Research Article

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Biomarkers in Medicine

The role of presepsin in the diagnosis of chronic obstructive pulmonary disease acute exacerbation with pneumonia

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Aim: In this study, we aimed to investigate the role of presepsin in detecting concomitant pneumonia in patients presenting with acute exacerbation of chronic obstructive pulmonary disease (COPD) in the emergency department. **Patients & methods:** Three groups were formed in the study. Group 1: patients diagnosed with acute exacerbation of COPD; group 2: patients with acute exacerbation of COPD + pneumonia; group 3: healthy individuals. **Results:** Presepsin levels of the patients in group 2 were significantly higher than those of group 1 and group 3 ($p < 0.05$). There was a statistically significant difference in erythrocyte sedimentation rate, CRP, procalcitonin and presepsin values between two patient groups ($p < 0.05$). **Conclusion:** Presepsin can be used to diagnose pneumonia in patients with acute exacerbation of COPD admitted to the emergency department.

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Keywords: acute exacerbation • C-reactive protein • COPD • diagnosis • erythrocyte sedimentation rate • pneumonia • presepsin • procalcitonin

An exacerbation of chronic obstructive pulmonary disease (COPD) is defined as an acute worsening of respiratory symptoms that results in additional therapy [1,2]. In acute exacerbation of COPD, complicating events occur, such as an increase in airway inflammation and mucus production and an increase in aeration. These changes lead to an increase in dyspnea, a change in sputum volume and color, an increase in purulence, an exacerbation of cough and a high fever and/or impaired mental function [2]. Acute exacerbations of approximately one to four are observed in COPD patients every year [3]. Studies have shown that as the severity of COPD increases, the frequency of attacks increases. Infection and environmental factors play a role in the formation of acute exacerbations [4]. Bacterial and viral infections have an important role in the development of attacks [3]. However, 30% of the patients do not have a real reason to explain the exacerbation [4].

COPD is a risk factor for community-acquired pneumonia, and pneumonia is the most common cause of acute exacerbation of COPD [4]. Coexistence of COPD and pneumonia increases hospitalization and mortality rates [5]. Therefore, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline recommends initiation of antibiotics in the presence of purulent sputum in patients presenting with acute exacerbation of COPD [2].

In recent years, studies on the role of some systemic biomarkers in detecting etiology, prognosis and the risk of mortality in acute exacerbations of COPD are outstanding [6–9]. Procalcitonin and CRP are among these markers. Procalcitonin, which is accepted as a marker of bacterial infection, has been shown to correlate with the etiology and prognosis of pneumonia [6]. Procalcitonin is considered a guide in determining treatment with antibiotics because it can distinguish bacterial and viral infections [10]. CRP is an acute phase reactant that increases in cases of inflammation and infection [11]. CRP cannot differentiate bacterial infections from viral and other inflammatory

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conditions, but it is used to determine the prognosis of these conditions. CRP is much less affected in other conditions than other acute phase reactants, especially erythrocyte sedimentation rate (ESR) [11].

CD-14 is a protein of approximately 55 kDa that is present in the membranes of mononuclear cells, and it serves as a high-affinity receptor to lipopolysaccharides (LPS) and the LPS/LPS-binding protein complex (LPBP). The LPS-LPBP-CD14 complex is separated from the cell membrane and released into the circulation and forms sCD14. Another sCD14 produced by plasma protease activity is called sCD14-subtype (presepsin). Presepsin is a polypeptide with a weight of 13 kDa at the terminal end of CD14. Presepsin has no LPS-binding properties, so it cannot be captured by anti-CD14 antibodies; thus, this free molecule can be used as a biomarker. Numerous studies have shown that presepsin levels are increased in the early stages of bacteremia and sepsis, and presepsin is a biomarker that has been nominated for routine use [12–15].

Acute exacerbation of COPD is often accompanied by pneumonia, which changes the prognosis and treatment of the disease. In patients with acute exacerbation of COPD presenting to the emergency department, the diagnosis of concomitant pneumonia may be difficult.

In this study, we aimed to investigate the role of presepsin in detecting concomitant pneumonia in patients presenting with acute exacerbation of COPD to the emergency department.

Patients & methods

This observational prospective study was carried out in line with research regulations, including the approval of the Ethics Committee of our institute dated 19 March 2018 and numbered 47/10 and according to the principles of the 'World Medical Association Helsinki Declaration.' It was supported by scientific studies support board of our institute numbered 69/2.

The study included patients with acute exacerbation of COPD above 18 years of age. Patients under 18 years of age, those with malignancy, pulmonary embolism, pulmonary edema, bronchiectasis, other chronic lung disease, nonpneumonia infection and patients with sepsis were excluded from the study.

Three groups were formed in the study:

- Group 1: patients diagnosed with acute exacerbation of COPD (n = 65);
- Group 2: patients with acute exacerbation of COPD and pneumonia (n = 61);
- Group 3: healthy individuals (control; n = 44).

The healthy group was selected from volunteer patients' relatives and emergency department staff who did not have any disease. Patients who met the following criteria were diagnosed with acute exacerbation of COPD: exacerbated cough and dyspnea, increased sputum volume and increased sputum purulence.

