ORIGINAL ARTICLE

Eastern Journal of Medicine
East J Med 27(4): 579-584, 2022
DOI: 10.5505/ejm.2022.70745

Predictive risk factors for Intensive Care Unit mortality in Acute Exacerbations of COPD requiring Invasive Mechanical Ventilation

Aysel Sunnetcioglu[1*], Buket Mermit Çilingir[1], Maşuk Çelikel[1], Serhat Bedirhanoğlu[1], Hilmi Demirkiran[2]

[1]*Department of Chest Diseases, Yuzuncu Yil University Medical Faculty, Van, Turkey*
[2]*Department of Anesthesiology and Reanimation, Yuzuncu Yil University Medical Faculty, Van, Turkey*

ABSTRACT

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) frequently necessitate intensive care unit (ICU) admissions. The purpose of this study is to determine risk factors for ICU mortality in AECOPD who required invasive mechanical ventilation (IMV).

Patients requiring IMV for AECOPD between January 2013 and March 2019 were retrospectively reviewed. Patients' characteristics, comorbidities, and laboratory results were reviewed from the medical charts. Subjects' acute physiology and chronic health evaluation (APACHE) II score, Glasgow Coma Scale (GCS), IMV (days), and mortality were recorded. As an output or dependent variable, ICU mortality was considered. Other variables were considered to independent factors or risk factors. Then, Logistic regression analysis was performed to determine risk factors for ICU mortality in AECOPD.

The study, 134 patients were included. The mean duration of IMV were 11.6 ± 12.2 days. The ICU mortality were 51.4 %. On admission to ICU, patients had APACHE-II scores of 23.0 ± 6.2. Nonsurvivors had lower blood Mg levels (1.8 ± 0.2 mmol/L, p = 0.002), lower blood Ca levels (8.0 ± 0.7 mg/dL, p = 0.005), higher Uric Acid, (8.5±3.8 mg/dl, p = 004), higher CRP levels (87.2 ± 71.8 mg/dl, p = 0.048), higher leukocyte count (14.7 ± 10.2 103L, p= 0.040), higher serum lactate (2.3 ± 1.7 mmol, p = 0.003) compared to survivors.

APACHI score and uric acid level were found statististically significant risk factors for ICU mortality.

Keywords: Chronic Obstructive Pulmonary Disease, Acute Exacerbation, Invasive Mechanical Ventilation, Intensive Care Unit

Introduction

Chronic obstructive pulmonary disease (COPD) is a major global health problem due to its high prevalence, increasing incidence, and very serious personal, social and economic cost(1). It is associated with acut exacerbations which are required additional treatment, may occur during the clinical course of disease and increase the mortality (2).

Mortality ranges from 11% to 48% in following acute exacerbation of the disease (3-8). COPD has a high level of morbidity and progresses with acute attacks that require frequent admission to the intensive care unit(ICU)(5). Patients with COPD hospitalized in the ICU usually have more than one comorbidity, presenting with acute respiratory failure (ARF) as a result of an infection-related acute attacks(4,6).

Previous studies have focused on clinical parameters aiming to predict 30-day mortality following acute exacerbations of COPD (AECOPD) (8,9). These studies used parsiyel karbondioksit basıncı ($PaCO_2$), oxygen saturation, *Body Mass Index*, age, and comorbidities as predictors of in-hospital mortality during AECOPD. However, very little evidence is available on the determinants of ICU mortality in AECOPD patients.

In the present study, we aimed to identify risk factors for ICU mortality in AECOPD patients who required invasive mechanical ventilation (IMV). Predicting the risk factors for mortality is

*Corresponding Author: Prof. Aysel Sunnetcioglu, Department of Chest diseases, Yuzuncu Yil University School of Medicine, 65100, Van, Turkey
E-mail: izciaysel@mynet.com, Tel: +90(432) 216 47 05, Fax: +90 (432) 216 75 19
ORCID ID: Aysel Sunnetcioglu: 0000-0002-3379-3620, **Buket Mermit Çilingir:** 0000-0002-4946-7029, **Maşuk Çelikel**: 0000-0003-0671-6694, **Serhat Bedirhanoğlu:** 0000-0002-5598-0216, **Hilmi Demirkiran:** 0000-0001-8116-3933
Received: 01.09.2021, **Accepted:** 07.07.2022

an important issue during the management of critically patients.

