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ORIGINAL RESEARCH

Comparison of the value of different biomarkers as diagnostic and prognostic markers in AECOPD

Serkan Doğan[1,*], Türker Demirtakan[2], Efe Demir Bala[1], Ayşe Fethiye Basa Kalafat[1], Mahmut Kerem Avşaroğlu[1], Ramiz Yazıcı[1], Salih Fettahoğlu[1], Rabia Birsen Tapkan[1], Hilmi Kaya[1], Utku Murat Kalafat[1]

[1]Department of Emergency Medicine, Kanuni Sultan Suleyman Training and Research Hospital, University of Health Sciences, 34303 Istanbul, Turkey
[2]Department of Emergency Medicine, Taksim Training and Research Hospital, University of Health Sciences, 34433 Istanbul, Turkey

***Correspondence**
serkan.dogan2@sbu.edu.tr
(Serkan Doğan)

Abstract

Background: Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are a significant cause of admissions to emergency departments (ED) and play a key role in morbidity and mortality rates on a global scale. Patients with AECOPD are frequently treated by emergency medicine (EM) physicians who must accurately predict the severity and potential outcomes of these cases. Treatment decisions and the extent of intervention provided often hinge on these predictions. In our study, we aimed to evaluate and compare the efficacy of different biomarkers—Procalcitonin (PCT), Pro-Brain Natriuretic Peptide (Pro-BNP) and C-Reactive Protein (CRP)—in determining the severity and prognosis of AECOPD. **Methods**: We examined the data of 196 selected patients diagnosed with AECOPD who were admitted to our ED between 15 February 2023 and 15 February 2024. The Receiver Operating Characteristic (ROC) curve was used to demonstrate the sensitivity and specificity of the relevant biomarkers. **Results**: Pro-BNP was found to be a significant predictor for severe AECOPD at $\geq$1350 ng/L and for mortality at $\geq$1500 ng/L (the area under curve (AUC): 0.653, 0.758). PCT showed lower predictive performance for mortality compared to Pro-BNP (AUC: 0.627). Although CRP levels were elevated in both severity and mortality groups, it did not demonstrate significant differences in predicting disease severity or mortality. **Conclusions**: Pro-BNP and PCT hold promise as crucial biomarkers for the management of AECOPD. They could enable prompt initiation of advanced treatment and enhance the overall care for individuals with AECOPD. **Clinical Trial Registration**: The study was registered on ClinicalTrials.gov (NCT06514599).

Keywords

Chronic obstructive pulmonary disease; Exacerbations; Pro-BNP; Procalcitonin

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is an important health concern worldwide and causes serious mortality and morbidity. While the frequency of COPD may vary among nations, an estimated 480 million individuals were projected to have been impacted by the disease in 2020 [1].

COPD is defined by a persistent and irreversible inflammation in the airways, pulmonary vasculature and lung tissue. In the course of the disease, individuals may experience a persistent presence of symptoms such as cough, shortness of breath and sputum production. Additionally, COPD exacerbations may occur due to seasonal variations, impacting the patient's quality of life and potentially straining health care systems globally [2].

Frequent acute exacerbations have been found to be associated with poorer health status and higher mortality in patients [3]. COPD exacerbations are diagnosed with a detailed medical history, physical examination and necessary diagnostic tests. As per the 2024 guidelines from the Global Initiative for Chronic Obstructive Lung Disease (GOLD), essential diagnostic tests for identifying and categorizing a patient with a tentative diagnosis of a COPD exacerbation include the Visual Analogue Scale (VAS) dyspnea score, respiratory rate, heart rate, resting oxygen saturation, arterial blood gas analysis and levels of C-reactive protein (CRP) [2].

There are studies mentioning CRP and Procalcitonin (PCT) levels as independent diagnostic biomarkers for asthma and COPD exacerbations [3]. Some research findings also align with the concept of utilizing CRP and PCT levels as standalone biomarkers to direct antibiotic treatment in such patients [2, 4]. Apart from these indicators, Pro Brain Natriuretic Peptide (Pro-BNP) has emerged as a promising biomarker for forecasting the outlook of COPD patients. Numerous studies have indicated its potential efficacy, whether utilized alone or in conjunction with other cardiac biomarkers [5].

In this study we have aimed to compare the efficacy of CRP, PCT and Pro-BNP as prognostic markers in COPD patients to assess disease severity and predict mortality. We focused specifically on PCT and Pro-BNP and if there is any potential superiority of these biomarkers against CRP while evaluating COPD exacerbation patients.

2. Materials and methods

2.1 Study design and settings

This prospective, observational study was conducted in the emergency department (ED) of a tertiary care referral center located in the western part of Istanbul. On a daily basis, the ED attends to around 80–100 patients who exhibit a range of critical conditions that endanger their lives. Respiratory problems such as difficulty breathing, shortness of breath and sudden lung issues are commonly seen as the primary reasons for emergency hospitalizations in our facility. To ensure prompt and life-saving treatments, the ED is outfitted with a comprehensive critical care unit and specialized resuscitation zones. As a result, the research was carried out in an environment that offers top-notch infrastructure to address exacerbations in patients with COPD.

All patients included in the study had a prior diagnosis of COPD confirmed by a specialist. The patients were classified into three groups—mild, moderate and severe exacerbations—based on the GOLD 2024 guidelines. Classification depended on various factors such as the severity of breathlessness, heightened cough, increased sputum production, rapid breathing, rapid heart rate and pertinent laboratory results. As per the GOLD 2024 recommendations, distinguishing mild from moderate exacerbations involves meeting a minimum of three out of the five specified criteria. Similarly, differentiating between moderate and severe exacerbations is established by the presence of acidosis alongside the onset or exacerbation of hypercapnia [2].

