Research Article

Study of serum C-reactive protein levels in acute exacerbations of chronic obstructive pulmonary disease patients

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Abstract

Background: C-reactive protein (CRP) is an acute phase protein synthesized in response to tissue damage or inflammation and reflects total systemic burden of inflammation in individuals.

Objective: To assess the levels of serum CRP in acute exacerbations of chronic obstructive pulmonary disease (COPD) and wherever possible compare it with their stable state and to evaluate clinical severity of exacerbations viz a viz rise in serum CRP.

Materials and Methods: It was a prospective study in which cases (76) were patients with acute exacerbation of COPD and control group (30) comprised of patients with acute exacerbation of other respiratory diseases such as pneumonia (15 patients), acute exacerbation of asthma (10 patients), and 5 patients of acute respiratory distress syndrome (ARDS). CRP measurement was done by Nephlometry. CRP levels were measured at time of exacerbation and at time of recovery of the patients, which were compared with the overall prognosis of the patients and with the duration and stage of COPD and also the prognosis of patients in each group is correlated to CRP levels. To achieve this objective, receiver operating characteristic curve analysis has been used with the help of MedCalc software and logistic regression analysis has been used to study the role of different stages of COPD and role of comorbidity in the final outcome of the patients using SPSS software version 22.

Result: The serum CRP was significantly elevated in patients with COPD with acute exacerbation (mean value 14.78 mg/dL). There was significant elevation of CRP values in control group such as in asthma (mean value 2.71 mg/dL), pneumonia (mean value 20.28 mg/dL), and ARDS (mean value 27.02 mg/dL).

Conclusion: CRP is a good discriminator and it predicts poor outcome and also predicts admission in intensive care unit (ICU) or in ward for the patients of acute exacerbation of COPD. CRP value higher than 17.5 mg/dL and above had the poor final outcome of treatment. Positive correlation was found between CRP value and admission in ICU.

KEY WORDS: Chronic obstructive pulmonary disease, C-reactive protein, inflammatory marker.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality globally. The prevalence and mortality of COPD are expected to increase in the coming decades and it is predicted to become the third most common cause of death and the fifth most common cause of disability in the world by 2020.[1] Numerous studies performed in recent

years provide overwhelming evidence of COPD as a condition characterized by an abnormal inflammatory response beyond the lungs with evidence of low-grade systemic inflammation,[2–5] which causes systemic manifestations such as weight loss, skeletal muscle dysfunction, an increased risk of cardiovascular disease, osteoporosis, and depression, among others. Blood markers, such as IL-6, C-reactive protein (CRP), fibrinogen, and procalcitonin have attracted interest during recent years and further studies in this area will probably increase the understanding of systemic manifestations in COPD.[6] These markers are found in circulation with stable patients of COPD[3] and have been shown to be associated with impaired functional capacity,[7] reduced daily physical activity,[8] and decreased health status.[5] One of the inflammatory markers that is increasingly evaluated in patients with COPD is CRP.[9] CRP 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 in individuals[10] and has been shown to be increased in patients with COPD in stable condition[3] and during exacerbations.[11] It is also known as a predictive factor for the course of COPD as well as for hospitalizations and mortality in patients with chronic respiratory failure.[12] It has been accepted that levels of CRP relate to the presence of airflow obstruction,[5] however, there are very few studies evaluating the level of CRP and prognosis of patients with COPD during acute exacerbations.

This study was conducted to assess the levels of serum CRP in acute exacerbations of COPD and wherever possible compare these with their stable state and to evaluate clinical severity of exacerbations viz a viz rise in serum CRP.

Materials and Methods

This study was conducted in "Department of Tuberculosis and Respiratory Diseases" from January 2012 to August 2013, recruiting 106 patients of which 76 were affected with COPD and 30 in control group. The control group had three different diagnoses. In this, 10 patients of asthma (acute exacerbation), 15 patients of pneumonia, and 5 patients of acute respiratory distress syndrome (ARDS) were taken. Therefore analysis was separately done for all three categories of control group with study group. Patients with COPD who were clinically in exacerbations diagnosed according to GOLD criteria 2009, included in study group and exacerbations of other respiratory diseases such as bronchial asthma, bronchiectasis, tuberculosis, and patients of pneumonia were included in control group. Patients of COPD with diabetes mellitus would also be taken but analyzed separately. Patients of known chronic systemic infection or inflammatory conditions such as systemic lupus erythematosus, rheumatoid arthritis, chronic renal failure, history of ischemic heart disease in past 3 months, and history of cerebrovascular accidents in past 2 months were excluded.

