Hypertension and chronic cor pulmonale were the independent risk factors for a prolonged length of hospital stay in acute exacerbation of chronic obstructive pulmonary disease (AECOPD) patients: a multicenter cross-sectional study

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January 17, 2021

Abstract

Background: AECOPD is a severe status of COPD. The prolonged length of hospital stay (LHS) was associated with poor prognosis and higher medical costs in AECOPD patients. Identification of the risk factors for prolonged LHS will help physicians provide targeted and personalized interventions, reduce LHS, and avoid unnecessary health services in COPD patients. This study aimed to explore the risk factors for prolonged LHS in hospitalized AECOPD patients. Methods: In this multicenter cross-sectional study, 598 AECOPD patients were screened. In the end, the LHS of 111 were <7 days (Normal LHS, N-LHS), 218 were 7-10 days (Mild Prolonged LHS, MP-LHS), and 100 were[?]11 days (Severe Prolonged LHS, SP-LHS). Demographic data, underlying diseases, symptoms, and laboratory findings were collected. Multiple logistics regression was performed to investigate the independent risk factors for prolonged LHS in AECOPD patients. Results: The significant differences in 11 variables were found by univariate analysis. Since significant collinearities among white blood cells (WBC), neutrophils (NS), and NS% were observed, WBC and NS% were excluded. Therefore, 9 factors were included in multiple logistics regression. Subsequently, our results identified that the rates of hypertension and chronic cor pulmonale (CCP) were independently associated with prolonged LHS in AECOPD patients. Conclusions: Collectively, our results suggested that complications of hypertension and CCP were at a higher risk of prolonged LHS in AECOPD patients. It also indicated that AECOPD combined with hypertension and/or CCP probably more severe. Then, more extensive management should be initially administrated.

Introduction

Chronic obstructive pulmonary disease (COPD) is a worldwide public health problem and one of the leading causes of mortality and morbidity [1,2]. Acute exacerbation of COPD (AECOPD), a severe status of COPD, is characterized by worsening of respiratory manifestations and was associated with increased mortality [3,4]. It was reported that AECOPD accounted for about 13% of all admitted patients [5]. Mounting evidence showed that length of hospital stay (LHS) was independently associated with the severity of AECOPD [6]. Although the risk factors for hospitalization in AECOPD were well explored [7-10], the predictors for prolonged LHS in AECOPD patients were still not very clear.

In developing countries, AECOPD causes a heavy burden on the health care system [11,12]. The direct and indirect costs of AECOPD at least include health care resources devoted to the diagnosis, illness management, workability loss, premature mortality, and family caregiver costs [13,14]. Dalal AA, et al. found that the average cost was $9,745 for standard admission, and $33,440 for an ICU stay in hospitalized AECOPD patients [2]. Chen YH, et al. showed that length of ICU stay, non-invasive or invasive ventilation intervention,

and use of antibiotics and systemic steroids were the major predictors of hospitalization costs in AECOPD [15]. Therefore, LHS was noticeably associated with the medical costs of hospitalized AECOPD patients.

LHS was essential for the prediction of AECOPD severity [8,16-18]. However, the threshold of prolonged LHS in AECOPD was still in controversy [8,17,18]. In a cohort study, Mushlin AI et al. showed that the mean LHS was 6 to 7 days in AECOPD patients [19]. They also found that longer LHS was associated with increased PCO_2levels, symptoms of more than 1 day, and antibiotic treatment at the time of admission. In another prospective study, Crisafulli E et al. divided the AECOPD patients into normal ([?]7 days) and prolonged LHS (>7 days) groups [20]. Their results showed that prolonged LHS were independently associated with mMRC (modified Medical Research Council) dyspnea score [?]2 and the presence of acute respiratory acidosis. In a retrospective study, 8 days were obtained to define the prolonged LHS in hospitalized AECOPD [17]. Meanwhile, in a prospective cohort study, 9 days was used as the threshold of prolonged LHS in AECOPD [18]. They revealed that baseline dyspnea, physical activity level, and hospital variability were the independent predictors of prolonged LHS in hospitalized AECOPD patients. Simultaneously, Wang Y, found that LHS above the 75th percentile was 11 days in AECOPD patients. And, they also identified that admission between Thursday and Saturday, heart failure, diabetes, stroke, high arterial PCO_2, and low serum albumin level were independently associated with prolonged LHS in AECOPD patients.