In patients with acute exacerbation of COPD, new pulmonary infiltration in chest x-ray and/or computerized tomography (CT) was included in the COPD acute attack and pneumonia group. In addition to acute exacerbation symptoms of COPD, patients with new pulmonary infiltrations and signs of infection were included in group 2. Chest x-ray and/or CT was performed in all patients to detect pulmonary infiltration. Patients without a definite diagnosis of pneumonia and doubtful infiltrates were excluded from the study. Patients with pulmonary tuberculosis, pulmonary oedema, pulmonary thromboembolism, non-pneumonia infection were excluded. Patients using antibiotics were excluded from the study. All participants were informed about the study.

The patient's symptoms, vital signs, co-morbidities, demographic characteristics, symptoms and physical examination findings, laboratory results, imaging findings and treatments were recorded in the study form. There was no intervention in the follow-up and treatment of the patients. In addition to the routine blood tests performed for the patients, 5 ml of blood was taken from the patients to determine the serum presepsin level. Blood samples of the patients were collected at the time of admission to the emergency department before treatment was started. Blood samples were taken from healthy subjects only for presepsin levels. Blood samples taken from the patients were centrifuged at 3000 r.p.m. for 15 min, and the serum was pipetted into Eppendorf tubes and stored at -80°C until they were assayed. Serum presepsin levels were measured by ELISA, MBS766136, 0.1156–10 ng/ml in the biochemistry laboratory using a kit with a sensitivity of less than 0.094 ng/ml.

Other inflammatory markers (ESR, procalcitonin, CRP) were studied in the hospital laboratory with routine blood samples. Samples were tested for ESR (range: 0–20 mm/h) using a brand test 1 model device (Alifax S.p.A, Padova, Italy) with the Westergren method. CRP (range: 0–0.5 mg/dl) was studied in a Beckman Coulter Image 800 device (Beckman Coulter, CA, USA) with the nephelometric method. Procalcitonin was studied in an AQT90FLEX

analyzer device (Radiometer Medical Aps, Copenhagen, Denmark) with the time-resolved Fluorescence method (range: <0.05 μg/l).

Sputum samples of the patients were taken during the follow-up in the emergency department. Samples of sputum and tracheal aspirate were studied in our microbiology laboratory. Because of the intensity of the emergency room, only patients with acute exacerbation of COPD and pneumonia could be sampled for sputum culture. Stable COPD patients could not be included in the study because of the study was performed in the emergency department. This may have limited our study.

Statistical method

For the statistical analysis of the data obtained, the SPSS (Statistics Program for Social Scientists) 24, 0 program was used. When the power analysis of the cases was performed, sufficient cases were reached between healthy and patient cases. The Mann–Whitney U test was used to compare the data that did not fit the normal distribution among the groups, and Student's t test was used to compare the normally distributed data. $p < 0.05$ was considered statistically significant. A χ^2 test was used to compare frequency data between two groups. $p < 0.05$ was considered statistically significant.

The Kruskal–Wallis test was used to compare three groups (acute exacerbation of COPD, acute exacerbation of COPD and pneumonia, healthy subjects) because the presepsin levels did not conform to a normal distribution. *Post hoc* analysis was performed with the Bonferroni test. Correlation between presepsin and inflammatory markers was investigated. The Spearman test was used to examine correlations. Med Calc statistical program was used for the receiver operating characteristic (ROC) analysis.

Results

The study included 126 patients and 44 healthy individuals. While 51.6% (n = 65) of the patients were diagnosed with acute exacerbation of COPD, 48.4% (n = 61) were diagnosed with acute exacerbation of COPD + pneumonia. There were 26 female and 39 male patients with acute exacerbation of COPD. There were 27 female and 34 male patients with acute exacerbation of COPD + pneumonia. Of the 126 patients, 42.1% were female and 57.9% were male. The mean age of the patients with acute exacerbation of COPD (group 1) was 66.35 ± 13.1 (min 31–max 95); the mean age of the patients with COPD acute exacerbation + pneumonia (Group 2) was 72.82 ± 11.38 (min 40–max 91). The mean values of age and vital signs of all patients included in the study are shown in Table 1. A statistically significant difference was found between the ages of group 1 (COPD acute exacerbation) and group 2 (COPD acute exacerbation + pneumonia; $p < 0.05$; Table 1). There was a significant but weak correlation between presepsin and the ages of the cases ($p = 0.001$; r: 0.282). There was no significant difference between groups for systolic blood pressure, diastolic blood pressure, pulse, fever, respiratory rate or oxygen saturation ($p > 0.05$; Table 1). Significant correlations were found between presepsin and systolic BP ($p = 0.024$; r: -0.201), diastolic BP ($p = 0.035$; r: -0.182), pulse ($p = 0.008$; r: 0.235), fever ($p = 0.027$; r: 0.197), oxygen saturation ($p = 0.001$; r: -0,282). There was no correlation between presepsin and respiratory rate.

Hypertension was the most common cause of co-morbid diseases, with a prevalence of 42.9% in the patients included in the study, followed by diabetes with a prevalence of 20.6% (Table 2). There was no statistically significant difference in co-morbidity between the groups ($p > 0.05$).

