

**PROCALCITONIN AND CRP AS BIOMARKERS IN DISCRIMINATION OF COMMUNITY-ACQUIRED PNEUMONIA AND EXACERBATION OF COPD**

## PROKALCITONIN I CRP KAO BIOMARKERI U RAZLIKOVANJU VANBOLNIČKE PNEUMONIJE I POGORŠANJA HOBP

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**Background:** Serum procalcitonin (PCT) and C-reactive protein (CRP) are markers of systemic inflammation and bacterial infection. We aimed to compare the usefulness of procalcitonin and CRP in patients with community-acquired pneumonia and exacerbations of chronic obstructive pulmonary disease (COPD).

**Methods:** A total of 116 consecutive patients were included in the study: 76 with chronic obstructive pulmonary disease in group 1, and 40 with pneumonia in group 2.

**Results:** Median serum CRP level was 44 mg/L in the COPD group and 132 mg/L in the pneumonia group. Median value of serum PCT was found to be 0.07 in the COPD group and 0.14 ng/mL in the pneumonia group. Serum PCT and CRP levels were significantly higher in the pneumonia group compared to the COPD group ( $p < 0.001$ ). The area under the ROC curve was 0.788 (CI: 0.704–0.872) for CRP and 0.699 (CI: 0.599–0.800) for procalcitonin to identify pneumonia.

**Conclusions:** Procalcitonin and CRP levels were significantly higher in patients with community-acquired pneumonia presenting to the emergency department with indications for hospitalization than in patients with exacerbations of chronic obstructive pulmonary disease. Serum CRP and procalcitonin concentrations were strongly correlated. CRP might be a more valuable marker in these patients with lower respiratory tract infections.

**Keywords:** CRP, procalcitonin, pneumonia, respiratory diseases, sensitivity

**Kratak sadržaj**

**Uvod:** Serumski procalcitonin (PCT) i C-reaktivni protein (CRP) markeri su sistemske inflamacije i bakterijske infekcije. Naš cilj bio je da se uporedi korisnost procalcitonina i CRP-a kod pacijenata sa vanbolničkom pneumonijom i pogoršanjima hronične opstruktivne bolesti pluća (HOBP).

**Metode:** Ukupno 116 uzastopnih pacijenata je uključeno u ovu studiju: 76 sa hroničnom opstruktivnom bolešću pluća u grupi 1 i 40 sa pneumonijom u grupi 2.

**Rezultati:** Srednji nivo CRP-a u serumu bio je 44 mg/L u grupi sa HOBP i 132 mg/L u grupi sa pneumonijom. Srednja vrednost PCT-a u serumu bila je 0,07 u grupi HOBP i 0,14 ng/mL u grupi sa pneumonijom. Nivo PCT-a i CRP-a u serumu bio je značajno viši u grupi sa pneumonijom u poređenju s grupom sa HOBP ( $p < 0,001$ ). Oblast ispod ROC krive bila je 0,788 (CI: 0,704–0,872) za CRP i 0,699 (CI: 0,599–0,800) za procalcitonin za identifikovanje pneumonije.

**Zaključak:** Nivoi procalcitonina i CRP-a bili su značajno povišeni kod pacijenata sa vanbolničkom pneumonijom koji su se javili odeljenju hitne službe i imali indikacije za hospitalizaciju nego kod pacijenata sa pogoršanjem hronične opstruktivne bolesti pluća. Koncentracije CRP-a i procalcitonina u serumu bile su u jakoj korelaciji. CRP bi mogao imati veću vrednost kao marker kod ovih pacijenata sa infekcijama nižeg respiratornog trakta.

**Ključne reči:** CRP, procalcitonin, pneumonija, respiratorne bolesti, osetljivost

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List of abbreviations: CAP: community-acquired pneumonia; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; PCT: procalcitonin.

## Introduction

Community-acquired pneumonia (CAP) is a severe disease which occurs in a society during daily life and is encountered frequently despite of effective antibiotic use and effective vaccines. Regardless of advanced diagnostic opportunities, the detection rate of CAP etiology is about 50–70% (1, 2).

Chronic obstructive pulmonary disease (COPD) is a significant public health concern which has an increasing prevalence and mortality rate. It is one of the most common causes of admission to hospital emergency departments (3, 4).

In order to restore hemostasis which is impaired in bacterial and viral infections, many physiological changes occur in the host. These systemic changes are generally known as the acute phase response. Macrophages which are activated by infectious agents or their products trigger an acute phase response with cytokines they release (TNF, IL-1, IL-6) (4). In the differentiation of bacterial and viral infections, leukocyte count, absolute neutrophil count, number and rate of rods, erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) level are the most commonly used acute phase reactants.

