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A Risk Prediction Model for Prolonged Length of Stay in Patients with Acute Exacerbations of Chronic Obstructive Pulmonary Disease: A Retrospective Study of 225 Patients in a Single Center in Kunming, China

Authors' Contribution:
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Statistical Analysis C
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Manuscript Preparation E
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Background: We aimed to develop an effective prediction model of prolonged length of stay (LOS) in patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD).

Material/Methods: We systematically enrolled 225 patients admitted for AECOPD to our hospital and divided them into a normal LOS group (≤7 days) and prolonged LOS group (>7 days). To analyze differences in laboratory data at different times, 3 logistic regression models were established. To develop the prediction model, all variables with statistical significance were included in the model. The area under the curve (AUC) was used to evaluate discrimination, and the Hosmer-Lemeshow test was used to assess the calibration of the model.

Results: Factors found to be independently associated with the increased risk of prolonged LOS included the use of corticosteroids during hospitalization, elevated HCO_3^-, decreased pH, and reductions in platelets (PLTs) and procalcitonin (PCT) between the fourth and first day of hospitalization. The risk prediction model including these factors had an AUC of 0.795, suggesting the good discrimination of our model. The Hosmer-Lemeshow test also showed good calibration of the model, which confirmed its good predictive performance.

Conclusions: A clinical prediction model was developed with good predictive performance, which could help clinicians identify patients with a higher risk of prolonged LOS, help shorten hospital stay, reduce the disease burden of patients, and improve the outcomes of AECOPD.

Keywords: Clinical Decision Rules • COPD, Severe Early-Onset • Disease Progression

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Background

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disorder characterized by persistent respiratory symptoms and airflow limitation. COPD is rarely reversible and can lead to chronic respiratory failure [1,2]. COPD remains the most prevalent disease-specific chronic respiratory disease, having a 5.9% relative increase in overall prevalence and killing of over 3 million people each year worldwide [3,4]. According to the World Health Organization, COPD is predicted to become the third leading cause of mortality worldwide by 2030 [5]. Acute exacerbation of COPD (AECOPD), which is characterized by episodes of worsening respiratory symptoms, has significant adverse consequences for patients [6,7]. Respiratory viruses and bacteria are the primary causes of AECOPD. Bacteria, such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis,* usually colonize the lower respiratory tracts of patients with COPD. This chronic bacterial colonization is related to defects in the uptake (phagocytosis) of bacteria by macrophages and may be a factor that drives chronic airway and systemic inflammation and immune responses in these patients [2,8,9]. Greater frequency of exacerbations can lead to accelerated lung function decline, poor quality of life, and even increased mortality [10]. Further, exacerbations are associated with subsequent hospital admissions, accounting for more than 70% of COPD costs due to emergency department visits and hospitalizations [11-14]. Meanwhile, prolonged length of stay (LOS) is related to worse lung function, poorer quality of life, and an increased risk of mortality. Thus, identifying factors related to prolonged LOS could help provide interventions for lessening the severity of AECOPD, shortening LOS, and avoiding the unnecessary use of health services.

According to previous studies, prolonged LOS is associated with various clinical variables, such as advanced age, reduced body mass index (BMI), smoking history, presence of comorbidities, more severe AECOPD, higher prevalence of oxygen therapy, and use of mechanical ventilation [15-21]. Some vital sign parameters, such as greater respiratory rate on admission, systolic pressure > 140 mmHg, and diastolic pressure >90 mmHg, were also found to be related to prolonged LOS in patients with AECOPD [17,22]. Pathogen infection is also associated with prolonged AECOPD LOS [23-25]. As suggested by Mushlin et al, the medically required LOS for patients with AECOPD should be between 6 and 7 days based on clinical characteristics [26]. Crisafulli et al regarded over 7 days as extended LOS [15]. To the best of our knowledge, some models have been established to predict the risk of prolonged LOS in patients with AECOPD based on various predictors, including heart failure, diabetes, low serum albumin level, BMI, dyspnea, and physical activity level [14,17,20]. Whether there are other variables that can be used to build a valuable predictive model is as yet unknown.

Thus, we aimed to identify the predictors of prolonged LOS (defined as > 7 days) and tried to develop an effective prediction model using clinical and laboratory variables before and after admission, which may help clinicians to identify the patients who would require a prolonged stay and to develop corresponding interventions.

Material and Methods

Study Design

In this retrospective study, we systematically enrolled patients admitted for AECOPD to the First Hospital of Kunming. The inclusion criteria were: (1) patients aged ≥18 years and (2) patients who met the diagnostic criteria for COPD specified by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Initiative of 2017 [6]; specifically, COPD should be considered in any patient with the symptoms of dyspnea, chronic cough, or sputum production, and a post-bronchodilator forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC) ratio <0.70 by spirometry, confirming the presence of persistent airflow limitation. AECOPD was defined as an acute worsening of respiratory symptoms that required additional therapy [6]. The exclusion criteria were: (1) patients with other respiratory diseases, such as pneumothorax or pulmonary embolism, asthma, pulmonary fibrosis, bronchiectasis, pulmonary tuberculosis sequelae, or pleural thickening; (2) patients with acute heart failure; (3) patients with extremely low immune function, severe infection, renal dysfunction, hepatobiliary diseases, pancreatic diseases, hyperthyroidism or hypothyroidism, malignant tumors, or blood system or connective tissue disorders; (4) patients with poor compliance who could not be contacted or were unwilling to make contact after discharge; (5) patients who took other investigational drugs within 1 month before our enrollment or were participating in other clinical studies; and (6) patients who were deemed unsuitable for this study by the physician in charge.

