# Association between C-Reactive Protein and Chronic Obstructive Pulmonary Disease

## C-reaktif Proteini ile Kronik Obstrüktif Akciğer Hastalığı Arasındaki İlişki

KOAH ve CRP/ COPD and CRP

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**Özet**

Amaç: Bu çalışmadaki amacımız C-reaktif protein'nin (CRP) Akut eksezervasyonda kronik obstrüktif akciğer hastalığı (AEKOAH) ve stabil kronik obstrüktif akciğer hastalığında( SKOAH) artıp artmadığını tespit etmek, CRP deki artışın diğer inflamatuar markırlarla olan korelasyonunu belirlemektir. Gereç ve Yöntem: Anthonisen'in akut eksezervasyon kriterlerini taşıyan ve KOAH akut eksezervasyonu (AEKOAH) tanısı nedeniyle hastaneye yatan hastaların dosyaları retrospektif olarak tarandı. Tüm hastaların göğüs radyologrefileri değerlendirildi. Göğüs radyografisinde yeni infiltrasyon, konsolidayon, hava bronkografi vb varsa pnömoni (PKOAH) olarak değerlendirildi. İki ay boyunca eksezervasyonu olmayan hastalar SKOAH olarak değerlendirildi. Aynı yaş ve cinsiyetten oluşan sağlıklı kontrol grubu oluşturuldu. Tüm hastaların İlk 24 saate yapılan solunum fonksiyon testi, arter kan gazı, venöz kan lökosit, nötrofil ve CRP ölçümleri kaydedildi. Bulgular: Ortalama CRP seviyesi akut ataktaki KOAH hastalarda kontrol grubuna ve SKOAH göre anlamlı derecede yüksekti ($p<0.05$). Aynı zamanda serum CRP düzeyi PaCO2 artış düzeyi ile pozitif, pH, FEV1 ve FEV1/FVC değerleri ile negatif ilişki gösterdiği belirlendi. SKOAH hastalarda ortalama CRP seviyesi kontrol grubuna göre yüksekti. Serum lökosit değeri ile serum CRP değeri arasında anlamlı bir korelasyon olduğunu belirledik. Sonuç: KOAH şideti ile serum CRP arasında anlamlı ilişki olduğu belirlendi. KOAH alevlenmelerinde serum lökosit değeri ile serum CRP değeri arasında anlamlı bir korelasyon olduğunu belirledik.

**Anahtar Kelimeler**

C-Reaktif Protein; Ekzeserbason; İnflamasyon

**Abstract**

Aim: In this study, we aimed to find out if there is an increase in the C-reactive protein (CRP) levels in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) and in stable COPD (SCOPD) and to determine the correlation of a possible increase with other markers of inflammation. Material and Method: All patients with AECOPD were also categorized according to radiologic findings. Chest X-rays were evaluated and COPD patients who had new infiltrates, consolidation, air bronkogram were considered to have pneumonia (PCOPD). SCOPD patients without a history of exacerbation for the previous 2 months were recruited prospectively from our outpatient clinic. The pulmonary function test results and the values of arterial blood gas analyses, leukocytes, neutrophils, and CRP measured within 24 hour of admission were obtained from the records of the patients with COPD,. Results: The mean serum CRP level during AECOPD was significantly higher compared to those in the control group and SCOPD patients. The mean CRP level was higher in the SCOPD patients compared to the control group as well. The serum CRP levels were positively correlated with the PaCO2 levels that showed the severity of the attack and negatively correlated with the pH, FEV1 and FEV1/FVC values. Positive correlation between leukocyte count and CRP was detected in all groups except the control group. Discussion: We indicated that there was an association between serum CRP levels and severity of COPD. In COPD exacerbations, leukocyte count and serum CRP levels had a significant positive correlation.