CRP is a polypeptide which is an important marker of inflammation, causes precipitation with C-polysaccharide on the cellular wall of pneumococcus and is responsible for activation of classical complement pathway and increased phagocytosis. CRP and leukocyte count do not have sufficient specificity in differentiating bacterial infections from noninfectious systemic inflammation and viral infections. Procalcitonin (PCT) has been added in recent years to the markers of infection that are currently used. Procalcitonin (PCT) is precursor of the hormone calcitonin. It was detected as a protein increasing in patients with sepsis and infection in the early 1990s. It has been accepted that PCT is specific to bacterial infections. Studies have revealed that bacterial endotoxin is the most potent stimulus for production of PCT. It is used to differentiate bacterial diseases from nonbacterial diseases, as viral, autoimmune, oncological diseases and local and limited infections do not cause an increase in PCT (5, 6). It has been reported that it is a more reliable marker than CRP in patients with heart failure, early diagnosis of bacterial infection, bacterial infections of lower respiratory tract, diagnosis and prognosis of patients with septic shock, patients with multiple trauma and early diagnosis of septic complications. No direct relationship of procalcitonin with calcium metabolism has been established yet. It is remarkable that in sepsis in which PCT reaches to higher levels, hypocalcemia is also present. In medullary thyroid cancer, PCT level increases, as well as calcitonin. However, in severe bacterial infections, although PCT increases, no change occurs in the calcitonin level. PCT with very low amounts (<0.1 ng/mL) is present in sera of healthy individuals. Clinical pre-

sentations of severe infections and noninfectious systemic inflammations are similar.

Differentiation between pneumonia and COPD exacerbation, both of which require different treatments and follow-ups, is clinically significant. It is important to prevent unnecessary use of antibiotics for the patients, to apply appropriate treatments and to reduce morbidities, mortalities and expenditures for care via performing differential diagnoses of these diseases (7, 8).

In this prospective study, we aimed to observe the clinical benefits of C-reactive protein and procalcitonin in hospitalized patients with COPD exacerbation and community-acquired pneumonia and to investigate their usability in differential diagnosis.

## Methods and Materials

### Patients

Patients diagnosed with COPD exacerbation and pneumonia who were indicated for hospitalization following their admission to the emergency department of Dr Suat Seren Chest Diseases and Surgery Training and Research Hospital between January and July 2013 were included in the study. The hospital is located in a low income area of the city and the patient population of the hospital mostly consists of people with low socioeconomic status. A great majority of the study group were over 50 years old (91%) and male (85%). Forty patients who had symptoms and physical examination findings consistent with pneumonia and newly-formed infiltrative appearance in chest x-rays comprised the pneumonia group and 76 patients who had known COPD were admitted to hospital with complaints of difficulty breathing and purulent sputum expectoration and no infiltrative appearance that was not consistent with pneumonia and/or any other diseases comprised the COPD group. Sputum cultures were performed in 58 patients (50%) and 14 sputum cultures (31%) were positive. There were 48 patients with previous antibiotic use. Of 116 patients, 114 were given antibiotic treatment during hospital stay. Cefuroxime axetil + macrolide antibiotics were used in most of the patients and fluoroquinolones were given to a few patients with kidney failure. Hospital stay duration of the patients ranged from 2 to 25 days with a median of 8 days.

### Methods

The study was approved by the local ethical committee and written informed consents were taken from all patients. Demographical, clinical and radiological findings, serum CRP and serum PCT levels of the patients were investigated. Serum CRP level was assayed with a nephelometric method using the Beckman Array 360 System. Intra-assay CVs for CRP assay were 10.1% at 27 mg/L and 2.1% at 69.2 mg/L; total

CV was 13.9% at 27 mg/L and 3.6% at 69.2 mg/L. Serum PCT level was assayed with a chemiluminescence method in an analyzer Cobas E 411. Intra-assay CV for the procalcitonin assay was 2.1% at 0.622 ng/mL and 2.1% at 41.2 ng/mL; inter-assay CV was 4.1% at 0.622 ng/mL and 4.9% at 41.2 ng/mL.

#### Statistical analysis

Statistical analysis was performed with the SPSS Package Program (SPSS version 15.0). Data was given as median (25<sup>th</sup>–75<sup>th</sup> quartile) and mean  $\pm$  standard deviation. Data was checked for normality of distribution with the Shapiro-Wilk test. In the comparison between groups, chi-square test, independent samples T-test and Mann-Whitney U test were used and  $p < 0.05$  was accepted as significant. Receiver operating characteristics analysis was used to analyze the diagnostic accuracy of biomarkers. Spearman correlation coefficient was performed to evaluate the correlation between CRP and procalcitonin. Youden index was used to determine the optimal cut-off value on a ROC curve (9).