The study was approved by the Ethics Committee of our hospital (approval no. SLKY2018-53) and was conducted according to the requirements of the Good Clinical Practice guidelines and Declaration of Helsinki.

Data Collection

Before admission, demographic and clinical data, including age, sex, BMI, history of drug and other allergies, surgery history, smoking and alcohol use, comorbidities (hypertension and diabetes), medication history (the use of systemic corticosteroids and antibiotics), home care medications (long-term oxygen therapy, short-acting β2-agonists, long-acting β2-agonists, and anticholinergics), season of COPD exacerbation (referring

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to the season of prior exacerbation in the last year), number of exacerbation attacks in the last year, and dyspnea grade were recorded. The dyspnea grade was evaluated by the modified Medical Research Council (mMRC) scale, which consists of a 5-level categorization, with a score of 2 as the symptomatic cutoff point. The severity of AECOPD was assessed by the Charlson weighted index of comorbidities, a method of categorizing comorbidities based on the International Classification of Diseases diagnosis codes. Each comorbidity category has an associated weight ranging from 1 to 6, based on the adjusted risk of mortality or resource use, and the sum of all the weights results in a single comorbidity score for an individual patient. The higher the score, the more likely the predicted outcome will result in mortality or higher resource use. On admission, all patients also underwent laboratory and microbial tests, and relevant variables, including white blood cells (WBCs), red blood cells (RBCs), packed-cell volume (PCV), hemoglobin (Hb), platelets (PLT), neutrophils (NEUT), lymphocytes (LY), pH, partial arterial carbon dioxide pressure ($PaCO_2$), the ratio of partial arterial oxygen pressure to the fraction of inspired oxygen (PaO_2/FiO_2), HCO_3^-, base excess (BE), C-reactive protein (CRP), procalcitonin (PCT), amyloid, interleukin (IL)-6, and bacteria in sputum, were recorded. On the fourth day of admission, clinical and laboratory variables (corticosteroid and antibiotic use during hospitalization and laboratory variables as specified above, except bacteria in sputum) were collected. LOS was recorded at the time of discharge.

On admission, we collected sputum from spontaneous cough samples, which was processed by Gram staining and culture if sufficient (with >25 WBCs and <10 epithelial cells per field). In patients who did not provide spontaneous sputum samples, we obtained induced sputum production by inhalation of 5% hypertonic saline solution (via nebulization for 5 to 10 min).

Laboratory and Microbial Tests

The laboratory tests conducted were blood cell analysis, arterial blood gas analysis, and infection markers test. The blood cell analysis for WBC, RBC, PCV, Hb, PLT, NEUT, and LY was carried out with a Sysmex XN-1000 automated hematology analyzer (Sysmex Corporation, Kobe, Japan). An ABL80 blood gas analyzer (Radiometer Medical A/S, Copenhagen, Denmark) was used for the arterial blood gas analysis to obtain data on pH, $PaCO_2$, PaO_2/FiO_2, HCO_3^-, and BE. The infection markers test for CRP, PCT, amyloid, and IL-6 was performed using a Roche Cobas 8000 electrochemical analyzer (Roche Diagnostics, Mannheim, Germany).

The microbial test was a sputum culture. The sputum sample was homogenized with sputolysin and inoculated in blood agar, chocolate agar, and MacConkey agar media, which were incubated in 5% CO_2 at 35 for 18 to 24 h. If no growth was observed after overnight incubation, the culture plates were incubated for an additional 24 h. Bacterial agents are classified as potentially pathogenic microorganisms (PPM) or non-PPM. Only when PPMs reached >10^6/colony forming units (CFUs) were they considered significant, while 10^5/CFU was regarded significant for *Streptococcus pneumoniae*.

Statistical Analysis

The included patients were divided into the normal LOS group (≤7 days) and the prolonged LOS group (>7 days). The Shapiro-Wilk test was used to test the normality of the quantitative data. Normally distributed quantitative data were described as mean±standard deviation, and the *t* test was performed for comparison between groups. Non-normally distributed data were described as median and quartile (M [Q_1, Q_3]), and the rank-sum test was used for comparisons between groups with the Z statistic. Qualitative data were expressed as the number of cases and the constituent ratio (n [%]). The chi-squared test or Fisher exact test was used for comparison between groups.

Logistic stepwise regression analysis was performed to screen the variables. For differences in the laboratory data at different times, 3 logistic regression models were established. Age, sex, long-term home oxygen therapy, short-acting β2 agonists, COPD-exacerbated, autumn, and Charlson index were included in models 1, 2, and 3. In addition, laboratory data on admission was included in model 1, laboratory data on the fourth day of hospitalization was included in model 2, and changes in laboratory data between the fourth and first day of hospitalization was included in model 3. Then, the final model included all variables with statistical significance in models 1, 2, and 3 to develop a prediction model of prolonged LOS. The area under the curve (AUC) was used to evaluate the discrimination and the Hosmer-Lemeshow test was used to assess the calibration of the final model.

Data were statistically analyzed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Receiver operating characteristic (ROC) curves were plotted using R 4.0.2 (R foundation for Statistical Computing, Vienna, Austria). $P<0.05$ was considered statistically significant.

