Review Article

# The importance of C-reactive protein and other inflammatory markers in patients with chronic obstructive pulmonary disease

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**Received:** 13 Dec 2011
**Revised:** 20 Jan 2012
**Accepted:** 4 Feb 2012

## *Abstract*

Chronic obstructive pulmonary disease (COPD) is a condition associated with inflammation in lungs and airways. The impacts of inflammatory process is not limited to respiratory system but extend to extrapulmonary organs with resultant complications involving endocrine, metabolic and cardiovascular systems. The extent and severity of inflammation may be partly estimated by serum measurement of several markers including serum CRP. Assessment of these markers can be useful not only for diagnostic or prognostic purpose but also for treatment evaluation of COPD patients. However, due to inconsistent results of published studies, at present the diagnostic or prognostic importance of inflammatory markers as well as their values in the evaluation of treatment outcome has not been accepted by all investigators. and so their routine applications require further studies. This review presents data in regard to the status of inflammatory markers at different stages of COPD patients and evaluates their predictive ability as well as their values in differential diagnosis or treatment evaluation.

***Keywords:*** COPD, CRP, ESR, Inflammation, Markers of inflammation.

***Caspian J Intern Med 2012; 3(2): 428-435***

Chronic obstructive pulmonary disease (COPD) is one of the most important causes of morbidity and mortality all over the world. It is characterized by cellular inflammation and structural remodeling of small airways and progressive deterioration of lung function due to airway obstruction (1-4). COPD is not an isolated condition with pathological mechanisms specifically localized to lungs but a heterogeneous disease with chronic inflammatory process accompanied by high comorbidity and systemic manifestations linked to other systemic diseases such as cardiovascular disease, diabetes ,metabolic syndrome and osteoporosis (3, 5). The causes of death in COPD is not limited to respiratory failure but also due to cardiovascular complications, lung cancer or other causes which often remain unrecognized (5).

The mainstay of treatment for COPD is suppression of inflammation to prevent its consequences. Hence, identification of inflammatory process and estimating its severity is important for treatment decision. Several parameters have been investigated for evaluation as well as follow up treatment and prediction of outcome. At present, the C- reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are the most common markers of inflammation that are usually used for both evaluation and treatment of inflammatory disorders such as rheumatoid arthritis (6, 7). However, many other markers are also available for these purposes which have been used for the assessment of inflammatory process in COPD (8-15). Nevertheless, CRP and ESR in particular, CRP is more often used because of their availability as well as their lower cost (7). Both markers are sensitive to changes in response to changes in severity of inflammation, disease exacerbation or treatment in patients with stable COPD, the serum CRP levels correlate negatively with pulmonary function volumes and arterial oxygen saturation (16).

However, CRP has been shown to be more useful in assessing the severity of COPD in patients presenting to primary care medical centers (17, 14). Markers of inflammation particularly CRP, changes with alterations of lung function volumes, severity of disease, and development of pneumonia. These markers can also be considered for the differentiation of COPD exacerbation from superinfection as well as in the evaluation of treatment efficacy (8, 16, 18). Furthermore, these parameters can be considered for prediction of outcome (11).

**Markers of inflammation in COPD:** Several chemical factors are involved in the development and continuation of inflammation. A number of them may be generated during the inflammatory process. These factors can be used not only for diagnostic purpose but also for the evaluation of inflammatory response, prediction of complications or treatment evaluation (6-8,10).

Up to now, many factors such as CRP, ESR,TNF-alpha, IL-8 (table 1) had been recognized as inflammatory markers and were used for these purposes. A number of these markers were used as predictors of future complications or predictors of lung function (table 1).

