



## Serial estimation of serum CRP levels in patients of COPD with acute exacerbation

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### ABSTRACT

**Objectives** By representing the C-reactive protein (CRP) levels with the dates of determining CRP, the status of disease can be known. The serial levels of CRP in patients of COPD were assessed to evaluate them as a determinant of the status of disease.

**Methods** A total of 100 known patients of COPD were evaluated at the time of admission, discharge from the ward, follow-up at six weeks. Serum CRP was measured by quantitative turbidimetric test and was correlated with Forced expiratory volume in 1 second (FEV<sub>1</sub>), arterial oxygen tension and total leukocyte count.

**Results** The mean value of the CRP at acute exacerbation was 50.712± 22.642 mg/l, 10.435± 9.325 mg/l at discharge and 8.318± 9.099mg/l at follow-up (p< 0.05). CRP showed statistically significant negative correlation with FEV<sub>1</sub>, FEV<sub>1</sub>% predicted and Sp O<sub>2</sub> at acute exacerbations. Significant negative correlation was found between CRP and FEV<sub>1</sub>, FEV<sub>1</sub>% predicted at discharge. CRP showed statistically significant negative correlation with FEV<sub>1</sub> and Sp O<sub>2</sub> at follow-up.

**Conclusion** The findings have shown that serial CRP estimation is useful as early marker of the exacerbation and also beneficial in assessing efficacy of treatment.

**Keywords:** Chronic obstructive pulmonary disease, C- reactive protein, serial estimations

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### INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality throughout the world. It is the fourth leading cause of death. According to the Global Burden of Disease Study, it results in 1.68 years of living with disability (YLD) per 1,000 population, representing 1.8% of all YLDs, with a greater burden in men than in women (1.93% vs. 1.42%).<sup>[1]</sup> Considering global trends of the present

day, increases in the prevalence and mortality due to the disease have been predicted in the coming decades.

COPD arises from an interaction between various causal factors, both host factors and environmental exposures. Worldwide, tobacco smoking is the most commonly encountered risk factor.<sup>[2]</sup> Alongwith, indoor and outdoor pollutants like exposure to particulate matter, irritants, organic dusts, chemical

agents, fumes and motor vehicle emissions have been documented to cause COPD.<sup>[3]</sup> The genetic risk factor is rare hereditary deficiency of alpha-1-antitrypsin( $\alpha$ 1-AT).<sup>[4]</sup> A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease. It is usually a progressive disease, characterized by exacerbation of symptoms.<sup>[5]</sup> Exacerbation is triggered by infection with bacteria or viruses or by environmental pollutants. Worsening of ventilation perfusion (VA/Q) abnormalities occur resulting in severe hypoxemia.

In COPD, innate and adaptive immune responses to long term exposure to noxious particles and gases, particularly cigarette smoke result in poorly reversible airflow obstruction and an abnormal inflammatory response in the lungs. There is increased numbers of neutrophils, macrophages, and T-lymphocytes (CD8 more than CD4) in the lungs. Reactive oxygen and nitrogen species are released from the inflammatory cells. They create oxidative stress. Many markers of oxidative stress and systemic inflammation are increased in stable COPD.<sup>[6]</sup> The levels of these markers increase further during acute exacerbation. Weight loss, cachexia, osteoporosis, chronic anemia, cardiovascular disorder and derangement of cognitive function have been observed in these patients along with chronic respiratory insufficiency which influences quality of life (limitation of activity, missed work, economic impact, effect on family routines, feelings of depression or anxiety).<sup>[7]</sup> Reflecting the multicomponent nature of the disease there is extensive heterogeneity among patients with COPD in terms of clinical presentation, disease severity and rate of disease progression.

There are various markers in COPD for assessment of severity of disease. Markers related to inflammatory processes, structural changes and systemic effects

