The Relationship between C-Reactive Protein and COPD Patients

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

Original Research Article

ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable, and treatable chronic inflammatory respiratory disease that affects 210 million people globally. Due to inflammation the resultant IL_6 increases the level of C-REACTIVE PROTEIN (CRP) from hepatocytes. This study was conducted to evaluate the association of C-Reactive Protein in COPD patients. The study also includes the key role of C-reactive protein (CRP) in assessing the acute exacerbations of Chronic Obstructive Pulmonary Disease (COPD), which has proven to be more valuable. This was a prospective study conducted over a period of three months between February 2021 and April 2021 at the department of General Medicine in Saveetha Medical College Hospital, Chennai. In a study of 50 patients, 25 were patients with COPD and 25 were a control group of healthy people. High Sensitivity C-Reactive Protein (hs-CRP), blood gases, spirometry, Body Mass Index (BMI), 6 Minute Walk Distance (6MWD) and GOLD stage of severity were measured. The serum hs-CRP was then evaluated for any correlation with the predictors of outcomes of COPD subjects. hs-CRP levels were higher in patients with COPD than in healthy individuals (4.82 / 0.8 mgl). A correlation was found between hs-CRP and the following variables:
FEV1 (r = -0.813; p < 0.01), 6MWD (r = -0.876; p < 0.01), GOLD stage (r = 0.797; p < 0.01) and evaluated. This study revealed that there is certain increase in hs-CRP in COPD patients due to inflammation. It acts not only as an inflammatory diagnostic marker, but also plays a role as predictor for the outcome of the disease and reducing the mortality rate.

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1. INTRODUCTION

According to GOLD (Global initiative for chronic Obstructive Lung Disease), Chronic Obstructive Pulmonary Disease (COPD) is a condition in which airflow is limited and not fully reversible [1]. (http://www.goldcopd.com)

Airflow obstruction related COPD have chronically reduced ratio of FEV1 / FVC. In COPD, increased air trapping (increased residual volume and increased ratio of residual volume to total lung capacity) and progressive hyperinflation are often observed late in the disease [1]. Forced expiratory flow rates are lowered in the lungs of people with COPD, which is the most common diagnosis.

Smoking cigarettes was a major risk factor for death from COPD [1]. There is higher prevalence of COPD in men due to smoking than women. Even childhood respiratory infections may lead to COPD. Studies have shown that as the intensity of smoking increases, the volume of air exhaled within the first second of a Forced Exhalation Maneuver (FEV1) rapidly decreases in a dose response relationship, which is usually expressed as Pack-years. This intensity is the reason why the prevalence rates of COPD increase with age [2].

Occupations involving severe specific exposures, including coal mining, gold mining, cotton textiles, fertilizers, and wood industries, are suggested as risk factors for COPD [3]. Specific chemical fume cadmium exposures lead to decline in FEV1, FEV1 / FVC and DL_{co} will lead to COPD. Indoor Biomass, smoke by wood and charcoal which are used for cooking, heating and in baking can also lead to COPD in children and reduces lung growth. It also leads to lung cancer in women such that it causes 2.7% Disability Adjusted Life Years (DALYS) worldwide [4]. Alpha 1 anti-trypsin deficiency will also lead to COPD.

According to the World Health Organization, COPD is an increasingly important public health problem around the world. COPD is the fourth leading cause of death. COPD will soon be, by 2023, the third most common cause of death worldwide, as predicted by GOLD.

COPD is a chronic inflammatory disease that is focused on inflammation in recent research. The airflow obstruction in COPD usually progresses over years. Inflammation in the COPD patients activates epithelial cells and increases alveolar macrophages and other inflammatory cells which release IL_6 [5]. This in turn leads to acute phase response and increases the CRP level. IL_6 increases the number of CD_8 and CD_4 cells, and macrophages which leads to pathology of COPD.

C-reactive protein is an acute phase protein mainly produced in the liver (hepatocytes), and is released in response to tissue damage and inflammation. CRP and other inflammatory markers reveal the overall status of inflammation occurring in the body of COPD patients in exacerbation and stable conditions.

In the natural history of COPD, exacerbations have a big effect on mortality especially in those who need to be admitted to the hospital. The severity of the disease increases, and so does the frequency and severity of the exacerbation [6]. Though the causes of an exacerbation vary, the most common cause is infectious etiology, i.e. up to 78% of hospital admissions for COPD patients. Both bacterial and viral respiratory infections can cause a major and systemic inflammatory response, which leads to a high level of CRP. The CRP biomarker have been extremely studied and used as a diagnostic tool in acute exacerbations.