**Table 1.** Types of inflammatory markers which can be used for identification of inflammatory process in chronic obstructive pulmonary disease

C-reactive protein (CRP)
Erythrocyte sedimentation rate (ESR)
TNF-alfa
Interlukin-6 (IL-6)
Interlukin-8 (IL- 8)
Vascular endothelial growth factor (VEGF)
TGF-beta1
Alfa1 - antitrypsine
Procalcitonin
Leptin
Fibrinogen
MMP-9
Adiponectin
H2O2

However, CRP and ESR were used in many studies for years and these markers were more familiar among the practitioners, because the data in this context were larger than the other inflammatory parameters. Leptin in the sputum is also a marker of inflammation in moderate COPD. There is a correlation between leptin and inflammatory markers. The presence of leptin in the sputum indicates a contributive role for leptin as an indicator of local inflammatory response in patients with COPD (19). ESR is also a well-known marker which is used in routine practice. Due to its lower cost, it is usually considered as an alternative to CRP test or in combination with it for the detection of inflammation. However, CRP is more sensitive than ESR in detecting inflammatory process due to its rapid changes in response to inflammation. In hospitalized patients with pneumonia, almost all patients show increased levels of CRP at the time of hospitalization whereas, raising of ESR appears later and ESR alone can not detect inflammatory process in stable COPD. Whereas, serum CRP particularly high sensitive CRP can detect minor level of inflammation even in asymptomatic patients with COPD (20). Shorter half life of CRP makes it more useful for following antibiotic therapy of pneumonia.

**Pathogenic mechanisms of COPD, contribution of inflammation:** The processes leading to COPD development are heterogenous. Several mechanisms such as apoptosis, cell proliferation, release of metalloproteinase and fibrosis of the small airways are contributing factors

In advanced diseases, development of autoimmunity, with activation of dendritic cells and T-helper cells may also be responsible. During the exacerbation period, macrophages are unable to ingest apoptotic cells and bacteria (1). Inflammation has an important contributive role not only in the development of lungs and small airways disease but also in the evolution of disease process to extra pulmonary organs and overall morbidity and mortality. Inflammation in the airways begins in response to chronic exposure to cigarette smoke, or other environmental factors and causes airway damage and ultimate destruction of alveolar walls as well as elastic recoil and vascular injuries (21-23). The initial reaction may be elicited in response to smoke inhalation and its outcome may be self- limited or due to prolong interaction with some environmental factors such as cigarette smoke may become progressive and leads to COPD (23).

Cellular infiltration in patients with chronic airflow limitation due to smoking composed of CD8-positive T lymphocytes and in severe conditions, neutraphillic infiltration was prominent. However, the precise roles of the CD8 T lymphocyte and the neutrophil in the pathogenesis of COPD still has not been recognized (21). In the early stage of COPD, systemic oxidative stress and pro-inflammatory cytokines are contributing factors to the pathogenesis of lung

damage. Arteial hypoxia can activate TNF-alfa and its receptor system and results to lung inflammation (22). Inflammation and pathologic reactions in the lungs may result in several endocrine and metabolic responses. These conditions may lead to catabolic activities such as gluconeogenesis, release of glucagon, insulin, adrenocorticotropic hormone, growth hormone, thyroxin, and catecholamines. Concentrations of iron and zinc decrease these conditions and lead to decrease erythropoesis and subsequent anemia.

In symptomatic COPD, the levels of proinflammatory cytokines increase and the number of inflammatory cells such as T-lymphocytes is greater than those without symptoms (21). The inflammatory reaction can be detected in the airways through bronchoalveolar lavage with examination of sputum, exhaled breath condensate, blood, urine, and tissue obtained at surgery or autopsy (19). Concentration of leptin in the sputum increases in moderate COPD in correlation with other inflammatory markers suggesting local inflammation (19).

**Markers of inflammation in COPD versus healthy controls:** High levels of CRP in COPD compared with control subjects without COPD have been demonstrated in several studies. Even in patients with stable COPD, serum CRP may be elevated (16). In a study of 324 patients with COPD and 110 reference subjects, patients with COPD had higher levels of CRP. In addition, the levels of TNF-alpha, IL-6, alpha-1 antitrypsine, fibrinogen were also greater in patients than in controls. There was an independent association between COPD and systemic inflammation (21). In some patients with mild COPD in the absence of any clinical sign and /or exacerbation, the levels of inflammatory markers are elevated (17, 24). In patients with exacerbation of COPD and with pneumonia, the levels of circulating CRP increase further (15, 18, 25). Sometimes, in COPD, the demonstration of inflammation is difficult to be detected by conventional serum CRP measurement. Meanwhile, the application of a new method defined as high sensitive CRP (hs-CRP) provides opportunity for the detection of minor CRP elevation (26).