61 of the patients included in the study were active smokers. There was no significant difference between presepsin levels of smokers (5.33 ± 5.3; min: 0.1–max: 27.8) and nonsmokers (6.16 ± 5.9; min: 0.1–max: 27.8; $p = 0.4$). No significant difference was found between the two patient groups in terms of smoking, presence of oxygen condensers, living in a home for the aged or history of intubation. In addition, 51.6% of the total patients were using oxygen condensers at home. The rate of smoking among all patients was 48.4%. There was no statistically significant difference in corticosteroid and β2 agonist drug use between the two groups (Table 2). When the symptoms of the cases were examined, cough was found in 65.1%, followed by sputum in 63.5% of patients. There was a significant difference only in cracles in terms of physical examination findings ($p < 0.05$; Table 2).

Chest x-ray and CT were performed in 53 patients. Chest x-ray was performed in 73 patients. In the COPD + pneumonia group, 67.2% (n = 41) of the patients had x-ray + tomography and 32% (n = 20) had chest x-ray.

There was a significant difference between the two patient groups in terms of white blood cells (WBC), urea, creatine and PCO_2 values ($p < 0.05$). There was no statistically significant difference between the other blood parameters ($p > 0.05$; Table 1). Significant correlations were found between presepsin and WBC ($p = 0.015$; r:

Table 1. Comparison of age, vital signs and laboratory values between patient groups.

Vital signs and laboratory values	Acute exacerbation of COPD (n = 65)	Acute exacerbation of COPD + pneumonia (n = 61)	p-value
Age (years)	66.3 ± 13.1 (31–95)	72.8 ± 11.4 (40–91)	0.003*
Systolic blood pressure (mm/Hg)	134.1 ± 27.1 (90–220)	122.4 ± 21.5 (70–170)	0.44
Diastolic blood pressure (mm/Hg)	76.83 ± 13.84 (50–113)	71.18 ± 13.30 (40–115)	0.20
Pulse rate/minute	93.64 ± 18.84 (18–130)	100 ± 19.60 (69–150)	0.12
Body temperature	36.82 ± 0.528 (36–38.5)	37.1 ± 0.94 (35.6–95)	0.214
Respiratory rate/minute	21.58 ± 4.05 (12–32)	20.57 ± 3.60 (12–30)	0.252
Pulse oxygen saturation	86.44 ± 11.85 (52–100)	84.3 ± 10.88 (54–99)	0.130
White blood cell	10,173 ± 3502 (4500–20,000)	13,555 ± 6875 (4800–41,200)	0.001*
Hemoglobin	13.85 ± 2.168 (7.5–18.20)	13.31 ± 2.28 (7.2–17.9)	0.122
Hematocrit	42.50 ± 8.53 (4.80–58.80)	41.68 ± 7.39 (23.10–59.80)	0.339
Platelets	235,507 ± 81,641 (68,000–518,000)	260,278 ± 128,783 (98 000–676,000)	0.712
Urea	47.69 ± 28.39 (13–155)	61.32 ± 36.13 (16–208)	0.014*
Creatinine	1.06 ± 0.336 (0.61–1.94)	1.33 ± 0.889 (0.52–6.97)	0.029*
AST	104.5 ± 465.53 (9–3388)	40.73 ± 51.50 (13–340)	0.213
ALT	103.2 ± 479.65 (6–3520)	36.86 ± 65.66 (5–336)	0.498
Glucose	134.33 ± 53.24 (52–360)	155.09 ± 74.56 (82–495)	0.096
Sodium	136.47 ± 3.67 (125–142)	135.83 ± 4.52 (124–145)	0.272
Potassium	4.44 ± 0.571 (3.30–6.14)	4.55 ± 0.719 (3.06–6.03)	0.253
pH	7.34 ± 0.83 (7.07–7.70)	7.34 ± 0.84 (7.17–7.51)	0.758
SpO_2	64.80 ± 22.59 (15–97.9)	64.57 ± 22.68 (12.7–98.2)	0.973
PaO_2	46.2 ± 22.16 (15.6–135)	43.95 ± 17.50 (1.90–91.30)	0.903
PCO_2	58.76 ± 15.26 (29.20–96.80)	52.81 ± 16.86 (22.80–96.20)	0.048*
FEV1 %	46.5 ± 21.1 (12.6–91.7)	51.6 ± 18.4 (22.2–95.3)	0.23
FEV1/FVC %	47.01 ± 14.4 (53.5–69.4)	47.5 ± 15.4 (34.7–69.2)	0.8
GOLD stage	2.8 ± 0.9 (1–4)	2.5 ± 0.7 (1–4)	0.15†
Number of exacerbation in the previous 12 months	3 ± 6 (0–29)	3 ± 7 (0–34)	0.28

Data was shown as mean ± SD (min–max) unless otherwise stated. p-values were calculated by Mann–Whitney U test.
†Student's t test.
*Statistically significant p-values (<0.05).
COPD: Chronic obstructive pulmonary disease; FEV1: Forced expiratory volume in 1 s; FVC: Forced vital capacity; GOLD: Global initiative for chronic obstructive lung disease; PaO_2: Partial oxygen pressure; PCO_2: Partial carbon dioxide pressure; SD: Standard derivation; SpO_2: Oxygen saturation.

0.282), hemoglobin (p = 0.014; r: -0.219), hematocrit (p = 0.016; r: -0.215), urea (p = 0.000; r: 0.443), creatinine (p = 0.000; r: 0.438), AST (p = 0.000; r: 0.318), sodium (p = 0.001; r: -0.303), potassium (p = 0.005; r: 0.251). There was no correlation between presepsin and glucose, ALT, platelets and blood gas values.