CRP is also predictor for the severity of the disease for the hospitalization and mortality in chronic respiratory failure [7]. In COPD patients, there is a relationship between the plasma CRP level and the severity of the disease & the quality of life, and a high sensitivity CRP level is a marker of the disease.

The aim of this study was to evaluate the levels of hs-CRP in the serum and assess its connection with lung function in patients with COPD who are experiencing an acute exacerbation.

2. METHODOLOGY

This was a prospective study conducted at the department of the General Medicine, Saveetha Medical College Hospital, Chennai over a period of three months between February 2021 and April 2021. A total of 50 subjects including 25 normal control patients and 25 patients of Chronic Obstructive Pulmonary Disease (COPD) were selected for this study.

Dysponea, chronic cough with sputum production, severe airflow obstruction and severity with FEV1 / FVC below < 0.7% after 400 mgs of inhaled Salbutamol were the main inclusion criteria for the COPD patients.

Diseases such as pneumothorax, acute coronary disease, recent MI, pulmonary embolism, vascular aneurysm, renal insufficiency, cirrhosis and other liver diseases, recent surgery, any history of malignancy and acute infection are the exclusion criteria for the COPD patients group. A history of asthma and FEV1 / FVC increased more than 12% following inhalation of 400 mgs of Salbutamol were added in this COPD patients group.

For the control group no history of COPD, Dysponea, and coughing are the inclusion criteria. They should also be with no signs of exclusion criteria.

Both groups of individuals, the control group and the COPD group, were examined and their medical history was taken. Demographic details like age, sex, address, occupation, and history of risk factors like smoking were plotted. Medical history of patients and vital signs were recorded. Anthropometry (height, weight, BMI) and relevant physical and systemic examinations were conducted to determine the exclusion criteria. For all subjects, BMI was calculated by dividing weight by height, kg/m^2.

The thorough history of acute symptoms like dyspnea, cough and sputum production was recorded together with fever, respiratory rate and upper respiratory symptoms like nasal congestion, increased rhinorrhea and sore throat. The chest X-ray was taken.

Blood investigation like CBC, blood gas analysis (levels of O_2 and CO_2), blood sugar, albumin level, albumin and globulin ratio, fibrinogen, total bilirubin, blood urea and nitrogen (BUN), blood creatinine level, alpha 1 anti-trypsin level (AAT) and blood cholesterol level were carried out. The high sensitive C-Reactive Protein (hs-CRP) was measured by using the UBI-MAGIWEL-CRP-Quantitative AD-401 Kit, a solid phase ELISA test, according to the instructions of the manufacturer. The reference range for CRP is 0.0 - 0.8 mg / dl. For hs-CRP measurement, the collected blood samples were separated into three parts and centrifuged. One more sample was collected and stored at $-20^{o}C$ for backup. Due to the high sensitivity of the hs-CRP measurement, the measurement was repeated three times in each sample and the mean was considered as the average result.

Lung Function Test (LFT) was performed accordingly, Forced Expiratory Volume in 1 second (FEV1) and Forced Vital Capacity (FVC) using a PR MORGAN & KENT spirometer. The patient was advised to sit on a chair with the clip on the nose to keep both nostrils closed. A breathing mask was connected around mouth which in turn was linked to spirometer.

The patient was instructed to take deep inhalation, then hold his breath for few seconds and then to exhale as hard as he can into breathing mask. The greatest total amount of air that the patient can forcibly breathe out after deep inhalation was recorded as the Forced Vital Capacity (FVC) in liters. The total amount of air that was exhaled by the patient in the first second after a full inhalation was recorded as Forced Expiratory Volume 1 (FEV1). The three values of FEC and FEV1 are plotted and the mean value was taken. FEV1/ FVC ratio was calculated by dividing the FEV1 / FVC (%). The 6MWD test was conducted in a 50-meter-long corridor. In 6MWD test the distance walked in 6 minutes was calculated.

The results were plotted in the SPSS 17.0 software. As per Gaussian distribution, continuous variables were expressed as mean ± standard deviation. T tests were used to compare the data between two groups. Linear relationships between variables were analyzed using Pearson's correlation coefficient. A multiple regression analysis was used to study the relationship between different variables and CRP.