Furthermore, the mortality condition of patients was evaluated throughout their hospitalization. Hospital stay duration was specified as the period from admission to release, with those discharged within 24 hours categorized as having a one-day stay. The ventilation assistance given to patients was also identified based on the GOLD 2024 guidelines [2]. Patients suffering from respiratory acidosis, respiratory muscle fatigue, increased work of breathing, paradoxical abdominal motion and intercostal retractions received non-invasive mechanical ventilation (NIMV). In cases where NIMV was insufficient or contraindicated, invasive mechanical ventilation (IMV) was used.

Patients received detailed information about their medical condition and the scientific context of the research. In cases where a patient was incapable of giving consent (such as being unconscious), permission was obtained from a legal representative acting on their behalf. The study protocol was carried out following the principles outlined in the Declaration of Helsinki. In preparing the manuscript, we followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines to enhance the accuracy and completeness of our reporting. The study received ethical approval from the institutional ethics committee of our hospital (Approval date: 08 February 2023, Approval No: KAEK/2023.02.21) and was registered on ClinicalTrials.gov (NCT06514599).

2.2 Selection of participants

The patients for this study were recruited from the ED between 15 February 2023 and 15 February 2024. A data collection form was developed for each patient to create a research database. This form included measurements taken upon admission, such as oxygen saturation (without supplemental oxygen), heart rate (in beats per minute), blood pressure (with separate systolic and diastolic values), body temperature, electrocardiogram (ECG) and respiratory rate. Furthermore, a comprehensive medical background was documented, encompassing details about past and ongoing illnesses, prescribed drugs, past surgeries or medical interventions, as well as smoking patterns.

These data were collected to identify potential confounders associated with COPD exacerbation, such as pulmonary embolism, heart failure, pneumonia, pneumothorax, myocardial infarction and arrhythmias (*e.g.*, atrial fibrillation). We also calculated the VAS dyspnea score, Modified Early Warning Score (MEWS) and Charlson Comorbidity Index (CCI). The VAS dyspnea score measures the severity of dyspnea on a scale from 0 (no dyspnea) to 10 (the most severe dyspnea the patient has experienced). The MEWS is employed as a tool for evaluating the likelihood of unfavorable outcomes in patients presenting at the ED. It takes into account vital signs including respiratory rate, heart rate, blood pressure, oxygen saturation and level of consciousness. A MEWS score exceeding 5 signifies the requirement for immediate medical intervention or admission to the intensive care unit. The CCI is a scoring system designed to predict a patient's 10-year mortality based on their comorbidities and the severity of these conditions.

2.2.1 Inclusion criteria

Patients eligible for inclusion in the study had to be over 18 years of age, diagnosed with COPD by a specialist, and meet the GOLD 2024 criteria for COPD exacerbation. This includes increased dyspnea, cough and sputum production over a period of less than 14 days, with or without tachypnea and tachycardia. Additionally, patients had to sign the consent and approval form to participate.

2.2.2 Exclusion criteria

Patients were excluded if they did not meet the criteria for acute exacerbation of COPD as defined by GOLD 2024, if they declined to participate in the study, if their test results could not be analyzed due to technical issues, if they were referred to external facilities and follow-up was not possible, or if they refused treatment.

2.3 Potential sources of bias

Since the clinician in charge of assessing patient eligibility was also the one deciding on participation in the study, it was not possible to blind the primary physician. To mitigate this potential bias, additional physicians and study authors who were not part of the initial patient evaluation independently

reviewed data from the patient database.

2.4 Study size

The sample size was determined using Statistical Package for Social Sciences (SPSS; ver. 26, IBM Corp., Armonk, NY, USA) and G*Power 3.1 (Universität Düsseldorf, Düsseldorf, NRW, Germany) software. In statistical analyses based on *F*-tests, the Partial Eta Squared value represents the effect size. Data from the pilot study indicated a Partial Eta Squared value of 0.28 (Type III sum of squares: 565.025, mean square: 282.513). With an alpha error of 5%, a target power of 80%, and three groups, the effect size of 0.28 was used. Based on these parameters, the total required sample size is at least 129 participants.

The study enrolled a consecutive total of 307 patients who arrived at the Emergency Department with a preliminary diagnosis of AECOPD. Among them, 54 patients were disqualified as they did not meet the exacerbation criteria according to GOLD 2024 guidelines. Twelve patients opted out of participation, 11 had test results that were unanalyzable due to technical glitches, and 30 patients were unable to provide follow-up data, leading to their exclusion. Additionally, 4 patients declined all treatment and testing. Following the application of all the specified inclusion and exclusion criteria, the final study cohort consisted of 196 patients (Fig. 1).

2.5 Statistical analysis

Hypotheses tests were performed to compare the variables of mild, moderate and severe COPD exacerbation groups. Categorical variables were shown as frequency and percentage. Kolmogorov-Smirnov test measured the normality of numerical variables. If the numerical variables fit the normal distribution, they were expressed with mean and standard deviation (SD); otherwise, they were expressed with median value and interquartile range (IQR). Pearson Chi-square test was used to compare categorical variables. One-way Analysis of Variance (ANOVA) test was applied to compare the normally distributed numerical variables. Dunnet or Tukey tests were selected for *post-hoc* analysis according to the homogeneity of variances. Kruskal-Wallis test was applied for not normally distributed numerical variables in three groups. Mann Whitney-U test was used for pairwise comparison. This study particularly