There was no statistically significant difference in forced expiratory volume in 1 s (FEV1; p = 0.23), FEV1/forced vital capacity (FVC; p = 0.8), GOLD (p = 0.15) between the groups (Table 1). According to the GOLD staging, 8% of the patients were stage 1, 32% were stage 2, 44% were stage 3 and 16% were stage 4.

There was no significant correlation between the levels of presepsin and FEV1 (r = 0.248; p = 0.08), FEV1/FVC (r = 0.121; p = 0.40).

The mean number of exacerbation in the previous 12 months was 3 ± 6 (min 0–max 34). There was no significant difference in the number of exacerbation in the previous 12 months between the groups (p = 0.28; Table 1). The exacerbations of the patients included in the study were not added to these numbers.

The values of ESR, CRP and procalcitonin were compared statistically between groups. ESR, CRP and procalcitonin values were significantly higher in the COPD acute exacerbation + pneumonia group ($p < 0.05$; Table 3).

Presepsin levels were significantly higher in the COPD acute exacerbation + pneumonia group than in the COPD acute exacerbation group ($p < 0.05$; Table 3 & Figure 1). Presepsin levels of the three groups were compared statistically, and a statistically significant difference was determined ($p < 0.05$). A *post hoc* analysis Bonferroni test was used to determine by which groups the difference was caused. The level of presepsin in the

Table 2. Demographic characteristics of the patients.

Characteristics	All patients (n = 126)	Acute exacerbation of COPD (n = 65)	Acute exacerbation of COPD + pneumonia (n = 61)	p-value
Co-morbidity				
Diabetes mellitus	26 (20.6)	14 (21.5)	12 (19.7)	0.80
Hypertension	54 (42.9)	24 (36.9)	30 (49.2)	0.16
Cardiovascular disease	37 (29.4)	19 (29.2)	18 (29.5)	0.97
Congestive heart failure	26 (20.6)	11 (16.9)	15 (24.6)	0.29
Cerebrovascular disease	3 (2.4)	2 (3.1)	1 (1.6)	0.6
Chronic renal disease	8 (6.3)	4 (6.2)	4 (6.6)	0.92
History				
Smoker	61 (48.4)	32 (49.2)	29 (47.5)	0.85
Use of oxygen condenser (supplemental oxygen)	65 (51.6)	33 (50.8)	32 (52.5)	0.85
Stay in the nursing home	15 (11.9)	4 (6.2)	11 (18.0)	0.40
History of intubation	2 (1.6)	1 (1.5)	1 (1.6)	0.96
Use of β2 agonist	92 (73)	50 (76.9)	42 (68.8)	0.29
Use of corticosteroid	78 (61.9)	42 (64.6)	36 (59)	0.47
Symptoms and physical examination findings				
Increase of sputum production	80 (63.5)	39 (60.0)	41 (67.2)	0.4
Cough	82 (65.1)	42 (64.6)	40 (65.6)	0.91
Fever	41 (32.5)	20 (30.8)	21 (34.4)	0.66
Increase of sputum purulence	31 (24.6)	16 (24.6)	15 (24.6)	0.99
Wheezing	65 (51.6)	44 (67.7)	21 (34.4)	0.91
Crackles	68 (54)	20 (30.8)	48 (78.6)	0.04*
Mortality	36 (28.6)	20(30.8)	16 (26.2)	0.57

Data is shown as n (%) unless other wise stated. p-values were calculated by χ^2, $p < 0.05$ statistical significant.
*p-values statistically significant.
COPD: Chronic obstructive pulmonary disease.

Table 3. Comparison of inflammatory markers of patients.

Inflammatory markers	Acute exacerbation of COPD (n = 65)	Acute exacerbation of COPD + pneumonia (n = 61)	p-value
Presepsin (ng/ml)	3.62 ± 3.08 (0.1–18.8)	8.03 ± 6.69 (0.2–27.8)	<0.001
Procalcitonin (ng/ml)	1.09 ± 6.94 (0–56)	5.65 ± 16.37 (0–100)	<0.001
CRP (mg/l)	44.54 ± 60.03 (0.48–299)	98.43 ± 82.99 (7.35–312)	<0.001
ESR (mm/h)	26.66 ± 19.0 (2–90)	36.03 ± 25.06 (120)	0.03

Data shown as mean ± SD (min–max) unless otherwise stated. p-values were calculated by Mann–Whitney U test, $p < 0.05$ statistically significant.
COPD: Chronic obstructive pulmonary disease; ESR: Erythrocyte sedimentation rate; SD: Standard derivation.

Table 4. Relationship of presepsin with mortality and other inflammatory markers.

Presepsin		ESR	CRP	Procalcitonin
Presepsin	r	0.209	0.482	0.590
	p	0.02	<0.001	<0.001

Spearman correlation test, $p < 0.05$ statistically significantly.
ESR: Erythrocyte sedimentation rate.

group with acute exacerbation of COPD acute exacerbation + pneumonia was statistically significantly higher than the levels in both the healthy group and in the COPD acute exacerbation group ($p < 0.001$; Figure 1).

A significant positive correlation was found between the levels of presepsin and ESR, CRP and procalcitonin (Table 4).