yield valuable information to compliment that provided by Forced expiratory volume in 1 second (FEV<sub>1</sub>) airflow limitation.<sup>[8]</sup> Increased levels of various inflammatory proteins such as C-reactive protein (CRP), tumor necrosis factors- $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6) are found in systemic circulation in COPD patients.<sup>[9]</sup> Additional markers are needed to provide a more comprehensive and clinically meaningful assessment so as to provide a more informed basis for treatment decisions. There has been a shift in the focus of biomarker discovery away from lung sources and towards blood specimens.<sup>[10]</sup> Serum or plasma biomarkers are attractive because blood is readily available and their measurement can be easily standardized.<sup>[11]</sup> Out of these blood based biomarkers, COPD has shown great promise. Raised blood CRP levels are associated with major outcomes of interest in COPD, including reduced lung function, hospitalization, and mortality, independent of the effects of smoking.<sup>[12]</sup> The role of systemic inflammation is being assessed by using CRP increase upto 10000 fold in response to a stimulus and inflammation. CRP has been found to be elevated in stable COPD patients as a marker of persistent low-grade systemic inflammation<sup>[13]</sup>, which seems to increase with increasing severity of COPD<sup>[14]</sup>. CRP elevation has been found in patients irrespective of infection. Thus, it is possible that while it is a marker for COPD exacerbation, it is not necessarily a marker of bacterial infection. These features have made CRP useful as a clinical marker of an inflammatory process.<sup>[15]</sup> In spite of the relation between systemic inflammation and CRP in COPD, only a few studies have assessed the role of CRP in measuring the level of systemic inflammation in COPD to evaluate the status of disease. In this study we have estimated the serial levels of CRP in patients of COPD presenting with acute exacerbation to evaluate it as a determinant of the status of disease.

The CRP levels were correlated with disease duration, spirometric lung function FEV<sub>1</sub>, arterial

oxygen tension( SpO<sub>2</sub>) and total leucocyte count (TLC) to have three dimensional picture of CRP levels in patients of chronic obstructive pulmonary disease presenting with acute exacerbation, at discharge and at follow up after 6 weeks to evaluate it as a marker of status of COPD

## METHODS

The present study was conducted on 100 known patients of COPD as per GOLD guidelines (n=100) presenting with moderate acute exacerbation in the Department of Tuberculosis and Respiratory Medicine[16]after obtaining their informed consent and approval from Institutional Ethical Committee. All COPD patients were having airflow limitation with FEV<sub>1</sub> of less than 70% predicted with reversibility of less than 200ml after administration of 400µg of salbutamol via metered dose inhaler. Serum CRP was measured at the time of acute exacerbation, at the time of discharge when patients were stable and at follow-up after six weeks and correlated with FEV<sub>1</sub>, SpO<sub>2</sub>, TLC. The best of FEV<sub>1</sub> was taken during the course of disease from acute exacerbation to recovery to measure the baseline COPD. Patients on oral steroids and having any other chronic disease besides COPD were excluded from the study.

A detailed history, thorough physical examination and routine investigations were done for all the cases (complete haemogram with ESR, serum bilirubin, SGOT/PT, blood urea, blood sugar, serum sodium/potassium, serum protein, blood gas analysis, urine examination, skiagram chest). Smoking pack years were calculated from mode of smoking, daily consumption, total years smoked. One pack year was 20 cigarettes smoked per day for one year. For bidis, cigarette equivalents were calculated by applying a weight of 0.5 to bidis and for hooka, 12.5g of loose tobacco was equivalent to one packet of 20 cigarettes.<sup>[17,18]</sup> FEV<sub>1</sub> was measured using a Micro Plus

Spirometer before and after inhalation of 400 µg of salbutamol via a metered dose inhaler. Inhaled short acting bronchodilators were withheld 6 hours before test, long acting β-agonists 12 hours before test and sustained release theophylline 24 hours before test. The patient was explained to take a deep breath and fill his lungs completely and then exhale as quickly as possible into the mouthpiece. Test was repeated three times and the best effort was taken for recording. Peripheral venous blood sample was collected in a plane vacutainer (blood collecting tubes) under aseptic conditions for CRP estimation. Serum was separated by centrifugation and CRP was measured by quantitative turbidimetric test.<sup>[19]</sup> Fresh sample was analyzed on the same day. CRP values in serum was measured three times in all the patients, first at the time of acute exacerbation, second at the time of discharge and third at the time of follow-up after six weeks. All patients were treated as per global initiative for chronic obstructive lung disease guidelines 2007 for the management of acute exacerbation of COPD in the form of oxygen therapy, short acting inhaled β<sub>2</sub> agonists, glucocorticoids, antibiotics and ventilatory support wherever required.