**Markers of inflammation in COPD vs. asthma:** Since inflammation in asthma has also a contributive role in airway obstruction, therefore a similar increased levels of inflammatory markers as observed in COPD is expected to be seen in this condition. However, the severity of inflammation and types of reactions may be different between the two conditions and so they may be used to differentiate asthma from COPD. In one study of 111 patients with COPD, 46 ashtma and 75 healthy controls, serum alfa1-antitrypsin levels were significantly higher in COPD patients and TGF-beta1 levels were higher in asthma patients than in COPD patients. Smoking status did not affect the levels of markers in COPD or asthmatic patients (27).

**CRP and lung function:** In COPD, lung function volumes decrease in correlation with severity of airway obstruction. Regarding the positive relation between the disease severity and inflammation, it is expected that inflammatory markers and lung functions show comparable changes.

Therefore, serum CRP measurement may predict the status of pulmonary function volumes including forced expiratory volume in 1 second (FEV1) or other lung function parameters (28). This issue has been investigated in several studies. Both CRP and ESR were useful for this purpose. In stable COPD, both parameters were negatively correlated with FEV1 (8, 16, 20). However, in most studies, CRP was preferred rather than ESR which was a better predictor of FEV1 (15, 20, 29). This marker may also be useful in the evaluation of FEV1,FVC or arterial oxygen saturation in stable COPD (16). Higher levels of CRP correlate with the reduction of these volumes. In a study of 938 patients with COPD, changes in FEV1 and FVC were compared with variations in CRP and IL-6. The increased levels of both factors were independently related to lower FEV1 and FVC values. In individuals with the highest quartiles of CRP and IL-6, the values of FEV1 and FVC were 7.5% and 3.9% respectively lower than the predicted values. The negative relationship with CRP was strongest in men rather than women (11.4% vs. -.0.4% (30). Corsonello et al. in a study of 223 patients with stable COPD aged 65 years old assessed more the relation of CRP and ESR with FEV1 % more. In this study, serum CRP but not ESR was weakly and inversely correlated with the FEV1 % (20).

Sin et al. in another study of 6629 patients from the Third National Health and Nutrition Examination Survey aged >50 years old, showed that moderate to severe airflow obstruction was associated with low grade systemic inflammation defined as higher levels of serum CRP and fibrinogen compared with control group without airway obstruction. In severe obstruction, the differences in fibrinogen in particular CRP were higher compared with controls and the levels of circulating CRP were greater by

2.18 times as compared with controls, whereas, in patients with moderate obstruction, the differences were lower but statistically significant (31).

**CRP and COPD exacerbation:** Exacerbation of COPD due to airway obstruction and/or superinfection is associated with the increased levels of inflammatory markers (32). The extent of inflammation correlates with the severity of disease. The several markers were tested in these patients to evaluate COPD exacerbation.

The serum CRP has shown to be very sensitive to change in response to exacerbation and so its measurement provides additional data in confirming COPD exacerbation. In a study of patients with COPD by Bircan et al. the increased level of CRP indicated acute exacerbation with sensitivity of 72.5% and specificity of 100%. Serum CRP in patients with purulent sputum and patients with leukocytosis was greater than those with mucoid sputum or patients without leukocytosis, respectively (32). The findings in another study of 90 patients with COPD demonstrated that CRP alone was not sufficiently specific or sensitive to diagnose exacerbation. But its combination with dyspenea ; sputum volume; or sputum purulence increased the diagnostic accuracy (18).

