Factors Associated with Inpatient Length of Stay among Hospitalized Patients with Chronic Obstructive Pulmonary Disease, China, 2016-2017: a retrospective study

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Factors Associated with Inpatient Length of Stay among Hospitalized Patients with Chronic Obstructive Pulmonary Disease, China, 2016-2017: a retrospective study

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ABSTRACT

Objectives: To identify factors associated with length of stay (LOS) in Chronic obstructive pulmonary disease (COPD) hospitalized patients, which may help shorten LOS and reduce economic burden accrued over hospital stay.

Design: A retrospective cohort study

Setting: This study was performed in a tertiary hospital in China.

Participants: New COPD patients who were aged ≥40 years and admitted between 2016 and 2017.

Primary and secondary outcome measures: LOS at initial admission was the primary outcome and health expenditures were the secondary outcome. To identify factors associated with LOS, we collected information at index hospitalization and constructed a conceptual model using directed acyclic graph (DAG). Potential factors were grouped into five blocks: demographic information, disease severity, comorbidities, hospital and environmental factors. Negative binomial regression model was fitted for each block of factors and then a parsimonious analysis was performed.

Results: Totally, we analyzed 565 COPD patients. The mean±SD age was 69±11 years old and 69.4% were male. The median LOS was 10 days with an interquartile range of 8-14 days. In modelling each block of factors, venous thromboembolism (rate ratio [RR] =1.38, 95% confidence interval (CI): 1.07-1.76), pulmonary encephalopathy (RR=1.53, 95%CI: 1.06-2.20), respiratory infection (RR=1.12, 95%CI: 1.01-1.24), osteoporosis (RR=1.45, 95%CI: 1.07-1.96), and emergence admission (RR=1.08, 95%CI: 1.01-1.16) were associated with longer LOS. In parsimonious analysis, all the aforementioned factors remained significant except emergency admission, strengthening their associations with hospital stay. Additionally, total hospitalization cost and patients' out-of-pocket cost increased monotonically with LOS (both P_{trend} <0.0001).

Conclusion: Patients' concomitant morbidities predicted excessive LOS in COPD patients. Hospitalization healthcare cost increased over the length of stay. Quality improvement initiatives may need to identify patients at high risk of longer stay and implement early interventions such as thromboprophylaxis to avoid lengthy stay, which could help reduce the high economic burden of COPD.

Keywords: Pulmonary disease, Chronic obstructive; Length of Stay; Risk Factors; DAG

Article Summary

Strengths and limitations of this study

- LOS and economic burden were analyzed in newly admitted COPD patients in developing countries.
- The primary data analysis was based on conceptual model and theoretical model driven
- Real experiences of hospitalized patients in the real-world clinical setting were analyzed
- Analysis in this single center study may not reflect the comprehensive profile of LOS in Chinese patients.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a burdensome chronic respiratory disease. It's estimated to cause 2.6% Disability-Adjusted Life Years (DALYs) globally and ranked as the third top cause of DALYs in China.[1] The prevalence of COPD in Chinese adults is 8.6%, with approximately 100 million COPD patients.[2] People aged over 40 years are particularly at high risk due to its onset in later life. During COPD progress, acute worsening respiratory symptoms can be easily triggered,[3,4] leading to hospitalizations and increased use of health service.[5] Spending on hospital-based care constitute the major healthcare cost in COPD patients, accounting for 65.9%-77% of medical costs in China.[6,7] The direct medical cost of COPD was estimated at $1732.24 per patient annually in 2006[8,9] and hospitalization cost per admission increased to $3669.33 in 2016.[10] COPD is also a costly disease in developed countries. In US, it consumes $72 billion in direct healthcare cost each year[11] and the tremendous cost is projected to be on the rise.[11,12] Given the large prevalent population and substantial economic burden imposed by COPD, interventions targeted to hospitalization are needed. Hospital stay is an important outcome for health care systems[13] and indicates the acute impact of exacerbation on patients.[14] Length of stay (LOS) correlates with hospitalization cost.[15] Shortening LOS might be one way to slow down the escalating healthcare cost.

Owing to disparities in healthcare systems or service use, there exists a high heterogeneity of LOS across countries.[12,16,17] In China, some patients stay longer under certain circumstances, eg, discharged and readmitted on the same day due to complicated conditions, prolonging their actual stay for the same hospitalization. Two prior studies in Chinese COPD patients demonstrated that respiratory coinfection and eosinopenia were associated with longer stay.[14,18] However, these studies focused more on single exposure-outcome relationship between one risk factor of interest and LOS. The lengthy stay is multifactorial and a diversity of factors can contribute to prolonged LOS, such as poor patients' health status, complicated disease conditions, and organization operation et al.[17,19-22] Some of these factors are related to health system and some are at patient level. To effectively reduce LOS and COPD disease burden, it's of paramount importance to identify important factors associated with LOS.