### ***Remission Criteria for Patients with Exacerbation of COPD***

The patient is considered to be in remission when inhaled β<sub>2</sub>-agonist therapy is required no more frequently than every 4 hour; patient is able to walk across room; eat and sleep without frequent awakening by dyspnea; has been clinically stable for 12-24 hours; arterial blood gases have been stable for 12-24 hours; fully understands correct use of medications; family and physicians are confident that patient can be managed successfully at home.<sup>[20]</sup>

The patients were discharged when they were in remission and followed up regularly till six weeks. The data so obtained was analyzed by standard statistical method. The association between two quantitative variables was evaluated with Pearson's correlation

coefficient. The results were expressed as the means and standard deviation for the quantitative variable. To compare the means of two groups, student's t-test was used while several groups were compared with Analysis of Variance (ANOVA) test. Least significant difference (LSD) was calculated between each pair of the groups where ANOVA test was applied.

## RESULTS

The mean age of the patients was 59.38  $\pm$  11.70 years with a Male: Female ratio of 81:19. All the patients had airflow limitation that was not fully reversible.

The comparison of the laboratory profile of the patients at the time of acute exacerbation, at remission and at follow-up after six weeks is shown in Table 1.

**Table 1: Laboratory Profile of the patients at admission, discharge and follow-up**

	At Admission (Mean $\pm$ S.D.)	At discharge (Mean $\pm$ S.D.)	At follow-up (Mean $\pm$ S.D.)	p-value
<b>TLC(/mm<sup>3</sup>)</b>	11839.00 $\pm$ 3808.47	8476.00 $\pm$ 1122.96	7806.00 $\pm$ 948.88	<0.001
<b>FEV<sub>1</sub>(L)</b>	0.8193 $\pm$ 0.2482	1.3359 $\pm$ 0.2326	1.4105 $\pm$ 0.2307	<0.001
<b>FEV<sub>1</sub> % predicted</b>	28.13 $\pm$ 7.29	57.413 $\pm$ 7.814	60.089 $\pm$ 7.078	<0.001
<b>SpO<sub>2</sub> (%)</b>	79.998 $\pm$ 14.238	97336 $\pm$ 1.604	87.844 $\pm$ 2.016	<0.001
<b>CRP(mg/L)</b>	50.712 $\pm$ 22.642	10.435 $\pm$ 9.325	8.318 $\pm$ 9.099	<0.001

As per age-wise distribution of the CRP level of the patients at follow-up seen in Figure 1, mean CRP level was found to be highest in the age group of 75-84 years but the difference was not statistically significant ( $p = 0.527$ ). Mean CRP at follow-up was 7.9938  $\pm$  9.2353 mg/dL in males while it was 9.7000  $\pm$  8.5898 mg/dL in females, which was higher in females but this difference was not statistically significant ( $p = 0.465$ ).

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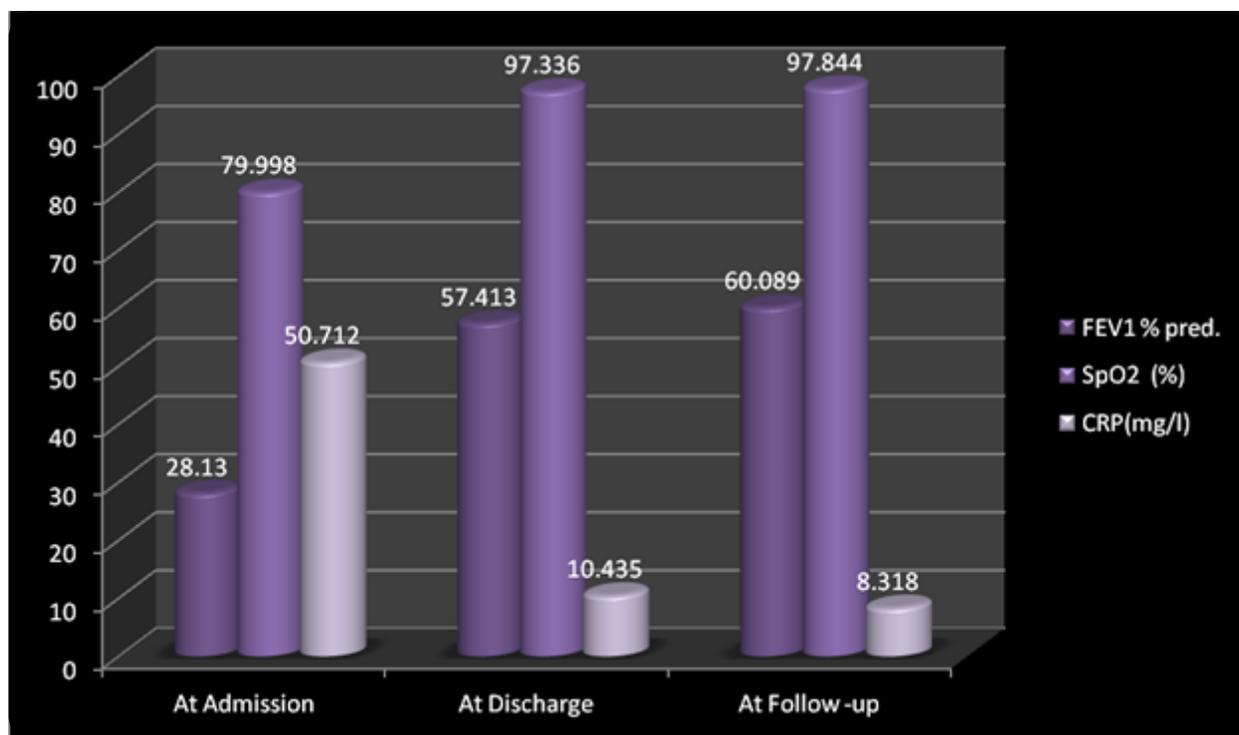


