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CHARACTERISTICS AND TREATMENT OUTCOMES OF PATIENTS WITH SEVERE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

KARAKTERISTIKE I ISHOD LEČENJA BOLESNIKA SA TEŠKOM EGZACERBACIJOM HRONIČNE OPSTRUKTIVNE BOLESTI PLUĆA

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Abstract

Introduction. Chronic obstructive pulmonary disease is the fourth leading cause of death worldwide. Acute exacerbations often require hospitalization, and are associated with high mortality. Identifying risk factors associated with mortality may improve medical treatment and reduce mortality. This study aimed to analyze outcomes of patients with acute exacerbations of chronic obstructive pulmonary disease treated in the intensive care unit, and to identify factors associated with mortality. **Material and Methods.** This retrospective study was conducted at the Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica, Serbia, between April 2015 and January 2019. Inclusion criteria were a diagnosis of acute exacerbation of chronic obstructive pulmonary disease, intensive care unit admission, and treatment with invasive mechanical ventilation. **Results.** A total of 127 patients were included, of whom 79 (62.2%) were male, with mean age ($\overline{X}$ ± SD) of 66.96±8.57 years. Intensive care unit mortality was 33/127 (26%), with a mean length of stay of 3.5 days (interquartile range 2.0-8.0). Overall in-hospital mortality was 56/127 (44%), with a median hospital stay of 15.0 days (interquartile range 7.0-24.0). Multivariate analysis identified the PaO_2/FiO_2 ratio (odds ratio 0.99; 95% confidence interval 0.98-0.99; p=0.013), Glasgow Coma Score (odds ratio 0.82; 95% confidence interval 0.69-0.96; p=0.014), and presence of septic shock (odds ratio 50.9; 95% confidence interval 8.58-549.52; p< 0.001) as predictors of intensive care unit mortality. **Conclusion**. Mortality among patients with acute exacerbations of chronic obstructive pulmonary disease treated in the intensive care unit remains high. Reduced PaO_2/FiO_2 ratio, lower Glasgow Coma Score, and septic shock are independent predictors of mortality.

Key words: Pulmonary Disease, Chronic Obstructive; Symptom Flare Up; Risk Factors; Mortality; Intensive Care Units; Respiration, Artificial

Sažetak

Uvod. Hronična opstruktivna bolest pluća je četvrti vodeći uzrok smrtnosti u svetu. Akutne egzacerbacije bolesti često zahtevaju hospitalizaciju i značajno doprinose povećanju mortaliteta. Otkrivanje faktora rizika povezanih sa mortalitetom može doprineti boljoj terapiji bolesnika i smanjenju smrtnosti. Cilj rada bio je da se analizira ishod lečenja bolesnika sa akutnim egzacerbacijama hronične opstruktivne bolesti pluća u jedinici intenzivne terapije, kao i utvrditi faktore rizika za mortalitet kod ovih bolesnika. **Materijal i metode.** Studija je retrospektivnog karaktera. Sprovedena je na Institutu za plućne bolesti Vojvodine u Sremskoj Kamenici, Novi Sad, Srbija u periodu od aprila 2015. do januara 2019. godine. Uključujući kriterijumi su dijagnoza akutne egzacerbacije hronične opstruktivne bolesti pluća, prijem u jedinicu intenzivne terapije i lečenje invazivnom mehaničkom ventilacijom. **Rezultati.** Uključeno je 127 ispitanika, 79 (62,2%) muškog pola, prosečne starosti ($\overline{X}$ ± SD) 66,96 ± 8,57 godina. U jedinici intenzivne terapije mortalitet je iznosio 33/127 (26%) a prosečna dužina lečenja 3,5 dana (interkvartilni raspon 2–8), dok je bolnički mortalitet iznosio 56/127 (44%), a dužina lečenja 15 (interkvartilni raspon 7–24) dana. U multivarijantnoj analizi prediktori mortaliteta bili su odnos PaO_2/FiO_2 (odnos šansi, 0,99; 95% interval pouzdanosti, 0,98–0,99; p = 0,013), Glazgov koma skor (odnos šansi, 0,82; 95% interval pouzdanosti, 0,69–0,96; p = 0,014) i septički šok (odnos šansi, 50,9; 95% interval pouzdanosti, 8,58–549,52; p < 0,001). **Zaključak.** Mortalitet pacijenata sa akutnim egzacerbacijama hronične opstruktivne bolesti pluća lečenih u jedinici intenzivnog lečenja je visok. Niže vrednosti PaO_2/FiO_2, Glazgov koma skora i prisustvo septičnog šoka nezavisni su prediktori mortaliteta kod ovih pacijenata.