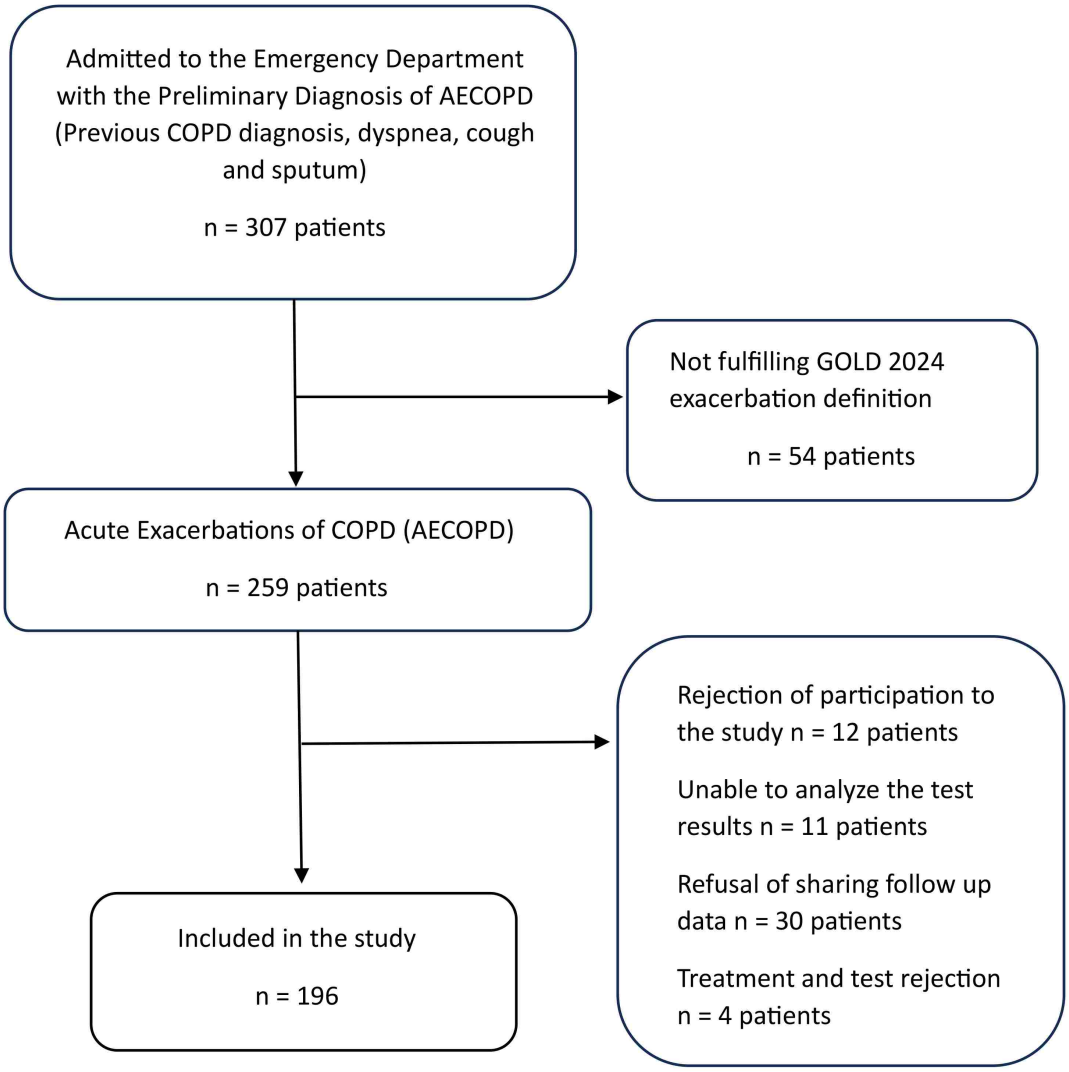

FIGURE 1. Flowchart of the study. AECOPD: acute exacerbations of chronic obstructive pulmonary disease; COPD: chronic obstructive pulmonary disease; GOLD: global initiative for chronic obstructive lung disease.

focused on the clinical value of procalcitonin, Pro-BNP and CRP on mortality prediction and severe COPD exacerbation. Therefore, the severe COPD exacerbation group and the other mild and moderate COPD exacerbation group were additionally compared with each other using Mann Whitney-U test. Survivor and non-survivor patients' PCT, Pro-BNP and CRP levels also compared with Mann Whitney-U test. The Receiver Operating Characteristics (ROC) analysis was performed to reveal the sensitivity and specificity of PCT, Pro-BNP and CRP levels to predict the severe exacerbations and mortality. Area under curve (AUC) for each variable was demonstrated via ROC curve. All the statistical tests were applied in a 95% confidence interval and 0.05 significance level. All data analyses were performed using IBM SPSS Version 26.

3. Results

3.1 Clinical characteristics

This study included 196 patients, who were classified into three groups based on the severity of exacerbation: mild, moderate and severe. The clinical characteristics of the patients are presented in Table 1.

Breath rate, heart rate and oxygen saturation:

Oxygen saturation (SpO_2) was found to be significantly affectd by the severity of the COPD exacerbation itself. Patients with mild exacerbations had a median SpO_2 value of 93% [90%–96%], while those with moderate exacerbations had a median SpO_2 value of 90% [83%–95%]. In severe exacerbations, the median SpO_2 value of 86.5% [75%–96%]. A statistically significant decrease in SpO_2 was observed in patients with severe exacerbations compared to those with mild exacerbations (p = 0.002). Moreover, patients experiencing moderate and severe exacerbations displayed notably elevated heart rate and respiratory rate in comparison to those with mild exacerbations. Nonetheless, there were no remarkable variances detected in blood pressure or body temperature across the three groups (Table 1).

A total of 71 patients (36.4%) in the study required NIMV support in our critical care and resuscitation units. Out of the total, 44 individuals (77.2%) experienced severe exacerbations, while 25 patients (33.8%) faced moderate exacerbations and 2 patients (3.1%) had mild exacerbations. Our examination of this data unveiled a notable correlation between the severity of COPD exacerbations and the necessity for NIMV in the emergency environment ($p < 0.001$).