Collectively, in our study, 7 days and 11 days were used as the thresholds of mild prolonged LHS and severe prolonged LHS in AECOPD patients, respectively. The purpose of this cross-sectional study was to identify the independent risk factors for prolonged LHS in hospitalized AECOPD patients.

Methods

Study design and population

This multicenter cross-sectional study was performed at respiratory departments of the Second Affiliated Hospital of Chongqing Medical University and the First People's Hospital of Suining City from January 2019 to August 2020. This study was approved by the Research Ethics Committees of the Second Affiliated Hospital of Chongqing Medical University (No. 2019-23) and the First People's Hospital of Suining City (NO. 2020-37) in accordance with the Declaration of Helsinki. The heights of the two hospitals were 305 meters and 801 meters above sea level, respectively. All AECOPD patients had no plateau living history. Informed consent was obtained from all the patients by the responsible physician or an appropriately trained staff member. Standard care and treatments were provided in our study according to current clinical guidelines [21,22].

Sample size determinations

As for sample size, a minimum amount of 246 (82 in each group) was required to detect at least a 20% difference in effect size for an 80% power, assuming $\alpha = 0.05$ and allocation ratio = 1:1:1. Furthermore, 20% more (98 in each group) patients were recruited.

Inclusion and exclusion criteria

The inclusion criterion was an acute exacerbation of COPD requiring hospitalization with age [?]40 years [22,23]. Exclusion criteria were as follows: non-respiratory failure patients without lung function test; active pulmonary tuberculosis (TB); asthma; bronchiectasis; pneumoconiosis; interstitial lung diseases (ILDs); pulmonary edema; pulmonary embolism; other chronic lung diseases; dysphagia and aspiration; dementia; hospital-acquired pneumonia (HAP); antibiotics within the last 2 weeks; immunosuppressive status (immunosuppressive drugs in the previous 2 weeks, organ transplant, and/or HIV infection); system steroid use within the last 2 weeks; the history of malignant diseases; renal failure; and liver failure. A total of 598 patients with hospitalized AECOPD were enrolled. And 169 were excluded. In the end, 111 patients were <7 days of LHS (Normal LHS, N-LHS), 218 patients were 7-10 days of LHS (Mild Prolonged LHS, MP-LHS), and 100 patients were [?]11 days of LHS (Severe Prolonged LHS, SP-LHS) (Figure 1).

Definitions

According to Global Initiative for Chronic Obstructive Lung Disease (GOLD) [22], the diagnosis of COPD was confirmed by the pulmonologists, based on noxious stimuli exposure history, risk elements, clinical symptoms, and spirometry (FEV1/FVC% <0.7 after bronchodilator inhalation). AECOPD was defined as an event in the natural course of the disease characterized by acute changes in clinical symptoms beyond normal day-to-day variation, resulting in additional therapy [22-24]. Chronic cor pulmonale (CCP) was defined as right ventricular hypertrophy resulting from the diseases affecting the function and/or structure of the lungs except when these pulmonary alterations were the result of diseases that primarily affect the left side of the heart [25,26]. And, the diagnosis of CCP was based on the findings of clinical presentations, echocardiography, and electrocardiogram (ECG) [25,26]. The ex-smoker was defined as abstaining from smoking [?] for 6 months. Neutrophils-to-lymphocytes ratio (NLR) was defined as neutrophils divided by lymphocytes in blood [24].