Finally, among the COPD group, a brief history of acute infectious exacerbations of COPD was taken. It was recorded as per Anthonisen's Scale for acute exacerbation and categorized according to that from grade I to III. The number of episodes is also plotted. The great III categories COPD patients add more number of acute exacerbation and hospitalization.

CRP measurements were taken when the patients are at stable and also at exacerbation. The CRP was also measured at 7, 14 and 35th day of post exacerbation.

3. RESULTS

In this prospective study 50 patients were investigated. (25 COPD patients and 25 individuals as control group).

The COPD group consisted of 20 male (80%) and 5 female (20%) subjects. In control group 18 were male (72%) and 7 were female (28%). There was no significant difference between these two groups, but the number of male COPD patients was higher in male patients (>75%).

In both the groups the age limit is above 45 to 70 years. The mean age was almost matched in both the groups.

The mean age is 64.78 + 10.3 years in COPD group and 66.50 + 8.7 in control group.

In the COPD groups 16 subjects (64%) were noted as cigarette smokers during the study and 8 subjects (32%) were found to be quitters of smoking and 1 subject (4%) related to baking as occupation.
In the control group there is no history of smoking or any other risk factors for COPD.

According to the GOLD stage of severity of COPD 5 patients on stage 1, 12 patients on stage 2, 6 on stage 3 and 2 patients were in 4th stage.

The mean hs-CRP value in the control group was 0.88 ± 0.48 mg/l. (ranging from 0.4 - 0.8 mg normally). But in COPD group hs-CRP values showed raised levels of 4.82 ± 1.97 mg (ranging from 1.7 - 8.1 mg/l). When patients with COPD were compared with controls by independent samples T-test, the mean value of hs-CRP was significantly higher in the former (11.574; $p < 0.01$).

Table 1.1. Gender

Gender	Control	COPD
Male	18 (72%)	20 (80%)
Female	7 (28%)	5 (20%)

Table 1.2. Age

Variables	Control	COPD	P Value
Age	66.50 + 8.7	64.78 + 10.3	0.63

Table 2. Smoking/risk factors

Smoking	16 (64%)
Non-Smoking	8 (32%)
Baking	1 (4%)

Table 3. GOLD stage of severity

GOLD stage	No. of subjects	Percentage
Stage I	5	20 %
Stage II	12	48 %
Stage III	6	24%
Stage IV	2	8%

The COPD group underwent spirometry, blood gas measurement, FEV1, FEV1%, FVC and FEV1 / FVC. Parameters were measured and severity was mentioned as per GOLD stage.
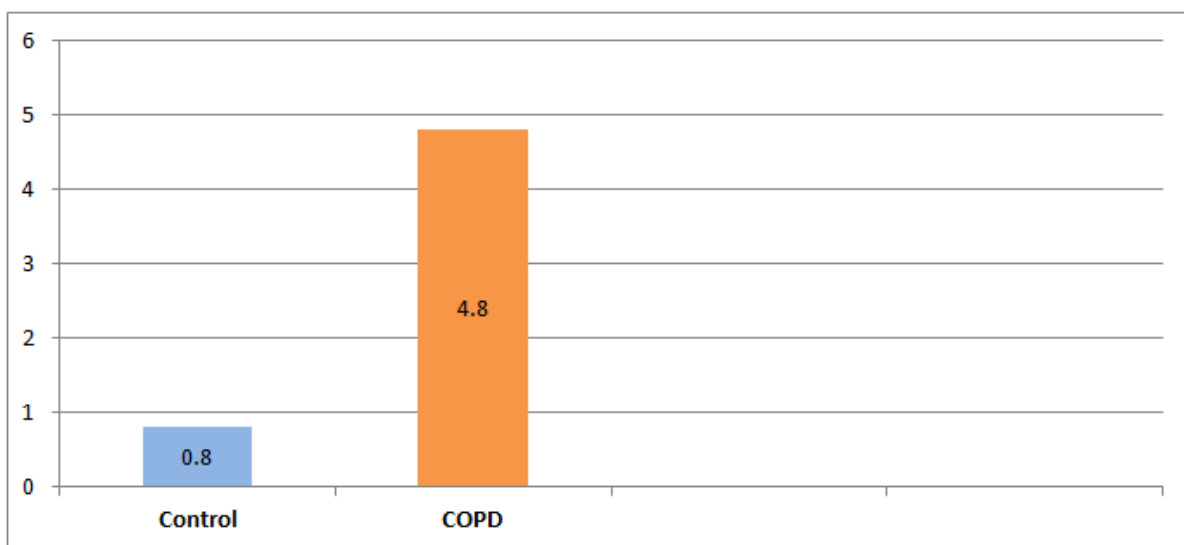