Ključne reči: hronična opstruktivna bolest pluća; egzacerbacija; faktori rizika; mortalitet; jedinica intenzivnog lečenja; mehanička ventilacija

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a common, progressive respiratory disorder characterized by persistent airway inflammation and incompletely reversible airflow limitation [1]. It results from an abnormal inflammatory response of the lungs to inhaled noxious particles or gases and remains a major global health burden [2]. According to the World Health Organization, COPD was the fourth leading cause of death worldwide in 2021, accounting for approximately 5% of all global mortality [3]. Na-

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Abbreviations

COPD – chronic obstructive pulmonary disease
AECOPD – acute exacerbation of chronic obstructive pulmonary disease
ICU – intensive care unit
FEV_1 – forced expiratory volume in one second
ICD – international disease classification
IQR – interquartile range
OR – odds ratio
CI – confidence interval
PaO_2 – partial pressure of oxygen in arterial blood
$PaCO_2$ – partial pressure of carbon dioxide
FiO_2 – fraction of inspired oxygen
CVI – cerebrovascular insult
TIA – transient ischemic attack
CAT – COPD Assessment Test
mMRC – modified Medical Research Council dyspnoea scale
MAP – mean arterial pressure
CRP – C-reactive protein

tional epidemiological data from Serbia indicate that COPD affected 3.5% of the population in 2019, reflecting a modest decline compared with earlier estimates from 2006 (4.3%) and 2013 (4.5%) [4]. In some patients, COPD may be associated with anatomical airway variations, such as a saber-sheath trachea [5].

Acute exacerbations of COPD (AECOPD) are episodes of clinical deterioration marked by worsening dyspnea, cough, and sputum production that necessitates medical intervention and adjustment of therapy [6]. Beyond exacerbating respiratory symptoms, these events can precipitate or aggravate chronic comorbidities, particularly cardiovascular and cerebrovascular diseases [7]. AECOPD is most frequently triggered by viral or bacterial infections or exposure to air pollutants [2]. Recommended management strategies include bronchodilators, systemic corticosteroids, antibiotics, and oxygen therapy, while non-invasive or invasive mechanical ventilation is reserved for severe cases [8]. In addition to improving arterial oxygenation, supplemental oxygen has been shown to enhance cerebral oxygen delivery and neurovascular function, potentially influencing cognitive outcomes and reducing cerebrovascular risk in patients with COPD [9].

Acute exacerbations of substantially accelerates disease progression and are associated with increased morbidity, mortality, and prolonged hospital stays [12]. Approximately 10% of exacerbations require hospitalization [10], and among patients admitted to intensive care units (ICUs), post-discharge mortality remains high. Data describing outcomes in the most severe exacerbations and associated mortality determinants are still limited [13]. A previous study from the Institute for Pulmonary Diseases of Vojvodina reported that among patients who died within the first 24 hours of admission for AECOPD, the leading causes of death were heart failure (37%), pneumonia (28%), pulmonary embolism (21%), and COPD itself (14%) [10]. In the United States, a 2012 study demonstrated that patients may experience up to 16 episodes of respiratory symptom worsening within the first two years following COPD diagnosis, reflecting the recurrent nature of exacerbations [11].

