedies, hukkas , cigarettes and consuming tobacco as kheni or chewing. It is the leading respiratory disease in terms of prevalence, having gross socio-economic impact worldwide[1-3] and will be third leading cause of death in the world by year 2020.[4]

The present study is undertaken to predict role of C-reactive protein as a prognostic indicator of outcome in both stable and unstable COPD patients.

The study is important in terms of annual global expenditure and in-hospital stay of COPD cases, which are tremendously growing because of increasing smoking habits and as well due to increasing pollution from vehicles discharging fumes.

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## MATERIALS AND METHODS

The study was conducted on 100 COPD patients attending OPD/ICU of NIMS Hospital, Jaipur between July 2014 to September 2015 and 50 controls.

Inclusion Criteria - Age 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 400 µg of salbutamol. Patients presenting in acute exacerbation. Written informed consent obtained prior to participation of the patient in the study. Due clearance from scientific and ethical committee of the Medical College have been obtained.

Exclusion Criteria-Following are the diseases excluded from the study-Bronchial asthma, tuberculosis, bronchiectasis, IHD within past 6 months, congestive heart failure, collagen vascular disease/autoimmune disease, pulmonary embolism, malignancy, renal in-sufficiency, liver cirrhosis, use of statins and hormone replacement therapy in the past.

Body mass index or BMI was calculated using the equation: BMI= Weight (kg)/ Height$^2$ (m$^2$).

6-Minute walk distance (6MWD) 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). Measurement of the forced expiratory volume in 1 second (FEV1) and a forced vital capacity (FVC) using RMS Spirometer (Helios_v 3.1.80) on the day of enrolment into the study and 20 minutes following the administration of salbutamol nebulization.

**Following is the MMRC dyspnea scale given below[5,6]** [Table 1].

**Table 1:** Modified MRC Dyspnoea Scale

| Modified MRC Dyspnoea Scale | |
|---|---|
| 0 | Not troubled by breathlessness except on strenuous exercise |
| 1 | Shortness of breath when hurrying on the level or walking up a slight hill |
| 2 | Walks slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level |
| 3 | Stop for breath after walking about 100 meters or after a few minutes on the level |
| 4 | Too breathless to leave the house or breathless when dressing or undressing |

**BODE Index**[7]: It 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).

**Table 2:** BODE Index

| BODE score | 0 | 1 | 2 | 3 |
|---|---|---|---|---|
| FEV1 | >=65 | 50-64 | 36-49 | <=35 |
| 6-min walk distance | >350 | 250-349 | 150-249 | <149 |
| Dyspnoea scale | 0-1 | 2 | 3 | 4 |
| BMI | >21 | <21 | | |

BODE stage I- 0-2, BODE stage II- 3-4 BODE stage III- 5-7, BODE stage IV- 8-10 [Table 2].

Quantitative determination of C-Reactive Protein[8-10]:-Blood samples were obtained when the patients were at rest, after 4 hours of fasting ,and CRP levels calculated by Latex agglutination (CRP turbilatex) using kit number TK1107001.

Statistical Analysis was done using Chi square ( $\chi^2$) test and Pearson's correlation coefficient was used to find correlation between serum CRP and other variables

## RESULTS

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 (mean 60.14±14.08) and location.

Among the cases 88 patients were male and 12 were females. Among the controls 38 were males and 12 were females. With P=0.098, there is no significant difference between sex distribution of cases and controls, hence both cases and controls are sex matched.

**Table 3:** Clinical and physiological characteristics of the study subjects.

| Parameters | Group | N | Mean | Std. Deviation | 'p' Value* |
|---|---|---|---|---|---|
| **CRP (Mg/L)** | **Case** | 100 | 13.55 | 10.83 | <0.001 |
| | **Control** | 50 | 2.07 | 0.82 | |
| **Age** | **Case** | 100 | 62.06 | 8.72 | 0.739 |
| | **Control** | 50 | 60.98 | 11.41 | |
| **Ht** | **Case** | 100 | 1.64 | 0.08 | 0.692 |
| | **Control** | 50 | 1.63 | 0.10 | |
| **Wt** | **Case** | 100 | 56.66 | 6.72 | 0.074 |
| | **Control** | 50 | 60.16 | 12.79 | |
| **BMI** | **Case** | 100 | 21.05 | 2.49 | 0.043 |
| | **Control** | 50 | 22.33 | 4.02 | |
| **MMRC** | **Case** | 100 | 2.19 | 1.07 | <0.001 |
| | **Control** | 50 | 0.26 | 0.44 | |
| **FVC** | **Case** | 100 | 67.46 | 18.02 | <0.001 |
| | **Control** | 50 | 94.14 | 5.69 | |
| **FEV1** | **Case** | 100 | 45.40 | 13.28 | <0.001 |
| | **Control** | 50 | 97.32 | 9.23 | |
| **FEV1/FVC** | **Case** | 100 | 57.83 | 10.71 | <0.001 |
| | **Control** | 50 | 103.38 | 9.76 | |
| **6MD (Meters)** | **Case** | 100 | 211.76 | 66.13 | <0.001 |
| | **Control** | 50 | 562.88 | 41.89 | |
| **BODE Index** | **Case** | 100 | 5.41 | 2.10 | <0.001 |
| | **Control** | 50 | 0.40 | 0.49 | |

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) [Table 3, Figure 1].

