ORIGINAL ARTICLE

Parameters in predicting the risk of a prolonged hospital stay in patients with acute exacerbation of chronic obstructive pulmonary disease: a single-centre experience

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ABSTRACT

Aim To identify clinical and laboratory parameters on admission and/or during a hospital stay that would predict prolonged hospital stay in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD).

Methods A retrospective cross-sectional study was conducted at the Clinic for Pulmonary Diseases and Tuberculosis, Clinical Centre University of Sarajevo for the period 2019-2021 accounting patients admitted due to AECOPD. The need for hospitalization was evaluated according to the current GOLD criteria and certain clinical parameters. Spirometry testing and laboratory analysis were performed for all patients on the day of admission and on the 10th day of hospital stay. Linear regression was used to show the relationship between multiple independent predictor variables and LOS.

Results A total of 50 patients were evaluated during their hospital stay due to AECOPD. Median of LOS was 22.02±1.06, with 90% hospital survival rate. Due to AECOPD the median of LOS in the intensive care unit (ICU) was 4±0.68 days with pH<7.35 in 34% of hospitalized patients. According to spirometry classification on the day of admission, 56% of patients were assigned to group 3 and 16% to group 4 with significant improvement identified on spirometry findings on discharge. Platelets on the day of admission were the only statistically significant positive predictors of the length of hospital stay.

Conclusion Identifying chronic obstructive pulmonary disease patients at risk of frequent exacerbations and appropriate disease management could reduce the disease burden.

Key words: chronic obstructive pulmonary disease, hospitalization, therapeutics

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INTRODUCTION

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is defined as acute worsening of respiratory symptoms such as dyspnoea, and/or increased sputum purulence and volume and/or cough which result from increased airway inflammation, mucus production and/or air trapping demanding the use of additional therapeutic modalities (1). Potential risk factors indicating the need for hospital treatment include worsening of resting dyspnoea, high respiratory rate, decrease in peripheral oxygen saturation, acute respiratory failure, depressed mental status, cyanosis and new onset of peripheral oedema, failure of prehospital medical treatment, comorbidities (e.g. heart failure, new onset of cardiac arrhythmias) (1,2). Chronic obstructive pulmonary disease (COPD) exacerbations usually last for 7-10 days, but 20% of patients after eight weeks of follow-up are still recovering from the previous exacerbation state (2). Frequent exacerbations are usual sign of uncontrolled disease and serious disease progression (3). Factors independently associated with poor outcome of AECOPD treatment are comorbidities, older age, low body mass index (BMI), history of frequent COPD exacerbation and long-term oxygen therapy use (4). The number of exacerbations experienced in the prior year remain the strongest predictor of future exacerbation history, along with worsening forced expiratory volume in the first second (FEV1) according to the spirometry findings (5). Exacerbations of COPD are often triggered by viral or bacterial infections presented by an increase in neutrophil and eosinophil count along with increased values of nonspecific inflammatory markers (6). The multiple comorbidities accompanying AECOPD are strongly associated with poor prognosis and worsening of the inpatient costs (1). Therefore, adequate and timely goal-directed treatment according to current guidelines (1) is crucial for AECOPD's favourable outcome with the least possible in-hospital stay.

The aim of this study was to identify both clinical and laboratory parameters on admission and/or during a hospital stay that would predict prolonged hospital stay in patients with AECOPD.

PATIENTS AND METHODS

Patients and study design

A retrospective cross-sectional study was conducted at the Clinic for Pulmonary Diseases and Tuberculosis, Clinical Centre University of Sarajevo for the period 2019-2021 accounting 50 patients admitted due to AECOPD.

Methods

The need for hospitalization was evaluated according to the current GOLD criteria (1) COPD exacerbation was classified as moderate, severe and/or very severe, and the following clinical parameters: smoking status, dyspnoea evaluation according to the modified medical researching council scale (mMRC scale), change in sputum colour and volume, chest pain, signs of upper respiratory tract infection verified at least five days prior admission, increase in body temperature, chest x-ray findings on the day of admission, number of exacerbations in the previous year and comorbidities on admission.