Early recognition and prompt management of AECOPD confer several clinical benefits. Early treatment mitigates the immediate impact of exacerbation, slows subsequent symptom deterioration, and reduces the likelihood of rehospitalization [14]. Prompt therapeutic intervention has been associated with faster symptom resolution, improved health-related quality of life, and decreased hospital admission rates [15]. Frequent exacerbations contribute to accelerated decline in pulmonary function, as reflected by reductions in FEV_1 [16]. Long-term outcomes remain poor, with hospitalized patients with AECOPD demonstrating an 82% lower 15-year survival compared with the general population [17]. Moreover, management of moderate-to-severe exacerbations imposes a substantial economic burden on healthcare systems [18].

Despite the recognized impact of AECOPD, evidence identifying predictors of mortality in patients requiring intensive care remains limited, particularly in region-specific settings. Identifying clinical, physiological, and treatment-related factors associated with mortality is essential for improving prognostication, guiding therapeutic decisions, and optimizing the allocation of critical care resources.

The aim of this study was to analyze treatment outcomes in patients with severe COPD exacerbations admitted to the intensive care unit and to identify risk factors associated with mortality in this patient population.

Material and Methods

This retrospective study was conducted at the Institute for Pulmonary Diseases of Vojvodina, Novi Sad, Serbia, and included patients treated between April 2015 and January 2019. The study was approved by the Ethics Committee of the Institute for Pulmonary Diseases of Vojvodina.

The study included patients with AECOPD requiring invasive mechanical ventilation. Patients were identified through the electronic medical records of the intensive care unit (ICU). Eligibility was based on a diagnosis of COPD, defined according to ICD-10 codes J44.1, J44.8 and J44.9. AECOPD was defined as worsening of cough, sputum production, and dyspnea requiring intensified therapy, including systemic bronchodilators. Inclusion criteria were admission to the ICU due to AECOPD, and requirement of invasive mechanical ventilation. Exclusion criteria included

diagnosis of asthma, pulmonary fibrosis, obesity hypoventilation syndrome (Pickwickian syndrome), transfer from another hospital, ICU admission for a primary condition other than AECOPD with concomitant COPD, or absence of clinical criteria fulfilling the diagnosis of AECOPD. The data extracted from medical records included demographic characteristics, length of hospital and ICU stay, smoking history, laboratory parameters, blood gas analyses, comorbidities, complications, and clinical outcomes.

During the study period, 234 patients with a diagnosis of COPD were treated in the ICU. Of these, 36 patients who did not require invasive mechanical ventilation were excluded. An additional 71 patients were excluded because ICU admission was not related to an episode of AECOPD.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) for normally distributed data or as median with interquartile range (IQR) for skewed data. Categorical variables are expressed as counts and percentages. Comparison between survivors and non-survivors were performed using Student's t-test or the Kruskal-Wallis test for continuous variables, depending on data distribution, and the chi-square (χ^2) test for categorical variables. Variables demonstrating statistical significance in univariate analysis were entered into a multivariate logistic regression model to identify independent predictors of mortality. Results are presented as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). A p-value < 0.05 was considered statistically significant [19].

Results

The study cohort comprised 127 patients, of whom 79 (62.2%) were male, with a mean age of 66.96 ± 8.57 years. Overall, 92 patients (72.4%) were current or former smokers, with a median smoking exposure of 40.0 pack-years (IQR 30–61.25). The emphysematous phenotype of COPD was documented in 36 patients (28.35%). At the time of ICU admission, type II respiratory failure was present in 99 patients (77.95%). The median PaO_2/FiO_2 ratio was 157.88 (IQR 109.69–230.06). Non-invasive ventilation was initially applied in 83 patients (65.35%), while percutaneous tracheostomy was required in 26 patients (20.47%).