Figure 1: Comparison of FEV1 % pred., SpO2 and CRP at Admission, Discharge and Follow-up

Table 2: Correlation of CRP with the Study parameters

	CRP at Admission		CRP at Discharge		CRP at Follow – up	
	Pearsons' coefficient	p - Value	Pearsons' coefficient	p - Value	Pearsons' coefficient	p – Value
Age	-0.013	0.901	-0.081	0.42	0.073	0.472
Duration of Illness	0.032	0.751	0.212*	0.034	0.207*	0.039
Duration of Smoking	0.047	0.644	-0.024	0.816	-0.002	0.988
Pack –Years	-0.023	0.819	-0.131	0.195	-0.085	0.402
FEV1	-0.442**	0	-0.297**	0.003	-0.287**	0.004
FEV1% predicted	-0.410**	0	-0.261**	0.009	-0.195	0.051
TLC	0.560**	0	0.328**	0.001	0.364**	0
SpO2	-0.237*	0.018	-0.091	0.37	-0.315**	0.001

\*\* Correlation is significant at the 0.01 level (2-tailed)

\* Correlation is significant at the 0.05 level (2-tailed)

Table 3 shows the relation between mean CRP at follow-up and smoking status. In Chronic smokers, mean CRP was  $8.2446 \pm 10.7307$  ranging from 2.0 to 77.6 mg/l. Mean CRP was  $7.1741 \pm 4.4392$  in Ex-smokers ranging from 2.30 to 20.10 mg/l. In Non-smokers, mean CRP was  $10.3765 \pm 8.8144$  ranging from 3.30 to 40.40 mg/l. This difference is not statistically significant ( $p=0.527$ ).

**Table 3: Distribution of subjects w.r.t. Follow-up CRP and Smoking Status**

Smoking Status	Follow-up CRP (mg/l) (Mean±S.D.)
Chronic Smoker	$8.2446 \pm 10.7307$
Ex- Smoker	$7.1741 \pm 4.4392$
Non Smoker	$10.3765 \pm 8.8144$

## DISCUSSION

CRP is an acute phase protein produced by liver in response to IL-6 stimulation. CRP is raised in most conditions associated with infection, inflammation or tissue damage, for which it is a sensitive marker.<sup>[15]</sup> COPD is associated with increased systemic inflammation compared with control subjects, and there is further up- regulation of systemic inflammation at the time of exacerbation.<sup>[6, 21]</sup> Markers reported to be higher in blood during exacerbation compared with the baseline state include CRP, IL-6, IL-8, tumor necrosis factor- alpha, leptin, endothelin-1, eosinophil cationic protein, myeloperoxidase and fibrinogen.<sup>[9, 22, 23]</sup> Many deaths at exacerbation are due to cardiovascular disease and an elevated CRP concentration is associated with increased cardiovascular morbidity.

An exacerbation represents an acute deterioration in symptoms which is beyond the patient's usual day-to-day variations. This definition requires subjective assessment by both the patient and the physician which is difficult. Up to 50% of exacerbations go unreported to health care professionals, and therefore definitions of exacerbation based solely on health care use criteria underestimate the true impact of these events. As there are difficulties in objectively assessing symptom changes, there has been great interest in the

development of a biomarker that is present at different concentrations during exacerbation from that present in stable disease. A useful biomarker should reflect confidently the exacerbation, severity or etiology. However, no studies have specifically reported the use of such assessment in the confirmation of exacerbation. CRP provides a link between airway inflammation, systemic inflammation and cardiovascular disease in COPD. The serum CRP concentrations at exacerbation are correlated with selected markers of airway inflammation, and are higher in the presence of a bacterial pathogen. This suggests that assay of systemic inflammatory markers to some extent reflect inflammatory load in the airway.<sup>[14]</sup> Also, CRP is elevated in stable COPD patients due to the presence of low-grade systemic inflammation.