Moderate exacerbation is defined according to the following parameters: 50%≤FEV1<80% <3 exacerbation/year, no need for hospitalization during the past one-year period. Severe exacerbation is defined as: 30%≤FEV1<50%, ≥3 exacerbation/year, the need for one hospitalization during the past one-year period, ≥65 years of age. Very severe exacerbation is defined as FEV1<30%, ≥3 exacerbation/year, ≥2 hospitalizations during the past one-year period, ≥65 years of age.

Sputum colour (serous/white/yellow-green/haemoptysis) was evaluated on admission as well as sputum volume appearance, and classified as moderate, increased or not detected.

Modified medical research council scale (mMRC) (7) was used for dyspnoea classification according to the following: mMRC grade 1- dyspnoea only within the strenuous exercise, mMRC grade 2 - walks slower than people of the same age because of dyspnoea or has to stop for breath when walking at own pace, mMRC grade 3 - stops for breath after walking 100 yards (91 meters) or after a few minutes, mMRC grade 4 - too dyspnoeic to leave house or breathless when dressing.

Spirometry testing needed for recordings of forced expiratory volume in the first second (FEV1)

and laboratory analysis including erythrocyte sedimentation rate (ESR), complete (CBC) and differential blood cell count including neutrophils (Neu), lymphocytes (Lym), monocytes (Mono), basophils (Bas) and eosinophils (Eos), C-reactive protein (CRP) and parameters of arterial blood gas analysis (ABG) according to the reference range values were performed for all patients on the day of admission and on the 10th day of hospital stay. The 10th day for the laboratory parameters control was determined as cut-off in concordance to an average time of AECOPD duration according to GOLD criteria (1). Reference ranges for evaluated laboratory parameters were: erythrocytes 4.34 -5.72 x10^{12}/L and 3.86 -5.08 x10^{12}/L for males and females respectively; leukocytes 3.4-9.7x10^{9}/L; haemoglobin 137-175 g/L in males and 119-157 g/L in females; haematocrit 0.41-0.53 % in males and 0.35-0.47% in females; platelets 158-424 x10^{9}/L for males and females; neutrophils 44-72%; lymphocytes 20-46%; monocytes 4-8 %; basophils 0-1 %; eosinophils 2-4 %; CRP up to 5.0 mg/L.

Spirometry findings on admission and discharge related to FEV1 were classified into four different categories: FEV1≥80% (mild), 50%≤FEV1<80% (moderate), 30%≤FEV1<50% (severe); FEV1<30% (very severe) assigned with category 1, 2, 3 and 4, respectively.

On the day of admission physical examination was performed including measurements of vital parameters such as heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) values. Patients were followed during the hospital stay with repeated/daily notification of vital parameters values and timed lab test analysis according to objective clinical improvement or deterioration of the patient's condition.

Statistical analysis

Data were evaluated by standard statistical procedures and presented in tables. The Shapiro-Wilk test was used to evaluate the normal distribution of continuous variables. The results were statistically evaluated and presented as mean value (X) and standard error mean (SEM) for variables. Linear regression was used to show relationship between multiple independent predictor variables and LOS (length of stay). The $p<0.05$ was considered as statistically significant.

RESULTS

Fifty patients were evaluated during their hospital stay due to AECOPD; 30% were females, and 70% were males. The median of length of hospital stay (LOS) was 22.02±1.06, with 90% of hospital survival rate. Due to AECOPD the median of LOS in the intensive care unit (ICU) was 4±0.68 days with pH<7.35 in 34% of hospitalized patients. Elevations in partial arterial pressure of CO_2 ($paCO_2$) were identified in only 18% of patients on the day of admission. The majority of patients were passive smokers, 22 (44%), while 18 (36%) were current smokers, and only 1 (2%) was ex-smoker. Twenty-seven (54%) patients did not experience any previous COPD exacerbations, while exacerbations appeared in the last three, six and twelve months in 12 (24%), 7 (14%) and 4 (8%) of patients, respectively. Upper respiratory tract infection was a clinical finding in 27 (54%) of patients. Most patients were classified in groups 2 and 3 according to mMRC on the day of admission, accounting for 14 (28%) and 36 (72%), respectively.