Chart 1. Mean hs-CRP in both study group

hs-CRP levels significantly correlate with GOLD stage (r = 0.797; p < 0.01). A negative correlation, which is significant, of hs-CRP was found with BMI (r = -0.710; p < 0.01), FEV1 (r = -0.813; p < 0.01) and 6MWD (r = -0.876; p < 0.01). Pearson's correlation coefficient of hs-CRP levels with other variables are shown in the following table.

The correlation between hs-CRP and sex, smoking and GOLD stage was taken into study by Spearman correlation.

To find out significant predictors of hs-CRP, which are 6MWD and FEV1, was carried out by stepwise multiple regression analysis.

Graph Pad Prism Version 7.0 was used to analyze the data of acute exacerbations. Categorical value results were shown as absolute and relative frequencies. And, continuous variables were shown in terms of Mean Value and Standard Deviations (SDS) /Median and Inter Quartile Ranges (IQR) and a T value less than 0.1. Most of the study participants were classified under the second or third degree of Anthonisen's criteria with median exacerbation rate of 1.70 (IQR 0.90 – 2.66) episodes per year.5 patients were reported having a single exacerbation episode, whereas 12 patients with 2 episodes and the remaining 8 patients with more than 3 episodes.

CRP level analyses were higher in cases of both bacterial (58.3 mg/l, IQR 21.0 – 128.2) as well as viral infections (36.4 mg/l, IQR 10.8 – 93.7) (p < 0.04). CRP also reached the highest level of (74.1, IQR 42.0 – 220.7) in some exacerbation episodes.

In almost all cases CRP shows persistently higher levels during exacerbation and also at 7, 14, 35 day of post exacerbation. Most of the patients showed rise in CRP even during the recovery period. Patients who have had more than one recurrence of exacerbation within 50 days have significantly higher levels of serum CRP compared to those without any recurrences, as noted.

Table 4. Pearson's correlation coefficient of hs-CRP levels with other variables

hs-CRP mgl	Correlation Coefficient (r)
Smoking	790
Sex	- 600
BMI kg/m^2	-690
FEV1	-800
6MWD	-870
GOLD Stage	790

Table 5. Significant predictors of hs-CRP

Model	Variable	R	R2	B
1	6MWD	0.878	0.778	-0.878
2	6MWD	0.924	0.863	-0.490
	FEV1			0.478