The most frequent concomitant diagnoses was pneumonia in 61 patients (45.03%), cardiac decompensation in 12 (9.45%), and pulmonary embolism in 7 (5.51%). Influenza infection was confirmed in 7 patients (5.51%). The median duration of invasive mechanical ventilation was 2.0 days (IQR 1.0–5.5) days. Median ICU length of stay was 3.5 days (IQR 2.0–8.0), while total hospital length of stay 15.0 days (IQR 7.0–24.0) days. ICU mortality was 33/127 (26%), while overall in-hospital mortality reached 56/127 (44%). No statistically significant difference was found between ICU mortality and length of ICU stay (p=0.06). Although a downward trend in hospital mortality was observed over the study period, this did not reach statistical significance (p=0.29).

Comparison between survivors and non-survivors identified several factors significantly associated with mortality. Non-survivors had a significantly lower PaO_2/FiO_2 ratio (median 113.06, IQR 82.1–192.76 vs. 173.44, IQR 123.38–237.25; p=0.004), and lower Glasgow Coma Scale (GCS) scores at admission (median 10, IQR 6–13.5 vs. 13, IQR 10–14; p=0.03). Septic shock was markedly more frequent among non-survivors (n=12 (36.36%) vs. n=2 (2.13%); p<0.001), as was acute renal failure (ARF) (n=10 (30.3%) vs. n=13 (13.83%); p=0.03) **(Table 1).**

In multivariate logistic regression analysis, independent predictors of mortality were identified as PaO_2/FiO_2 ratio (OR 0.99; 95% CI 0.98–0.99; p=0.013), GCS (OR 0.82; 95% CI 0.69–0.96; p=0.014), and the presence of septic shock (OR 50.9; 95% CI 8.58–549.52; p<0.001).

Discussion

In this study, we evaluated the clinical characteristics, treatment outcomes, and predictors of mortality among patients requiring invasive mechanical ventilation for acute exacerbations of chronic obstructive bronchopulmonary disease (AECOPD). Multivariate analysis identified three statistically significant independent predictors of ICU mortality: impaired oxygenation reflected by low PaO_2/FiO_2 ratio, decreased level of consciousness as measured by the Glasgow Coma Scale (GCS), and the presence of severe infection manifested as septic shock). These findings underscore the central prognostic importance of gas-exchange failure, neurological status, and infection severity in critically ill patients with AECOPD.

The ICU mortality rate in our cohort was 26%, with an overall in-hospital mortality of 44%. These rates exceed those reported in several earlier studies, where ICU mortality ranged from 13.3% to approximately 25% and hospital mortality from 11–33% [13,14,20–24]. However, our findings are comparable with more recent data reporting ICU mortality of 25% and 28-day mortality of 34% [13]. Variability across studies likely reflects differences in patient selection, disease severity, comorbidity burden, and healthcare system characteristics. Long-term outcomes reported in the literature further highlight the poor prognosis of this population, with mortality rates of 4.5% at 12 weeks post-discharge [25], 26.2%