According to spirometry classification on the day of admission, 23 (56%) patients were assigned to group 3, 13 (26%) to group 2 and 8 (16%) to group 4 with significant improvement identified on spirometry findings on discharge, accounting for 22 (44%) in group 1 and 19 (38%) in group 2.

An increase in mean values of nonspecific inflammatory markers such as leucocytes and CRP was noted on admission, accounting for 12.1±0.84 and 73.77±12.95, respectively. Total leukocyte counts as well as a neutrophil-to-lymphocyte ratio (NLR) and neutrophil count were increased on admission, accounting for 12.1±0.84, 8.51±1.47 and 80.11±1.71 respectively, with the decrease in number after ten days of hospital stay. However, the eosinophil count was elevated on the 10th day of hospital stay in comparison to the admission result (1.46±0.23 and 1.06±0.29 respectively) (Table 1).

In a univariant linear regression analysis model, by examining independent predictors in patients with acute exacerbation of COPD, parameters such as chest pain, platelets, and eosinophils on the 10th day of hospital stay were identified as statistically significant positive predictors of the length of hospital stay.

The parameters such as elevated body temperature, sputum, sputum volume and respiratory

Table 1. Clinical and laboratory parameters of patients with acute exacerbation of chronic obstructive pulmonary disease (COPD)

Parameter	Value
Length of hospital stay/LOS (days)	22.02±1.06
Hospitalization outcome (death/survival) (%)	10/90
Gender (female/male) (%)	30/70
Smoking status (non-smoker/smoker/passive smoker/ex-smoker) (%)	18/36/44/2
Number of AECOPD (without exacerbation/in last 3 months/in last 6 months/in last 12 months) (%)	54/24/14/8
Upper respiratory tract infection (yes/no) (%)	54/46
Elevated body temperature (<37/37.5/38/38.5 C) (%)	76/2/16/6
mMRC (0/1/2/3/4) (%)	0/0/28/72/0
Sputum (without/serous/white/yellow-green/haemoptysis) (%)	6/38/28/16/10
Sputum volume (without/moderate/increased) (%)	8/6/86
Chest pain (yes/no) (%)	30/70
Spirometry on admission (1/2/3/4) (%)	2/26/56/16
Spirometry on discharge (1/2/3/4) (%)	44/38/18/0
SBP<90mmHg (yes/no) (%)	6/94
paCO2>6.5kPa (yes/no) (%)	18/82
pH<7.35 (yes/no) (%)	34/66
ICU stay (days)	4±0.68
ESR on admission	45.34±5.55
CRP on admission (mg⁄L)	73.77±12.95
Erythrocytes on admission (x10^{12}⁄L)	4.57±0.11
Haemoglobin on admission (g⁄L)	132.6±2.51
Haematocrit on admission (%)	40.68±0.89
Platelets on admission (10^9⁄L)	295±16.71
Leucocytes on admission (10^9⁄L)	12.1±0.84
Neutrophils (%)	80.11±1.71
Lymphocytes (%)	10±1.34
Eosinophils (%)	1.06±0.29
NLR	8.51±1.47
ESR on the 10th day of hospital stay	25.98±4.07
CRP on the 10th day (mg⁄L)	23.91±6.96
Erythrocytes on the 10th day (x1012⁄L)	4.26±0.08
Haemoglobin on the 10th day (g⁄L)	125.5±2.5
Haematocrit on the 10th day (%)	39.07±1.04
Platelets on the 10th day (x109⁄L)	237.58±18.05
Leukocytes on the 10th day (x109⁄L)	9.22±0.46
Lymphocytes on the 10th day (%)	21.58±1.54
Neutrophils on the 10th day (%)	67.85±1.93
Eosinophiles on the 10th day (%)	1.46±0.23
NLR on the 10th day of hospital stay	3.09±0.78

Data are shown as number of patients (percentage) or mean±SEM (standard error of mean), unless otherwise stated. Percentages are calculated for non-missing days; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; CRP, C reactive protein; mMRC, modified medical research council dyspnoea scale; SBP, systolic blood pressure; ICU, intensive care unit; ESR, erythrocyte sedimentation rate; NLR, neutrophil to lymphocyte ratio

rate higher than 30 were identified as statistically significant negative predictors of the length of hospital stay ($p<0.05$). In a multivariant linear regression analysis model, by examining the independent predictors with acute exacerbation of COPD, platelets on the day of admission were the only statistically significant positive predictors of the length of hospital stay. At the same time, elevated body temperature and sputum volume were identified as statistically significant negative predictors of the length of hospital stay ($p<0.05$) (Table 2).