Lacoma, in a study of 318 patients with COPD consisting of 46 stable COPD, 217 undergoing an exacerbation, and 55 with pneumonia levels of serum PCT and CRP were different across the three comparison groups . The levels especially in pneumonia were greater followed by exacerbated COPD. In 23 patients whose serum levels for both PCT and CRP were available before and after the treatment, the serum concentrations remained elevated until one month after discontinuation of treatment. The patients with higher values of CRP and procalcitonin had earlier death (33).

Changes in other inflammatory markers such as VEGF, IL-6 are similar to CRP and in patients with acute exacerbated COPD, the circulating concentrations of these markers are higher as compared with the stable COPD and healthy controls and change correlated with CRP (34).

The levels of inflammatory markers may remain elevated after subsidence of exacerbated clinical signs or symptoms (35). In one study by Perera et al., the patients with frequent exacerbation of COPD had persistent elevation of inflammatory markers .Persistently the elevated markers had predictive values. A high serum CRP 14 days after an exacerbation, indicated recurrent exacerbation within 50 days. This observation indicates that persistent elevation of inflammatory markers can be considered as a predictor of recurrent exacerbation in the future (36). Nevertheless, the elevated levels of inflammatory markers such as CRP or ESR are only determinants of inflammatory process but not the severity of COPD (37).

**CRP in predicting COPD outcomes:** In patients with COPD inflammation is contributed to the development of several nonpulmonary complications like coronary artery disease and chronic heart failure. These conditions are expected to be developed in patients with prolonged inflammatory process along with persistent elevation of inflammatory markers such as CRP (38).

This issue was shown in a prospective study of 1, 302 individuals with airway obstruction who were selected from the ongoing Copenhagen City Heart Study. These patients were followed up for a median period of 8 years. The subjects with baseline levels of CRP higher than 3 mg /L had greater hospitalization and death due to COPD versus less than 3 mg/L. The adjustment for the other variables baseline CRP was 1.2 mg/L greater in those who subsequently were hospitalized or died. The absolute 10-yr risks for COPD hospitalization and death in individuals with CRP above 3 mg/L were 54% and 57% respectively (39). Local or systemic inflammation leading to progression of atherosclerosis has been shown in animal studies as well (40).

In COPD patients of the Third National Health and Nutrition Examination Survey, aged >50 years old, both severe and moderate airflow obstruction was associated with increased occurrence of ischemic changes on electerocardiograms. Circulating CRP and fibrinogen was positively associated with severity of airflow obstruction (31). In the 4803 participants of Lung Health Study with mild to moderate COPD, in patients with CRP concentration at highest quintile, all -cause mortality was 1.79 times greater than those at lowest quintile. The odds of death due to cardiovascular events and cancer were 1.51 and 1.85, respectively. The risk of mortality between the highest and lowest quintiles was 4.03, 3.3, 1.82 after 1 year, 2 years and 5 years, respectively (24). Additionally, the high concentration of CRP may be indicative of future pulmonary hypertension developing. Pulmonary hypertension is associated with higher levels of serum CRP and TNF-alfa in comparison to those without hypertension. These observations suggest a pathogenetic role for low-grade

systemic inflammation for development of pulmonary hypertension (41). The development of future lung cancer in COPD patients with high levels of inflammation is greater than the patients with lower level of inflammation. In a study of 103 newly diagnosed lung cancer patients, the serum levels of CRP,ESR, CEA, CA19-9 and CA125 were analyzed and compared with 85 homochronous hospitalized patients with chronic respiratory diseases including COPD, asthma, bronchiectasis and pulmonary fibrosis. Both ESR and CRP were significantly higher in the lung cancer group, as compared with chronic respiratory diseases group. A significantly positive correlation was seen between ESR and CRP, the ESR and CA125 as well as CRP and CA125. The CRP was associated with an increased risk of lung cancer. After adjusting to the other confounding factors such as age, gender and smoking condition, the risk of cancer increased along with the increasing CRP values (42). However, the results of studies that assessed the outcomes of patients with COPD based on CRP values were not consistent. In a study of patients with moderate to severe COPD by de Torres et al., serum CRP levels were not associated with future mortality. It seems that the predictive ability of CRP in severe COPD is different from asymptomatic or minimally symptomatic patients. In more severe diseases, CRP loses its predictive ability. However, CRP is a general marker of systemic inflammation which is synthesized by the hepatocytes and may be influenced by several nonpulmonary factors such as age, sex, drugs, and inflammatory process in other anatomical regions. Therefore, its clinical application in prediction of outcome in COPD is partly limited and the results should be explained with caution (16).