Table 6. Anthonisen's criteria

| GOLD Stage	No. of Patients	Anthonisen's Criteria	No. of Exacerbation Episodes	CRP Level
GOLD I	5	Grade I The Occurrence of Dysponea, Sputum Volume, Sputum Purulent	1 Episode	Ranges from 36.4 mg/l to 58.3 mg/l something up to 74.1 mg/l in some cases
GOLD II	12	Grade II Two of the above symptoms	2 Episodes	
GOLD III	6	Grade III One of the above symptoms	Three or More Episodes	
GOLD IV	2	Increased Fever, RR and Cough		
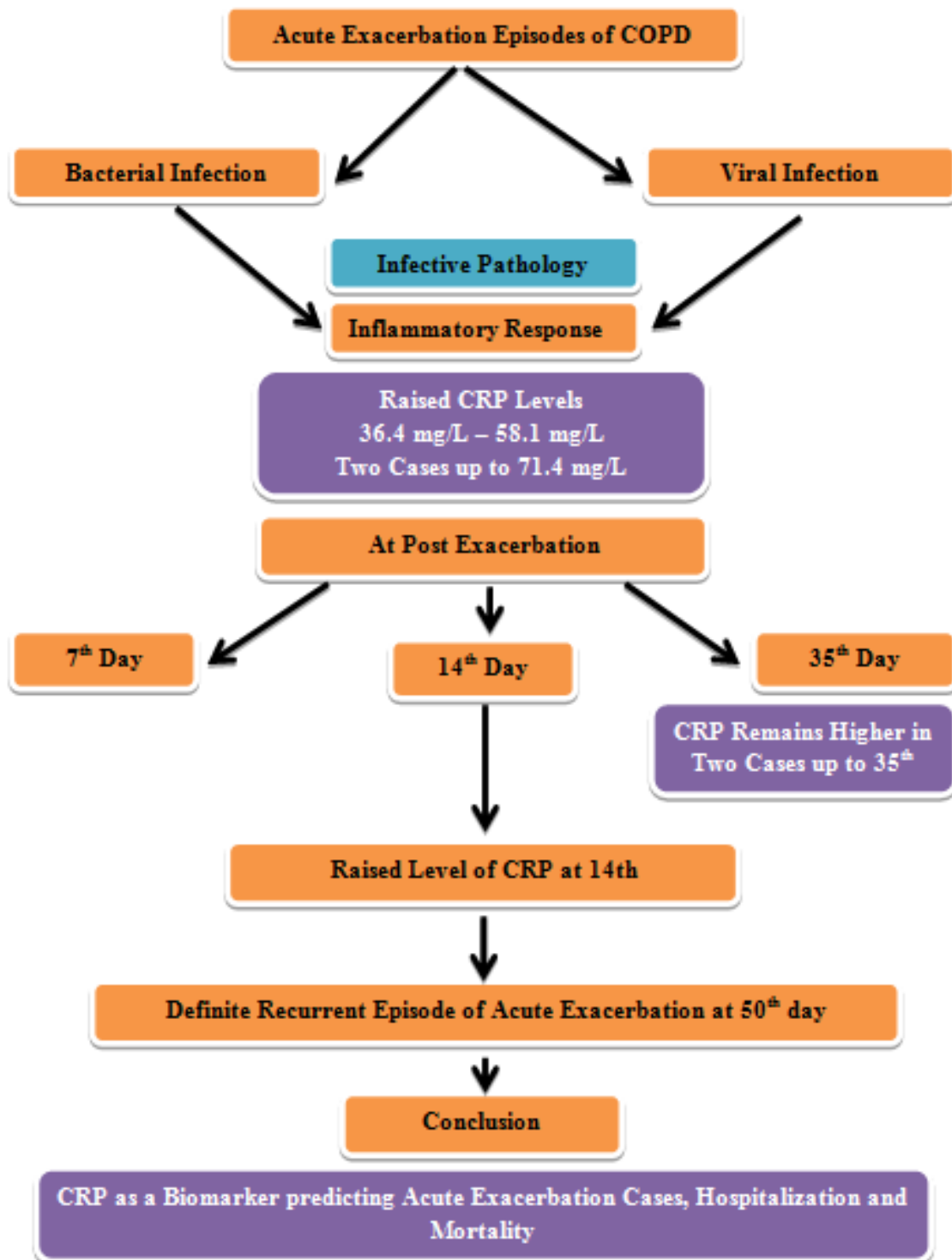
Chart 2. Acute exacerbation episodes of COPD

Between community-attended and hospitalized COPD acute exacerbation episodes, significant differences in the levels of CRP were found. The levels ranged from (37.3 mg/l, IQR 12.8 – 82.7) in community based cases to (67.4 mg/l, IQR 27.0 – 189.0) in hospitalized patients. There was a significant association between the increase in CRP and the increase in RR and leucocytes and a fall in SAO2.

Table 7. Markers of exacerbation severity (N=50)

	Reference values	Community-managed, n = 15	Hospital admitted, n = 35	P-value
CRP	<5 mg/L	38.5 (12.8–82.7)	70.5 (27.0–189.0)	<0.0001
WBC count	4,000–11,000	9,500 (7,860–11,460)	11,000 (8,500–14,002)	0.001
RR	12–16 breath/min	22 (20–28)	24 (24–30)	0.002
SaO$_2$	96%–100%	93 (92–95)	88 (85–92)	<0.0001
PaO$_2$+	10.6–13.3 KPa	7.6 (7.3–8.6)	6.9 (6.2–7.6)	0.002
PaCO$_2$+	4.6–5.9 KPa	5.4 (5.2–6.6)	6.0 (5.4–7.5)	0.001
pH+	7.35–7.45	7.40 (7.40–7.44)	7.42 (7.39–7.44)	0.443

Table 8. The factors associated with hospital admission were analyzed. Results were as follows