#### Results

A total of 116 patients (40 with pneumonia and 76 with COPD exacerbation) were included in the study. In the COPD exacerbation group, there were 9

female patients and 67 male patients and in the pneumonia group, there were 8 female patients and 32 male patients. No difference was found between both groups in terms of gender distribution ( $p = 0.238$ ). Mean age of COPD group was  $67.4 \pm 10.2$  and mean age of pneumonia group was  $62.9 \pm 16.7$  ( $p = 0.124$ ). Cigarette consumption was 57/packs year in COPD group and 41 packs/year in pneumonia group. Cigarette consumption rate was higher in COPD group compared to pneumonia group ( $p < 0.007$ ). In the hemogram values at hospitalization, the mean value of white blood cells was  $12.2 \pm 4.5$  ( $10^9/L$ ) in COPD group and  $12.4 \pm 5.6$  ( $10^9/L$ ) in pneumonia group. No difference was found between the groups in terms of white blood cell count ( $p < 0.549$ ). Mean neutrophil count prior to hospitalization was  $8.7 \pm 3.9$  ( $10^9/L$ ) in COPD group and  $8.5 \pm 3.9$  ( $10^9/L$ ) in pneumonia group. No difference was found between the groups in terms of neutrophil values ( $p < 0.461$ ). There were significantly increased levels of hemoglobin and hematocrit in COPD exacerbation group compared to pneumonia group ( $p < 0.008$  and  $p < 0.009$  respectively) (Table I).

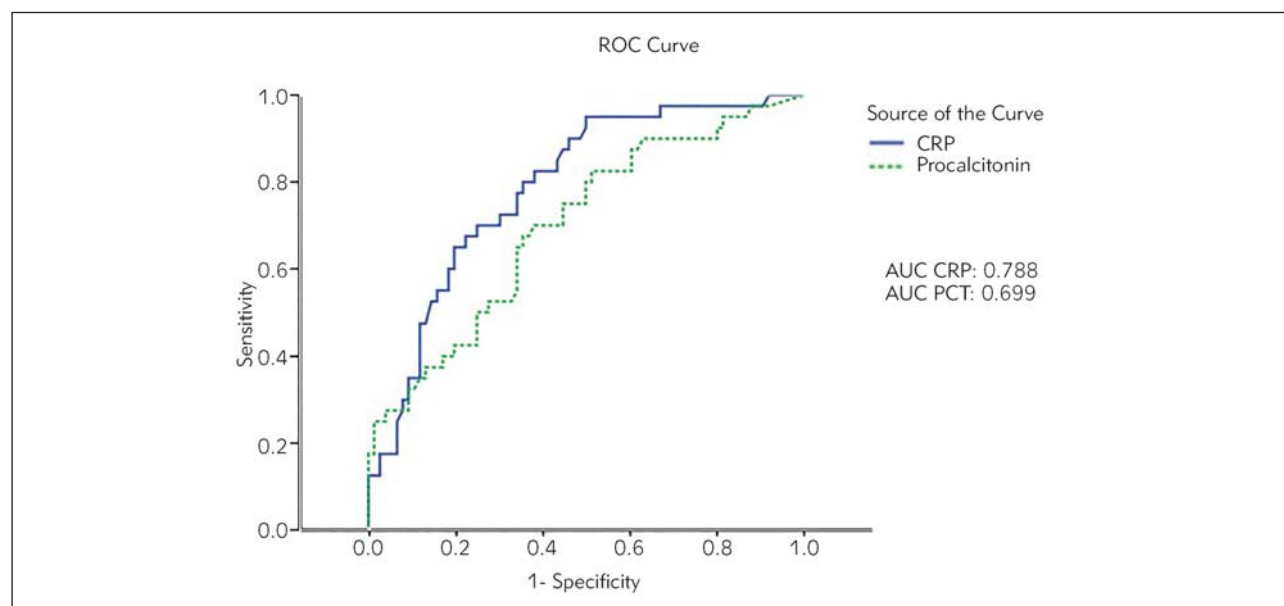
As a median value, serum CRP level was 44 mg/L in COPD group and 132 mg/L in pneumonia group. Serum CRP level was significantly higher in pneumonia group compared to COPD group ( $p < 0.001$ ). Median value of serum PCT was found

**Table I** Clinical, demographical and laboratory parameters of the patients.

		COPD Exacerbation	Pneumonia	p
Gender	Female Male	9 67	8 32	0.238
Age (mean)		$67.4 \pm 10.1$	$62.9 \pm 16.7$	0.124
Cigarette consumption (pack/year)		47 (35–71)	20 (4–60)	0.007
White blood cells ( $10^9/L$ )		12 (9–16)	11 (8–16)	0.549
Neutrophils ( $10^9/L$ )		$8.7 \pm 3.9$	$8.5 \pm 4.0$	0.461
Hemoglobin (g/L)		$132 \pm 25$	$119 \pm 16$	0.008
Hematocrit (%)		$41.8 \pm 7.7$	$37.8 \pm 5.0$	0.009