Complete clinical examination of patients was performed. Hemoglobin, total and differential leukocyte count, chest X-ray (PA view) spirometry, serum creatinine, serum bilirubin, SGPT, urine routine and microscopy, urine sugar and albumin, erythrocyte sedimentation rate, and CRP were investigated. And again after the exacerbation has improved or worsened during treatment, CRP levels were measured along with other investigations mentioned earlier. CRP measurements were done using nephlometry. Baseline CRP of patients with COPD under study would also serve as another control. Interpretation of qualitative determination of CRP by presence of agglutination within 2 min indicates a CRP level in the sample ≥0.6 mg/dL (positive result). Lack of agglutination within 2 min (a smooth homogeneous suspension) indicates a CRP level <0.6mg/dL (negative result). CRP measurement by semi-quantitative method was interpreted as ($D \times 0.6$) mg/dL, where D is the highest dilution factor for which a positive result is seen.

The hypothesis of our work was that CRP levels can be used as a predictor of poor prognosis in patients with COPD with acute exacerbation. To achieve this aim, the receiver operating characteristic curve (ROC) analysis has been used with the help of MedCalc software and logistic regression analysis has been used to study the role of different stages of COPD and role of comorbidity in the final outcome of the patients using SPSS software version 22.

Results

Mean age of the patients with COPD with acute exacerbations was 62 years. Among patients with pneumonia, mean age was 47.74 years and among those with asthma and ARDS the mean age was 48.40 and 30.8 years, respectively. Among patients of COPD 67.1% were males and 32.9% were females. Among patients with pneumonia, 73.33% were males and 26.67% were females. Among patients of asthma, 70% were males and 30% were females. Of the five patients of ARDS, three (60%) were males and two (40%) were females. Maximum (93.42%) patients were of GOLD stage 3 and 4, whereas only 6.58% patients were having stage 1 and 2. Of all, 60.52% patients of COPD were having comorbidities, 34.20% patients were diabetic, and 36.83% were hypertensive. Among patients with pneumonia, 26% were diabetic and 13% were hypertensive. In patients with asthma, both diabetic and hypertensive were 20%, whereas in patients of ARDS only one (20%) was diabetic.

At the time of admission in hospital, mean CRP value of study group was 14.78 ± 13.52 (mg/dL), maximum 80.26% being in the range of 0.6–20, and in control group among patients with pneumonia mean CRP was 20.28 ± 9.66 (mg/dL), maximum 66.66% being in the range of 10–30. In patients with asthma, mean CRP was 2.71 ± 3.35 (mg/dL) and the maximum patients being in the range of 0.6–10. In patients with ARDS, mean value of 27.02 ± 6.034 (mg/dL) was found with maximum 80% in the range of 20–30 [Table 1]. After recovery of patients, mean CRP of study group was 1.13 ± 0.706 mg/dL, with maximum 69.5% patients having CRP

below 1.2. In control group, among patients with pneumonia, the mean CRP value was 1.13 ± 0.411 mg/dL, with 66.67% patients having CRP levels below 1.2. Of the patients with asthma, the mean CRP value was 0.633 ± 0.33 mg/dL, all the patients of asthma had values below 1.2, and in case of patients with ARDS the mean CRP was 1.08 ± 0.38 mg/dL with 60% patients having CRP levels below 1.2 [Table 1].

ROC curve analysis of level of CRP in predicting the prognosis showed that area under the curve (AUC) was 0.814 with a 95% confidence interval (CI) of 0.73–0.883. The AUC is statistically significant with *z*-value 6.154 and $p < 0.0001$. The high value of AUC (lower bound of 95% CI being 0.73) indicates that CRP is a good discriminator and predicts poor outcome in patients with COPD coming in acute exacerbation. Since the sensitivity and specificity of the CRP values are maximum at the 17.5 mg/dL, so the cutoff value for predicting poor prognosis is 17.55 mg/dL. Above this value, the chances of poor prognosis are high. Correlation of CRP with prognosis of patients in study group was established and it showed that of the 17 deaths among patients with COPD, maximum patients were with CRP >20. Of the total 14 patients, 8 (57.14%) died with CRP value in the range of 20–30. One (100%) patient died with CRP value >30. Six (18.18%) of 33 patients died with the CRP value in the range of 10–20. The difference in the improved % in ranges 0.6–10 and 10–20 was not statistically significant [Table 2]. In correlation of CRP with prognosis of patients in control group, we found that there were three (20%) deaths in patients of pneumonia of the total 15 patients. Of the three deaths, CRP of one patient was between 10 and 20, two patients were having CRP >30 [Table 3]. Among the 10 patients with asthma, there was only one (10%) death [Table 4]. No deaths were recorded in patients of ARDS.