Results

Baseline Description

In the present study, a total of 225 patients were enrolled and divided into a normal LOS group (≤7 days, n=73) and prolonged LOS group (>7 days, n=152). The median LOS was 7 days. Most patients (86.22%) were men and 78.67% of patients had a smoking history. The mean age was 71.23±8.43

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years, and the mean BMI was 22.34±2.72 kg/m^2. For comorbidities, 107 (47.56%) patients had hypertension, and 26 (11.56%) patients had diabetes. The most frequent medication history was antibiotic use. For home therapy, long-term home oxygen therapy was the most frequently used treatment, followed by short-acting β2 agonists. Concerning COPD exacerbation, most patients (56.89%) reported COPD exacerbation in winter. Nearly half of patients (48.44%) had 0 to 1 exacerbations within the last year.

Differences in Baseline Characteristics

Based on the clinical and laboratory data collected at baseline, the univariate analysis suggested that age (t=-2.515, P=0.013), proportions of long-term home oxygen therapy (χ^2=11.615, P<0.001), short-acting β2 agonists (χ^2=6.426, P=0.011), and the incidence rate of autumn exacerbation (χ^2=6.513, P=0.011) in the prolonged LOS group were all significantly higher than those in the normal LOS group. For laboratory data, the prolonged LOS group showed a significantly higher pH (t=-2.69, P=0.008), dyspnea grade (χ^2=14.581, P<0.001), and Charlson index (χ^2=7.769, P=0.005) but significantly lower $PaCO_2$ (t=2.33, P=0.021) and HCO_3^- (t=2.23, P=0.027) compared with the normal LOS group (**Table 1**).

Differences in Characteristics on the Fourth Day of Hospitalization

As shown in **Table 2**, analysis on the fourth day of hospitalization showed that PaO_2/FiO_2 (Z=-2.600, P=0.009), HCO_3^- (t=2.10, P=0.037), BE (Z=-2.112, P=0.035), and the proportion of corticosteroid use during hospitalization (χ^2=14.060, P<0.001) in the prolonged LOS group were significantly higher than those in the normal LOS group.

Differences in Characteristic Changes Between the Fourth and First Day

The results showed that changes in laboratory variables between the fourth and first day of hospitalization were similar between the prolonged LOS group and the normal LOS group (all P>0.05; **Table 3**).

Variables Associated with the Risk of Prolonged LOS

In multivariate regression model 1, which incorporated the laboratory data on admission, 1-year increase in age (day 1) was revealed to be associated with a 0.039-fold increase (OR 1.039, 95% CI 1.002-1.078) in the risk of prolonged LOS. Compared with patients with an mMRC scale (day 1) score of 0 to1, the risk of prolonged LOS increased 1.796-fold (OR 2.796, 95% CI 1.490-5.245) in those with scores of 2 to 4. In addition, the risk decreased 0.996-fold (OR 0.004, 95% CI 0.001-0.441) for every increase in pH (day 1), and the risk increased 0.077-fold (OR 1.077, 95% CI 1.006-1.153) for every 1 mmol/L increase in HCO_3^- (day 1) (**Table 4**).

In multivariate regression model 2, which included laboratory data on the fourth day of hospitalization, the risk of prolonged LOS increased 1.384-fold (OR 2.384, 95% CI 1.195-4.757) in patients whose exacerbations occurred in autumn (day 1). Compared with patients with mMRC scale (day 1) scores of 0 to 1, a 1.394-fold elevation (OR 2.394, 95% CI 1.274-4.501) in risk was shown in those with scale scores of 2 to 4. In addition, the risk increased by 2.007-fold (OR 3.007, 95% CI 1.539-5.877) for patients who used corticosteroids during hospitalization (day 4) (**Table 4**).

In multivariate regression model 3, which included changes in laboratory data between the first and the fourth day of hospitalization, the results demonstrated that long-term home oxygen therapy (day 1) raised the risk of prolonged LOS 1.396-fold (OR 2.396, 95% CI 1.310-4.383). For each point increase in the Charlson index (day 1), the risk increased 0.546-fold (OR 1.546, 95% CI 1.093-2.187). For each 1×10^9/L decrease in ΔPLT, the risk increased 0.006-fold (OR 1.006, 95% CI 1.000-1.012). In addition, the risk increased 1.119-fold (OR 2.119, 95% CI 1.185-3.790) for every 1 μg/L decrease in ΔPCT (**Table 4**).

Development of the Final Model

Variables with statistical significance in models 1, 2, and 3 were then included in the final prediction model. The model suggested that patients who used corticosteroids during hospitalization had a 2.514-fold increased risk (OR 3.514, 95% CI 1.677-7.362) of prolonged LOS. For every 1 mmol/L increase in HCO_3^-, the risk increased 0.069-fold (OR 1.069, 95% CI 1.000-1.142). For every increase in pH, the risk decreased 0.574-fold (OR 0.426, 95% CI 0.246-0.737). In addition, the risk increased 0.007-fold (OR 1.007, 95% CI 1.001-1.014) for every 1×10^9/L decrease in ΔPLT, and the risk increased 1.021-fold (OR 2.021, 95% CI 1.081-3.778) for every 1 μg/L decrease in ΔPCT (**Table 5**).

According to the ROC curve, the AUC of the combined prediction model was 0.795 (95% CI 0.730-0.861), with a sensitivity of 0.743 (95% CI, 0.674-0.813) and a specificity of 0.753 (95% CI, 0.65-0.852), which suggested the good discrimination of our model (**Figure 1, Table 6**). The results of the Hosmer-Lemeshow test (χ^2=9.648, P=0.291) indicated the good calibration of the model. The calibration curve of the model is shown in **Figure 2**.