**Table II** Serum CRP and PCT levels of pneumonia and COPD groups.

		COPD	Pneumonia	p
CRP (mg/L)	Mean Median Range	74 44 23–379	176 132 50–519	$< 0.001$
PCT (ng/mL)	Mean Median Range	0.16 0.07 0.02–1.04	0.64 0.14 0.02–3.15	$< 0.001$



**Figure 1** Diagnostic accuracy of procalcitonin and CRP for pneumonia discrimination.

to be 0.07 in COPD group and 0.14 ng/mL in pneumonia group. Serum PCT level was significantly higher in pneumonia group compared to COPD group ( $p < 0.001$ ). In addition to this, a positive relationship was determined between PCT and CRP in all study groups ( $r = 0.55$ ,  $P < 0.001$ ) (Table II).

The area under the ROC curve was 0.788 (CI: 0.704–0.872) for CRP and 0.699 (CI: 0.599–0.800) for procalcitonin. The optimal cut-off value to identify pneumonia was 4.35 mg/dL for CRP, with a sensitivity of 0.95 and a specificity of 0.50. The optimal cut-off for procalcitonin was 0.09 with a sensitivity of 0.67 and a specificity of 0.65 (Figure 1).

When we evaluated the duration of hospital stay, the mean duration of hospital stay was  $8 \pm 4$  days in COPD group and  $10 \pm 5$  days in pneumonia group. Duration of hospital stay in pneumonia group was higher than that of patients with COPD. A significant difference was found between both groups in terms of duration of hospital stay (0.009).

## Discussion

Community-acquired pneumonia constitutes a serious problem in terms of morbidity, mortality and healthcare services, and delays in diagnosis and treatment increase complication and mortality rates (10). Early detection of infections is a significant problem for clinicians nowadays. Due to bacterial resistance, use of antibiotics for each suspected infection is not recommended and, therefore, specific markers of bacterial infections have become important in the diagnosis (11).

In our study, serum procalcitonin and CRP values were found to be significantly higher in patients

with pneumonia compared to patients diagnosed with COPD exacerbation. Additionally, it was determined that PCT correlated with CRP. Based upon these data, it can be said that PCT is not significantly different from CRP. In many studies in which serum CRP and PCT levels were compared, it was shown that CRP increases in bacterial, viral and autoimmune diseases, while PCT increases generally in bacterial infection. Therefore, serum CRP levels are more sensitive and specific in the determination of nonspecific inflammation compared to serum PCT levels (12). In patients with CAP, evaluation with PCT is important in differentiating from other noninfectious infiltrates and guiding duration of antibiotic use. PCT guidance for exacerbations in patients with COPD provides a continuous advantage in antibiotic use, compared to the standard treatment (13, 14). Considering the correlation between procalcitonin and CRP, CRP may be an alternative to procalcitonin. In a previous study, PCT and CRP showed very similar performances in the detection of bacterial origin in patients with exacerbation of COPD (15). Our results also show that PCT and CRP have similar performances in distinguishing CAP from exacerbations of COPD. In addition, the optimal CRP and procalcitonin threshold values to identify pneumonia were very close to the values reported by Bafadhel et al. (16).

Durations of hospital stays of patients with pneumonia and the ones diagnosed with COPD exacerbation were found to be different. We think that clinical approach and patient profile of the hospital involved in the study are effective in this result. Since pneumonia treatment requires 1–3 weeks of antibiotic therapy, this may be a factor for increased hospital stay of patients with pneumonia compared to COPD patients. In the study by Bafadhel et al. (16), in which they

evaluated procalcitonin and CRP in patients diagnosed with pneumonia or exacerbation of asthma or COPD, the mean hospital stay of patients diagnosed with CAP was 6 days. We, as well, found the mean duration of hospital stay of patients with CAP as 10 days in our study. In the patients diagnosed with COPD exacerbation, the mean duration of hospital stay was found to be 5 days (16). In this study, we, as well, found the duration of hospital stay in patients with COPD exacerbation as 8 days. We think that clinical approach of the hospital involved in the study may also influence the duration of hospital stay. In the study by Menedez et al. (17) the hospital type was a significant factor related to length of hospital stay.

This study has some limitations. One limitation of the study is the lack of blood culture confirmed diagnosis. Second, use of antibiotic drugs by some

patients before inclusion in this study may have altered some biomarkers. The third limitation is that we measured PCT and CRP values only once.

## Conclusion

It may be said that CRP, which is cheaper and a common marker compared to PCT, can be used in the differential diagnosis of lower respiratory tract infections and it may avoid unnecessary antibiotic use in hospitalized patients with respiratory diseases.

## Conflict of interest statement

The authors stated that they have no conflicts of interest regarding the publication of this article.

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