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Risk factors for prolonged hospitalization as a marker for difficult-to-manage exacerbations of chronic obstructive lung disease (COPD): the DiMECO Study

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Abstract

Background Exacerbation is an independent risk factor for chronic obstructive pulmonary disease (COPD)-related morbidity and mortality. Despite optimal care, there may be risk factors that lead to difficulties in managing exacerbations that may be associated with prolongation of length of hospital stay (LOS).

Methods This is a multicenter prospective observational study of COPD patients hospitalized with exacerbations. Prolonged LOS was calculated according to the 50th percentile and defined as ≥ 9 days. Potentially predicting factors of LOS were stratified into 4 pillars as patient-related, disease and exacerbation-related, treatment-related and, hospital utility-related. These categories were systematically documented throughout the duration of the hospitalization.

Results A total of 434 patients, 361 males and 73 females, with a mean age of 69.2 ± 9.3 years, were included in the study. Variables of each pillar were tested with univariate analysis to identify potential risk factors for prolonged LOS. Subsequently significant factors excluding factors associated with hospital utility were tested with multivariate logistic regression analysis for detecting potential associated factors for difficult-to-manage COPD exacerbation. Biomass exposure, past history of non-invasive mechanical ventilation (NIMV), low bicarbonate levels at admission, antibiotic switching, need for theophylline, increasing oxygen requirement, need for in-hospital non-invasive mechanical ventilation, nutritional support and physiotherapy were found as defining factors.

Conclusions The DiMECO study can help to identify COPD exacerbators who are at risk for prolonged hospitalizations that may associate with difficult-to-manage COPD exacerbations. Difficult to manage COPD exacerbation may serve as a provocative framework, underscoring the necessity for a better understanding of

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the multifaceted approaches to the management of COPD exacerbations. This conceptualization warrants further investigation across diverse clinical settings to validate its applicability and efficacy.

Keywords COPD, Exacerbation, Prolonged hospitalization, Difficult to manage COPD exacerbation

Introduction

Chronic obstructive pulmonary disease (COPD), the third leading cause of death worldwide, is characterized by varying severity of exacerbations which is an independent risk factor for COPD-related mortality [1]. Twenty-two–40% of all COPD patients experience at least one moderate or severe exacerbation annually, while 9–16% of patients experience more than one exacerbation [2].

The cause, severity, impact, treatment and time course of the exacerbations vary among patients, communities, health care systems and countries. It is not unusual that, according to the former classification of exacerbation proposed by the Global Initiative for Obstructive Lung Disease (GOLD), patients with non-severe exacerbations may be hospitalized frequently [3]. This may result in unfair healthcare utilization and increased burden on hospitals. Recently, the GOLD proposed a new and more objective classification of exacerbations, delineating severe exacerbations characterized by respiratory insufficiency. This classification highlights the significant burden of COPD-related morbidity and mortality [4, 5]. Although there are no comprehensive integrated clinical guidelines covering multiple dimensions of the management of COPD exacerbation, there are several evidence-based recommendations for the management of respiratory insufficiency, antibiotic therapy, bronchodilation and corticosteroid usage [1, 6, 7]. The main goals of the management of exacerbations are to relieve symptoms, to prevent readmission and mortality, to return the level of oxygen and other supportive therapy to the home-maintenance level, to control comorbidities and to reassure patient engagement in follow-up bundles. The required length of hospital stay (LOS) for those goals is not certain and varies depending on several factors. This is usually 5–14 days in general [8–11].

The LOS is prolonged in some patients who do not respond in a timely manner to therapies and supportive care, which may lead to additional complications and costs and certainly vicious cycles for patients. We hypothesized that the situation could be defined as a "difficult to manage COPD exacerbation", for which a prolonged LOS could be a surrogate marker. A literature review revealed that there is also heterogeneity in defining prolonged LOS, which varies from 4 to 14 days. The risk factors for prolonged LOS have been analyzed in different settings [8–11]. Heterogeneity in exacerbation phenotypes, comorbidities that mimic and aggravate exacerbation symptoms, baseline characteristics of disease severity, utilized pharmacological and nonpharmacological treatment modalities and available healthcare services may all affect patient care and exacerbation-related outcomes that may affect the LOS.

In this study, we aimed to investigate different sets of variables to predict prolonged LOS in hospitalized COPD exacerbators that may associate with "difficult to manage COPD exacerbations".