**Inflammatory markers and pneumonia in COPD:** Both exacerbation and superinfection of pneumonia in COPD patients can cause serum CRP raising. CRP measurement can differentiate COPD exacerbation from pneumonia. Furthermore the persistence of pneumonia and response to treatment may be assessed with high sensitivity by CRP measurement (15).

Both CRP and ESR are capable to change with development of pneumonia. However, CRP raise is rapid and serum level is high at the time of hospitalization. The level of ESR also increases during pneumoniac but the velocity of rising and declining is slower than CRP. Therefore CRP is more sensitive than ESR in this condition. In addition, short half life of CRP makes it a more useful means both for evaluation and treatment of pneumonia (7).

In addition, changes in serum CRP levels can be predictive of changes in pulmonary function volumes. This relationship was shown in a study of COPD patients. In a study by Lee et al., both serum CRP and procalcitonin were used as predictors of pneumonia in COPD. While both markers increased in the presence of pneumonia, CRP predicted the presence of bacteria better than procalcitonin, whereas, the ability of serum precalcitonin in the diagnosis of pneumonia was better than CRP or ESR (14.)

**Levels of inflammatory markers in response to treatment:** The levels of inflammatory markers are expected to be affected in response to treatment aimed to suppress inflammation. The effect of inhaled therapies using inhaled corticosteroids alone or in combination with long-acting beta-2 agonists bronchodilators which are the mainstay of COPD treatment has been evaluated in several studies. In one study, treatment of COPD with inhaled corticosteroid resulted in the reduction of serum CRP levels as compared with the nontreated patients (43). In another study, two weeks treatment with inhaled corticosteroid reduced serum CRP levels as compared with baseline levels and continuation of treatment for longer duration resulted in further CRP reduction lower than baseline values, while the withdrawal of treatment resulted in serum CRP elevation toward pretreatment level. However, in this study, treatment with placebo did not affect CRP level.

The combination of tiotropium/fluticasone or tiotropium alone did not have effect on the inflammatory cells and inflammatory mediators obtained from sputum of these patients. Furthermore, the FEV1, FVC and CRP or quality of life have not been affected as well (44). These observations indicate that serum inflammatory markers decrease by appropriate treatment and reduction of serum CRP by appropriate treatment may be associated with improved cardiovascular outcome.

In another double-blind randomized placebo-controlled trial study across 11 centers which included 289 patients with low levels of FEV1 values, treatment with inhaled corticosteroid in conjunction with long-acting beta 2 - adrenergic agonist for four weeks resulted in significant improvement of FEV1 without affecting CRP and IL-6 levels, while serum surfactant protein D levels decreased. These findings suggest that in patients with COPD inhaled corticosteroid therapy affects lung-specific biomarkers rather than inflammatory markers (45). In conclusion, there is much information in regard to contributive role of

inflammation in the development and progression of COPD. These observations provided a clue for assessing inflammatory process or follow up treatment efficacy by the measurement of CRP, ESR or other markers. In addition, these markers have potentials of predicting future complications. In this context, serum CRP has shown valuable ability for the prediction of COPD exacerbation or the development of pneumonia.

The follow up of changes in these markers are helpful for the prediction of lung function and response to bronchodilators. Since inflammation in other organs can also increase these markers, high serum level of CRP, ESR or other parameters in patients with COPD should be explained with caution. Any changes in the concentration of these markers are required to be correlated with clinical findings or other appropriate laboratory parameters. However, despite the many studies in this context, the application of these markers for diagnostic or prognostic purposes require further investigations.

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