Additionally, we noted a substantial reduction in pH levels that corresponded with the exacerbation severity of COPD. Patients experiencing mild exacerbation displayed an average pH of 7.36 $\pm$ 0.38, whereas those with moderate exacerbation exhibited an average pH of 7.36 $\pm$ 0.05. Significantly greater pH reduction was evident in the severe exacerbation cohort, with an average arterial blood gas pH of 7.29 $\pm$ 0.09 ($p <$ 0.001). Correspondingly, the mean pCO_2 level was significantly higher in the severe exacerbation group compared to both the mild and moderate exacerbation groups (Table 1).

In our study, pneumonia was identified in 67 out of 196 patients, accounting for 34.5% of the total. Specifically, 12 cases (18.8%) were reported in the mild exacerbation group, 32 cases (42.7%) in the moderate exacerbation group, and the severe exacerbation group recorded 23 cases. Our analysis revealed a statistically significant correlation between the severity of COPD exacerbation and the presence of pneumonia (p = 0.005).

The median length of hospital stay for all patients was 1 [1–6.75] day, with mild exacerbation patients spending significantly less time in the hospital compared to those with moderate and severe exacerbations. In this study, a total of 196 patients were observed, and the general mortality rate was determined to be 17.3%, with 34 patients succumbing to the condition. Specifically, among the deceased patients, 6.3% belonged to the mild exacerbation group, 17.3% to the moderate exacerbation group and 29.8% to the severe exacerbation group. Analysis of the data revealed a notable increase in mortality rates among patients classified in the severe exacerbation group (p = 0.003) (Table 1).

The median VAS dyspnea score was calculated as 4 [4–5] in patients with mild exacerbations, 6 [5–8] in patients with moderate exacerbations and 9.5 [8–10] in those with severe exacerbations. A statistically significant difference in VAS scores was observed between the three groups ($p < 0.001$).

The median MEWS was 1 [1–2] in the mild exacerbation group, 2 [2–3] in the moderate group and 3 [2–5] in the severe group. Statistically significantly higher MEWS values were found in moderate and severe exacerbations compared to mild exacerbations ($p < 0.001$). However, no significant differences were found between the groups for CCI scores (Table 2).

3.2 Pairwise comparison between Pro-BNP, PCT, CRP and exacerbation severity

In our study, we performed a pairwise comparison and analysis of PCT, Pro-BNP and CRP levels in relation to the severity of COPD exacerbations. The results of this analysis are presented in Tables 3a,3b.

Pro-BNP, PCT and CRP:

Comparisons of inflammatory markers and Pro-BNP levels represent key findings in this study. The mean PCT level was the highest in patients with severe exacerbation. The median levels of PCT in the severe, moderate and mild exacerbation categories were 0.10 μg/L, 0.12 μg/L and 0.10 μg/L, correspondingly. It is noteworthy that, despite the lack of a significant disparity among the three groups according to the Kruskal-Wallis test, upon pairwise comparisons, it was evident that the median PCT level showed a remarkable increase in the severe exacerbation category when compared to both the mild and moderate groups. In the study, CRP, which is another inflammatory marker, exhibited a median value of 34.40 mg/dL within the entire study cohort. However, no statistically significant differences in median CRP levels were found among the three groups, nor in pairwise comparisons.

Significantly elevated median Pro-BNP levels were observed in both the severe exacerbation group and the non-survivor group. More precisely, the median Pro-BNP level reached 1366 ng/L in the severe exacerbation group, 1476 ng/L in the moderate exacerbation group and 508.40 ng/L in the mild exacerbation group. Substantial differences

TABLE 1. The distribution of patients' clinical and laboratory findings in accordance with the severity of COPD exacerbations.