Materials and methods

Study design

This is a prospective observational study of patients with COPD exacerbation who were admitted to the general ward of pulmonology department from emergency room (ER) or outpatient clinic between October 1^{st,} 2018, and September 30^{th,} 2019. This study was approved by the local institutional ethics committee of Gazi University. Written informed consent for participation was obtained from each enrolled participant. The study was conducted in accordance with the Declaration of Helsinki. *The clinical trial number is 687/2018.*

Inclusion criteria

Patients with a confirmed diagnosis of COPD by spirometry for at least one year who experienced severe exacerbation, requiring hospitalization based on symptoms, physical signs and respiratory insufficiency were included in the study [1]. Patients who developed hospital-acquired pneumonia, pulmonary edema, congestive heart failure, or lung cancer during hospitalization were also included. However, patients with a pre-existing history of stable heart failure or lung cancer prior to hospitalization were included only if their condition remained stable before admission.

Exclusion criteria

Patients who had not undergone a pulmonary function test in the past year, those with COPD admitted directly to the intensive care unit or transferred from the intensive care unit to a general ward, and those with stable COPD hospitalized primarily for other reasons—such as community-acquired pneumonia, heart failure, or lung cancer—were excluded. Additionally, patients with both COPD and asthma were excluded from the study.

The GOLD 2017 COPD report was accepted as a reference for COPD diagnosis, staging, definition of COPD exacerbation, treatment of exacerbation, criteria for transfer to the intensive care unit and discharge [1]. All attending physicians agreed to follow the GOLD document for guiding patient management.

Study parameters

Parameters that may potentially be associated with prolonged length of hospital stay were recorded prospectively during hospitalization. These parameters were classified into 4 pillars as patient-related, disease and exacerbation-related, treatment-related and hospital utility-related factors. The first 3 pillars were analyzed using multivariate logistic regression model to predict LOS that may associated with "difficult to manage COPD exacerbation". Hospital utility factors, waiting time in ER were intentionally excluded from the model, as they reflect institutional characteristics contributing to prolonged stays and may not be directly associated with the difficulties in management. A detailed description of the pillars is given by Baha et al. [8]. The definitions of the recorded variables that constitute the pillars are detailed in the appendix.

Laboratory work-up, including total blood count; biochemistry, including liver and kidney function tests; C-reactive protein (CRP); arterial blood gas; chest X-ray; and electrocardiogram (ECG), were examined for all patients on the day of hospital admission and, if necessary, during hospitalization. The frequency of workup was contingent upon the decisions made by the attending physicians.

Comorbidities such as cardiovascular disease, diabetes mellitus, lung cancer, sleep apnea syndrome, depression and anxiety were actively sought with medical reports and with specific tools such as stop bang score, hospital anxiety and depression score (HAD). Any suspected conditions were further evaluated by the decision of the attending physician.

History of drug usage including antibiotics, bronchodilators, immunosuppressants, noninvasive mechanical ventilation (NIMV), long-term oxygen therapy (LTOT), nebulizers, were recorded in admission.

In hospital NIMV usage, supplemental oxygen levels, nutritional status, need for nutritional support and physiotherapy and specific examination tools ordered by attending physician during hospitalization were also documented. Accordingly, serum vitamin D levels, cardiac enzymes, N-terminal pro brain natriuretic peptide (NT-pro BNP), echocardiography (ECHO), hemoglobin A1c (HgbA1c), D-dimer, thorax computed tomography (CT), thorax CT-angiography and bronchoscopy were performed if needed.

Nutritional support was administered to patients with inadequate oral intake and malnutrition. Assisted physiotherapy was administered to patients with inadequate mobilization, cough and sputum mobilization. Appropriate consultations were obtained for complex comorbidity management.

At the end of the hospitalization period in pulmonology ward, the clinical outcomes were defined as discharge, transfer to intensive care, transfer to another department or death.

The length of hospital stay was calculated as the total hospitalization period both in the emergency room (ER) and in pulmonology ward. Since the length of hospital stay did not show a normal distribution, we evaluated prolonged LOS according to percentiles. The prolonged LOS was 6 days according to the 25th percentile, 9 days according to the 50th percentile (median value) and 14 days according to the 75th percentile. Those whose hospitalization duration was above the 50th percentile was considered to have a prolonged LOS. A cutoff value of 9 days or more was used for a prolonged LOS in this study.

Statistical analysis

The statistical analysis was performed using SPSS version 23.0 software (Chicago, USA). In the statistical analysis, categorical variables are presented as numbers and percentages, and continuous variables are presented as the mean ± standard deviation (SD) and as the median (25th −75th interquartile range) for descriptive analysis. For normally distributed data, the Mann-Whitney U test was used for comparative analysis between two independent groups, and the independent sample t test was used for normally distributed data. Normally distributed continuous variables are expressed as mean ± SD, while non-normally distributed continuous variables are expressed as median (25th −75th interquartile range). Comparisons of categorical variables between separate groups were performed with the chi-square test.