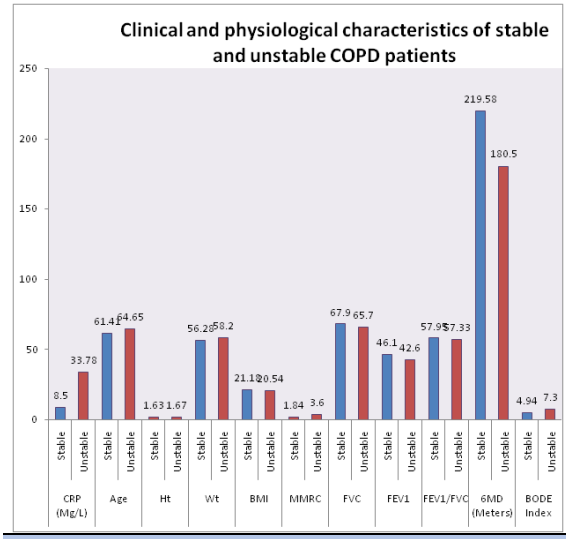


**Figure 1:** Clinical and physiological characteristics of stable and unstable COPD patients.

**Table 4:** Correlation of CRP in COPD Cases (N=100)

| Parameters | Correlation Coefficient | 'p' Value |
|---|---|---|
| **Age** | 0.131 | 0.193 |
| **Ht** | 0.207 | 0.039 |
| **Wt** | 0.086 | 0.398 |
| **BMI** | -0.119 | 0.237 |
| **FVC** | -0.162 | 0.107 |
| **FEV1** | -0.284 | 0.004 |
| **6MWD** | -0.364 | <0.001 |
| **MMRC** | 0.638 | <0.001 |
| **FEV1/FVC** | -0.305 | 0.002 |
| **GOLD Stage** | 0.529 | <0.001 |
| **BODE INDEX** | 0.780 | <0.001 |
| **BODE Stage** | 0.726 | <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> 6 mg/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 [Table 4].

## 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.

The mean age of the patients was 62.06±8.72 years and that of the controls was 60.98±11.41 years, the difference being statistically insignificant (p=0.739). Age itself did not correlate to severity of COPD in this study, its correlation with CRP also being statistically insignificant. Uppalet al[11] also failed to observe a significant correlation between age and disease severity, and age and quality of life albeit there was a trend towards worsening of disease with advancing age. They reasoned that this might be due to the cumulative effect of smoking with increased age and the age related physiological deterioration in lung function.

In our study, 88 patients were males and only 12 were females, which is in accord with previous studies. Male dominance in prevalence of COPD has been reported earlier also.[12]

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 extra-pulmonary complications and it may be used as a long term predictor of future outcomes.

A meta-analysis by Y Zhang, H Bunjhoo, W Xiong et al.[17] suggested that patients with stable COPD had higher serum CRP concentrations than healthy controls and that the serum CRP concentration might be an indicator of disease severity. Our study confirms that circulating CRP levels are higher in stable COPD patients and thus may be regarded as a valid biomarker of low grade systemic inflammation. Furthermore CRP was 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) which is statistically highly significant. This is in line 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)[18].John R. Hurst et al. assessed 36 biomarkers in patients of acute exacerbation of COPD. Plasma CRP concentration, in the presence of a major exacerbation symptom, is useful in the confirmation of COPD exacerbation while other Systemic biomarkers were not helpful in predicting exacerbation severity[19].A multicenter trial by Karin H. Groenewegen et al. established that stable COPD patients are associated with low grade inflammation and acute phase reactants are increased in these patients. It was further established that patients presenting with acute exacerbation had higher levels of acute phase proteins like CRP than stable patients[20].

In our study, CRP is inversely correlated with FEV1(r= -0.284, p=0.004) that was statistically significant which is in accordance with study

conducted by SJ Wu,PChen et al[21], Andrea Corsonello et al.[22] and Yihua Lin[23] who also found negative correlation of CRP with FEV1. Study by Rakesh Kumar and P Nigam[24] 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. It has been proposed that inflammatory cytokines could be secreted by adipocytes and by inflammatory cells present in adipose tissue. But study by Reshu Agarwal et al.[25] 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 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.[26] Further research is needed to elucidate the effect of different cytokines on body composition and vice versa.

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.[27] ,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.[28] on COPD patients who presented with acute exacerbation, concluded that physical activity was associated with reduced levels of CRP. Thus, more physically active COPD patients show better functional status.

In our study, CRP is inversely correlated with 6-minute walk distance(r= -0.364, $p<0.001$) that was found to be statistically significant. Our study duplicates the work of Broekhuizen et al[14], Reshu Agarwal et al.[25]and Rakesh Kumar & P Nigam[24] 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[29] 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[30] states that higher values of CRP are associated with reduced physical activity in patients with COPD.

Sarioglu et al.[31] investigated the relationship between the BODE index and disease duration, annual exacerbation and hospitalization rates, health related quality of life and systemic inflammatory markers like C-reactive protein and concluded that BODE index is a comprehensive, feasible and simple clinical scoring system in the evaluation of COPD. BODE index was significantly correlated to serum CRP levels (r=0.419, $p<0.001$). 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[24]. 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

The study of COPD on 100 patients along with 50 controls showed CRP to be a reliable marker of inflammation, inversely correlated to FEV1, BMI, 6MWD and having positive correlation with MMRC dyspnoea scale. As BODE index is a multidimensional index to predict outcome in COPD, CRP can be used as a marker of prognosis in COPD.

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