**Keywords**

C-Reactive Protein; Exacerbation; Inflammation

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## Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow obstruction which is usually progressive, not fully reversible and does not change markedly over several months. The disease is predominantly caused by smoking [1]. The frequent occurrence of exacerbations is an important feature of chronic obstructive pulmonary disease (COPD). Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is defined as deterioration in clinical picture with increased dyspnea, decrease in daily performance, increase in sputum production and its purulent nature, increased coughing, high fever and/or mental deterioration. Furthermore, chest discomfort, wheezing, tachypnea, and 20% increase in basal pulse rate may accompany the clinical picture [2,3]. Although many factors that trigger exacerbations are defined, tracheobronchial infections are particularly blamed [4,5]. Though infectious exacerbations are mainly caused by bacteria; it is difficult to differentiate whether the etiology is bacterial or non-bacterial [6,7] . During the exacerbations, purulent nature of the sputum due to neutrophil collection might be an indicator of bacterial infections [8]. C-reactive protein (CRP) is an acute phase protein that is synthesized as a response to tissue damage and inflammation mainly by hepatocytes. It shows the total systemic inflammation in cardiovascular disorders and in COPD [9-12]. In many studies, serum CRP levels are reported to be an important marker of bacterial infections [13,14]. On the contrary, there are reports that show increased serum CRP levels in patients with AECOPD and stable COPD (SCOPD) as well [15,16].

In this study, we aimed to find out if there is an increase in CRP levels in patients with AECOPD and SCOPD and to determine the correlation of this possible increase with the other markers of inflammation.

## Material and Method

### Study Subjects

The study was conducted in a hospital for chest diseases. The medical records of all COPD patients admitted to the hospital between April 2008 and April 2009 were retrospectively evaluated. Patients were considered to have AECOPD if they experienced any of the 3 symptoms that constitute Anthonisen criteria [3]. Patients with AECOPD were categorized according to the nature of expectoration as having purulent (yellow-green coloration) sputum or not. All patients with AECOPD were also categorized according to radiologic findings. Chest X-rays were evaluated and COPD patients who had new infiltrates were considered to have pneumonia (PCOPD). Patients were excluded from the study if they had bronchiectasis (radiologically proven or history of persistent phlegm expectoration), tuberculosis or other inflammatory diseases such as malignancy, arthritis or connective tissue disorders [17]. SCOPD patients without a history of exacerbation for the previous 2 months were recruited prospectively from our outpatient clinic [17]. A group of asymptomatic nonsmokers who were all age and sex-matched with the patients were also included in the study as controls. The SCOPD patients and control subjects gave written informed consent.

### *Measurements*

The demographic features, the pulmonary function test results and the values of arterial blood gas analyses measured within 24 hour of admission were obtained from the records of the patients with AECOPD, while they were performed in the outpatient clinic for the SCOPD patients and the control group. Forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC) and FEV1/FVC% were obtained using a spirometer (MIR Spirolab S/FNA23) according to the standards of the American Thoracic Society [17]. For arterial blood gas analyses, blood was drawn from the radial artery while the patients were breathing room air. Arterial oxygen and carbon dioxide tensions were analyzed with a blood gas analyzer (Rapid Lab 248). Venous blood samples for leukocyte count and CRP were taken and analyzed on the day of admission. The CRP levels were measured by nephelometry (Siemens BnProSpec). Normal range of CRP was 0-3 mg/l.

### *Statistical Analyses*

In the statistical evaluation Chi- Square Test, Pearson correlation analysis, one-way ANOVA and, for multiple comparison, Tukey test were used.

## Results

The mean age of 160 people (125 males, 35 females) included in the study was 63.70±7.81. The mean age did not significantly differ between the groups. The means of some variables were given in Table 1.

The mean serum CRP level during acute exacerbations of COPD was significantly higher compared to those in the control group and SCOPD patients. The mean serum CRP level in the PCOPD group was significantly higher compared to that

Table 1. The means of some variables in different groups.

| | AECOPD(a)* n:40 | PCOPD(b)* n:40 | SCOPD(c)* n:40 | CONTROL(d)* n:40 |
|---|---|---|---|---|
| FEV1 ( L) | 958.95±78.95cd | 1023.85±236.62cd | 1534.18±743.57abd | 2830.50±397.72abc |
| %FEV, % predicted | 36.05±5.95cd | 36.40±5.43cd | 53.43±23.75abd | 90.98±2.14abc |
| FEV1/FVC | 39.78±9.52cd | 41.13±10.31cd | 52.35±9.94abd | 85.63±5.10abc |
| CO2 (mm Hg) | 48.18±10.76cd | 51.08±11.72cd | 40.42±4.44ab | 39.15±2.49ab |
| O2, (mm Hg) | 50.88±5.47cd | 52.68±7.36cd | 74.15±9.83ab | 91.05±2.24abc |
| Leukocyte count (/mm3) | 9248.83±3477.44bd | 15626.50±5597.47acd | 9892.50±2175.55bd | 6462.50±1706.35abc |
| Neutrophil (/mm3) | 56.25±6.41b | 78.90±15.71acd | 60.85±14.30b | 56.15±6.25b |
| CRP (mg/l) | 34.55±15.87bcd | 86.73±24.53acd | 10.18±13.24ab | 2.15±0.89ab |
| Smoking history (Pack-years) | 59.89±6.60d | 56.08±12.26d | 54.87±29.10d | - |