Material and Methods

Patients: This was a study of patients with COPD who were admitted to a tertiary care hospital between January 2013 and March 2019. Ethics approval was obtained from the local ethics committee (degree no: 2019/17-15). All data were collected retrospectively, and all patient records were evaluated individually. COPD patients older than 40 years of age who required mechanical ventilation for acut respiratory failure were included in the study. Patients with asthma, COPD without hypercapnia, bronchiectasis, interstitial lung disease, malignancy, acute respiratory distress syndrome, were excluded from the study.

A detailed history and demography of all patients was taken including age, gender, smoking status, biomass exposure, comorbidities, history of hospitalization and acute exacerbations in the previous year.

Descriptions: COPD was diagnosed by a pulmonologist who evaluated airflow limitation on spirometry, limitation being defined as a forced expiratory volume in 1 s/*forced vital capacity* (FEV_1/FVC) ratio below 0.7 or below the lower limit of normal in patients with a history consistent with the diagnosis (10). An AECOPD was defined as an acute alter in respiratory symptoms that is beyond normal variability and is sufficient to guaranty a change in therapy (11). Patients admitted to the ICU for IMV were included if any of the following conditions: 1.severe dyspnea with the use of accessory muscles, paradoxical respiration, respiratory arrest, 2. a respiratory frequency > 35 breaths/minute; 3. impaired mental status; 4. respiratory acidosis (pH < 7.26); hypoxemia (arterial oxygen tension < 60 mmHg)(12). Acute physiology and chronic health evaluation (APACHE) II scores were calculated by using the most unfavorable values available during the first day in the ICU, as described in the literature (13).

Measurements: Arterial blood gas results, hemogram parameters, blood sugar levels, serum albümin, protein, magnesium, calcium, fosfor levels, C-reactive protein (CRP) and procalcitonin levels, neutrophil-to-lymphocyte ratio were retrieved from their medical records. Spirometry could not be performed in all of the patients, because those with COPD and hypercapnic respiratory failure had severe obstruction. Therefore, the general health status of those patients precluded examination by spirometry.

Statistical analysis : Descriptive statistics for the studied variables (characteristics) were presented as mean, standard deviation, minimum and maximum values. Normality assumption of the continuous variables was tested with Kolmogov-Simirnov test. After normality test, Student t test was performed to compare group means. Chi-square test was used to determine the relationship between categorical variables. As an output or dependent variable, ICU mortality was considered. Other variables were considered to independent factors or risk factors. In order to determine the possible risk factors that may be associated with ICU mortality, first, forward logistic regression was performed. Then logistic regression for ICU mortality were analyzed using the enter method and odds ratios aswell as confidence intervals were calculated. Statistical significance level was considered as 5% and SPSS (ver: 13) statistical program was used for all statistical computations.

Results

We included 134 COPD patients requiring IMV for ARF. Of all patients, 83 were male (61.9%) and the mean age was a 71.7 ± 9.6 years. The ICU mortality rate was 51.4%. The majority of the patients (56.3%) had previously been admitted to the hospital for an AECOPD.

Of the 134 patients, 98 (73.1%) had at least one comorbidity (Table 1), the most common of which were hypertension (n=36, 26.8%), followed by Coronary artery disease (n=30, 22.3%), Congestive heart failure (n=23, 17.1%), diabetes mellitus (n=23, 17.1%), Chronic renal failure (n=12, 0.89%).

The mean APACHE II score was 23.0 ± 6.2. Mean duration of IMV were 11,6 ± 12,2 days.

Those who died had a low albumin levels (26.1± 6.9 g/L, p < 0.001) , a low Protein levels (54.5 ± 8.2 g/L, P .008), a low blood Magnesium (Mg) levels (1.8± 0.2 mmol/L, P .002), a low blood Calcium (Ca) levels (8.0± 0.7 mg/dL, p = 0.005), high Uric Acid, (8.5±3.8 mg/dl, p= 0.004), high CRP levels (87.2± 71.8 mg/dl, p = 0.048), high Leukocyte count(14.7± 10.2 10^3L, p=0.040) , high serum lactate (2.3± 1.7 mmol, p = 0.003) when compared with those who survived, on ICU admission (Table 2). In order to determine the risk factors for ICU mortality, result of the logistic regression analysis were presented in Table 3. From the risk factors, odds ratios of APACHE - II and uric acid were found statistically significant.