Thus, we conducted a retrospective longitudinal study in COPD patients who were newly admitted to National Clinical Research Center for Respiratory Diseases (NCRCRD), a 354-bed, medical and clinical research center in a tertiary hospital in Beijing, China. To comprehensively analyze factors associated with hospital stay, we performed a hypothesis-driven analysis by constructing a conceptual model using directed acyclic graph (DAG). We hypothesized individuals with the aforementioned risk factors were at increased risk for lengthy stay. This was the first clinical epidemiological study to examine factors associated with LOS in Chinese COPD inpatients by the use of conceptual model. It provided some new information about health-care for COPD patients in developing countries and might offer one way to reduce the heavy burden of COPD.

METHODS

We retrospectively analyzed patients consecutively admitted between Jan.1st 2016 to Dec.31th 2017. The eligible patients were Chinese inpatients with primary diagnosis of COPD at initial admission in respiratory units, ≥40 years, undergoing pulmonary function testing, and not hospitalized for COPD in preceding one year. Considering the goal to identify patients at high risk of prolonged hospital stay, patients discharged against medical advice were excluded. To ensure that patients were not hospitalized due to COPD in previous one year, data on hospitalizations in 2015 were collected as well. Patients once hospitalized for COPD in 2015 were excluded to remove the influence of preceding COPD admissions within 12 months on the first admission,[20] Patients staying longer than 30 days were also excluded.

All diagnoses, including primary and five secondary diagnoses, were determined by International Classification of Diseases, 10th Revision (ICD10) coding system. COPD was defined as J40-J44 in ICD-10 codes. Unique individuals with primary diagnosis of COPD at index admission were identified. To guarantee accuracy of ICD10 coding, diagnoses were ascertained by checking details in medical records.

Hospital stays

LOS was calculated as days by subtracting the admission date from discharge date at the index admission, which was the initial hospital stay. For patients readmitted frequently during study period, their initial hospital stays were included for analyses. If patients were discharged and readmitted on the same day, the readmissions were recorded as the same hospitalization as the initial one. LOS for the same-day discharge and readmission were calculated as the summed days of hospital stay in each consecutive admission.

Direct economic burden

As data on days off from work due to COPD disabling effect were unavailable, we only analysed direct health care expenditures during hospitalization for COPD economic burden. Information on total costs and patients' out-of-pocket costs were obtained and converted to U.S. dollars using annual currency exchange rate in 2017 (1 dollar=6.7518 yuan).[23]

Potential factors

COPD is a complex disease involving airflow obstruction and multisystem diseases,[24] We combined secondary diagnoses to characterize COPD's concomitant diseases, including comorbidities and complications according to guidelines[25] and researches.[24,26-28] Comorbidities were cardio/cerebro-vascular diseases, diabetes, respiratory infection, bronchiectasis, gastroesophageal reflux, obstructive sleep apnea syndrome (OSAS), lung cancer, depression or anxiety, and osteoporosis. Complications included respiratory failure, pulmonary heart diseases, hypoxemia, venous thromboembolism (VTE), pneumothorax and pulmonary encephalopathy. As particulates in the air can trigger worsening respiratory symptoms and lead to emergency visiting or hospitalization,[29-31] we collected data on ambient air pollutants at admission. Data on daily concentrations of particulate matter with a diameter of <2.5 μm ($PM_{2.5}$) and ozone were obtained from the Environment Monitoring Station nearest to the study site. Considering the varying air pollutant concentrations across seasons and potential impact of seasonal changes (temperatures, humidity),[32] we also analyzed seasons when the admissions occurred. Emergency admission and day of week of admission were analyzed as hospital factors. The weekday of admission was dichotomized into Thursday-Sunday and Monday-Wednesday.

Patient and public involvement

Patients were not involved in this retrospective study.

Statistics

Data were summarized as number (percentage) for categorical variables and mean±SD or median (interquartile ranges [IQR]) for continuous variables as appropriate. To comprehensively analyze potential risk factors for longer LOS and identify important factors, we first developed a conceptual model using DAG. According to the model, baseline covariates were grouped into five blocks: patient demographic characteristics, COPD complications, comorbidities, hospital and environmental factors. Given the overdispersion in distribution of LOS, negative binomial regression was modelled to estimate the effect of potential covariates on hospital stay in each block. Rate ratios (RR, also known as relative risk) with 95% confidence interval (CI) were reported for the changes in percent of association between covariates and LOS. Then we fitted a final parsimonious model with significant variables obtained in aforementioned models. Hospitalization costs among patients with different LOS were compared using Kruskal-Wallis test. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, North Carolina, USA) with two-tailed $p<0.05$.