*The groups which showed statistically significant differences in terms of mean in Tukey test are shown with superscripts.
a Acute exacerbation of chronic obstructive pulmonary disease
b Pneumonia and chronic obstructive pulmonary disease
c Stable chronic obstructive pulmonary disease
d Control group

in SCOPD group. The mean CRP levels were higher in SCOPD patients compared to the control group as well. Furthermore, the serum CRP levels in this study were positively correlated with the PaCO2 level that showed the severity of the attack and negatively correlated with the pH, FEV1 and FEV1/FVC values. This study also showed that, compared to the SCOPD group, serum leukocyte and neutrophil counts in severe exacerbations of COPD were higher in the PCOPD group. We noticed a significant correlation between the serum leukocyte level and serum CRP level. Similarly, the serum leukocyte and neutrophil counts also had a positive correlation with the PaCO2 level that showed the severity of attack and a negative correlation with pH, FEV1 and FEV1/FVC.

The lowest mean FEV1 value was detected in AECOPD patients. The mean FEV1 values did not significantly differ between AECOPD and PCOPD patients. These two groups had lower mean FEV1 values than the SCOPD patients and the control group. The means of FEV1% and FEV1/FVC in all groups were detected to be lower than the control group. The mean arterial blood PaO2 was detected to be lower in AECOPD and PCOPD patients; however, the mean arterial blood PaCO2 was detected to be higher than the other two groups. The mean WBC count in all groups was higher than the control group. The groups did not differ in terms of cigarette pack-years.

The mean values of arterial blood CO2 and O2, WBC count and CRP levels of SCOPD patients were not different from those of the control group. However, these values were different from those in the other two groups. The distribution of some variables according to groups is given in Table 2.

Table 2. The distribution of some variables according to groups.

| | AECOPD n=40 | | PCOPD n=40 | | SCOPD n=40 | | CONTROL n=40 | | TOTAL |
|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n |
| Gender (x2=0.40, p=0.94) | | | | | | | | | |
| Male | 31 | 77.5 | 32 | 80.0 | 32 | 80.0 | 30 | 75.0 | 125 |
| Female | 9 | 22.5 | 8 | 20.0 | 8 | 20.0 | 10 | 25.0 | 35 |
| Sputum (x2=123.95, p=0.00) | | | | | | | | | |
| Absent | 13 | 32.5 | - | - | 40 | 100.0 | 40 | 100.0 | 93 |
| Purulent | 27 | 67.5 | 40 | 100.0 | - | - | - | - | 67 |
| pH (x2=45.12, p=0.00) | | | | | | | | | |
| Acidosis | 11 | 27.5 | 13 | 32.5 | - | - | - | - | 24 |
| Normal | 27 | 67.5 | 27 | 67.5 | 32 | 80.0 | 40 | 100.0 | 126 |
| Alkalosis | 2 | 5.0 | - | - | 8 | 20.0 | - | - | 10 |
| Partial blood CO2 pressure (x2=31.11, p=0.00) | | | | | | | | | |
| <35 | - | - | - | - | 3 | 7.5 | - | - | 3 |
| 35-45 | 18 | 45.0 | 14 | 35.0 | 33 | 82.5 | - | - | 65 |
| 45> | 22 | 55.0 | 26 | 65.0 | 4 | 10.0 | - | - | 52 |
| Smoking status (x2=161.57, p=0.00) | | | | | | | | | |
| Smoker | 8 | 20.0 | 12 | 30.0 | 10 | 25.0 | - | - | 30 |
| Ex-smoker | 28 | 70.0 | 25 | 62.5 | 27 | 67.5 | - | - | 80 |
| Non-smoker | 4 | 10.0 | 3 | 7.5 | 3 | 7.5 | 40 | 100.0 | 50 |

Purulent sputum was present in all PCOPD patients and in 67.5% of the AECOPD patients. Acidosis frequency was 32.5% and 27.5% in PCOPD and AECOPD patients, respectively. The partial blood CO2 pressure was above 45 mm Hg in 55% of AECOPD and 65% of PCOPD patients. Twenty percent of AECOPD and 30% of PCOPD patients were current smokers.