After performing univariate analysis in each pillar, statistically significant risk factors were tested in one multivariate logistic regression analysis to identify the factors associated with prolonged LOS that may associate with "difficult to manage COPD exacerbation". Hospital utilization factors, such as extended emergency room stays exceeding one day and inability to discharge patients due to incomplete work-up, were excluded from the multivariate model deliberately. Although these factors are associated with prolonged length of stay, they are obviously out of the scope of the definition "difficult to manage" COPD exacerbations. The details of this model are explained in the supplementary material (suppl.). A p value < 0.05 was considered to indicate statistical significance. This study is a multicenter investigation utilizing real clinical data. Consequently, we did not employ imputation methods or other techniques to handle missing data. Instead, analyses were conducted using only the available data. For variables with missing information, the sample sizes (n values) are clearly indicated in the tables to ensure transparency.

Results

The patient enrollment and the outcome are summarized by the flow chart (Fig. 1). The baseline sociodemographic characteristics and comorbidities of the patients are shown in Table 1.

A total of 434 patients from 13 centers (9 university hospitals and 4 training and research hospitals) were included in the study. Among them 361 (83.2%) were male, and 73 (16.8%) were female. The mean age was 69.2±9.3 years. A total of 22.1% of the patients were active smokers, and 43.3% had biomass exposure. Two hundred and two (46.5%) patients were on LTOT, whereas 95 (21.9%) were on noninvasive mechanical ventilation (NIMV) at admission. Two hundred and eighty-six (65.9%) patients had a history of nebulizer usage. A total of 356 (82%) patients had at least one comorbidity. The most frequent comorbidities were cardiovascular conditions, including hypertension (54.1%) and coronary artery disease (32.9%). Diabetes mellitus was present in 28.1% of the patients.

Patients who did not experience prolonged hospitalization had a mean hospital stay of 5 days (R: 1–8), whereas patients in the prolonged group were hospitalized for a mean of 14 days (R: 9–70). At the end of the study, the clinical outcome of the patients was as follows: the majority of patients were discharged (n=420), 9 patients (6 from the prolonged group) died, and 5 (all from the prolonged group) were referred to another department for extrapulmonary reasons.

Univariate analysis

Patient-related factors

Past history of smoking (p<0.001), biomass exposure (p<0.001), presence of any comorbidity (p=0.016), being on LTOT (p=0.001), being on NIMV (p=0.018), being on nebulizer (p=0.028), increased hospital anxiety-depression score (HAD score 16–21) (p<0.001) and Stop Bang score (score 5–8 for high risk for obstructive sleep apnea (OSA)) (p=0.006) were significantly more frequent in patients with prolonged LOS. Among the comorbidities, heart failure (p=0.007), arrhythmia (p=0.014), chronic renal failure (p=0.012) and lung cancer (p=0.004) were more common in patients with a prolonged LOS.

Disease- and exacerbation-related factors

The COPD grades and stages and features of exacerbations are shown in Table 2. The annual number of exacerbations, time from symptoms` onset to hospital admission, and waiting time in ER were greater in patients with a prolonged LOS (Table 2). In addition, partial oxygen levels at room temperature were lower in these patients than in the non- prolonged patients (Table 2).

CRP (p=0.004) and troponin (p=0.028) were greater in patients with a prolonged LOS than in patients with a non-prolonged LOS, while the albumin/protein ratio (p=0.003) and levels of vitamin D (p=0.04) were lower.

Pneumonic infiltration and bronchiectasis were detected via chest X-ray more often in the prolonged-LOS vs. non-prolonged group (p=0.011). Thorax CT was performed more often in patients with a prolonged LOS