Table 1. Differences In Baseline Characteristics Between Survivors and Non-Survivors

P-value	All patients (n=134)	Survivors (n=65)	Non-survivors (n=69)
Age (years) (Mean ± SD) 0.566	71.7±9.6	71.2±10.0)	72.1±9.2
Gender (M/F) 0.330	83/51	43/22	40/29
APACHE skoru (Mean ± SD) 0.001	23.0±6.2	19.4±4.5	26.4±5.6
GCS 0.001	7.2±2.2	8.1±2.4	6.3±1.8)
Mechanical ventilation stays, days 0.018	11.6±12.2	9.0±7.7)	14.0±14.9
(Mean ± SD)			
Current Smoker 0.436	54	25	30
Ex-Smokers n(%) 0.162	18	11	7
Non-smoker n(%) 0.230	40	21	19
Biomass n(%) 0.080	46	18	18
Patients with ≥2 previous AECOPD n(%) 0.981	75	36	39
Patients with ≥1 previous AECOPD 0.046	72	39	33
Requiring hospitalisation n(%)			
Comorbidities			
Diabetes n(%) 0.230	23(17.1%)	10	13
Hypertension n(%) 0.388	36(26.8%)	19	17
Coronary artery disease n(%) 0.807	30(22.3%)	15	15
Congestive heart failure n(%) 0.439	23(17.1%)	8	15
Chronic renal failure n(%) 0.889	12(0.89%)	5	7

Abbreviations: APACHE: Acute Physiology and Chronic Health Evaluation, GCS: Glasgow Coma Scale, AECOPD: Acute Exacerbations of Chronic Obstructive Pulmonary Disease, SD: Standard Deviation

Thus, it can be stated that a 1-unit increase in the APACHI score are likely to increase 1.43 times the risk of ICU mortality. Similarly, it has been observed that a 1 unit increase in the amount of uric acid are likely to increase 1.76 times the risk of ICU mortality.

Discussion

In the present study involving patients with AECOPD requiring invasive mechanical ventilation for respiratory failure, mortality rate was 51.4%. Uric acid levels were found as risk factor associated with ICU mortality. Additionally, nonsurvivors had lower albumin levels, lower protein levels, lower blood Mg levels, lower blood

Table 2. Differences In Laboratory Data Between Survivors and Non-Survivors

P-value	All patients (n=134)	Survivors (n=65)	Non-survivors (n=69)
Arterial blood gases			
pH (Mean ± SD) 0.144	7.23±0.9	7.22±0.1	7.20±0.9
PaO2, mmHg (Mean ± SD) 0.828	43.4±17.0	44.1±15.1	42.7±18.7
PaCO2, mmHg (Mean ± SD) 0.842	65.5±15.7	65.7±14.4	65.2±17.0
HCO3, mEq/L (Mean ± SD) 0.426	26.3±9.1	27.0±6.6	25.7±11
Serum Lactate, mmol/L (Mean ± SD) 0.003	1.9±1.4	1.3±0.7	2.3±1.7
Laboratory variables			
Leukocyte Count, 10^3L(Mean ± SD) 0.040	13.3±8.5	11.7±6,0	14,7±1.0
Hemoglobin, g/dL(Mean ± SD) 0.163	13.7±2.8	14.1±2.5	13.4±3.0
Hematocrit, % (Mean ± SD) 0.224	44.2±9.7	45.2±8.9)	43.2±10.9
Albumin, g/L (Mean ± SD) 0.001	28. 4±6.4	31.0±4.6)	26.1±6.9
Protein, g/L (Mean ± SD) 0.008	56.7±8.2	58.8±7.8)	54.5±8.2
Magnesium (Mg), mg/dL (Mean ± SD) 0.002	2.0±0.5	2.1±0.6)	1.8±0.2
Calcium (Ca), mg/ dL (Mean ± SD) 0.005	8.2±0.8	8.4±0.8	8.0±0.7
Phosphorus, mg/ dL (Mean ± SD) 0.462	3.8±1.6	3.6±1.2	3.9±1.9
Uric Acid, mg/ dL (Mean ± SD) 0.004	7.5±4.0	6.4±2.8	8.5±3.8
Blood glucose, mg/dL (Mean ± SD) 0 .737	160.2±89.0	157.5±89.8	162.7±88.8
CRP, mg/dL (Mean ± SD) 0.048	76.3±64.5	64.7±53.8	87.2±71.8
Procalcitonin, ng/mL (Mean ± SD) 0.324	3.02±7.5	2.1±7.9	3.8±7.0
Neutrophil /Lymphocyte Ratio (Mean ± SD) 0.650	15,6±19.0	14.9±16.5)	16.4±21.3