Table 1. Risk factors for mortality in the intensive care unit

Variable	Deceased (N=33)	Survivors (N=94)	p-value
Age (years), mean ± SD	65.73 ± 8.75	67.39 ± 8.51	0.41
Male gender, n (%)	23 (69.7%)	56 (59.57%)	0.30
Female gender, n (%)	10 (30.3%)	38 (40.43%)	0.30
Non-invasive ventilation, n (%)	13 (39.39%)	70 (74.47%)	<0.001
Duration of invasive ventilation (days), median (IQR)	2.5 (0–5)	2 (1–6)	0.47
PaO_2 (kPa), median (IQR)	8.69 (6.61–9.76)	9.09 (6.54–12.03)	0.29
PaO_2/FiO_2 ratio, median (IQR)	113.06 (82.1–192.76)	173.44 (123.38–237.25)	0.004
$PaCO_2$ (kPa), median (IQR)	7.635 (6.28–9.40)	7.56 (5.92–9.23)	0.85
pH, median (IQR)	7.26 (7.12–7.36)	7.28 (7.22–7.35)	0.12
Hemoglobin (g/L), median (IQR)	118.0 (98–143.5)	130.0 (113.5–145)	0.10
Hematocrit, median (IQR)	0.38 (0.31–0.45)	0.39 (0.34–0.45)	0.47
Leukocytes (×10^9/L), median (IQR)	16.0 (9.5–19.65)	10.8 (8.5–16.18)	0.06
Eosinophils (×10^9/L), median (IQR)	0.1 (0.02–0.2)	0.1 (0.03–0.2)	0.53
CRP (mg/L), median (IQR)	47.8 (27.4–133.73)	56 (13.66–135.07)	0.80
Procalcitonin (ng/mL), median (IQR)	1.4 (0.22–3.64)	0.22 (0.08–1.3)	0.10
Fibrinogen (g/L), median (IQR)	3.6 (2.70–5.58)	4.15 (3.32–6.14)	0.31
GCS score, median (IQR)	10 (6–13.5)	13 (10–14)	0.03
Smoker or former smoker, n (%)	26 (78.79%)	66 (70.21%)	0.34
Pack-years, median (IQR)	37.5 (24.38–50)	40 (30–65)	0.23
Emphysema, n (%)	6 (18.18%)	30 (31.91%)	0.13
Pneumonia, n (%)	20 (60.61%)	41 (43.62%)	0.09
Pleural effusion, n (%)	4 (12.12%)	14 (14.89%)	0.69
Pulmonary embolism, n (%)	4 (12.12%)	3 (3.19%)	0.05
Acute myocardial infarction, n (%)	5 (15.15%)	12 (12.77%)	0.72
Heart failure, n (%)	1 (3.03%)	6 (6.38%)	0.46
Atrial fibrillation, n (%)	5 (15.15%)	6 (6.38%)	0.12
Arterial hypertension, n (%)	20 (60.61%)	64 (68.09%)	0.43
Coronary artery disease, n (%)	5 (15.15%)	10 (10.64%)	0.49
CVI/TIA, n (%)	2 (6.06%)	10 (10.64%)	0.43
Hyperlipidemia, n (%)	0 (0%)	2 (2.13%)	0.40
Liver disease, n (%)	1 (3.03%)	3 (2.96%)	0.59
Diabetes mellitus without complications, n (%)	1 (3.03%)	9 (9.57%)	0.42
Diabetes mellitus with complications, n (%)	2 (6.06%)	8 (8.51%)	0.42
Acute renal failure, n (%)	10 (30.3%)	13 (13.83%)	0.03
Septic shock, n (%)	12 (36.36%)	2 (2.13%)	<0.001
Chronic renal failure, n (%)	3 (9.09%)	6 (6.38%)	0.60
Influenza, n (%)	1 (3.03%)	6 (6.38%)	0.47
Charlson comorbidity index, median (IQR)	4 (3–5)	4 (3–5)	0.70
Duration of ICU stay (days), median (IQR)	2 (0–5)	4 (2–10)	0.003
Total hospital stay (days), median (IQR)	5 (2–9.5)	18.5 (11–27)	<0.001

IQR – interquartile range; PaO_2 – partial pressure of oxygen in arterial blood; $PaCO_2$ – partial pressure of carbon dioxide; FiO_2 – fraction of inspired oxygen; CRP – C-reactive protein; GCS – Glasgow Coma Scale; CVI – cerebrovascular insult; TIA – transient ischemic attack; ICU – intensive care unit.

at one year, and up to 64.3% at five years [26]. Although specific causes of in-hospital death were not evaluated in this analysis, the discrepancy between ICU and total hospital mortality likely reflects advanced age, substantial comorbidity burden (Charlson index 4.05 ± 1.42), and severity of underlying COPD. Formal assessment of COPD severity was not feasible due to the absence of spirometric data, as spirometry is contraindicated during AECOPD. Furthermore, symptom burden (CAT, mMRC) and prior exacerbation history were unavailable due to the retrospective study design.