This study was approved by China-Japan Friendship Hospital Clinical Research Ethics Committee (approval no. 2018-163-K119). Privacy and confidentiality of all patient's information were maintained. Patient informed consent was not required.

RESULTS

Altogether, 565 new COPD patients were analyzed (Figure S1). The cohort was mostly elderly men residing in local areas. The mean±SD age was 69±11 years. Table 1 summarized the general information of eligible patients. Respiratory failure, pulmonary heart diseases, cardiovascular or cerebrovascular diseases, diabetes and respiratory infection were the top co-existing morbidities. Most admissions occurred on Monday-Wednesday. Outpatient departments were the main source for COPD admissions. Inpatient numbers were similar across seasons. Median exposure to ambient O_3 and $PM_{2.5}$ were 92 ug/m^3 and 52 ug/m^3, respectively. LOS was 10 (IQR: 8-14) days and total hospitalization cost was $2080.7 (1501.6, 2877.17).

Conceptual model for LOS

A conceptual model was developed based on existing knowledge about COPD and its LOS (Table S1).[17,19,20,29-35] Figure 1 presented the links from individual-level characteristics, health system-related factors, and environmental factors to LOS.

Factors associated with LOS

Based on the conceptual model, we grouped potential factors into five blocks: patient demographic characteristics (age, gender, marital status, residence), lung function and COPD complications, comorbidities, hospital factors (emergency admission, weekday) and environmental factors (season, ozone and $PM_{2.5}$ at admission).

In single model with each block of factors, concomitant VTE (RR 1.38, 95% CI 1.07-1.76) and pulmonary encephalopathy (RR 1.53, 95% CI 1.06-2.20) were associated with an increased risk of longer stay. Lung function was negatively associated with LOS with marginal insignificance. Respiratory infection (RR 1.12, 95% CI: 1.01-1.24), osteoporosis (RR 1.45, 95% CI: 1.07-1.96), and emergence admission (RR 1.08, 95% CI: 1.01-1.16) emerged as significant risk factors for longer LOS. Regarding demographic and environmental factors, no significant associations were observed (Table 2).

In final parsimonious analysis, concomitant VTE, pulmonary encephalopathy, respiratory infection, and osteoporosis remained significant for increased risk in lengthy stay (all P<0.05) (Table 3).

COPD economic burden

Patients having prolonged LOS were supposed to consume greater health resources. We further analyzed the changes in COPD healthcare cost over LOS and observed an upward trend in both total hospitalization cost and patients' out-of-pocket cost (both P_{trend} <0.0001). Figure 2 depicted the increase in costs among patients with LOS ≤8 days, 9-14 days, and >14 days divided by quantiles.

DISCUSSION

COPD is costly and shortening hospital stay is one way to reduce its high economic burden. In this retrospective study involving nearly 600 COPD patients admitted between 2016 and 2017, we analyzed factors associated with LOS from multiple aspects, aiming to identify high-risk population and risk factors that could be utilized to deliver preventive interventions toward targeted population. COPD complications (VTE, pulmonary encephalopathy) and comorbidities (respiratory infection and osteoporosis) were identified as important factors for prolonged LOS. Direct healthcare cost was in a graded increase with longer LOS.

Existing evidence on LOS in COPD patients showed a high heterogeneity and geographical variation.[17,19,20,36-40] The analysis of COPD audit data across 13 European countries demonstrated an average LOS of 7 days in COPD patients.[17] In a study of COPD comorbidity and LOS in US, mean LOS exceeded one week.[40] A real-life study in Norway showed a much longer LOS among patients admitted to rehabilitation unit, which were longer than 30 days.[39] In our study, the median LOS was 11 days. Risk factors for longer LOS also varied across different studies. Such variance are probably due to disparities in health systems in which patients are managed differently,[17] diverse study population defined by different in/exclusion criteria, and various ways to deal with data, e.g., outcome definitions.[19,39] In this study, there was a subgroup of patients who were discharged and readmitted immediately on the same day for the same cause of hospitalization. To reflect their real-life experience, we took the same-day discharge and readmission into consideration.