Discussion

In the present study, we aimed to develop a clinical prediction model for the risk of prolonged LOS >7 days in patients with

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Table 1. Differences in baseline characteristics.

Variable	Total (n=225)	Group		Statistic	*P*
		LOS ≤7 days (n=73)	LOS >7 days (n=152)		
Sex, n(%)				χ^2=2.811	0.094
Male	194 (86.22)	67 (91.78)	127 (83.55)		
Female	31 (13.78)	6 (8.22)	25 (16.45)		
Age (years), mean±SD	71.23±8.43	69.21±8.22	72.20±8.36	t=-2.515	0.013
BMI (kg/m^2), mean±SD	22.34±2.72	22.37±2.16	22.33±2.95	t=0.137	0.891
Nationality, n(%)				–	1.000
Han	223 (99.11)	73 (100.00)	150 (98.68)		
Others	2 (0.89)	0 (0.00)	2 (1.32)		
Past medical history, n(%)					
Drug or other allergies	65 (28.89)	22 (30.14)	43 (28.29)	χ^2=0.082	0.775
Surgery	122 (54.22)	35 (47.95)	87 (57.24)	χ^2=1.715	0.190
Hypertension	107 (47.56)	34 (46.58)	73 (48.03)	χ^2=0.042	0.838
Diabetes	26 (11.56)	9 (12.33)	17 (11.18)	χ^2=0.063	0.801
Smoking	177 (78.67)	59 (80.82)	118 (77.63)	χ^2=0.299	0.585
Alcohol use	97 (43.11)	33 (45.21)	64 (42.11)	χ^2=0.193	0.660
Medication history, n(%)					
Corticosteroids	32 (14.22)	9 (12.33)	23 (15.13)	χ^2=0.318	0.573
Antibiotics	77 (34.22)	22 (30.14)	55 (36.18)	χ^2=0.801	0.371
Home therapy, n(%)					
6Long-term oxygen therapy	126 (56.00)	29 (39.73)	97 (63.82)	χ^2=11.615	<0.001
Short-acting β2 agonists	174 (77.33)	49 (67.12)	125 (82.24)	χ^2=6.426	0.011
Long-acting β2 agonists	103 (45.78)	31 (42.47)	72 (47.37)	χ^2=0.478	0.490
Anticholinergics	18 (8.00)	7 (9.59)	11 (7.24)	χ^2=0.371	0.543
Season of COPD exacerbation, n(%)					
Spring	82 (36.44)	32 (43.84)	50 (32.89)	χ^2=2.549	0.110
Summer	91 (40.44)	28 (38.36)	63 (41.45)	χ^2=0.196	0.658
Autumn	72 (32.00)	15 (20.55)	57 (37.50)	χ^2=6.513	0.011
Winter	128 (56.89)	37 (50.68)	91 (59.87)	χ^2=1.696	0.193
Number of exacerbations last year, n(%)				Z=-1.845	0.065
0-1	109 (48.44)	41 (56.16)	68 (44.74)		
2	49 (21.78)	16 (21.92)	33 (21.71)		
≥3	67 (29.78)	16 (21.92)	51 (33.55)		
Blood routine examination					
WBC (10^9/L), M(Q_1, Q_3)	7.02 (5.64, 9.85)	7.05 (5.51, 10.02)	7.00 (6.02, 9.51)	Z=0.308	0.758

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Table 1 continued. Differences in baseline characteristics.

Variable	Total (n=225)	Group		Statistic	*P*
		LOS ≤7 days (n=73)	LOS >7 days (n=152)		
RBC (10^{12}/L), Mean±SD	4.93±0.83	4.93±0.82	4.92±0.85	t=0.08	0.936
PCV, Mean±SD	0.46±0.08	0.46±0.07	0.46±0.08	t=0.27	0.785
Hb (g/L), Mean±SD	150.47±24.16	150.16±23.94	151.10±24.77	t=-0.27	0.787
PLT (10^9/L), M(Q_1, Q_3)	184.00 (147.00, 229.00)	181.00 (145.50, 227.50)	193.00 (152.00, 233.00)	Z=0.683	0.495
NEUT (10^9/L), M(Q_1, Q_3)	4.80 (3.78, 7.20)	4.90 (3.84, 7.78)	4.66 (3.53,6.26)	Z=-1.230	0.219
LY (10^9/L), M(Q_1, Q_3)	1.20 (0.80,1.70)	1.10 (0.80, 1.50)	1.40 (0.80, 1.90)	Z=1.906	0.057
Blood gas analysis					
pH, Mean±SD	7.42±0.08	7.41±0.09	7.43±0.04	t=-2.69	0.008
$PaCO_2$ (mmHg), Mean±SD	43.68±13.07	44.95±13.95	41.04±10.60	t=2.33	0.021
PaO_2/FiO_2 (mmHg), M(Q_1, Q_3)	238.00 (206.00, 270.00)	244.00 (211.00, 272.50)	234.00 (189.00, 270.00)	Z=-1.666	0.096
HCO_3^- (mmol/L), Mean±SD	27.93±5.33	28.48±5.34	26.80±5.16	t=2.23	0.027
BE (mmol/L), M(Q_1, Q_3)	2.00 (1.00, 5.30)	2.55 (1.10, 5.70)	1.90 (0.80, 4.10)	Z=-1.727	0.084
Infection markers test, M(Q_1, Q_3)					
CRP (mg/L)	8.17 (2.60, 35.93)	6.81 (2.69, 31.90)	10.31 (2.44, 44.70)	Z=0.806	0.420
PCT (μg/L)	0.06 (0.04, 0.11)	0.06 (0.04, 0.10)	0.06 (0.04, 0.13)	Z=1.625	0.104
Amyloid (mg/L)	97.00 (28.10, 199.00)	108.15 (33.95, 202.00)	61.70 (17.20, 181.00)	Z=-1.752	0.080
IL-6 (pg/mL)	10.80 (4.70,28.90)	11.35 (4.90, 31.45)	9.60 (4.40, 23.40)	Z=-0.410	0.682
Bacteria in sputum, n(%)	186 (83.04)	62 (86.11)	124 (81.58)	χ^2=0.712	0.399
mMRC scale, n(%)				χ^2=14.581	<0.001
0-1	67 (29.78)	34 (46.58)	33 (21.71)		
2-4	158 (70.22)	39 (53.42)	119 (78.29)		
Charlson index, n(%)				χ^2=7.769	0.005
1	183 (81.33)	67 (91.78)	116 (76.32)		
2	42 (18.67)	6 (8.22)	36 (23.68)		