Comorbidities were common in our cohort, with systemic hypertension (66.1%), bronchiectasis (21.3%), diabetes (15.7%), pulmonary hypertension (12.6%), and

coronary artery disease (11.8%) being most prevalent. This pattern is consistent with prior studies, including a large cohort of 606 COPD patients in which hypertension (63.4%) and diabetes (35.8%) were similarly frequent, while the same study reported higher prevalence of heart failure, coronary artery disease, and dyslipidemia compared with our findings [27]. Other recent work from China reported respiratory failure, hypertension, coronary disease, and chronic heart failure as the most frequent comorbidities [21], findings largely consistent with our results, although respiratory failure was evaluated in our cohort as a gas-exchange parameter rather than as a comorbidity. Similar comorbidity profiles were noted in a Shanghai cohort of post-ICU AECOPD patients [25].

While autopsy studies have identified heart failure and pulmonary embolism as major causes of death in AECOPD [10], these conditions were not common in our cohort and did not significantly influence mortality. A study from Taiwan identified longer hospitalization and ICU admission as mortality predictors [28]; however, ICU treatment was an inclusion criterion in our study, precluding its assessment as a prognostic factor. Length of stay did not emerge as a significant predictor of mortality, though the shorter length of stay observed among non-survivors likely reflects early death in the most critically ill patients.

Our findings regarding PaO_2/FiO_2 ratio, GCS, and septic shock as independent mortality predictors are consistent with the previous reports. Prior studies have identified systemic hypertension, pneumonia, sepsis, acute renal failure, hypoglycemia and elevated serum creatinine [23,29–35]. In contrast, systemic hypertension and pneumonia were not independent predictors in our analysis, and variables such as serum creatinine and blood glucose were not included. Age has been widely reported as a mortality predictor [14,22,31,36,37], although several studies – consistent with our findings – have demonstrated no significant association [30,38,39]. Admission hypercapnia was also not associated with increased mortality, in line with previous observations [22,31,34].

A 2020 study identified advanced age (>80 years), respiratory failure on admission, fever, leukocytosis, elevated serum creatinine, and MAP <65 mmHg as mortality predictors [39]. Leukocytosis and hypotension – clinical markers of sepsis – support the strong prognostic role of infection severity. In our cohort, septic shock emerged as a significant independent predictor of mortality, emphasizing the importance of early detection and aggressive management of infectious complications in patients with AECOPD.

Notably, 45% of patients were admitted with concomitant pneumonia. Differentiating AECOPD from pneumonia can be clinically challenging due to overlapping symptoms; however, all included patients met established criteria for AECOPD, with documented symptom worsening necessitating intensified bronchodilator therapy. The high prevalence of pneumonia and its association with septic shock underscore the clinical relevance of infectious complications. This is particularly important in the context of chronic inhaled corticosteroid use and increased pneumonia risk, especially in patients with low eosinophil counts [4].

This study has several limitations. Its retrospective design restricts causal inference and is associated with incomplete clinical data. COPD severity could not be assessed due to the lack of spirometric measurements, symptom scales, and exacerbation history. Additionally, variables such as vaccination status and long-term inhaled therapy could not be statistically analyzed, limiting insights into their potential prognostic relevance.

Conclusion

Mortality among patients with acute exacerbations of chronic obstructive pulmonary disease requiring invasive mechanical ventilation in the intensive care unit is high. The PaO_2/FiO_2 ratio, Glasgow Coma Score, and the presence of septic shock were identified as independent predictors of mortality. Careful assessment of these parameters at admission and during ongoing clinical management may improve risk stratification and support timely therapeutic decision-making.

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