ROC curve analysis of level of CRP in predicting the admission in intensive care unit (ICU)/ward showed that AUC was 0.792 with a 95% CI of range 0.702 to 0.864. The AUC is statistically significant ($z = 5.366$ and $p < 0.0001$). The high value of AUC (lower bound of 95% CI being 0.702) indicates that CRP is a good discriminator and predicts admission of patients with COPD with acute exacerbation in ICU/ward. Since the sensitivity and specificity of the CRP values are maximum at the 11.25 mg/dL. So the cutoff value for predicting admission in ICU is 11.25 mg/dL. Correlation of CRP with admission of patient in ICU/ward among study group and controls was established and we found that maximum patients with COPD had CRP > 10 and required admission in ICU. 87.87% patients in the CRP range of 10–20 required ICU admission, 100% in the CRP range of 20–30 required ICU admission, whereas 57.14% in range of 0.6–10 required ICU admission. Among controls of total 15 patients with pneumonia; 33.33% required ICU admissions, 10% patient out of total 10 patients with asthma required ICU, whereas all patients with ARDS were treated in ICU [Table 5].

The outcome of COPD stage 3 and stage 4 has been compared with stage 2 as baseline since there was no patient in stage 1. Both the regression coefficient was statistically significant ($p < 0.008$ for stage 3 and 0.001 for stage 4). This predicts that the chances of mortality are three times more in stage 3 and stage 4 COPD as compared to stage 2.

Logistic regression analysis has been used to study the role of comorbidity in patients of COPD in the final outcome. The regression coefficient was statistically not significant ($p < 0.375$ and odds ratio of 0.658). So this analysis shows that presence of comorbidity is neither a predictor nor a contributor in poor outcome of patients with COPD coming in acute exacerbation.

Discussion

The American Thoracic Society/European Respiratory Society consensus states: "Although COPD affects the lungs, it also produces significant systemic consequences." These consequences can be detected clinically and appear to be associated with the presence of systemic inflammatory markers. CRP is one of these systemic inflammatory markers. We opted for serum CRP because it is cheaper and easily accessible. At the time of admission in hospital, mean CRP values of study group was 14.78 ± 13.52 (mg/dL), and in control group among patients with pneumonia mean CRP was 20.28 ± 9.66 (mg/dL), in patients with asthma mean CRP was 2.71 ± 3.35 (mg/dL), and in patients with ARDS mean CRP value was 27.02 ± 6.034 (mg/dL) [Table 1]. After recovery of patients, mean CRP value of study group was 1.13 ± 0.706 mg/dL. However, in control group, the mean CRP value was 1.13 ± .411 mg/dL in patients with pneumonia, 0.633±0.33 mg/dL in those with asthma, and 1.08 ± 0.38 mg/dL in those with ARDS [Table 1].

Valipour et al.[13] conducted a study and found that serum CRP was significantly higher in acute exacerbation of patients with COPD than in stable patients and healthy control subjects ($p < 0.001$). Similarly, in our study we found that CRP was elevated in all patients of COPD with acute exacerbation whether the patient was of any stage. Takemura et al.[14] conducted a study to assess the level of CRP in patients with asthma and found that serum hs-CRP levels were significantly increased in steroid-naive patients, but not in patients on inhaled corticosteroid. Similarly in our study, in patients of asthma CRP levels were elevated. The mean CRP was 2.71 mg/dL that reduced to 0.68 mg/dL after exacerbation got over. Garcia Vazquez et al.[15] studied the levels of CRP in community-acquired pneumonia and found that CRP was elevated in all patients of pneumonia. Similarly, in our study CRP levels in patients of pneumonia (mean CRP 27.28 mg/dL) and ARDS (mean CRP 20.28 mg/dL) were also elevated. Their values retuned to almost normal as the acute phase got over.[15] Man et al.[16] found that the CRP measurements provided incremental prognostic information beyond that achieved by traditional marker of prognosis in mild to moderate COPD, and may enable more accurate detection of patient at high risk of mortality. In our study, ROC analysis

Table 1: Mean CRP during admission and recovery among study group and different controls

Characteristics	Study group	Controls		
	Chronic obstructive pulmonary diseases	Pneumonia	Asthma	+ARDS
During admission Mean *CRP (mg/dL)	14.78 ± 13.52	20.28 ± 9.66	2.71 ± 3.35	27.02 ± 6.034
During admission Median CRP (mg/dL)	13.90	19.80	1.20	26.20
During recovery Mean CRP (mg/dL)	1.13 ± 0.706	1.13 ± 0.411	0.633 ± 0.33	1.08 ± 0.38
During recovery Median CRP (mg/dL)	1.10	1.20	0.500	1.20