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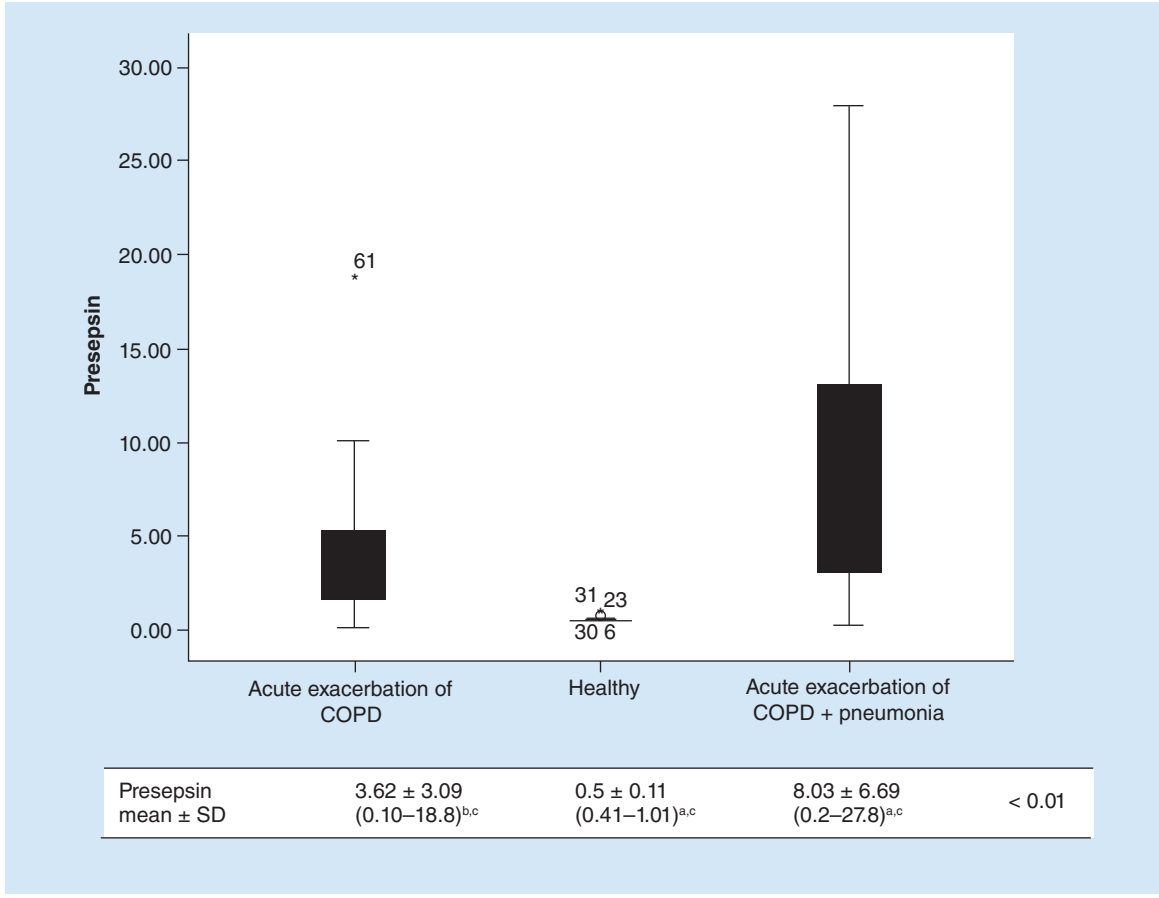

Figure 1. Comparison of presepsin levels between three groups. [a]Indicates the statistical difference to acute exacerbation of COPD. [b]Indicates the statistical difference to acute exacerbation of COPD + pneumonia, [c]Indicates the statistical difference to healthy individual. Kruskal Wallis Test, $p < 0.05$ statistical significant, post hoc Benforrini test was used.
COPD: Chronic obstructive pulmonary disease.

Table 5. Presepsin levels in patients with and without mortality.

Groups	Patients with mortality	Patients without mortality	p-value
All patients	6.36 ± 5.53 (0.1–18.4)	5.52 ± 5.63 (0.1–27.8)	0.33
AECOPD	3.98 ± 2.77 (0.1–10)	4.47 ± 3.23 (0.1–18.8)	0.33
AECOPD + Pneumonia	9.33 ± 6.69 (1.2–18.40)	7.57 ± 6.71 (0.2–27.8)	0.35

Data shown as mean ± SD (min–max) unless otherwise stated. p-values were calculated by Mann–Whitney U test, $p < 0.05$ statistically significant.
AECOPD: Acute exacerbation of chronic obstructive pulmonary disease; ESR: Erythrocyte sedimentation rate; SD: Standard derivation.

Receiver operating characteristic (ROC) analysis was performed for the ability of presepsin and other inflammatory markers to determine the possibility of pneumonia in COPD patients. The area under the curve (AUC) site was the highest in CRP, followed by procalcitonin, presepsin and ESR (Table 5 & Figure 2). The AUC area of the presepsin was 0.70, and the cut-off value was 7. When the cut-off value of 7 was used, the specificity of the presepsin was 92.31% and the sensitivity was 42.62% (Table 5).