Clinical characteristics	Total N = 196	Mild exacerbation N = 64	Moderate exacerbation N = 75	Severe exacerbation N = 57	*p* value
Male Gender, n (%)	140 (71.4)	47 (73.4)	53 (70.7)	40 (70.2)	0.909¶
Age, yr, mean ± SD	70.68 ± 10.73	71.06 ± 11.13	70.13 ± 11.37	70.89 ± 9.57	0.863*
Breath rate, Median [Q1–Q3]	20 [18–22]	20 [18–20][b,c]	20.50 [18–22.25][a]	20 [18–24][a]	**0.037**†
Heart rate, bpm, mean ± SD	98.78 ± 20.34	91.09 ± 12.60[b,c]	100.14 ± 21.55[a]	102.50 ± 25.76[a]	**0.001***
Systolic pressure, mmHg, Median [Q1–Q3]	136 [120–157.25]	140 [123.25–150]	132 [110.75–154]	136 [121–160]	0.466†
Diastolic pressure, mmHg, Median [Q1–Q3]	80 [68–87.75]	80 [69.25–82]	80 [64.25–85.50]	80 [70–90]	0.201†
Fever, °C, Median [Q1–Q3]	36.55 [36.40–36.70]	36.7 [36.40–36.78]	36.60 [36.40–36.70]	36.60 [36.40–36.70]	0.976†
Oxygen saturation, %, Median [Q1–Q3]	91 [84–96]	93 [90–96][c]	90 [83–95]	86.50 [75–96][a]	**0.002**†
Pro-BNP, ng/L, Median [Q1–Q3, min–max]	982.50 [352–3739, 10–35,000]	508.40 [114–1220, 10–10,272][b,c]	1476 [592–3547, 55–31,059][a]	1366 [557–8964, 10–35,000][a]	**0.007**†
NIMV, n (%)	71 (36.4)	2 (3.1)	25 (33.8)	44 (77.2)	<**0.001**¶
IMV, n (%)	28 (14.4)	0	1 (1.4)	27 (47.4)	
Procalcitonin, µg/L, Median [Q1–Q3, min–max]	0.11 [0.06–0.21, 0.02–100]	0.10 [0.05–0.18, 0.02–2.15]	0.12 [0.06–0.20, 0.02–8.79]	0.10 [0.06–0.14, 0.02–100]	0.855†
C-Reactive Protein, mg/L, Median [Q1–Q3]	34.40 [12.93–92.75]	24.44 [7.12–51.60]	60.56 [19.23–103.42]	49.01 [14.62–107.12]	0.157†
pH, mean ± SD	7.34 ± 0.07	7.36 ± 0.38[c]	7.36 ± 0.05[c]	7.29 ± 0.09[a,b]	<**0.001***
pO_2 (<60 mmHg), n (%)	144 (73.8)	46 (73.0)	52 (69.3)	46 (80.7)	0.333¶
pCO_2, mmHg, mean ± SD	54.17 ± 35.03	45.45 ± 7.30[c]	50.15 ± 13.31[c]	59.15 ± 14.92[a,b]	<**0.001***
Lactate, mmol/L, Median [Q1–Q3]	2.05 [1.42–2.97]	1.85 [1.30–2.50]	2.30 [1.60–2.80]	1.85 [1.40–3.50]	0.439†
Leucocyte, 10^3/µL, mean ± SD	11.29 ± 4.68	10.49 ± 4.59	10.69 ± 3.53	11.96 ± 5.57	0.293*
Neutrophile, 10^3/µL, mean ± SD	8.91 ± 4.35	8.00 ± 4.66	8.72 ± 3.15	9.58 ± 4.58	0.247*
Congestive heart failure, n (%)	47 (24.1)	10 (15.6)	18 (24.0)	19 (33.9)	0.065¶
Pneumonia, n (%)	67 (34.5)	12 (18.8)	32 (42.7)	23 (41.8)	**0.005**¶
Length of stay, days, Median [Q1–Q3]	1 [1–6.75]	1 [1–1][b,c]	1 [1–11][a]	2 [1–12.25][a]	**0.001**†
Mortality, n (%)	34 (17.3)	4 (6.3)	13 (17.3)	17 (29.8)	**0.003**¶

COPD: Chronic Obstructive Pulmonary Disease; SD: Standard Deviation; NIMV: Non-invasive mechanical ventilation; IMV: Invasive mechanical ventilation; Pro-BNP: Pro-Brain Natriuretic Peptide; pO_2: partial pressure of oxygen; pCO_2: partial pressure of carbon dioxide.

**One Way ANOVA test was used in the analysis of continuous variables, Dunnet or Tukey tests were selected for post-hoc analysis according to the homogeneity of variances;*

¶: Pearson chi square test was used to analyze categorical variables;

†: Kruskal Wallis test was used to compare, Bonferroni correction was used to adjust significance values;

[a]: According to post-hoc tests there is a significant difference with Mild exacerbation group;

[b]: According to post-hoc tests there is a significant difference with Moderate exacerbation group;

[c]: According to post-hoc tests there is a significant difference with Severe exacerbation group.

The bolded numbers had significant p values.

TABLE 2. Clinical severity scores and comorbidities in COPD exacerbation patients.

Clinical characteristics	Total N = 196	Mild exacerbation N = 64	Moderate exacerbation N = 75	Severe exacerbation N = 57	*p* value
VAS (dyspnea), Median [Q1–Q3]	6.00 [5–8]	4.00 [4–5][b,c]	6.00 [5–8][a,c]	9.50 [8–10][a,b]	<**0.001**†
MEWS, Median [Q1–Q3]	2 [1–3]	1 [1–2][b,c]	2 [2–3][a]	3 [2–5][a]	<**0.001**†
CCI, Median [Q1–Q3]	5 [4–6]	5 [4–6]	5 [4–6]	5 [4–7]	0.524†
Smoker, n (%)	35 (20.0)	9 (15.8)	18 (26.9)	8 (15.7)	0.202¶
Obesity, n (%)	126 (69.2)	39 (63.9)	51 (73.9)	36 (69.2)	0.469¶
Hypertension, n (%)	95 (48.5)	30 (46.9)	35 (46.7)	30 (52.6)	0.757¶
Diabetes Mellitus, n (%)	57 (29.1)	20 (31.3)	21 (28.0)	16 (28.1)	0.897¶
Coronary artery disease, n (%)	50 (25.6)	17 (26.6)	17 (22.7)	16 (28.6)	0.730¶
Malignancy, n (%)	33 (16.8)	6 (9.4)	16 (21.3)	11 (19.3)	0.144¶

COPD: Chronic Obstructive Pulmonary Disease; VAS: Visual Analogue Scale; MEWS: Modified Early Warning Score; CCI: Charlson Comorbidity Index.
†: Kruskal Wallis test was used to compare, Bonferroni correction was used to adjust significance values;
¶: Pearson chi square test was used in the analysis of categorical variables;
[a]: According to post-hoc tests there is a significant difference with Mild exacerbation group;
[b]: According to post-hoc tests there is a significant difference with Moderate exacerbation group;
[c]: According to post-hoc tests there is a significant difference with Severe exacerbation group.
Values with a statistically significant p-value are written in bold.

TABLE 3a. Pairwise comparison of mild, moderate and severe exacerbation groups.