*CRP: C-reactive protein
+ARDS: Acute respiratory distress syndrome

Table 2: Correlation of CRP with prognosis of patients in study group

C-reactive protein levels (mg/dL)	Chronic obstructive pulmonary diseases			
	Total	Improved	Expired	Improved (%)
<0.6	0	0	0	0
0.6–10	28	26	2	92.85
10–20	33	27	6	81.81
20–30	14	6	8	42.85
>30	1	0	1	0
Total	76	59	17	77.63

Table 3: Correlation of CRP with prognosis of patients in control (Pneumonia) group

C-reactive protein levels (mg/dL)	Pneumonia			
	Total	Improved	Expired	Improve (%)
<0.6	0	0	0	0
0.6–10	3	3	0	100
10–20	5	4	1	80
20–30	5	5	0	100
>30	2	0	2	0
Total	15	12	3	80

Table 4: Correlation of CRP with prognosis of patients in control (asthma) group

C-reactive protein levels (mg/dL)	Asthma			
	Total	Improved	Expired	Improve (%)
0.6–10	9	8	1	88.89
10–20	1	1	0	100
20–30	0	0	0	0
>30	0	0	0	0
Total	10	9	1	90

Table 5: Correlation of CRP with admission of patient in ICU/ward among study group and controls

C-reactive protein levels (mg/dL)	Chronic obstructive pulmonary diseases		Pneumonia		Asthma		*ARDS	
	Ward	ICU	Ward	ICU	Ward	ICU	Ward	ICU
<0.6	0	0	0	0	0	0	0	0
0.6–10	12	16	3	0	8	1	0	0
10–20	4	29	1	4	1	0	0	0
20–30	0	14	4	1	0	0	0	4
>30	0	1	2	0	0	0	0	1
Total	16	60	10	5	9	1	0	5

*ARDS: Acute respiratory distress syndrome.

was carried out to compare the CRP levels with the outcome of the patients of COPD and we found that CRP is a good discriminator and predicts poor outcome in patients with COPD coming in acute exacerbation.[16] Nordestgaard[17] determined rates of COPD-related hospitalization and death during a follow-up of 8 years and found that the baseline CRP level more than 3 mg/dL was associated with more cumulative incidences of COPD-related hospitalization and death. Similarly in our study, we found that as the level of CRP increases in patients of COPD with acute exacerbation the prognosis became poor and we found that chances of poor outcome are high when a patient will presents with initial CRP values of more than or equal to 17.5 mg/dL.[17] Azevedo et al.[18] conducted a study to find the correlation of ratio of CRP/albumin in patients of COPD hospitalized in ICU with the prognosis of the patient. They found that higher the ratio, poorer the outcome of the patient. In our study, we found that initial CRP levels in patients of COPD can predict admission in ICU/ward and we concluded that any patient of COPD coming with acute exacerbation with CRP levels equal to or more than 11.2 mg/dL needs admission in ICU.[18]

The strength of this study is that CRP is a single, cheap, easily available systemic inflammatory marker, which can guide us regarding prognosis in COPD, pneumonia, asthma, and ARDS and its values correlate with improvement and poor outcome. As positive correlation was found between CRP value and admission in ICU, therefore CRP can guide us about the site of management. The limitation of this study is that CRP is a nonspecific inflammatory marker so other inflammatory condition should be ruled out. Most common comorbidities found in our patients with COPD were hypertension and diabetes mellitus. However, they were not significantly associated with poor outcome due to less number of patients included in the study (76), no final conclusion can be drawn on this aspect.

The serum CRP was significantly elevated in patients with COPD with acute exacerbation, asthma (mean value 14.78 mg/dL), pneumonia (mean value 20.28 mg/dL), and ARDS (mean value 27.02 mg/dL). The value of CRP during acute exacerbation of COPD was significantly associated with mortality, value higher than 17.5 mg/dL and above had the poor final outcome of treatment. Positive correlation was found between CRP value and admission in ICU, the cutoff above which admission in ICU is to be considered is 11.2 mg/dL. Thus CRP values have important prognostic value in COPD, pneumonia, asthma, and ARDS and values correlate with improvement and poor outcome. They should be considered in taking decision to document severity of the disease and for admission in ICU.

Conclusion

CRP is a good discriminator and it predicts poor outcome and also predicts admission in intensive care unit (ICU) or in ward for the patients of acute exacerbation of COPD. CRP value higher than 17.5 mg/dL and above had the poor final outcome of treatment. Positive correlation was found between CRP value and admission in ICU.

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