The mortality rate was 28.6% (n = 36). The mortality rate in group 1 (acute exacerbation of COPD) was 30.8% (n = 20), while in group 2 (COPD acute exacerbation and pneumonia), the mortality rate was 26.2% (n = 16). There was no statistically significant difference between the two groups in terms of mortality ($p > 0.05$; Table 2). In addition, presepsin levels in patients with and without mortality were compared in all cases. There was no statistically significant difference in presepsin levels between the groups with and without mortality in

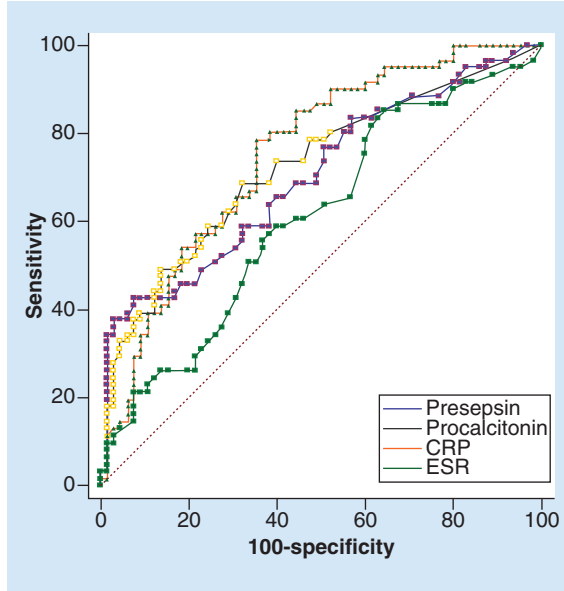

Figure 2. Comparison of presepsin, procalcitonin, CRP and erythrocyte sedimentation rate values for receiver operating characteristic curves in determining pneumonia.
ESR: Erythrocyte sedimentation rate.

Table 6. Receiver operating characteristic analysis of inflammatory biomarkers to determine the possibility of pneumonia in chronic obstructive pulmonary disease patients.

Inflammatory Markers	AUC	Sensitivity	Specificity	Cut-off	SE	95% CI
Presepsin	0.70	42.62	92.31	7	0.0467	0.613–0.780
Procalcitonin	0.72	68.85	67.69	0.16	0.0447	0.636–0.799
CRP	0.75	78.69	64.62	25.7	0.0431	0.668–0.826
ESR	0.62	85.25	35.38	15	0.0505	0.518–0.695

AUC: Area under the curve; ESR: Erythrocyte sedimentation rate; SE: Standard Error.

Table 7. Comparison of inflammatory markers according to sputum culture results.

Inflammatory markers	Culture negative (n = 37)	Culture positive (n = 15)	p-value
Presepsin (ng/ml)	8.21 ± 6.30 (1.20–27.8)	8.14 ± 8.91 (0.6–27.8)	0.57
Procalcitonin (ng/ml)	3.05 ± 6.14 (0–22)	11.41 ± 33.22 (0–100)	0.71
CRP (mg/l)	116.66 ± 100.01 (9.2–312)	107.3 ± 82.63 (23.8–236)	0.96
ESR (mm/h)	35.00 ± 22.97 (3–78)	46.44 ± 31.43 (17–120)	0.40

p-values were calculated by Mann–Whitney U test.
ESR: Erythrocyte sedimentation rate; SD: Standard Derivation

the COPD acute exacerbation + pneumonia group. The same results were obtained in the acute exacerbation of COPD group (Table 4).

Sputum or tracheal aspirate samples were taken from 52 patients with COPD acute exacerbation + pneumonia, and the cultures were studied. In all, 32.7% (n = 17) of the patients had no growth in their cultures. Normal respiratory tract flora was found in 38.5% (n = 20) of the patients, and 28.8% (n = 15) of the patient cultures showed growth of pathogen microorganisms. The groups with positive cultures and negative cultures + normal respiratory flora was compared with each other. No statistically significant difference was found between the two groups in presepsin (p = 0.57), procalcitonin (p = 0.71), CRP (p = 0.96) or ESR (p = 0.40; Table 6). In the 20 blood cultures performed, no growth was observed.

The distribution of pathogenic microorganisms was as follows: Gram-negative microorganisms were obtained in eight patients (*Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia, Acinotobacter haemolyticus, Klebsiella Pneumoniae, Gram-negative laktobasil, Hemofilus influenza*), Gram-positive microorganisms in six patients (*Streptococcus pneumonia*, *Staphylococcus aureus*) and *Candida albicans* in one case. No statistically significant difference was found

Table 8. Comparison of inflammatory markers according to sputum culture results.

Inflammatory markers	Gram-negative bacteria (n = 8)	Gram-positive bacteria (n = 6)	p-value
Presepsin (ng/ml)	7.42 ± 6.67 (0.6–17.7)	9.32 ± 9.67 (1.5–27.8)	0.67*
Procalcitonin (ng/ml)	7.98 ± 21.82 (0–62)	17.31 ± 40.52 (0–100)	0.65
CRP (mg/l)	122.25 ± 90.95 (23.8–285)	167.19 ± 127.95 (7.87–312)	0.46*
ESR (mm/h)	48 ± 33.4 (17–120)	46.7 ± 32.8 (2–82)	0.94*

p-values were calculated by Mann–Whitney U test.
*Student's t test, $p < 0.05$ statistically significant.
ESR: Erythrocyte sedimentation rate; SD: Standard Derivation

between presepsin levels of patients with pneumonia due to Gram-positive (9.32 ± 9.67; min: 1.5–max: 27.8) and Gram-negative (7.42 ± 6.67; min: 0.6–max: 17.7) bacteria (p = 0.67; Table 6).