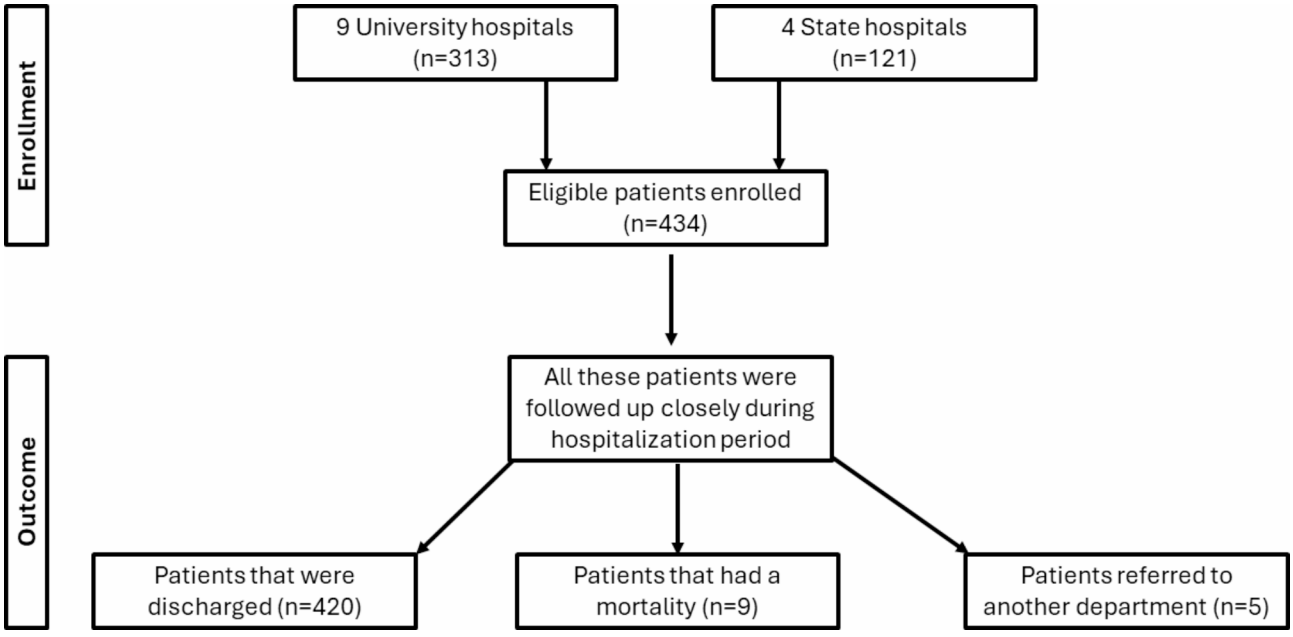

Fig. 1 Flow chart of the study for patient enrollment and outcome

Table 1 Baseline sociodemographic characteristics and comorbidities of patients

	Total	Non-prolonged LOS	Prolonged LOS	P
	N = 434	n = 197 (45.4%)	n = 237 (54.6%)	
Age, years	69.2 ± 9.3	68.6 ± 9.9	69.6 ± 8.9	0.2641
Age, n (%)				0.1192
< 65 years	127 (29.3)	65 (33.0)	62 (26.2)	
Gender, n (%)				0.4192
Male	361 (83.2)	167 (84.8)	194 (81.9)	
BMI, kg/m^2	n = 420	n = 187	n = 233	0.8081
	25.2 ± 5.7	25.3 ± 5.4	25.4 ± 5.7	
Smoking status, n (%)				**< 0.001**[2]
Never smoked	24 (5.5)	8 (4.1)	16 (6.8)	
Ex-smoker	301 (69.4)	122 (61.9)	179 (75.5)	
Passive smoker	13 (3.0)	5 (2.5)	8 (3.4)	
Active smoker	96 (22.1)	62 (31.5)	34 (14.3)	
Biomass exposure, n (%)				**< 0.001**[2]
Yes	188 (43.3)	64 (32.5)	124 (52.3)	
Comorbidity, n (%)				**0.0162**
Yes	356 (82.0)	152 (77.2)	204 (86.1)	
LTOT, n (%)				**0.0012**
Yes	202 (46.5)	75 (38.1)	127 (53.6)	
NIMV, n (%)				**0.0182**
Yes	95 (21.9)	33 (16.8)	62 (26.2)	
Nebulizer use, n (%)				**0.0282**
Yes	286 (65.9)	119 (60.4)	167 (70.5)	
HAD (total point)	n = 399	n = 176	n = 223	**< 0.001**[3]
	16.0 (11.0–22.0)	15.0 (8.0–19.0)	18.0 (12.0–23.0)	
HAD, n (%)	n = 399	n = 176	n = 223	**0.0082**
≥ 16 (median)	220 (55.1)	84 (47.7)	136 (61.0)	
Stop Bang, n (%)	n = 405	n = 180	n = 225	**0.0062**
Low risk for OSA	83 (20.5)	31 (17.2)	52 (23.1)	
Intermediate risk for OSA	187 (46.2)	99 (55.0)	88 (39.1)	
High risk for OSA	135 (33.3)	50 (27.8)	85 (37.8)	
Comorbidities				
Heart Failure, n (%)				**0.0072**
Yes	106 (24.4)	36 (18.3)	70 (29.5)	
Arrhythmia, n (%)				**0.0142**
Yes	74 (17.1)	24 (12.2)	50 (21.1)	
CRF, n (%)				**0.0122**
Yes	37 (8.5)	9 (4.6)	28 (11.8)	
Lung Cancer, n (%)				**0.0042**
Yes	22 (5.1)	3 (1.5)	19 (8.0)	

[1]*Student's t test* [2]*Chi-square test* [3]*Mann-Whitney U test* Abbreviations: BMI; Body Mass Index, LTOT; Long Term Oxygen Therapy, NIMV; Noninvasive Mechanical Ventilation, HAD; Hospital Anxiety and Depression (0–7 normal, 8–10 mild, 11–15 moderate and 16–21 severe), Stop Bang (score used to assess the risk for obstructive sleep apnea, 0–2 low risk, 3–4 intermediate and 5–8 high risk), CRF; Chronic Renal Failure

and mass appearance was more common on thorax CT in patients with a prolonged LOS ($p=0.003$).