Abbreviations: PaO_2: Partial Arterial Oxygen Pressure, $PaCO_2$: Partial Carbon Dioxide Pressure, HCO_3: Bicarbonate, CRP: C-Reactive Protein, SD: Standard Deviation

Ca levels, higher CRP levels, higher leukocyte count, more elevated serum lactate compared to survivors.

Previous studies have shown that the APACHE II score is an risk factor for ICU mortality in AECOPD patients admitted to the ICU (3,14-16). The mean APACHE II scores reported in the literature range from 11 to 22 (17), comparable to the mean of 23 in our sample. This data suggests that APACHE II score may predict mortality in AECOPD patients admitted to ICU.

Table 3. Results of Logistic Regression For ICU Mortality Risk

OR (95% CI)	p-value	
APACHE II score	1.430 (1.107–1.848)	0.006
Glasgow Coma Scale	1,049 (0.746–1.476)	0.174
Current Smoker	0.805 (0.018–22.315)	0.436
Ex-Smokers	3.082 (0.033-288,305)	0.162
Uric acid, mg/dL	1.762 (1.151–2.697)	0.043
Glucose	0.991(0.779–1.003)	0.152
Patients with ≥2 previous AECOPD	0.211 (1.721–3.109)	0.153
Patients with ≥1 previous AECOPD requiring hospitalisation	4.746(0.463–48,642)	0.190

AECOPD which requires hospitalization, is an important prognostic factor in decreasing survival in all COPD stages (18). Soler-Cataluña et al. showed that mortality increases with the frequency of severe exacerbations requiring hospitalization(19). In the present study, the risk of mortality is higher in patients with hospitalized AECOPD in the previous year.

Hypoalbuminemia may occur in patients with chronic disease as a result of inadequate caloric intake and combined effects of inflammation. Many studies in the literature show that hypoalbuminemia increases mortality in COPD patients(3,20). Magnesium deficiency can lead to exacerbations of pulmonary diseases as it helps in alleviating bronchospasm(21). Bhatt et al. found an inverse relationship between serum magnesium level and the frequency of AECOPD(22). Hypomagnesaemia was correlated with increased length of ICU stay, and mortality rate(23). This study, nonsurvivors had lower albumin, Mg, and Ca levels.

Although many studies have been conducted to evaluate the relationship between uric acid and COPD, few have evaluated the relationship between serum uric acid concentration and mortality in COPD patients(24,25). In a study conducted by Zhang et al., hyperuricemia was shown to be a predictor of mortality in patients with COPD(26). Previous studies have shown that uric acid has a certain significance due to its antioxidant properties(27). However, uric acid also has pro-inflammatory properties, especially in patients with high serum uric acid levels(28). Hyperuricemia might worsen COPD by increasing inflammation and oxidative stress.

Our study has some limitations. First, it was a single-center study. In addition, it was subject to all of the drawbacks inherent to a retrospective study design, including the possibility that patient histories were incomplete and that there were missing data related to factors that could influence the outcomes (e.g., Spirometry values). However, our data could lay the foundation for future studies.

Acute Exacerbations of COPD requiring IMV are related to high mortality in ICU. In the present study, hyperuricemia and high APACHE-II scores were independent factors associated with mortality for patients admitted to ICU for acute exacerbations of COPD.