LOS – length of stay; BMI – body mass index; COPD – chronic obstructive pulmonary disease; WBC – white blood cell; RBC – red blood cell; PCV – packed-cell volume; Hb – hemoglobin; PLT – platelet; NEUT – neutrophil; LY – lymphocyte; $PaCO_2$ – partial arterial carbon dioxide pressure; PaO_2/FiO_2 – the ratio of partial arterial oxygen pressure to the fraction of inspired oxygen; BE – base excess; CRP – C-reactive protein; PCT – procalcitonin; mMRC – modified Medical Research Council; SD – standard deviation; M(Q_1, Q_3) – median and quartile; n(%) – the number of cases and the constituent ratio; -: using Fisher's test.

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Table 2. Differences in characteristics on the fourth day of hospitalization.

Variable	Total (n=225)	Group		Statistic	*P*
		LOS≤7 days (n=73)	LOS >7 days (n=152)		
Blood routine examination					
WBC (10^9/L), mean±SD	6.60±2.09	6.56±2.05	6.62±2.12	t=0.19	0.853
RBC (10^{12}/L), mean±SD	4.80±0.81	4.77±0.81	4.81±0.81	t=0.30	0.765
PCV, mean±SD	0.45±0.07	0.45±0.07	0.45±0.07	t=-0.16	0.877
Hb (g/L), mean±SD	147.81±23.52	148.05±22.61	147.69±24.01	t=-0.11	0.914
PLT (10^9/L), M(Q_1, Q_3)	181.00 (142.00, 220.00)	174.00 (136.00, 216.00)	185.50 (142.50, 228.00)	Z=-0.919	0.358
NEUT (10^9/L), M(Q_1, Q_3)	4.25 (3.21, 5.36)	4.25 (3.10, 5.35)	4.25 (3.22, 5.36)	Z=-0.413	0.679
LY (10^9/L), M(Q_1, Q_3)	1.50 (1.10, 1.90)	1.50 (1.10, 2.00)	1.40 (1.10, 1.90)	Z=0.973	0.331
Blood gas analysis					
pH, Mean±SD	7.43±0.05	7.43±0.04	7.42±0.05	t=-1.06	0.292
$PaCO_2$ (mmHg), Mean±SD	42.39±10.97	40.47±11.55	43.30±10.59	t=1.82	0.070
PaO_2/FiO_2 (mmHg), M(Q_1, Q_3)	265.00 (228.00, 310.00)	255.00 (215.00, 290.00)	269.50 (238.00, 320.50)	Z=-2.600	0.009
HCO_3^- (mmol/L), Mean±SD	27.95±5.19	26.92±5.67	28.45±4.88	t=2.10	0.037
BE (mmol/L), M(Q_1, Q_3)	2.70 (1.00, 5.40)	1.70 (0.20, 4.40)	3.00 (1.25, 5.70)	Z=-2.112	0.035
Infection markers test, M(Q_1, Q_3)					
CRP (mg/L)	5.72 (2.00, 12.56)	4.37 (2.00, 11.70)	6.59 (2.00, 12.95)	Z=-0.728	0.467
PCT (μg/L)	0.05 (0.03, 0.07)	0.05 (0.03, 0.07)	0.05 (0.03, 0.08)	Z=-0.233	0.816
Amyloid (mg/L)	10.70 (4.31, 23.60)	9.88 (4.09, 19.50)	10.90 (5.03, 25.85)	Z=-1.084	0.278
IL-6 (pg/mL)	6.50 (3.50, 11.90)	6.30 (3.40, 10.60)	7.25 (3.55, 12.65)	Z=-0.583	0.560
Medication during hospitalization, n(%)					
Corticosteroids	89 (39.56)	16 (21.92)	73 (48.03)	χ^2=14.060	<0.001
Antibiotics	211 (93.78)	66 (90.41)	145 (95.39)	–	0.154

LOS – length of stay; WBC – white blood cell; RBC – red blood cell; PCV – packed-cell volume; Hb – hemoglobin; PLT – platelet; NEUT – neutrophil; LY – lymphocyte; $PaCO_2$ – partial arterial carbon dioxide pressure; PaO_2/FiO_2 – the ratio of partial arterial oxygen pressure to the fraction of inspired oxygen; BE – base excess; CRP – C-reactive protein; PCT – procalcitonin; SD – standard deviation; M(Q_1, Q_3) – median and quartile; n(%) – the number of cases and the constituent ratio; -: using Fisher's test.