Data collection

In our study, demographic data, underlying diseases, comorbidities, symptoms, and the length of hospital stay (LHS) were recorded and collected. The blood samples for laboratory tests and lung function tests were all collected and performed within 24h after admission. However, for the safety and cooperation concerns, a spirometer test wasn't performed in patients with respiratory failure. All patients underwent computed tomography (CT) scans within 48h after admission. And the results were reviewed by one independent radiologist and one pulmonologist in each hospital, who were blinded to the study. Discrepancies were settled by consensus.

Statistical analysis

Data were analyzed using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as the Mean ± standard deviation (SD), and categorical data were expressed as frequencies. The data distribution was examined by the Kolmogorov-Smirnov test. Continuous variables with normal distribution were analyzed by one-way ANOVA with LSD and SNK's posthoc trial. Continuous variables with abnormal distribution and ordinal variables were measured by the Kruskal-Wallis H test. The Chi-square test was used to analyze categorical variables. Collinearity diagnostic was applied for selected variables before the regression model was built. Multiple logistics regression was performed to investigate the independent risk factors associated with LHS in AECOPD patients [24]. A threshold of $p< 0.05$ was thought to be significant.

Results

Baseline characteristics of AECOPD patients.

In this cross-sectional study, a total of 598 AECOPD patients were enrolled. In the end, the LHS of 111 patients (26%) were <7 days (Normal LHS, N-LHS), 218 patients (51%) were 7-10 days (Mild Prolonged LHS, MP-LHS), and 100 patients (23%) were[?]11 days (Severe Prolonged LHS, SP-LHS) (Figure 1). The demographic data of the patients were presented in Table 1. The significant differences in age and the rates of CAP, CCP, and hypertension were observed among 3 groups.

Clinical presentations and laboratory data of AECOPD patients.

As shown in Table 2, white blood cells (WBC), neutrophils (NS), NS%, lymphocytes%, erythrocyte sedimentation rate (ESR), PH, and albumin (ALB) were significantly different among the 3 groups.

Multiple logistic regression analysis in AECOPD patients.

To explore independent factors associated with LHS in AECOPD patients, multiple logistics regression was performed. Since significant collinearities among WBC, NS, and NS% were observed, WBC and NS% were excluded. In the multiple logistics regression model, 9 factors in significant association with LHS in univariate analysis, including age, the rates of CAP, CCP, and hypertension, NS, lymphocytes%, ESR, PH, and ALB were included. Subsequently, our data identified that the rates of hypertension and CCP were independently associated with LHS in AECOPD patients (Table 3).

Discussion

In this multicenter cross-sectional study, we enrolled 598 AECOPD patients. At last, 111 patients (26%) with LHS <7 days (Normal LHS, N-LHS), 218 patients (51%) with LHS 7-10 days (Mild Prolonged LHS, MP-LHS), and 100 patients (23%) with LHS [?]11 days (Severe Prolonged LHS, SP-LHS) were included. Then, the significant differences in 11 factors, including age, the rates of CAP, hypertension, and CCP, WBC, NS, NS%, lymphocytes%, ESR, PH, and ALB were identified among 3 groups by univariate analysis. Since collinearity among WBC, NS%, and NS were observed, WBC and NS% were excluded in multiple logistics regression. Subsequently, multiple logistics regression revealed that the rates of hypertension and CCP were independently associated with LHS in AECOPD patients.