Discussion

In our study, we wanted to investigate the role of presepsin as a new infectious mediator in patients with acute exacerbation of COPD. We evaluated the relationship of presepsin with procalcitonin and acute phase reactants (ESR and CRP), which are accepted markers used for antibiotic usage guidelines in bacterial infections.

In many studies reported that CRP and procalcitonin levels were significantly higher in the COPD exacerbation with pneumonia group compared with those of the COPD exacerbation group [7,8]. Taghizadieh *et al.* compared CRP and procalcitonin biomarkers in patients with COPD exacerbation and community-acquired pneumonia. They found a statistically significant difference in procalcitonin in the community-acquired pneumonia group compared with the COPD group but reported no significant difference in CRP values [9]. In a study by Klouche *et al.*, patients with acute respiratory failure, patients with sepsis due to pneumonia and noninfectious patients were compared. CRP and procalcitonin (cut-off: 0.5 ng/ml) were significantly higher in patients with sepsis due to pneumonia [16]. Since CRP and procalcitonin infection markers were accepted, most of the studies found these markers to be higher in patients with COPD + pneumonia. Both parameters are used to determine the presence of infection in patients presenting with acute exacerbation of COPD. In our study, procalcitonin and CRP levels in the COPD acute exacerbation + pneumonia group were found to be statistically significant. However, there are other studies in the literature with differing findings. Kawamatawong *et al.* did not find a significant difference in procalcitonin and CRP levels between bacterial infections and other etiologies (viral and noninfectious) in patients with acute exacerbations of COPD. They stated that the small number of patients in their study may have affected this result [10].

It has been shown in many studies that ESR, an inflammatory marker, is increased in COPD acute exacerbations and community-acquired pneumonia [17–20]. However, we did not find any study comparing ESR levels in patients with pneumonia in COPD acute exacerbation and in patients with acute exacerbation of COPD. In a study performed in COPD patients with lower respiratory tract infection, Van Beurden *et al.* reported that ESR increased and that this increase decreased with treatment [19]. In our study, ESR was found to be statistically higher in the group of patients with COPD acute exacerbation and pneumonia compared with the group without pneumonia. Acute exacerbation of COPD with increased inflammation is associated with pneumonia, leading to a further increase in ESR.

In this study, compared with healthy people and patients with acute exacerbation of COPD, presepsin was significantly higher in the acute exacerbation of COPD group. In the literature, there was no study showing the level of presepsin in patients with acute exacerbation of COPD. However, recent studies have shown that the level of presepsin increases during inflammation and infection [16,21]. High levels of presepsin in COPD may be attributed to acute exacerbation characterized by increased inflammatory mediators and airway inflammation. This may be the reason why presepsin levels increase above the cut-off value (7 ng/ml) in some of the patients with acute exacerbation of COPD. Since we performed the study in the emergency department, we could not include stable COPD patients. The lack of stable COPD patients has limited our study. More studies are needed to fully evaluate the potential role of presepsin in the diagnosis of acute exacerbation of COPD.

We compared the value of presepsin in acute exacerbation of COPD and acute exacerbation of COPD + pneumonia groups. The value of serum presepsin was significantly higher in patients with acute exacerbation of COPD with pneumonia. No similar study was found in the literature. However, Klouche *et al.* compared the levels of presepsin to differentiate patients with sepsis and noninfectious respiratory failure [16]. Presepsin (cut-off value:

588 pg/ml) was found to be significantly higher in patients with sepsis due to pneumonia [16]. There are also reports in the literature that presepsin can be used in the diagnosis and prognosis of patients with pneumonia [16,22,23]. In one study, Liu *et al.* investigated the role of presepsin in determining the severity of community-acquired pneumonia; they found that presepsin levels in patients with severe pneumonia were significantly higher than those in the other pneumonia cases [22]. In a study by Qi *et al.*, the levels of blood presepsin between community-acquired bacterial pneumonia and active tuberculosis patients were compared. In this study, the presepsin level of the pneumonia group was found to be significantly higher than that of the active tuberculosis group [23]. Proteolysis of sCD14 released into the circulation by cathepsin leads to presepsin formation. Thus, presepsin levels in the blood can indicate inflammation and infection. Presepsin can be detected in the blood as long as the infection continues. Presepsin, which may increase in acute exacerbation of COPD due to inflammation, was significantly increased with the addition of pneumonia.

It has been shown in several studies that concentrations of presepsin increase with age and renal impairment [24,25]. In the present study, there was a significant but weak correlation between presepsin and the ages of the cases. In additionally, the statistically significant difference was found between the ages of group 1 (COPD acute exacerbation) and group 2 (COPD acute exacerbation + pneumonia). The effect of age on the difference between presepsin levels of these two groups should also be considered. Age should be considered in the interpretation of presepsin levels and threshold values should be established accordingly.

Huerta *et al.* have reported that corticosteroid use affects patients' inflammatory markers [7]. In our study, no significant difference was found between the two groups in terms of corticosteroid use. Therefore, we think that steroid has no role in the levels of presepsin and other inflammatory markers.