Although the difference was not statistically significant, the frequency of microorganism isolation at the time of admission was greater in prolonged-LOS patients ($p=0.125$). Influenza was also detected more often in patients with a prolonged LOS ($n=7$ vs. $n=1$). Hospital-acquired pneumonia (HAP) and the detection of microorganisms in body fluids were more common in patients with a prolonged LOS ($p<0.001$).

Treatment-related factors

Table 3 shows information on the treatment-related variables` results. The history of frequent antibiotic use was more common in patients with a prolonged LOS ($p=0.002$). In both prolonged-LOS and non-prolonged-LOS patients, need for antibiotics was similar on the first day of hospitalization ($p=0.607$), however, need for an antibiotic switch during hospitalization was greater in patients with a prolonged LOS ($p<0.001$). Prolonged-LOS patients needed antibiotics and corticosteroids for a

Table 2 Disease condition and features of COPD exacerbation

	Total	Non-prolonged LOS	Prolonged	P
	N = 434	n = 197 (45.4%)	LOS	
	(%)		n = 237(54.6%)	
GOLD Stage, n (%)	n = 424	n = 189	n = 235	**< 0.001[2]**
A	20 (4.7)	18 (9.5)	2 (0.9)	
B	80 (18.9)	48 (25.4)	32 (13.6)	
C	39 (9.2)	21 (11.1)	18 (7.7)	
D	285 (67.2)	102 (54.0)	183 (77.9)	
GOLD Spirometry grade, n (%)	n = 335	n = 146	n = 189	**< 0.001[2]**
1	11 (3.3)	8 (5.5)	3 (1.6)	
2	76 (22.7)	47 (32.2)	29 (15.3)	
3	100 (29.9)	34 (23.3)	66 (34.9)	
4	148 (44.1)	57 (39.0)	91 (48.1)	
Number of moderate exacerbations in the last 1 year	n = 430	n = 196	n = 234	**0.0281**
	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	
Number of the patients who had moderate exacerbations in the last 1 year, n (%)	n = 430	n = 196	n = 234	**0.0272**
≥ 2	242 (56.3)	99 (50.5)	143 (61.1)	
Number of severe exacerbations in the last 1 year	n = 430	n = 196	n = 234	**< 0.001[1]**
	1.0 (0–2.0)	1.0 (0–2.0)	1.0 (0–2.0)	
Number of the patients who had severe exacerbations in the last 1 year, n (%)	n = 430	n = 196	n = 234	**0.0021**
≥ 1	281 (65.3)	113 (57.7)	168 (71.8)	
Time from symptom onset to hospitalization, day	n = 431	n = 195	n = 236	**< 0.001[1]**
	5.0 (3.0–7.0)	4.0 (2.0–7.0)	7.0 (3.0–10.0)	
Number of patients stratified according to time from symptom onset to hospitalization, n (%)	n = 431	n = 195	n = 236	**< 0.001[2]**
> 5 days	188 (43.6)	66 (33.8)	122 (51.7)	
Number of days in the emergency department	n = 349	n = 152	n = 197	**< 0.001[1]**
	1.0 (0–1.0)	0 (0–1.0)	1.0 (0–1.0)	
Number of patients stratified according to the number of days in the emergency department, n (%)	n = 349	n = 152	n = 197	**< 0.001[2]**
≥ 1 day	182 (52.1)	62 (40.8)	120 (60.9)	
CRP admission, n (%)				**0.0042**
High	330 (76.0)	137 (69.5)	193 (81.4)	
Hospital acquired pneumonia during follow up, n (%)				**0.0011**
Yes	43 (9.9)	9 (4.6)	34 (14.4)	
PO_2mmHg admission (ABG)	n = 377	n = 153	n = 224	**0.0431**
	59.1 (51.0-73.5)	63.0 (52.0-74.5)	57.9 (50.1–72.8)	
PO_2(ABG) admission, n (%)	n = 377	n = 153	n = 224	**0.0032**
< 60 mmHg	195 (51.7)	65 (42.5)	130 (58.0)	
HCO_3mEq/L(ABG) admission, n (%)	n = 373	n = 152	n = 221	**0.0182**
< 22	42 (11.3)	10 (6.6)	32 (14.5)	

[1]Mann-Whitney U test [2]Chi-square test

Abbreviations: ABG; Arterial blood gases, CRP: C-reactive protein, PO_2; Partial oxygen pressure, PCO_2; Partial carbon dioxide pressure, SO2; Oxygen saturation, HCO_3; Bicarbonate

longer period ($p<0.001$), and these patients needed more theophylline ($p=0.002$), diuretics ($p=0.002$), in hospital NIMV ($p<0.001$), nutritional support ($p<0.001$) and physiotherapy ($p<0.001$) than non-prolonged hospitalized patients (Table 3).