COPD is one of the leading causes of morbidity and mortality worldwide [24,27]. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), the prevalence of COPD was 11.7% (95% CI 8.4% to 15.0%), indicating globally about 384 million people suffering from COPD [28]. AECOPD is also one of the major causes of admission in COPD patients [29,30]. Mounting evidence showed that LHS was independently associated with the severity, cost burden, in-hospital mortality, and re-admission rates in COPD [2,5,9,15,31,32]. Some studies reported that comorbidities were independently associated with LHS in AECOPD patients [7,8]. In a retrospective study, Wang Y et al. showed that heart failure, diabetes, stroke, increased $PaCO_2$, and reduced albumin (ALB) were the independent risk factors for prolonged LHS in AECOPD patients [8]. Meanwhile, in a longitudinal retrospective observational study, Inabnit LS et al. revealed that LHS significantly correlated with the number of comorbidities in COPD patients [7]. Furthermore, they also noticed that congestive heart failure (CHF), fluid and electrolyte disorders, and renal failure were associated with 28%, 20%, and 50% greater LHS in COPD patients, respectively. However, the variables, obtained in these studies, were not comprehensive. Hence, some potentially important risk factors and predictors probably were not included. Furthermore, until now, the risk factors associated with prolonged LHS weren't well explored in Chinese AECOPD patients. Therefore, comprehensive data, including demographic data, underlying diseases, comorbidities, symptoms, lung function (GOLD stages), laboratory parameters, and CT scan, were collected in our study.

Simultaneously, an acknowledged definition of prolonged LHS was still in controversy. The varied definitions of prolonged LHS in COPD were used in different studies [8,20,33]. In a retrospective longitudinal study, the COPD patients, registered by London general practitioners and patients admitted to the emergency room with COPD from 2006 to 2010, were screened [33]. It was found that the average LHS was 7 days in COPD patients. Meanwhile, in a prospective study in the Hospital Clinic of Barcelona, 7 days also was used as the cut-off of prolonged LHS in AECOPD patients [20]. However, in another retrospective study, 11 days was used to define the prolonged LHS in AECOPD patients [8]. Therefore, two thresholds of prolonged LHS, both 7 days and 11 days were considered in the current study. Subsequently, multiple logistics regression identified that the rates of hypertension and CCP were independently associated with prolonged LHS in AECOPD patients.

Some studies identified the close relationship between COPD and hypertension [34,35]. In a retrospective cohort study, 314 AECOPD patients in Swiss were screened [34]. They found that new or worsening hypertension was an independent risk factor for re-exacerbation in AECOPD patients. Meanwhile, in a cross-sectional study, the association between COPD and comorbidities (presented by Charlson comorbidity scores) was explored [35]. The results revealed that Charlson comorbidity scores in COPD patients were higher than in non-COPD patients. Meanwhile, more than 40% of COPD patients were combined with cardiovascular diseases, hypertension, and hyperlipidemia. Several studies found that low-grade systemic inflammation contributed substantially to the pathogenesis of both hypertension and COPD [36-38]. Barnes PJ et al. showed that arterial constriction resulted from COPD-induced airway inflammation, lung hyperinflation, systemic inflammation, endothelial dysfunction, and oxidative stress was essential for hypertension in COPD patients [38]. Furthermore, several studies also revealed the benefits of blood pressure control in AECOPD combined with hypertension [39,40]. It was found that the angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) treatments were negatively associated with LHS in

AECOPD combined with hypertension [39]. In a retrospective national cohort study, Mortensen EM et al. showed that ARBs and ACE inhibitors were associated with decreased mortality in hospitalized AECOPD combined with hypertension [40].

Additionally, the impact of CCP on COPD prognosis wasn't well explored. To our knowledge, this was the first multiple center's cross-sectional study to explore whether CCP was associated with LHS in AECOPD patients. CCP was defined as the right ventricle hypertrophy resulting from diseases affecting the function and/or structure of the lungs except when these pulmonary alterations are the result of diseases that primarily affect the left side of the heart [25,26]. In this study, the diagnosis of CCP was based on the findings of clinical presentations, echocardiography, and electrocardiogram (ECG) [25,26]. In advanced COPD, endothelial dysfunction, pulmonary arterioles constriction, and vascular remodeling, featured by intimal hyperplasia and vascular smooth muscle hypertrophy/hyperplasia, were induced by hypoxia and persistent chronic pulmonary inflammation, eventually leading to pulmonary hypertension (PH) [22,41,42]. In chronic pulmonary diseases, such as COPD and idiopathic pulmonary fibrosis, PH, and CCP were considered to be a single disease in different stages [25,26]. Progressive PH could cause right ventricular hypertrophy and eventually lead to right cardiac failure. Lung disease associated PH was defined as mean pulmonary arterial pressure (mPAP) greater than 20mmHg at rest [43]. Additionally, it was found that the diameter of the pulmonary artery was independently associated with acute exacerbation in COPD [44]. Then, in the current study, our results first time identified that CCP was an independent risk factor for prolonged LHS in AECOPD patients.