DISCUSSION

Evaluation of the variation of the LOS for COPD exacerbation performed by Ruparel et al. identified that the mean LOS across Europe were higher than expected showing great variability in overall Europe, North America, Australia and Asia (8,9). The factors that are influencing the variability of LOS are patient-related, determined by the stage of the disease and exacerbation severity as well as treatment-related (10).

Predominantly related factors to a prolonged hospital stay in patients admitted with AECOPD are the place of admission and the need for more intensive care treatment (11). The study by Garcia-Sanz et al. (11) on 661 patients identified that prolonged stay due to AECOPD was primarily related to the unit patients are admitted to, the need for more intensive care treatment and the use of noninvasive mechanical ventilation. However, patients evaluated in our study were treated in ICU for a median of 4±0.68 days and continued treatment in the hospital ward with available medicamentous treatment due to satisfactory clinical improvement. The prospective study by Crisafulli et al. evaluated clinical variables predicting the risk of a hospital stay for longer than seven days in patients with severe AECOPD. They identified that the presence of an mMRC ≥2 and acute respiratory acidosis at admission independently increased the risk of a prolonged LOS for AECOPD (12). Most patients in our study were assigned with mMRC 3 on admission, which partially explains prolonged LOS with a median of 22.02±1.06 days. The study of Wang et al. exploring the independent predictors of prolonged LOS in AECOPD patients and identified three groups of patients with LOS <7 days, 7-10 days, and ≥11 days, respectively (13), and found that rates of hypertension and chronic cor pulmonale (CCP), neutrophil-lymphocyte ratio (NLR), and erythrocyte sedimentation rate (ESR) were independent predictors of prolonged LOS in AECOPD patients. The study of Gomez-Rosero et al. aimed to prove mean platelet volume (MPV), eosinophil count and neutrophil/lymphocyte ratio (NLR) as in-hospital prognostic factors, but identified only NLR as greater than 5 as a strong predictor of mortality or ICU admissions and a

Table 2. Independent clinical and laboratory predictors of length of hospital stay in patients with acute exacerbation chronic obstructive pulmonary disease (AECOPD)

Variable	Univariate linear regression analysis		Multivariate linear regression analysis	
	Regression coefficient (95% CI)	p	Regression coefficient (95% CI)	p
Gender	-3.00 (-10.48 – 4.48)	0.374		
Smoking status	3.75 (-4.90 – 12.40)	0.339		
Number of AECOPD	1.18 (-3.16 – 5.51)	0.541		
Upper respiratory tract infections	-3.80 (-19.21 – 11.61)	0.578		
Elevated body temperature	-7.20 [(-13.08 – (-1.32)]	0.023	-2.73 [(-4.68 – (-0.78)]	0.007
mMRC	2.85 (-4.63 – 10.33)	0.397		
Sputum	-4.36 [(-8.69 – (0.02)]	0.049	-0.77 (-2.63-1.09)	0.408
Sputum volume	-12.17 [(-20.95 – (-3.38)]	0.023	-5.92 [(-10.26 – (-1.17)]	0.009
Chest pain	12.37 (1.92 – 22.82)	0.027	2.55 (-1.89 – 6.99)	0.253
Spirometry on admission	-1.27 (-7.33 – 4.80)	0.637		
Respiratory rate >30/min	-19.51 [(-31.76 – (-7.26)]	0.007	-2.01 (-5.94 – 1.91)	0.307
ESR on admission	0.02 (-0.11 – 0.14)	0.761		
CRP on admission	0.15 (-0.11- 0.40)	0.220		
Erythrocytes (x10^{12}/L)	-4.45 (-19.61-10.70)	0.509		
Haemoglobin (g/L)	-0.34 (-1.62- 0.93)	0.545		
Haematocrit (%)	2.56 (-3.45 -8.58)	0.347		
Platelets (x10^9/L)	0.07 (0.02-0.12)	0.013	0.03 (0.01-0.04)	0.005
Leucocytes (x10^9/L)	-1.96 (-6.04- 2.12)	0.293		
Neutrophils %	-0.35 (-0.99 – 0.31)	0.249		
Eosinophils %	-0.97 (-5.82 – 3.88)	0.651		
Basophils %	10.82 (-1.64 – 23.27)	0.079		
Monocytes %	0.50 (-3.18 – 4.18)	0.756		
On the 10th day				
ESR	-0.21 (-0.76 – 0.35)	0.405		
CRP (mg/L)	-0.04 (-0.27 – 0.19)	0.722		
Erythrocytes (x10^{12}/L)	-21.38 (-48.67 – 5.91)	0.106		
Haemoglobin (g/L)	-0.18 (-1.68 – 1.32)	0.785		
haematocrit (%)	0.49 (-1.86 – 2.84)	0.637		
Platelets (x10^9/L)	-0.04 (-0.11 – 0.02)	0.161		
Leukocytes (x10^9/L)	1.95 (-0.28 – 4.19)	0.078		
Lymphocytes (%)	-0.73 (-2.11 – 0.66)	0.254		
Eosinophils (%)	4.01 (1.45 – 6.57)	0.008	0.95 (-0.17 – 2.07)	0.095
Basophils (%)	-9.95 (-44.80 – 24.90)	0.521		