Parameters	COPD exacerbation severity			*p* values		
	Mild	Moderate	Severe	Mild *vs.* Severe	Mild *vs.* Moderate	Moderate *vs.* Severe
PCT, Median [Q1–Q3, min–max]	0.10 [0.05–0.18, 0.02–2.15]	0.12 [0.06–0.20, 0.02–8.79]	0.10 [0.06–0.14, 0.02–100.00]	**0.004**	**0.044**	**0.002**
Pro-BNP, Median [Q1–Q3, min–max]	508.40 [114–1220, 10–10,272][b,c]	1476.00 [592–3547, 55–31,059][a]	1366.00 [557–8964, 10–35,000][a]	<**0.001**	**0.003**	**0.004**
CRP, Median [Q1–Q3]	24.44 [7.12–51.60]	60.56 [19.23–103.42]	49.01 [14.62–107.12]	0.692	0.796	0.413

COPD: Chronic Obstructive Pulmonary Disease; PCT: Procalcitonin; Pro-BNP: Pro-Brain Natriuretic Peptide; CRP: C-reactive protein. Mann-Whitney U test was used to compare.
Values with a statistically significant p-value are written in bold.

TABLE 3b. Comparison of survivor and non-survivor groups.

Parameters	Mortality		
	Survivor Median [Q1–Q3]	Non-Survivor Median [Q1–Q3]	*p*-value
PCT	0.10 [0.06–0.18]	0.16 [0.10–0.43]	**0.001**
Pro-BNP	801 [233–2544]	3476 [1390–16,374]	<**0.001**
CRP	29.00 [11–83]	60.50 [23–119]	0.066
Length of stay	1 [1–5]	1 [1–14]	0.332

PCT: Procalcitonin; Pro-BNP: Pro-Brain Natriuretic Peptide; CRP: C-reactive protein.
Mann-Whitney U test was used to compare.
Values with a statistically significant p-value are written in bold.

in Pro-BNP levels were noted not only between the groups but also in pairwise comparisons.

The predictive value of PCT, Pro-BNP and CRP for severe exacerbation and mortality was evaluated using ROC analysis (Fig. 2). Only Pro-BNP demonstrated a significant threshold value and AUC for predicting severe exacerbation. A Pro-BNP level greater than 1350 ng/L predicted severe exacerbation with 63% sensitivity and 62% specificity (p = 0.003, AUC = 0.653).

Regarding mortality prediction, both PCT and Pro-BNP were significant markers. The threshold for PCT in predicting mortality was 0.115 μg/L, with 64% sensitivity, 53% specificity and an AUC of 0.627 (p = 0.035). Pro-BNP was found to be a stronger predictor for mortality, with a threshold of 1500 ng/L, predicting mortality with 68% sensitivity and 66% specificity (p = 0.001, AUC = 0.758), (Fig. 3, Tables 3a,3b).

4. Discussion

In our study, we aimed to compare the diagnostic value and predictive efficiency of CRP, PCT and Pro-BNP as markers for assessing the severity of COPD exacerbations. We found that both PCT and Pro-BNP were statistically significantly better at predicting mortality in COPD exacerbations. Furthermore, Pro-BNP was found to be statistically significantly more effective than the other markers in predicting the severity of COPD exacerbations.

According to statistics from the Global Burden of Disease research, COPD-related fatalities make up approximately 4.72% of the total global death toll [5]. The year 2019 saw 3.23 million individuals succumb to COPD, underscoring the urgency of investigating the factors linked to mortality in patients with this condition [6]. Therefore, identifying reliable biomarkers for predicting clinical outcomes in COPD exacerbations is essential.