To our knowledge, this was the first multicenter cross-sectional study to explore the risk factor for prolonged LHS in AECOPD in the Chinese population. Meanwhile, two thresholds of prolonged LHS, 7 days and 11 days, were considered, making our data more convincible, which was one of the major strengths of this study. Additionally, comprehensive data, such as demographic data, underlying diseases, comorbidities, symptoms, lung function, and laboratory data, were collected. Particularly, a chest CT scan was performed on each patient, which effectively promoted the diagnosis accuracy and reduced confounders. The major limitation of our study included that the study was only performed in tertiary general hospitals in China. The results probably couldn't generalize to primary health care. Meanwhile, only Chinses AECOPD patients were included. Then, the results should be replicated in other ethnic groups in the future.

Conclusions

Taken together, our results identified that hypertension and chronic cor pulmonale (CCP) were independently associated with LHS in AECOPD patients. These results indicated that AECOPD patients combined with hypertension and/or CCP were more severe. Then, it was necessary to provide earlier and more effective interventions to AECOPD patients combined with hypertension and CCP. However, these findings should be validated in primary health care and other ethnic groups in the future.

Acknowledgments

We want to express our sincere appreciation to all the patients who participated in the study. This study was supported by the Natural Science Foundation of Guangdong Province (grant number 2017A030310286), Scientific Research Project of Guangzhou (grant number 201707010282), the Science and Technology Planning Project of Guangdong Province (grant number 2014A020212627 and 2016A020215099), and the Chongqing Natural Science Foundation (grant number cstc2018jcyjAX0245).

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Figure legend

Figure 1. A Flow chart of the study.

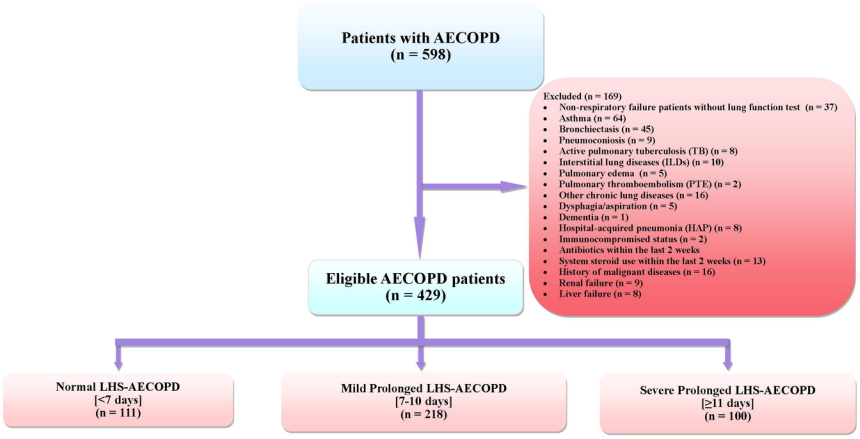

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Table 1-3.pdf available at https://authorea.com/users/389997/articles/504465-hypertension-and-chronic-cor-pulmonale-were-the-independent-risk-factors-for-a-prolonged-length-of-hospital-stay-in-acute-exacerbation-of-chronic-obstructive-pulmonary-disease-aecopd-patients-a-multicenter-cross-sectional-study