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Table 3. Differences in characteristic changes between the fourth and first day.

Variable	Total (n=225)	Group		Statistic	*P*
		LOS ≤7 days (n=73)	LOS >7 days (n=152)		
Blood routine examination					
ΔWBC (10^9/L), mean±SD	-0.87 (-2.42, 0.32)	-1.01 (-2.60, 0.16)	-0.83 (-2.37, 0.34)	Z=-0.443	0.658
ΔRBC (10^{12}/L), mean±SD	-0.14 (-0.43, 0.19)	-0.13 (-0.46, 0.23)	-0.15 (-0.42, 0.19)	Z=0.176	0.860
ΔPCV, mean±SD	-0.01 (-0.04, 0.02)	-0.01 (-0.03, 0.02)	-0.02 (-0.04, 0.01)	Z=1.112	0.266
ΔHb (g/L), mean±SD	-3.00 (-11.00, 6.00)	-3.00 (-11.00, 6.00)	-2.00 (-11.00, 6.00)	Z=-0.107	0.915
ΔPLT (10^9/L), M(Q_1, Q_3)	-3.00 (-27.00, 21.00)	-10.00 (-40.00, 20.00)	-2.00 (-22.50, 21.50)	Z=-1.433	0.152
ΔNEUT (10^9/L), M(Q_1, Q_3)	-0.89 (-2.44, 0.26)	-0.42 (-2.53, 0.50)	-1.03 (-2.43, 0.11)	Z=0.978	0.328
ΔLY (10^9/L), M(Q_1, Q_3)	0.20 (-0.10, 0.60)	0.20 (-0.20, 0.40)	0.20 (0.00, 0.60)	Z=-1.236	0.217
Blood gas analysis					
ΔpH, mean±SD	0.01 (-0.03, 0.05)	0.00 (-0.04, 0.03)	0.01 (-0.03, 0.05)	Z=-1.365	0.172
Δ$PaCO_2$ (mmHg), mean±SD	-1.00 (-7.00, 5.00)	0.00 (-5.00, 4.00)	-1.00 (-8.00, 5.50)	Z=0.209	0.834
ΔPaO_2/FiO_2 (mmHg), M(Q_1, Q_3)	26.00 (5.00, 57.00)	20.00 (5.00, 46.00)	32.00 (7.00, 59.50)	Z=-1.401	0.161
ΔHCO_3^- (mmol/L), mean±SD	0.10 (-3.10, 2.80)	0.10 (-2.70, 2.40)	0.10 (-3.25, 3.05)	Z=-0.124	0.902
ΔBE (mmol/L), M(Q_1, Q_3)	0.00 (-2.90, 2.60)	-0.20 (-2.90, 2.30)	0.05 (-2.85, 2.80)	Z=-0.265	0.791
Infection markers test, M(Q_1, Q_3)					
ΔCRP (mg/L)	-2.50 (-22.24, 0.70)	-5.27 (-32.18, 0.12)	-1.83 (-17.95, 1.09)	Z=-1.633	0.102
ΔPCT (μg/L)	-0.01 (-0.05, 0.01)	-0.02 (-0.09, 0.00)	-0.01 (-0.04, 0.01)	Z=-1.833	0.067
ΔAmyloid (mg/L)	-75.40 (-167.70, -18.80)	-48.90 (-153.57, -11.41)	-86.05 (-173.34, -21.32)	Z=1.675	0.094
ΔIL-6 (pg/mL)	-3.80 (-17.60, 1.20)	-4.20 (-18.40, 1.40)	-3.65 (-17.55, 0.90)	Z=-0.054	0.957

LOS – length of stay; WBC – white blood cell; RBC – red blood cell; PCV – packed-cell volume; Hb – hemoglobin; PLT – platelet; NEUT – neutrophil; LY – lymphocyte; $PaCO_2$ – partial arterial carbon dioxide pressure; PaO_2/FiO_2 – the ratio of partial arterial oxygen pressure to the fraction of inspired oxygen; BE – base excess; CRP – C-reactive protein; PCT – procalcitonin; SD – standard deviation; M(Q_1,Q_3) – median and quartile; n(%) – the number of cases and the constituent ratio; Δ – changes between the fourth and first day of hospitalization.

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Table 4. Variables associated with the risk of prolonged LOS in models 1, 2, and 3.

Variable	β	S.E	Wald	*P*	OR	Lower	Upper
Model 1							
Constant	35.508	17.811	3.974	0.046			
Age (day 1)	0.038	0.019	4.169	0.041	1.039	1.002	1.078
mMRC scale (day 1)	1.028	0.321	10.261	0.001	2.796	1.490	5.245
pH (day 1)	-5.558	2.418	5.282	0.022	0.004	0.001	0.441
HCO_3^- (day 1)	0.074	0.035	4.585	0.032	1.077	1.006	1.153
Model 2							
Constant	-1.347	0.547	6.059	0.014			
COPD-exacerbated autumn (day 1)	0.869	0.353	6.072	0.014	2.384	1.195	4.757
mMRC scale (day 1)	0.873	0.322	7.349	0.007	2.394	1.274	4.501
Corticosteroids use during hospitalization (day 4)	1.101	0.342	10.372	0.001	3.007	1.539	5.877
Model 3							
Long-term home oxygen therapy (day 1)	0.874	0.308	8.041	0.005	2.396	1.310	4.383
Charlson index (day 1)	0.436	0.177	6.079	0.014	1.546	1.093	2.187
ΔPLT	0.006	0.003	4.489	0.034	1.006	1.000	1.012
ΔPCT	0.751	0.297	6.405	0.011	2.119	1.185	3.790

LOS – length of stay; mMRC – modified Medical Research Council; PLT – platelet; PCT – procalcitonin; S.E – standard error; OR – odds ratio; Δ – changes between the fourth and first day of hospitalization.