Reference

1. Agusti A, Vogelmeier C, Faner R. COPD 2020: changes and challenges. Am J Respir Crit Care Med 2020, September 26.
2. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report: GOLD Executive Summary. Eur Respir J. 2017;49:1700214
3. Connors AF Jr, Dawson NV, Thomas C, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease: Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments. Am J Respir Crit Care Med. 1996;154:959–967.
4. Alaithan AM, Memon JI, Rehmani RS, Qureshi AA, Salam A. Chronic obstructive pulmonary disease: hospital and intensive care unit outcomes in the Kingdom of Saudi Arabia. Int J Chron Obstruct Pulmon Dis. 2012;7:819–823.
5. Breen D, Churches T, Hawker F, Torzillo PJ. Acute respiratory failure secondary to chronic obstructive pulmonary disease treated in the intensive care unit: a long term follow up study. Thorax. 2002;57:29–33.

6. Seneff MG, Wagner DP, Wagner RP, Zimmerman JE, Knaus WA. Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease. JAMA. 1995;274:1852–1857.
7. Roche N, Zureik M, Soussan D, Neukirch F, Perrotin D. Predictors of outcomes in COPD exacerbation cases presenting to the emergency department. Eur Respir J 2008; 32:95361.
8. Conti V, Paone G, Mollica C, et al. Predictors of outcome for patients with severe respiratory failure requiring non invasive mechanical ventilation. Eur Rev Med Pharmacol Sci. 2015;19(20):3855–3860.
9. Faustini A, Marino C, D'Ippoliti D, Forastiere F, Belleudi V, Perucci CA. The impact on risk-factor analysis of different mortality outcomes in COPD patients. Eur Respir J. 2008; 32:629-636.
10. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med. 2001;163:1256-1276.
11. GOLD (2011) Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. Available at: http://www.goldcopd.org (Ref list)
12. Vestbo J, Hurd SS, Agusti AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013;187:347-365.
13. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13:818–829.
14. Cheng AC, Cheng KC, Chen CM, Hsing SC, Sung MY. The outcome and predictors of failed extubation in intensive care patients. The elderly is an important predictor. Int J Gerontol. 2011;5:206-211.
15. Khalil MM, Abd Elfattah N, El-Qusy AS. Assessment of the outcome of mechanically ventilated chronic obstructive pulmonary disease patients admitted in the respiratory ICU in Ain Shams University Hospital. Egypt J Bronchol. 2014;8:138-142.
16. Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax 2002;57:847-852.
17. Afessa B, Morales IJ, Scanlon PD, Peters SG. Prognostic factors, clinical course, and hospital outcome of patients with chronic obstructive pulmonary disease admitted to an intensive care unit for acute respiratory failure. Crit Care Med. 2002;30:1610-1615.
18. Hana Müllerova, Diego J. Maselli, Nicholas Locantore, et al. Hospitalized Exacerbations of COPD: Risk Factors and Outcomes in the ECLIPSE Cohort. Chest. 2015;147:999-1007.
19. Soler-Cataluña JJ, Martinez-Garcia MA, Román Sánchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax. 2005;60:925–931.
20. Hasegawa W, Yamauchi Y, Yasunaga H, et al. Factors affecting mortality following emergency admission for chronic obstructive pulmonary disease. BMC Pulm Med. 2014;14:151.
21. Shabbir PM. Miracle of magnesium sulfate. Indian J Allergy Asthma Immunol. 2012;26:14–15.
22. Bhatt SP, Khandelwal P, Nanda S, Stoltzfus J C, Fioravanti GT. Serum magnesium is an independent predictor of frequent readmissions due to acute exacerbation of chronic obstructive pulmonary disease. Respiratory Medicine. 2008;102:999–1003.
23. Chen M, Sun R, Hu B. The influence of serum magnesium level on the prognosis of critically ill patients. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2015;27:213–217.
24. Garcia-Pachon E, Padilla-Navas I, Shum C. Serum uric acid to creatinine ratio in patients with chronic obstructive pulmonary disease. Lung. 2007;185:21–24.
25. Horsfall LJ, Nazareth I, Petersen I. Serum uric acid and the risk of respiratory disease: a population-based cohort study. Thorax. 2014;69:1021–1026.
26. Xin Zhang, Lijie Liu, Rui Liang, Shoude Jin. Hyperuricemia is a biomarker of early mortality in patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2015;10:2519–2523.
27. Alvarez-Lario B, Macarron-Vicente J. Is there anything good in uric acid? QJM. 2011;104(12):1015–1024.
28. Ghaemi-Oskouie F, Shi Y. The role of uric acid as an endogenous danger signal in immunity and inflammation. Curr Rheumatol Rep. 2011;13(2):160–166.