Hospital utility-related factors

Among the patients with a prolonged LOS, 156 (66.4%) were recruited from the ER, and 79 (33.6%) were recruited from outpatient clinics. Similarly, of the patients with a non-prolonged LOS, 126 (64.3%) were admitted from the ER, and 70 (35.7%) were admitted from outpatient clinics. Forty-two patients had delayed discharge

Table 3 In hospital treatment-related factors during follow-up

	Total	Nonprolonged LOS	Prolonged LOS	P
	N = 434	n = 197 (45.4)	n = 237(54.6)	
	(%)			
History of frequent usage of antibiotics, n (%)	n = 430	n = 195	n = 235	**0.0021**
Yes	176 (40.9)	64 (32.8)	112 (47.4)	
Antibiotic switch during hospitalization, n (%)	n = 419	n = 192	n = 227	**< 0.001**[1]
Yes	78 (18.6)	16 (8.3)	62 (27.3)	
Antibiotics longer than 7 days, n (%)	n = 421	n = 191	n = 230	**< 0.001**[1]
Yes	222 (52.7)	47 (24.6)	175 (76.1)	
Corticosteroid longer than 7 days, n (%)	n = 429	n = 197	n = 232	**< 0.001**[1]
Yes	138 (32.2)	23 (11.7)	115 (49.6)	
Additional doses of corticosteroids, n (%)	n = 431	n = 197	n = 234	**< 0.001**[1]
Yes	88 (20.4)	24 (12.2)	64 (27.4)	
SABA/SAMA more than 3 days n (%)	n = 432	n = 197	n = 235	**< 0.001**[1]
Yes	254 (58.8)	91 (46.2)	163 (69.4)	
Need for theophylline, n (%)	n = 429	n = 195	n = 234	**0.0021**
Yes	83 (19.3)	25 (12.8)	58 (24.8)	
Diuretics, n (%)	n = 430	n = 196	n = 234	**0.0021**
Yes	120 (27.9)	40 (20.4)	80 (34.2)	
Increasing O_2 requirement at follow-up, n (%)	n = 431	n = 197	n = 234	**< 0.001**[1]
Yes	168 (39.0)	44 (22.3)	124 (53.0)	
In hospital NIVM at follow-up, n (%)	n = 432	n = 197	n = 235	**< 0.001**[1]
Yes	145 (33.6)	44 (22.3)	101 (43.0)	
Increasing pressure of NIVM at follow-up, n (%)	n = 145	n = 44	n = 101	**< 0.001**[1]
Yes	72 (49.7)	12 (27.3)	60 (59.4)	
Nutritional support, n (%)	n = 431	n = 197	n = 234	**< 0.001**[1]
Yes	84 (19.5)	16 (8.1)	68 (29.1)	
Need for physiotherapy, n (%)	n = 432	n = 197	n = 235	**< 0.001**[1]
Yes	157 (36.3)	46 (23.4)	111 (47.2)	
Inability to be discharged due to the delay of the examination, n (%)	n = 431	n = 196	n = 235	**< 0.001**[1]
Yes	42 (9.7)	6 (3.1)	36 (15.3)	

[1] *Chi-square test*

Abbreviations: NIMV: Noninvasive mechanical ventilation, SABA/SAMA: short acting $beta_2$ agonist, short acting muscarinic antagonist

due to delayed workups that could not be arranged earlier. The number of patients with delayed workups from the prolonged LOS group was 6-fold higher than the non-prolonged one (Table 3). Delayed workup included unfinished examination(s) or consultation(s) ($p < 0.001$).

Multivariate logistic regression analysis

Multivariate logistic regression analysis of the risk factors for a prolonged LOS (≥9 days) that may be associated with "difficult to manage COPD exacerbation" is shown in Table 4. Among the factors identified as significant in the multivariate analysis, the highest odds ratios (OR) were associated with the need for non-invasive mechanical ventilation (NIMV) during hospitalization, low bicarbonate levels and the requirement for theophylline.

Discussion

This study is a multicenter prospective cohort study of severe COPD exacerbations with a comprehensive evaluation of multiple potential risk factors of prolonged hospital stay and "difficult-to-manage COPD exacerbations". The risk factors for prolonged LOS were stratified into 4 groups: patient-related, disease- and exacerbation-related, treatment-related and hospital-utility-related. Multivariate logistic regression analysis identified 9 variables that may be associated with prolonged hospital stay that may be associated with difficult to manage COPD exacerbation. These risk factors were biomass exposure, history of NIMV, low bicarbonate levels at admission, antibiotic switching, increasing oxygen requirement, in-hospital non-invasive mechanical ventilation, need for theophylline, nutritional support and physiotherapy.