Table 5. Variables associated with the risk of prolonged LOS in the final model.

Variable	β	S.E	Wald	*P*	OR	Lower	Upper
Age	0.038	0.022	3.149	0.076	1.039	0.996	1.084
Sex	0.720	0.541	1.772	0.183	2.055	0.712	5.933
mMRC scale	0.449	0.380	1.396	0.237	1.567	0.744	3.299
COPD-exacerbated autumn	0.583	0.378	2.371	0.124	1.791	0.853	3.760
Charlson index	0.859	0.543	2.505	0.113	2.360	0.815	6.837
Corticosteroids use during hospitalization	1.257	0.377	11.094	<0.001	3.514	1.677	7.362
LY	-0.356	0.245	2.105	0.147	0.701	0.433	1.133
HCO_3^-	0.067	0.034	3.888	0.049	1.069	1.000	1.142
pH	-0.853	0.280	9.298	0.002	0.426	0.246	0.737
ΔPLT	0.007	0.003	4.836	0.028	1.007	1.001	1.014
ΔPCT	0.704	0.319	4.863	0.027	2.021	1.081	3.778

LOS – length of stay; mMRC – modified Medical Research Council; PLT – platelet; PCT – procalcitonin; S.E – standard error; OR – odds ratio; Δ – changes between the fourth and first day of hospitalization.

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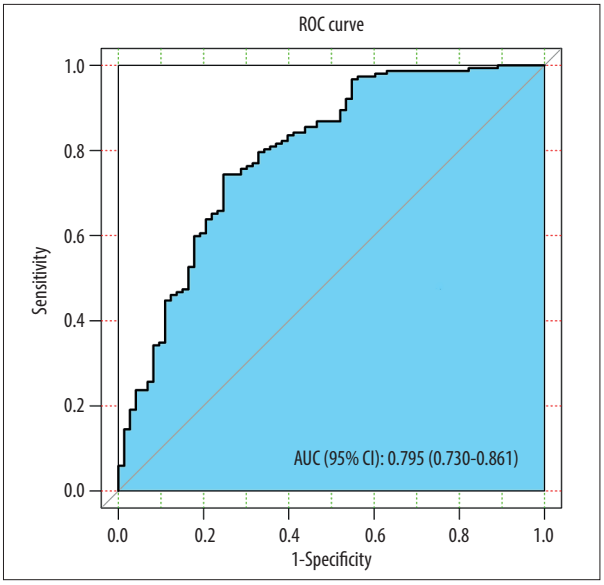

Figure 1. ROC curve of the prediction model. ROC – receiver operating characteristic; AUC – area under the curve.

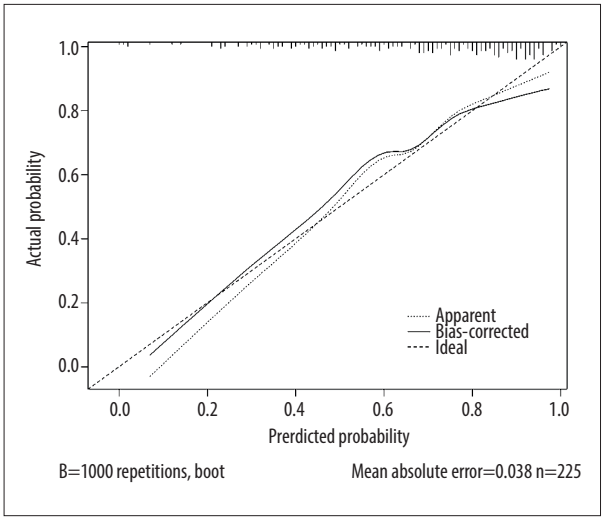

Figure 2. Calibration curve of the prediction model.

Table 6. Predictive value of the predictors for prolonged LOS in the final model.

Variable	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)	PPV (95% CI)
Combined	0.795 (0.730-0.861)	0.743 (0.674-0.813)	0.753 (0.655-0.852)	0.585 (0.486-0.685)	0.863 (0.804-0.922)
Age	0.596 (0.516-0.676)	0.816 (0.754-0.877)	0.342 (0.234-0.451)	0.472 (0.337-0.6061)	0.721 (0.654-0.788)
Sex	0.541 (0.498-0.585)	0.164 (0.106-0.223)	0.918 (0.855-0.981)	0.345 (0.278-0.412)	0.806 (0.667-0.946)
mMRC scale	0.624 (0.558-0.691)	0.783 (0.717-0.848)	0.466 (0.351-0.580)	0.507 (0.388-0.627)	0.753 (0.686-0.820)
COPD-exacerbated autumn	0.585 (0.524-0.645)	0.375 (0.298-0.452)	0.795 (0.702-0.887)	0.379 (0.302-0.456)	0.792 (0.698-0.885)
Charlson index	0.577 (0.531-0.624)	0.237 (0.169-0.304)	0.918 (0.855-0.981)	0.366 (0.296-0.436)	0.857 (0.751-0.963)
Corticosteroids use during hospitalization	0.631 (0.568-0.693)	0.480 (0.401-0.560)	0.781 (0.686-0.876)	0.419 (0.336-0.502)	0.820 (0.740-0.900)
LY	0.578 (0.494-0.663)	0.342 (0.267-0.418)	0.479 (0.365-0.594)	0.259 (0.185-0.333)	0.578 (0.476-0.680)
HCO3-	0.614 (0.532-0.695)	0.684 (0.610-0.758)	0.534 (0.420-0.649)	0.448 (0.344-0.553)	0.754 (0.682-0.826)
pH	0.566 (0.490-0.642)	0.566 (0.487-0.645)	0.288 (0.184-0.392)	0.241 (0.151-0.331)	0.623 (0.542-0.704)
ΔPLT	0.559 (0.474-0.645)	0.816 (0.754-0.877)	0.342 (0.234-0.451)	0.472 (0.337-0.606)	0.721 (0.654-0.788)
ΔPCT	0.580 (0.497-0.663)	0.849 (0.792-0.906)	0.301 (0.196-0.407)	0.489 (0.343-0.635)	0.717 (0.651-0.782)