	OR (95% CI)	P-value
GOLD stage IV	1.35 (0.75–2.18)	0.30
Charlson Comorbidity Index	1.20 (0.95–1.40)	0.16
Bronchiectasis	1.40 (0.78–2.47)	0.27
BODE	1.20 (0.93–1.37)	0.31
LTOT	1.99 (1.08–3.32)	0.03
Baseline hypercapnia	2.89 (1.56–4.64)	<0.0001
CRP (mg/L)		
< 18.6	1	
18.7–47.7	1.89 (0.91–3.33)	0.10
47.8–100	3.00 (1.25–5.24)	0.02
> 100	4.86 (2.25–8.78)	<0.0001

CRP emerged as predictive along with the oxygen therapy and baseline hypercapnia on exacerbation severity in the GEE model, which assesses the influence of inflammatory response. In adjusted models, both basal hypercapnia and CRP remained significant predictors of (a four-time risk of) hospitalization when the CRP level rises above 100 mg/l.

4. DISCUSSION

There is a remarkable rise in hs-CRP with COPD patients than with controls, as revealed by our study. Also, hs-CRP was remarkably higher in smokers than in quitters (r = 0.796; p < 0.01). As showed by Juan P de Toress et al. [8] that the active smokers have higher CRP levels, our study substantiated it exactly. Intriguingly, the non-smoking COPD patients had higher levels than the control group. COPD patients had a higher level of CRP (50.03 ± 1.51) than both the smoking and non-smoking control group, showed, on the contrary, by Pinto Plato et al. [9].

CRP and FEV1 values were inversely related with each other. The more increased in CRP level shows the faster reduction of FEV1. Cross-sectional and longitudinal variations between CRP and FEV1 decline, which shows FEV1 and CRP are negatively associated (p = 0.002), as plotted by Shabbon et al. [10]. The increased levels of hs-CRP that leads to accelerated decline in FEV1 and mortality in patients with mild to moderate COPD, as a recent study showed, denotes that the CRP measurements can enable identifying the risky patients.

The strong association of the CRP level in stable COPD patients with 6MWD and FEV1 is the most important finding in our study. Also, we found that there's an independent correlation between the CRP level and the other important prognostic values like BMI & GOLD-stage spirometric classification. A crucial increase in the CRP level in stable COPD patients indicates the persistent systemic inflammation, substantiated by Gan et al. [11]. The studies of Yende et al. [12] and Broekhuizen et al. proved the above results. Thus, the hs-CRP is a valid biomarker for low-grade systemic inflammation. In this study, there is an inverse correlation between CRP levels and 6MWD. CRP levels being inversely correlated with endurance found by Koechlin et al. [13] and the increase of CRP in those COPD patients with poor exercise found by Broekhuizen et al. [14] are similar to this study.

The inverse relation between the CRP levels and the distance achieved in 6MWD, independent of other factors like age, sex & smoking, found by Broekhuizen et al., is also consistent with our study.

BMI and CRP are inversely correlated in our study. This correlation was found by Marie and Breyer et al. [15], who found that obese COPD patients with a BMI of over 30 kg/m^2 were 3.3 times more likely to have a high level of CRP. On the contrary, patients with BMI lower than 21 kg/m2 were twice as likely to have higher CRP levels. Schols et al. observed that there is a correlation between high levels of CRP and high Resting Energy Expenditure (REE) & low Fat Free Mass (FFM). In our study we found that the more severe the GOLD criteria by spirometry the higher the levels of CRP were. But Pinto Plato et al found there was no significant increase of CRP with aggravation of disease. But De Torress and coworkers' study showed similar results to our study.

The relationship between acute exacerbation of COPD, recovery, recurrent exacerbation and inflammatory responses all are closely correlated with rise of CRP level irrespective of infective pathology. Most patients did not return to baseline even by day 35, as our study revealed. Persistently heightened systemic inflammation with high CRP levels is in association with the non-recovery of symptoms in COPD exacerbation. A persistent high serum CRP concentration on the 14th day of an index exacerbation episode might predict an additional episode within 50 days.

5. CONCLUSION

The levels of C-Reactive Protein are increased in Chronic Obstructive Pulmonary Disease (COPD) patients, as our study revealed.

So the plasma CRP is not only effective in the evaluation of inflammation but also useful as a marker in monitoring inflammation during COPD treatment. There are multiple clinical variables in association with the levels of CRP, which help in anticipating the outcome of the patients, as well as the mortality rates. Further following of cohort studies with greater samples will help to confirm our findings.

ETHICAL APPROVAL AND CONSENT

This study was approved by the Ethics Committee of Saveetha Medical University.

An informed and written consent was obtained from every patient prior to the study

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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