CRP showed statistically significant negative correlation with FEV<sub>1</sub>, FEV<sub>1</sub>% predicted and SpO<sub>2</sub> at acute exacerbation ( $r = -0.442$ ,  $p < 0.001$ ;  $r = -0.410$ ,  $p < 0.001$ ;  $r = -0.237$ ,  $p = 0.018$ , respectively). Significant positive correlation was evident between CRP and TLC at acute exacerbation ( $r = 0.560$  and  $p < 0.001$ ). No significant correlation was evident between CRP and age, duration of illness, duration of smoking and pack-years of smoking at acute exacerbation. It was also observed that there was statistically significant ( $p < 0.001$ )

difference between the mean TLC at the time of acute exacerbation; at discharge and at follow-up. The least significant difference (LSD) between TLC at admission and at discharge, between TLC at discharge and follow-up and between TLC at admission and follow-up was statistically significant ( $p < 0.001$ ,  $p < 0.05$  and  $p < 0.001$  respectively). It has been quoted in literature that a high serum CRP value may indicate an infectious exacerbation in COPD patients and it correlates with sputum purulence and increased serum TLC. Significant statistical difference in TLC between COPD patients with acute exacerbation and stable COPD groups ( $p = 0.005$ ) was observed.<sup>[24]</sup>

The difference in mean FEV<sub>1</sub> at acute exacerbation, at discharge, and at follow up was statistically significant ( $p < 0.001$ ). The LSD between FEV<sub>1</sub>% at admission and at discharge, between FEV<sub>1</sub>% at discharge and follow-up and between FEV<sub>1</sub>% at admission and follow-up was statistically significant ( $p < 0.001$ ,  $p < 0.05$  and  $p < 0.001$  respectively). Similar results were found by Bircan et al in which they found that there was significant statistical difference in FEV<sub>1</sub>% predicted between COPD patients with acute exacerbation and stable COPD groups.<sup>[24]</sup> The LSD between SpO<sub>2</sub> at admission and at discharge, between SpO<sub>2</sub> at discharge and follow-up was statistically significant ( $p < 0.001$  and  $p < 0.001$  respectively) while LSD between SpO<sub>2</sub> at discharge and follow-up was not statistically significant ( $p > 0.05$ ).

The mean value of the CRP at the time of acute exacerbation in the study was 50.712+22.642 mg/l, which decreased to 10.435+9.325 mg/l at discharge after the patients were treated as per GOLD (Global Initiative for Chronic Obstructive Lung Disease) guidelines in the ward and 8.318 + 9.099 mg/l at follow-up after six weeks. This difference was found to be statistically significant ( $p < 0.001$ ). The LSD between CRP at admission and at discharge, between CRP at admission and follow-up was statistically significant ( $p < 0.001$  and  $p < 0.001$  respectively) while LSD between CRP at discharge and follow-up was not statistically significant

( $p > 0.05$ ). Similar results were found by Bircan et al [24] in which, they detected mean CRP level of 36.8 + 43.9 mg/l in COPD patients with acute exacerbation and 7.9 + 1.9 mg/l in stable COPD patients. None of the stable COPD patients showed CRP levels of >10 mg/l.<sup>[14]</sup> The normal range of CRP was 0-10 mg/l. Torres et al<sup>[25]</sup> determined the mean CRP level in stable COPD patients to be 4.1 mg/l while it was 10.97+14.00 mg/l in the study by Karadag et al.<sup>[26]</sup> Dev et al evaluated the value of C-reactive protein measurements in exacerbations of COPD and found that CRP levels were elevated in patients with acute exacerbation. The average CRP level after adequate treatment was 33+4 mg/l ( $p < 0.001$ ).<sup>[15]</sup>