Co-existing morbidities have been mentioned as predictors of LOS.[20,21] As shown in our data, VTE predicted longer LOS. It can be provoked by immobilization, heightened systemic inflammation, venous stasis or other factors that place COPD patients at risk of thrombosis.[40] Patients presenting lower limb swelling, dyspnea or other symptoms usually undergo ultrasound or CT pulmonary angiogram for diagnosis. The additional examinations and antithrombotic therapy can prolong their LOS. Likewise, pulmonary encephalopathy may contribute to the prolonged stay. It occurs when neuronal damage is induced by oxygen and CO2 retention and acidosis[41], resulting in physical impairment and coma, subsequently prolonging hospital stay. Respiratory infections are a common trigger for COPD exacerbation. In our study, it was significantly associated with LOS. The greater bacterial load and inflammation could delay patients' recovery, which, in return, placed patients at greater likelihood of lengthy stay. In an AECOPD study on infectious phenotypes,[14] COPD patients with virus and/or bacteria infection had longer LOS than non-infectious patients. Besides, osteoporosis emerged as another contributor to lengthy stay. In GOLD 2020, osteoporosis is mentioned as a concomitant chronic disease that influences COPD patients' hospitalizations.[42] Some factors specific to COPD precipitate osteoporosis development, e.g., long-term inhaled corticosteroids use for maintenance therapy[40,43,44], and lung function deterioration in disease progress.[45] Systematic inflammation and oxidative stress through sarcopenia in COPD can lead to bone metabolic abnormalities and COPD-associated osteoporosis[45], placing COPD patients at an increased risk of fractures and longer stay.[46] The prolonged LOS in patients with aforementioned concomitant diseases underscore the need for effective management of COPD comorbidities and early prevention.

Additionally, we observed a monotonically increasing trend in both total hospitalization cost and out-of-pocket cost over LOS, indicating longer hospital stay cost more in COPD patients. The domestic and international studies concordantly showed that COPD is a highly expensive disease and hospital-based care cost represents the major cost driver.[7,12] The proportion varies across regions in China, ranging from 65.9% to 77%.[6,7] In 2016, COPD hospitalization cost was \$3669.33 per patient per admission.[10] In US, hospitalization is responsible for over 70% of total COPD healthcare costs.[19] The direct cost is estimated at \$72 billion annually[11] and is projected to be on the rise,[11,12] imposing substantial economic burden on society and individuals. The issue may be addressed through shortening hospital stay with tailored interventions taken.

There were several strengths in our study. First, we provided clinical epidemiological data on LOS and its risk factors in newly admitted patients for COPD. Currently, studies on hospital stay are mainly restricted to developed countries.[14,17-20,22,36,47,48] Our study demonstrated health care for Chinese COPD patients, including a comprehensive risk factor analysis for LOS and an increase of economic burden along with longer stay. Our study, together with the few prior studies in Chinese people,[14,18] would help fill the gap in knowledge of COPD inpatients' LOS in developing countries. Second, we took the same-day discharge and readmission into consideration when analyzing the collected routinely data in daily clinical practice, which reflected real experiences of hospitalized patients in the real-world clinical setting. The identified risk factors could help determine early interventions to prevent excessive stay, which further reduce economic burden accrued over hospital stay. Hence, the findings are clinically relevant and have clinical implications. In addition, as the analyzed data were from electronic medical records, data collection process was standardized and all data were under scrutiny before entering into electronic system in hospital. Diagnoses of COPD and other diseases were ascertained by reviewing medical records to ensure reliable data. Fourth, the primary data analysis was based on conceptual model by the use of DAG; the findings were theoretical model driven and the visually represented models in DAG made the assumptions about effects of exposures on LOS transparent and explicit.[49]

Hospital stay is a complex issue that is subject to patient, hospital and heath system factors. The underlying mechanisms have not been completely disentangled. It merits further investigations to figure out one way to prevent prolonged LOS. The monotonically increasing hospitalization cost with LOS underscores the great importance of shortening hospital stay in reducing COPD economic burden, which may keep rising with the growing and aging population.

There were several limitations. First, the study was performed in NCRCRD, one of top hospitals in respiratory field in China. LOS may differ in patients admitted to other health institutes that provide suboptimal care for respiratory disease. To obtain a more comprehensive profile of hospital stay in Chinese COPD patients, a multi-center study involving hospitals across different grades and regions is needed. Second, as information about patients' indirect costs were not available, we used hospitalization costs as a proxy for COPD economic burden. A profound analysis of COPD economic burden should evaluate indirect costs.