An accurate definition of prolonged hospitalization is very important for this study. The number of studies varied between 4 and 14 days in literature [9–15]. While some studies have used a cutoff value of the 75th percentile of total length [7, 8], others have considered hospitalization exceeding 7 days to indicate prolonged hospitalization [10]. There might be issues for both patients, as we might miss most of the patients when

Table 4 Multivariate logistic regression analysis of risk factors for prolonged LOS (≥ 9 days)

	Multivariate LR Model (Backward LR Method: Final Step)	
	Adjusted OR (95% CI)	***p***
Smoking (ref: active smoking)	1.9 (0.9–3.9)	0.057
Biomass exposure (ref: No)	**2.4 (1.3–4.4)**	**0.004**
Past history of NIMV (ref: No)	**2.9 (1.2–7.3)**	**0.018**
Heart failure (ref: No)	1.9 (0.9-4.0)	0.069
Lung cancer (ref: No)	3.4 (0.8–13.5)	0.087
Failure to apply to the hospital despite the presence of symptoms longer than 5 days (ref: ≤5 days)	1.7 (0.9-3.0)	0.099
PO_2<60 mmHg (ref: **≥60 mmHg)**	1.7 (0.9–3.1)	0.071
HCO_3 < 22 (ref:**≥22)**	**3.2 (1.2–8.8)**	**0.022**
High CRP (ref: normal)	1.9 (0.9–3.7)	0.060
Antibiotic change during hospitalization (ref: No)	**2.9 (1.2-7.0)**	**0.014**
Need for theophylline (ref: No)	**3.1 (1.3–7.1)**	**0.008**
Increasing O_2requirement in hospital (ref: No)	**2.2 (1.2–4.2)**	**0.014**
Need for NIVM in-hospital (ref: No)	**3.5 (1.5–8.1)**	**0.003**
Need for nutritional supplement in-hospital (ref: No)	**2.7 (1.1–6.4)**	**0.026**
Need for physiotherapy in-hospital (ref: No)	**2.6 (1.4–4.8)**	**0.003**

*Variables with $P<0,05$ as determined by univariate analysis were entered into multivariate logistic regression analysis. NIMV: noninvasive mechanical ventilation, CRP: C reactive protein, HCO_3: Bicarbonate, PO_2: partial oxygen pressure

we consider only the 75th percentile and misinterpret the findings if we consider a fixed duration without taking into consideration the features of the study groups, who might be not only severe but also accompanied by additional risk factors that might influence outcomes. Another important point is that the 75th percentile in different studies has pointed to different durations [14, 15]. For instance, while the 75th percentile for one study group was ≥9 days [12], for another group, the 75th percentile defined prolonged hospitalization as 14 days [14]. The population included in our study had a 50th percentile of ≥9 days and a 75th percentile of 14 days, which is in accordance with previous studies [11, 15].

Another important issue is the variety of risk factors that have been reported from different studies for prolonged LOS. The different study populations and different designs of the studies that included limited risk factors may explain the differences. Some known factors that have been described previously are the presence of severe symptoms and acute respiratory acidosis [10]; BMI < 25 kg/m2 [11]; low physical activity level; hospital variability [12]; the presence of comorbidities such as diabetes, stroke, heart failure and low serum albumin levels [13]; the severity of exacerbation and the winter season [14]; and older age [16]. Another study reported that age does not influence the length of stay, but factors related to the severity of disease influence the outcome [17].

Our study is quite comprehensive regarding the variety of risk factors and the number of centers that have been included. In contrast to the other studies, in this study, univariate analysis revealed increased hospital anxiety, depression and Stop Bang scores; low albumin/protein ratios and vitamin D levels; high CRP and troponin levels; the presence of bronchiectasis and HAP; antibiotic switching; a longer duration of antibiotic and corticosteroid administration; and the need for theophylline, which were found to be related to LOS.

One study has shown that up to 60.4% of individuals with COPD exacerbation have both anxiety and depression [18, 19]. OSA is also more frequent in patients with advanced COPD, and early recognition and prompt treatment with positive airway pressure therapy have been shown to significantly reduce readmissions [20]. Guidelines recommend that COPD patients be investigated for OSA by the Stop Bang Questionnaire [21]. Studies have shown that high CRP levels are predictors of COPD exacerbations and that high CRP levels, even after treatment for exacerbations, might indicate chronic inflammation, thus predicting the risk for re-exacerbation within 50 days (22–23). On the other hand, Pavasini et al. demonstrated that cardiac troponin elevation is an independent predictor of increased risk of all-cause mortality in patients hospitalized for COPD exacerbation [24].