Titova *et al.* examined the area under the ROC curve of procalcitonin (0.67) and CRP (0.73) to detect pneumonia [8]. In our study, the highest AUC value was found in CRP (AUC = 0.75), in accordance with the literature. In our study, the values of procalcitonin, ESR and presepsin were found to be 0.72, 0.61 and 0.70, respectively. In the study by Klauche *et al.*, presepsin and procalcitonin tests were performed for the diagnosis of pneumonia in patients admitted to the intensive care unit with acute respiratory failure. As a result of the analysis, the AUC value of presepsin was 0.75, the sensitivity was 81% and the specificity was 80%. The AUC value of procalcitonin was 0.82, the sensitivity was 69% and the specificity was 80% [16]. Klauche *et al.* found that both presepsin and procalcitonin AUC values were higher than those in our study. We attributed this difference to the fact that in the Klauche *et al.* study, all the patients with pneumonia were patients with sepsis. In recent studies, levels of presepsin were found significantly higher in septic than in nonseptic patients or those with systemic inflammatory response syndrome. Moreover, a specific increase was reported in the early stage of sepsis that also well correlated with severity. Especially in severe sepsis, impaired renal function and bleeding parameters increase presepsin levels more [16,26,27]. Since sepsis and septic shock patients were not included in this study, the levels of inflammatory markers may not be increased further.

In this study; FEV1, FEV1/FVC and GOLD values of the patients in the two groups were similar. Additionally, there was no relationship between the severity of COPD and presepsin levels. Therefore, we do not think that the degree of COPD affects the level of presepsin in our study.

In the study by Klauche *et al.*, patients with sepsis who had severe pneumonia had significantly higher values of presepsin and procalcitonin than those living with sepsis alone. There was no statistically significant difference in CRP values [16]. In our study, no significant difference was found in terms of mortality in both groups. We think that the result of the study by Klauche *et al.* was because all patients had severe pneumonia with sepsis. We did not include sepsis patients in the study.

Lacoma *et al.* reported that 39% of the patients with COPD exacerbations had normal flora, 35% had pathogen microorganisms and 24% had no growth in culture [6]. They found no significant difference in procalcitonin and CRP levels when compared with the normal flora + culture-negative and culture-positive groups. They did not find any significant difference between the etiologies of infection for either marker [6]. Titova *et al.* reported that in the sputum cultures of COPD patients with acute exacerbation and patients with COPD acute exacerbation + pneumonia, 27% had normal flora microorganisms and 30% had pathogenic microorganisms. They also showed that 42% of the patients were infected with viruses. Procalcitonin levels and these pathogens have not been reported to be correlated statistically. There was no growth in the blood cultures of the patients [8]. Our study was consistent with the above studies; 32.7% of the patients had no growth in culture. Normal respiratory tract flora was found in 38.5% of the patients, and 28.8% of the patients developed pathogen microorganisms. In the culture, the pathogen-producing group and the nonpathogen groups were compared; no statistically significant difference

was found for presepsin, procalcitonin, CRP or ESR levels. Endo *et al*. reported that there was no significant difference between presepsin levels in infections due to Gram-positive and Gram-negative pathogens [28]. Our results were consistent with this study. These findings indicate that infection and colonization cannot be differentiated according to culture results. In addition, none of the inflammatory markers used seems to be useful in determining the etiology of infection.

Conclusion

ESR, CRP, procalcitonin and presepsin levels were significantly higher in patients with COPD acute exacerbation + pneumonia compared with those of patients with isolated COPD acute exacerbation. Presepsin was significantly correlated with the other three inflammatory markers.

As a result, presepsin can be used to diagnose pneumonia in patients with acute exacerbation of COPD admitted to the emergency department.

Summary points

- The level of presepsin in the group with acute exacerbation of chronic obstructive pulmonary disease (COPD) + pneumonia was statistically significantly higher than the levels in both the healthy group and in the COPD acute exacerbation group. Presepsin levels were significantly higher in the COPD acute exacerbation + pneumonia group than in the COPD acute exacerbation group.
- Erythrocyte sedimentation rate (ESR), CRP and procalcitonin values were significantly higher in the COPD acute exacerbation + pneumonia group.
- A significant positive correlation was found between the levels of presepsin and ESR, CRP and procalcitonin.
- ROC analysis was performed for the ability of presepsin and other inflammatory markers to determine the possibility of pneumonia in COPD patients. The AUC area was the highest in CRP, followed by procalcitonin, presepsin and ESR.
- The groups with positive cultures and negative cultures + normal respiratory flora were compared with each other. No statistically significant difference was found between the two groups in inflammatory markers.

Author contributions

The authors contributed equally to this study. Constructing an idea or hypothesis for research: S Özkan, A Halıcı. Planning methodology: S Özkan, A Halıcı. Data collection: A Halıcı, İ Hür, K Abatay, F Halıcı. Biochemical analysis: E Çetin. Statistical analysis: S Özkan. Writing: A Halıcı, S Özkan.

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Ethical conduct of research

This observational prospective study was carried out in line with research regulations, including the approval of the Ethics Committee of our institute dated 19/03/2018 and numbered 47/10 and according to the principles of the 'World Medical Association Helsinki Declaration.'

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