PCT, a 116-amino-acid polypeptide, serves as a precursor

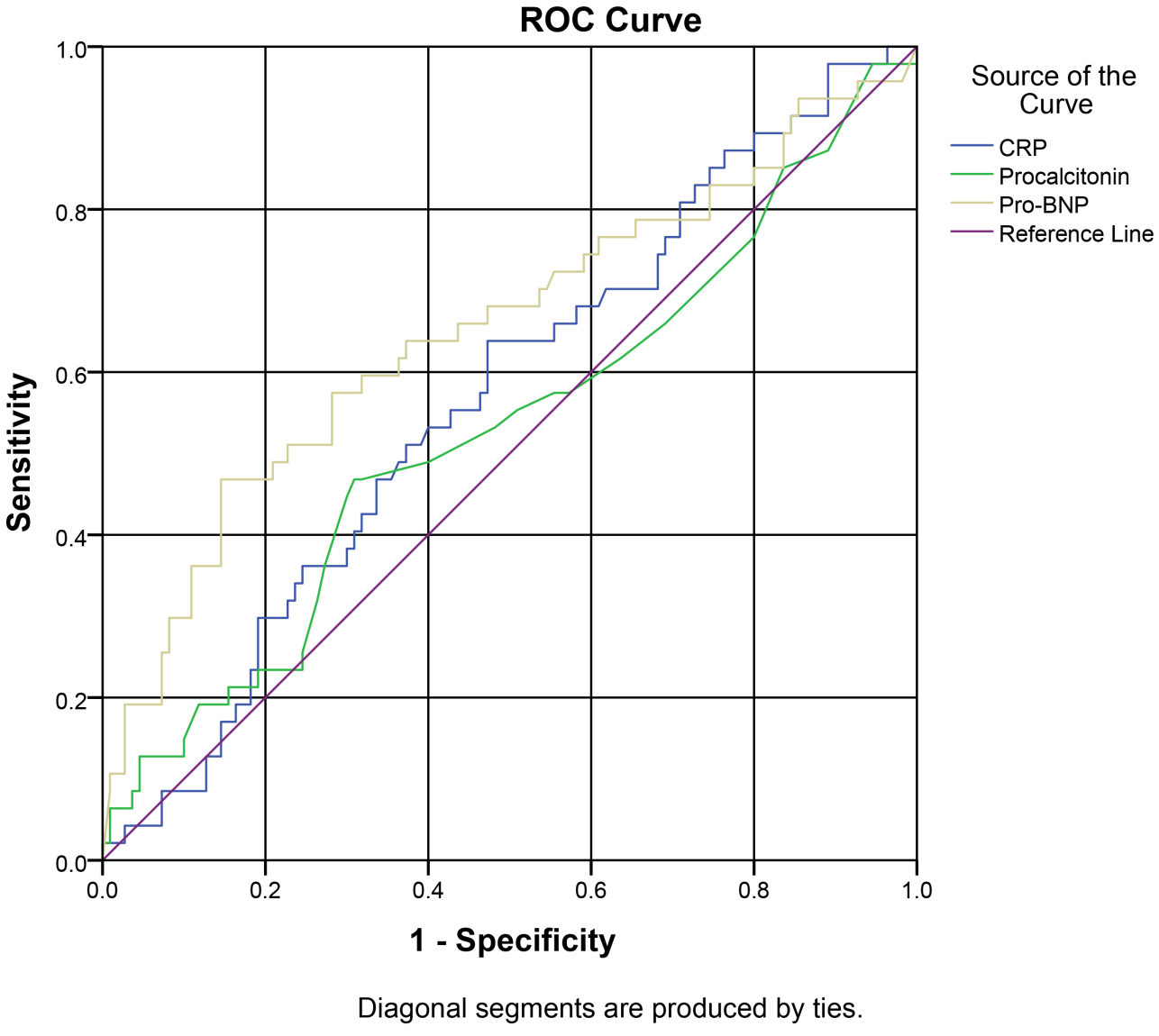

FIGURE 2. ROC curve for COPD severe exacerbation prediction. COPD: Chronic Obstructive Pulmonary Disease; ROC: Receiver Operating Characteristics; CRP: C-Reactive Protein; Pro-BNP: Pro-Brain Natriuretic Peptide.

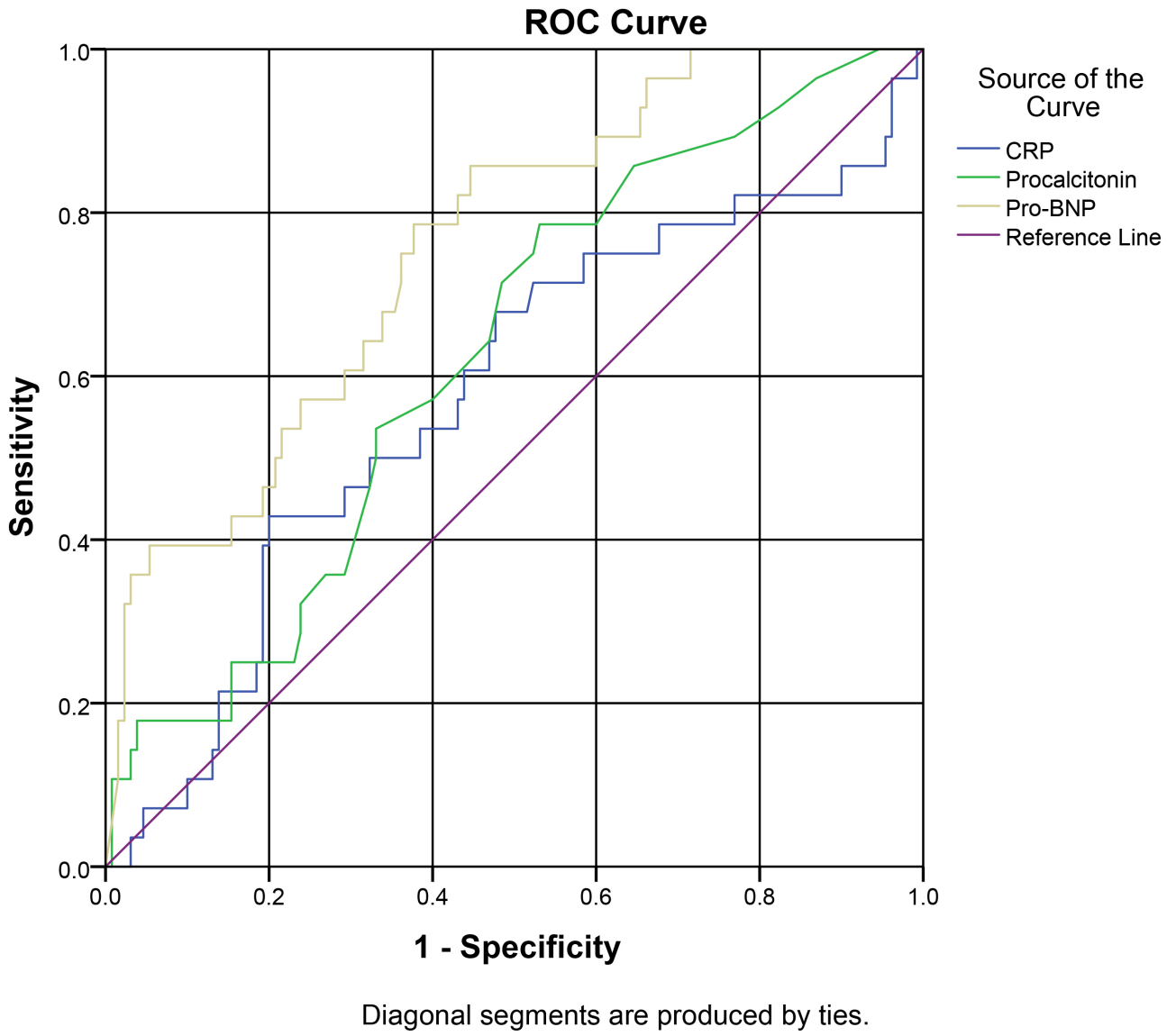

FIGURE 3. ROC curve for mortality prediction in patients with COPD exacerbation. COPD: Chronic Obstructive Pulmonary Disease; ROC: Receiver Operating Characteristics; CRP: C-Reactive Protein; Pro-BNP: Pro-Brain Natriuretic Peptide.