The results with treatment-related variables were quite remarkable in this study. In addition to longer antibiotic duration and switches, longer corticosteroid usage and longer supportive care are also related to prolonged LOS in univariate analysis. We do not know whether these factors are related to disease severity. A meta-analysis showed that serum CRP and procalcitonin levels can be used as biomarkers to tailor antibiotic treatment for COPD exacerbations [25]. The current literature recommends 5 days of antibiotic or systemic corticosteroid use for COPD exacerbations [26, 27]. When however, less is known about our indicated group, which we define as having difficult-to-manage COPD exacerbation. Most

likely, when the severity increases, the duration of antibiotic use and the probability of a switch increase. This might be related to resistant pathogens, hospital-acquired infections, hospital utilization and the local flora. Guidelines are needed to improve antibiotic and corticosteroid management in this selected group of COPD exacerbations. Interestingly low bicarbonate levels were also more prominent in the prolonged LOS group and was also significant risk factor in the multivariate analysis with an OR value of 3.2. Previous studies have shown that the presence of metabolic acidosis in addition to respiratory acidosis is a sign of bad prognosis as it determines an increased need for NIMV in acute exacerbators of COPD [28]. Indeed, NIMV usage in hospital was significantly higher in prolonged LOS with the highest OR 3.5 in the multivariate analysis.

Additional medications and management strategies, such as diuretics, theophylline, NIMV usage and an increase in need for oxygen therapy together with nutritional support and physiotherapy, are also more frequent in patients with prolonged LOS. These approaches, even though not directly cause exacerbation itself, are all indirect measurements of patients that need extra care and who do not respond to standard care, thus might show a more difficult-to-manage group in clinical practice. In clinical practice, it is obvious that patients with hypervolemia need more time to experience euvolemia.

The decision of the physician to discharge a patient might vary depending on hospital sources, patient preferences, patient support and local guidelines. One study showed that some physicians preferred observing patients for an extra day even though they were appropriate for discharge just to be sure that patients were going to cope with their disease at home [29]. Our study also showed that in the prolonged LOS group, patients were not discharged because consultations or other examinations could not be completed, and this might be an issue for many other countries as well. This could be a threat for patients who are exposed to hospital-driven problems for additional days. We think that this issue is newly raised in the literature and should be taken into consideration for patient management.

COPD exacerbation patients who need prolonged hospitalization consume more health resources, have poor control of disease despite receiving high-dose and multiple drugs and suffer from the side effects of all these treatments. This may also result in increased morbidity and mortality.

The study has several limitations

Its primarily observational nature makes it challenging to establish a clear causal relationship. Additionally, selection bias may affect the results, as the included centers are predominantly reference centers within the country. Consequently, the findings reflect local practices, which may vary across different geographical areas and countries. Therefore, further validation is necessary.

Conclusion

This study analyzed multiple variables for prolonged hospitalization in COPD exacerbations. A wide variety of risk factors, including patient-, disease-, and exacerbation-related features, as well as treatment- and hospital-related factors, have been included. This study also raised a new phenomenon, "difficult to manage exacerbations", which may overlap with the prolongation of hospitalization.

Abbreviations

COPD	Chronic obstructive pulmonary disease
LOS	Length of hospitalization
ER	Emergency room
CRP	C-reactive protein
ECG	Electrocardiogram
NT-proBNP	N-terminal pro brain natriuretic peptide
ECHO	Echocardiography
HgbA1c	Hemoglobin A1c
CT	Thorax computed tomography
LTOT	Long-term oxygen therapy
NIMV	Noninvasive mechanical ventilation
HAD	Hospital anxiety depression score
OSA	Obstructive sleep apnea
OR	Odds ratio
BMI	Body mass index
HAP	Hospital acquired pneumonia

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

A Baha, S Özkan, E Şen, F Çiftçi, B Öztürk, SK Cengiz, G Ulubay, İ Şerifoğlu, Y Varol, AMertoğlu, A K Çırak, O Turan, N Dursunoğlu, N Savurmuş, A Gürgün, F Elmas, L Çöplü, Ü Sertçelik, R Yıldız, İ Özmen, A Alpaydın, Mt Polatlı, EK Yeşiloğlu, D Çelik were responsible for collecting patient data; D Esendagli and N Köktürk were responsible for reviewing the patient data and manuscript writing; D Yapar was responsible for the statistical analysis. All authors have read and agreed to the published version of the manuscript.

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Data availability

The original contributions presented in the study are included in the article. The raw data supporting the conclusions of this article will be made available upon request to the corresponding author.

Declarations

Ethics approval and consent to participate

This study was approved by the local institutional ethics committee of Gazi University. *The clinical trial number is 687/2018.* Written informed consent for

participation was obtained from each enrolled participant. The study was conducted in accordance with the Declaration of Helsinki.

Competing interests
The authors declare no competing interests.

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