Positive correlation between leukocyte count and CRP was detected in all groups except the control group. Positive correlation between neutrophil and CRP was also detected in AECOPD patients and control group (Table 3).

Table 3. Correlations between leukocyte count and CRP values

| | CRP | | | |
|---|---|---|---|---|
| | AECOPD | PCOPD | SCOPD | Control |
| Leukocyte count | | | | |
| Pearson Correlation | 0.467** | 0.336* | 0.540** | -0.212 |
| p value | 0.002 | 0.034 | 0.000 | 0.179 |
| NEUTROPHIL | | | | |
| Pearson Correlation | 0.458** | 0.172 | 0.431 | 0.363* |
| p value | 0.003 | 0.289 | 0.006 | 0.021 |

*Correlation is significant at the 0.05 level, **Correlation is significant at the 0.01 level

## Discussion

Infection and acute exacerbations in chronic inflammations cause deterioration in the respiratory functions of patients with COPD [18] . A variety of measurable markers that can show the existence and severity of inflammation anywhere in the body are identified. Parameters such as serum CRP levels, leukocyte counts, neutrophilic predominance in the leukocyte formula are the ones that are used for evaluating the response to therapy and prediction of mortality [17]. Increased CRP level in COPD shows a severe attack and is negatively correlated with the respiratory functions.20 Pinto-Plata et al. showed that CRP levels in COPD patients are significantly higher compared to the control group and the CRP levels that increase much more during the acute attack is a predictor of mortality [21]. In our study, the mean CRP level during the acute attacks was significantly higher in the COPD patients compared to that in the control group. Also, in accordance to the literature, the CRP levels in this study are positively correlated with the PaCO2 that showed the severity of the attack and negatively correlated with pH, FEV1 and FEV1/FVC values.

The secretion of pro-inflammatory cytokines like IL-6 and TNF-α is increased in the circulation of patients with COPD [11,22,23]. IL-6 is known to be a powerful signaling cytokine for CRP expression by the liver and its serum levels have been reported to correlate with CRP levels in SCOPD patients [24]. Gan et al. reported that patients with COPD had higher levels of CRP than control subjects in all the studies evaluated, indicating the presence of a systemic inflammation in patients with SCOPD [11]. Several studies showed that the mean CRP levels were higher in the SCOPD than the control group [10,15]. In this study, we also showed that the mean CRP levels were higher in SCOPD patients compared to the control group in accordance to the current literature.

In COPD patients, bacterial infections cause intense inflammatory response. That is the reason why many studies recorded increased CRP levels in patients with AECOPD due to bacterial infections [25]. Bircan et al. showed that CRP levels were

significantly higher in patients with AECOPD compared to patients with SCOPD [17]. In the same study, the serum CRP levels were significantly higher in the PCOPD group compared to other groups. We also showed that serum CRP levels in the PCOPD group were significantly higher compared to the SCOPD group, in parallel to the studies that were published previously [17,25]. In our study, the mean serum CRP level of the PCOPD group was significantly higher than the levels in the AECOPD and SCOPD groups.

Some cytokines that are secreted from the macrophages which are on the first-line defense against the microorganisms that cause systemic infections induce hematopoiesis and cause an increase in serum leukocyte count that is another determinant of infection. Particularly in COPD, bacterial infections cause a more intense inflammation. The studies have shown that, in COPD exacerbations, both leukocyte and neutrophil counts are related to the severity [9,11]. During exacerbations, purulent change in character of sputum due to neutrophil collection in the respiratory tract may be an indicator of bacterial infection [8]. We have, in this study, showed that serum leukocyte and neutrophil counts in severe acute attacks of COPD are higher in the PCOPD group compared to the SCOPD group. We noticed a significant correlation between the serum leukocyte level and serum CRP level. In this study, in accordance with the current literature, serum leukocyte and neutrophil counts also had a positive correlation with the PaCO2 level that showed the severity of attack and a negative correlation with pH, FEV1 and FEV1/FVC. Similar to the previous studies, it was found that purulent sputum was more frequent in acute exacerbation of COPD and absent in SCOPD group.

### *Conclusion*

In conclusion, we determined an association of serum CRP levels and severity of the clinical status of COPD. In COPD, leukocyte count and serum CRP levels had a significant positive correlation.

### *Declaration of Interest*

None of the authors declared any conflict of interest regarding this study

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