to calcitonin. Unlike CRP or erythrocyte sedimentation rate, serum levels of PCT tend to increase earlier. PCT is notably effective in the identification of bacterial infections, holding a significant position in the immune response against such pathogens. Bacterial infections in both the upper and lower airways commonly provoke COPD exacerbations, indicating the potential of PCT as a valuable biomarker for individuals experiencing COPD exacerbations [7]. Hoult *et al.* [8], (2022) conducted a systematic review indicating that the levels of PCT, in conjunction with CRP levels, demonstrate differing degrees of significance in identifying the bacterial presence during a COPD exacerbation. Similarly, in our study, we observed significantly higher PCT serum levels in patients with severe COPD exacerbations.

Davies *et al.* [9] (2022), elevated PCT levels were associated with an increased probability of admission to the intensive care unit (ICU) admission. Another study conducted by Lin *et al.* [10] (2021) revealed that the utilization of procalcitonin changing rate can enhance patient survival by aiding in the adjustment of mechanical ventilation weaning for individuals experiencing respiratory failure in AECOPD. Our findings align with these studies, as we observed a statistically significant elevation in PCT levels in non-survivor patients compared to survivors.

Exacerbations in COPD are categorized as mild, moderate or severe according to the GOLD 2024 guidelines, with CRP serving as one of the criteria for such classification. A research study conducted on 110 COPD patients revealed that individuals testing positive for PCT exhibited elevated mortality rates and enhanced readmission frequencies in comparison to their PCT-negative counterparts [11]. Our findings are consistent with these results, as we found that PCT performed statistically better than CRP in classifying exacerbations. Due to its predictive capability, we are convinced that incorporating PCT, a biomarker known for its enhanced reliability, could greatly enhance the early detection of COPD patients at increased mortality risk during acute exacerbations, a condition that imposes a significant global burden of mortality.

Higher levels of Pro-BNP and troponin have been recognized as autonomous predictors of mortality in individuals with AECOPD, and are linked to the requirement for ICU admission and extended hospitalization durations [12]. The results of this study support these findings, with Pro-BNP levels also correlating with the severity of COPD exacerbations. The correlation can be elucidated by the pathophysiological development of COPD. With the passage of time, COPD can induce pulmonary hypertension by augmenting the resistance in lung tissue, subsequently leading to arterial rigidity and potentially culminating in heart failure. The findings of a study by Tian *et al.* [13] (2021) indicating that Pro-BNP holds diagnostic significance in AECOPD and shows a subtle connection with the severity of pulmonary hypertension in patients with AECOPD.

This study discovered that heightened Pro-BNP levels were indicative of the seriousness of exacerbations and the likelihood of death in patients with AECOPD. Likewise, another research conducted by Zhang *et al.* [14] identified Pro-BNP as a standalone risk factor for individuals hospitalized through the Emergency Department due to AECOPD. The findings of this study also suggest that, compared to CRP and PCT, Pro-BNP is a superior predictor for both mortality and the severity of exacerbations in AECOPD patients. Supporting this, a study by Pavasini *et al.* [15] (2016) highlighted Pro-BNP as a robust indicator of mortality in patients with AECOPD.

Triantafyllidou *et al.* [16] (2023) discovered a notable correlation between the MEWS and the intensity of COPD flare-ups. Their study revealed that the MEWS upon admission is associated with CRP levels. Despite being regarded as a less superior assessment tool for AECOPD severity in comparison to the National Early Warning Score upon admission, MEWS remains valuable in categorizing the seriousness of COPD exacerbations.

Nevertheless, our research did have its constraints. Being carried out in an emergency department environment, we faced challenges in obtaining thorough data regarding patients' adherence to prescribed medications. Furthermore, the study was confined to a solitary facility, potentially subjecting it to the impact of local variables. An additional limitation stemmed from the study's structure, rendering the implementation of double-blinding unfeasible. As the physician evaluating the patient in the ED could not be blinded, we minimized bias by ensuring that the physicians and authors involved in data analysis were blinded to the clinical conditions.

5. Conclusions

While our results do not conclusively prove the superiority of PCT and Pro-BNP as predictors, they do offer compelling evidence indicating the need for further exploration of these biomarkers. Discovering new biomarkers for risk assessment could facilitate quicker evaluations and the provision of customized care based on individual patient requirements and risk factors. This study offers a novel approach by directly comparing the diagnostic and prognostic utility of PCT and Pro-BNP with the widely used CRP in the management of AECOPD.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

SD, TD, MKA, EDB, UMK and AFBK—were responsible for the study concept and study design; critical revision of the manuscript for important intellectual content. RY and SF—performed data extraction. RY, SF, RBT and HK—were responsible for data analysis. SD, RY, UMK, RBT, HK and SF—drafting of the manuscript. All authors have read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was carried out following the principles outlined in the Declaration of Helsinki. In preparing the manuscript, we followed the STROBE guidelines to enhance the accuracy and completeness of our reporting. The ethics committee of Kanuni Sultan Süleyman Training and Research Hospital approved the study. (Approval date: 08 February 2023, Approval No: KAEK/2023.02.21) and was registered on ClinicalTrials.gov (NCT06514599). Informed consent was obtained from all individual participants included in the study.

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CONFLICT OF INTEREST

The authors of this paper have no conflicts of interest, including specific financial interests, relationships and/or affiliations relevant to the subject matter or materials included.

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