At the time of acute exacerbation, the mean CRP level in patients whose sputum was sterile on culture was 45.245+19.3372 mg/dl while in patients whose sputum yielded any of the organism, it was 79.4125+16.3852 mg/dl which is significantly higher ( $p < 0.001$ ). This finding is concordant with the previous study in which, they found that CRP level was elevated (>10mg/dl) in all COPD patients where recognized bacterial pathogens were isolated and in 62 % with no clear bacteriological source of infection. In the study, etiological bacteria could be cultured from sputum of 16 patients only at the time of acute exacerbation (16 %). *S. pneumonia* was the most common bacteria isolated, followed by *P. aeruginosa*, *H. influenza*, *Klebsiella* species and *Staph. aureus*. The finding is in accordance with the previous Indian study by Arora et al.<sup>[27]</sup>

In the present study, CRP showed statistically significant negative correlation with FEV<sub>1</sub> and FEV<sub>1</sub> % predicted at discharge ( $r = -0.297$ ,  $p = 0.003$ ;  $r = -0.261$ ,  $p = 0.009$  respectively). Significant positive correlation was found between CRP and total leukocyte count and duration of illness at discharge ( $r = 0.328$ ,  $p = 0.001$ ;  $r = 0.212$ ,  $p = 0.034$  respectively). No statistically significant correlation was evident between CRP value at discharge and age, duration of smoking, pack- years of smoking and SpO<sub>2</sub>. CRP showed statistically significant negative correlation with FEV<sub>1</sub> and SpO<sub>2</sub> at follow-up ( $r = -0.287$ ,

$p = 0.004$  and  $r = -0.315$ ,  $p = 0.001$  respectively). Statistically significant positive correlation was evident between CRP and total leukocyte count and duration of illness at follow-up ( $r = 0.364$ ,  $p < 0.001$  and  $r = 0.20$ ,  $p = 0.039$  respectively). No statistically significant correlation was evident between CRP value at follow-up and age, duration of smoking, pack-years of smoking and FEV<sub>1</sub>% predicted. Bircan et al found that CRP levels were negatively correlated with SpO<sub>2</sub>, FEV<sub>1</sub> and FEV<sub>1</sub>% in overall study population ( $r = 0.317$ ,  $p = 0.0001$ ;  $r = 0.203$ ,  $p = 0.0001$ ;  $r = 0.410$ ,  $p = 0.0001$ , respectively).

In literature several studies have stressed the importance of CRP estimations. In a multivariate study, CRP levels in stable COPD patients were best correlated with Pa O<sub>2</sub> and 6 minute walk distance(6MWD).[28] CRP has been confirmed as a valid marker of low- grade systemic inflammation in stable COPD patients.[26] CRP is a systemic marker of the inflammatory process that occurs in patients with COPD.[29] In a cohort study, CRP was found to be a strong and independent predictor of future COPD outcomes in individuals with airway obstruction.<sup>[30]</sup>

From the study, we can make out that if we investigate CRP regularly in a patient of COPD and write its value in a linear fashion like 8,7,3,2,5,60 with the dates of determining CRP; we can interpret the status of disease in that patient at that time. This signifies that in stable COPD patients, CRP levels can be compared in patients with different duration of illnesses. Similar findings were reported by Bircan et al and Dev et al.[24][15] In the above example, if the next value of CRP is 5, it means that acute exacerbation is present or is about to begin. This will help in early treatment and taking preventive measures whenever it has not begun. If the next value is 2 or 1, it means that patient is going towards stable state. The levels like 60 mean that patient is having bacterial infection. It indicates the need for use of antibiotics in the treatment. If the value of CRP rises, say for example, 8 or 9 and the disease is not in acute exacerbation, it means that any other disease or

cause of inflammation is present which needs further evaluation accordingly.

## CONCLUSION

CRP was found to be a strong and independent predictor of future COPD outcomes in individuals with airway obstruction.

- CRP is an important biomarker in COPD.
- It is an early maker of the exacerbation and also beneficial in assessing efficacy of the treatment.
- By representing the CRP levels with the dates of determining CRP, the status of the disease can be evaluated. The levels were significantly elevated at exacerbation and decreased substantially thereafter, with comparable levels at discharge and follow-up after six weeks.
- The lower levels in stable state can be compared in patients with different durations of illnesses to assess severity of disease since CRP elevation was also found in patients having non- infective exacerbation, so it is not a marker for infective exacerbation only.

CRP estimation should be a routine investigation in COPD patients to know the baseline level, as an indicator of exacerbation and for the evaluation of response to therapy in each patient.

## CONFLICT OF INTEREST

We declare that we have no conflict of interest.

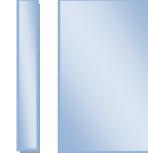
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