ESR, erythrocyte sedimentation rate; CRP, C reactive protein; mMRC, modified medical research council dyspnoea scale

longer hospital stay in patients hospitalized with AECOPD (14). However, the results of our study identified platelets on the day of admission as the only statistically significant positive predictors of the LOS. In addition, an increase in mean values of nonspecific inflammatory markers such as leucocytes, CRP, and NLR were noted on admission in our study, with a significant decrease after ten days of hospital stay, which correlates with previous results.

According to available studies, COPD is linked with comorbidities such as congestive heart failure (CHF), fluid and electrolyte disorders, and renal failure (15). Results of Inabnit et al. identified that CHF was associated with a 28% greater length of stay ($p< 0.0001$), electrolyte disorders were associated with a 2-fold greater length of stay ($p< 0.0001$) while renal failure was associated with a 50% greater length of stay ($p< 0.0001$) (15). However, comorbidities on the day of admission were not evaluated in our study due to the lack or inconsistency of data. A larger sample, along with the analysis of impact of comorbidities on outcome, would provide more significant conclusions for clinical practice. In AECOPD patients, an improvement in clinical outcome is the result of successful therapy (16). Data on sputum culture suggest that bacterial infections often cause AECOPD, and sputum purulence and the presence of bacteria are strongly correlated (17). Antibiotics are the usual treatment in AECOPD; however, some patients treated with antibiotics show incomplete resolution, persistence of symptoms/signs, leading to an in-hospital treatment failure. That imposes a question of antibiotic efficacy in resolving identified bacterial infections regarding the adequacy of its use leading to the likelihood of future relapse (18).

Among numerous clinical factors related to early readmission, lung function decline rate

and dyspnoea severity score are among the most common (19). Moreover, numerous studies performed with a period of one-year observation on AECOPD patients, identified airflow obstruction severity, measured by FEV1, to be an important predictor factor for AECOPD readmission during the stable phase (20). In general, FEV1 values below 50% of the predicted values are associated with a higher risk of COPD readmission (21). The results of our study identified more than half of patients assigned with group 3 on admission according to spirometry findings with significant improvement after one day follow-up, which also correlated with previous data.

Taking into consideration research findings, our study determined certain laboratory and clinical parameters influencing the prolonged hospital stay in patients with AECOPD.

In conclusion, future research should determine if better management of comorbidities can favourably impact the COPD disease burden. COPD patients frequently experience exacerbations. Increasing exacerbation frequency is associated with increased COPD-related costs, regardless of the cause. Future targets should be adjusted to identify COPD patients at risk of frequent exacerbations and appropriate disease management.

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TRANSPARENCY DECLARATION

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