LOS – length of stay; mMRC – modified Medical Research Council; LY – lymphocyte; PLT – platelet; PCT – procalcitonin; AUC – area under the curve; CI – confidence interval; NPV – negative predictive value; PPV – positive predictive value; Δ – changes between the fourth and first day of hospitalization.

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AECOPD. Several factors were found to be independently associated with the increased risk of prolonged LOS, including use of corticosteroids during hospitalization, elevated HCO_3^-, decreased pH, and reduced changes in PLTs and PCT between the fourth and first day of hospitalization. A risk prediction model including these factors had an AUC of 0.795, suggesting the good discrimination of our model. The Hosmer-Lemeshow test also showed the good calibration of the model, confirming the model's good predictive performance.

Owing to the clinical fact that 7 days was the median LOS of our study population, and based on previous studies that proposed the medically required LOS for patients with AECOPD should be between 6 and 7 days based on clinical characteristics [26] and over 7 days should be regarded as prolonged LOS [15], we chose the cutoff of 7 days for LOS in this study, although different cut-offs were used in other studies [14,17,19,20,27]. Further, the fourth day of hospitalization was selected to repeat the assessment of the same laboratory variables as those on the first day of hospitalization as well as corticosteroid and antibiotic use, because the efficacies of corticosteroids and antibiotics are generally evaluated 72 h after use in clinical practice, which was on the fourth day of hospitalization in this study. Moreover, in the present study, there were differences in the laboratory data between the fourth and first day of hospitalization.

The impact of HCO_3^- and pH at the time of admission on prolonged LOS have scarcely been investigated in patients with AECOPD. In the present study, an increase of HCO_3^- and a decrease of pH were associated with an increased risk of prolonged LOS. It was reported that a high $PaCO_2$ measured in the Emergency Department was associated with prolonged LOS [20], which could support our findings in some way. According to Wang et al, $PaCO_2$ and other blood-gas variables reflect the severity of respiratory failure [20]. Our results could be interpreted that due to upper respiratory tract obstruction, respiratory dysfunction, and carbon dioxide accumulation in the body, patients with COPD are prone to respiratory acidosis with an increase in HCO_3^- and a decrease in pH, which are associated with the occurrence of AECOPD and might contribute to a prolonged LOS. We recommend that clinicians should be cautious about a change in blood-gas variables, such as HCO_3^- and pH, in patients with COPD to identify those with a high risk of prolonged AECOPD LOS for early intervention.

We also found an association between the use of corticosteroids during hospitalization and the risk of prolonged LOS. The possible reason is that although the corticosteroids could inhibit the excessive inflammatory response, it could also lead to the spread of infection and other adverse effects, such as gastrointestinal bleeding and increased blood glucose [28,29]. Similarly, since the exacerbation of COPD and its treatment with corticosteroids can worsen comorbidities such as diabetes [30], it is understandable that a prolonged stay is needed to get these comorbid conditions under control [20]. Here, we suggested the proper use of corticosteroids during hospitalization to improve the outcome of AECOPD and shorten the hospital stay.

Currently, limited statistical models have been established that can effectively predict the risk of prolonged LOS in patients with AECOPD, which is based on varying definitions of prolonged LOS and different predictors [14,17,20]. There is no model to predict prolonged LOS for the Chinese population. In the present study, we developed a promising prediction model with good calibration and discrimination using data from a Chinese hospital comprising demographic, laboratory, and environmental variables. Increased knowledge of predictors and earlier prediction of the risk of prolonged LOS may help clinicians provide better and more timely treatment and intervention, which could shorten hospital stay, reduce the disease burden of patients, and improve the outcomes of AECOPD.

There are limitations in our study. First, the study may be limited by its retrospective design, and some important features, such as heart failure, stroke, need for mechanical ventilation, Intensive Care Unit admission, and even mortality, were not recorded in the hospital. Second, the sample size in our study was relatively small, and a prospective study with larger sample size is needed. Third, although the predictive ability of our model was good, external validation is preferred for improving the reliability of the model. Fourth, phenotyping of the groups was not comprehensive: the severity of AECOPD, the microbiological origin of AECOPD, and spirometric data were not available.

Conclusions

In the present study, we identified a group of predictors that were independently associated with prolonged LOS of more than 7 days. A clinical prediction model comprising these variables was then developed with good predictive performance. It may help clinicians identify patients with a higher risk of prolonged LOS and clarify which variables they should closely monitor when making treatment decisions to shorten hospital stay and improve the burden and outcomes of AECOPD for patients with COPD.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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