CONCLUSION

This study underscores the significance of concomitant morbidities and disease severity in predicting COPD hospital stay. Healthcare cost increased over hospital stay. Identification of high-risk patients for excess stay and delivery of early interventions such as thromboprophylaxis may offer one way to shorten LOS in COPD patients, which would help reduce the economic burden accrued over the stay.

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Author Contributions T.Y., J.J.J., C.W. were involved in conceptualization, funding acquisition and supervision. F.D., Y.Y.W., Y.L., X.S.L. collected data. F.D., X.X.R., K.H analyzed and interpreted the data. F.D. wrote the draft of manuscript: T.Y., J.J.J., F.D., C.W., K.H., X.X.R., S.W.Q, H.T.N., Y.Y.W., Y.L., M.Y.L., X.S.L. contributed to writing-review and approved the final manuscript.

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Competing interests None declared

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Table 1. Characteristics of patients hospitalized for COPD

Study patients N=565		Values [a]
Demographic characteristics	Age, years	69±11
	Men	392 (69.4)
	Married	544 (96.3)
	Local resident	361 (63.9)
Lung function and complications [b]	Pre-FEV1	1.16 (0.84, 1.73)
	Respiratory failure	63 (11.4)
	Pulmonary heart diseases	59 (10.7)
	Hypoxemia	10 (1.8)
	VTE	9 (1.6)
	Pneumothorax	2 (0.4)
	Pulmonary encephalopathy	4 (0.7)
Comorbidities [b]	Cardio/Cerebrovascular Diseases	340 (61.7)
	Diabetes	102 (18.5)
	Respiratory infection	67 (12.2)
	Bronchiectasis	47 (8.5)
	Reflux esophagitis	38 (6.9)
	OSAS	18 (3.3)
	Lung cancer	5 (0.9)
	Anxiety depression	12 (2.2)
	Osteoporosis	6 (1.1)
	Obesity	56 (9.9)
Admission	Admitted on Thursday-Sunday	252 (44.6)
	Admitted from emergency	173 (30.7)

Study patients N=565		Values [a]
Seasons at admission	March-May	164 (29.0)
	June-August	145 (25.7)
	Sep.-Nov.	94 (16.6)
	Dec.-Feb.	162 (28.7)
Air pollution at admission	O_3, ug/m^3	92 (63, 150)
	$PM_{2.5}$, ug/m^3	52 (25, 88)
Hospital stay and healthcare cost	Length of stay, days	10 (8, 14)
	Direct cost of hospitalization, $	2080.7 (1501.6, 2877.17)

[a] Data were represented as mean ± SD or median (Interquartile) for continuous variables where appropriate and n (%) for categorical variables.

[b] Fourteen patients' complications and comorbidities were missing due to their unavailable data on secondary diagnoses.

Table 2. Single model analysis for factors associated with hospital stay at index admission based on DAG

Block	Variable	RR 95%CI	P value
Demographic characteristics	Age, per 5 years	1.01 (0.998-1.03)	0.094
	Male	1.05 (0.97-1.13)	0.237
	Married	0.88 (0.74-1.05)	0.158
	Local residents	1.04 (0.96-1.12)	0.334
Lung function and complications	FEV1	0.97 (0.95-1.00)	0.055
	Respiratory failure	1.05 (0.94-1.18)	0.396
	Pulmonary heart diseases	1.03 (0.92-1.16)	0.624
	Hypoxemia	0.96 (0.74-1.24)	0.757
	VTE	1.38 (1.07-1.76)	0.012*
	Pneumothorax	1.63 (0.98-2.70)	0.057
	Pulmonary encephalopathy	1.53 (1.06-2.20)	0.023*
COPD comorbidities	Cardio/Cerebrovascular Diseases	1.05 (0.98-1.13)	0.184
	Diabetes	0.98 (0.90-1.07)	0.648
	Respiratory infection	1.12 (1.01-1.24)	0.035*
	Bronchiectasis	1.00 (0.88-1.13)	0.967
	Reflux esophagitis	1.00 (0.88-1.15)	0.959
	OSAS	1.17 (0.97-1.42)	0.094
	Lung cancer	1.09 (0.77-1.57)	0.620
	Anxiety depression	0.89 (0.69-1.13)	0.324
	Osteoporosis	1.45 (1.07-1.96)	0.018*
	Obesity	0.97 (0.86-1.08)	0.559
Hospital factors	Admitted on Thursday-Sunday	1.04 (0.97-1.11)	0.319

Block	Variable	RR 95%CI	P value
	Admitted from emergency	1.08 (1.01-1.16)	0.033*
Environmental factors	Season at admission, Mar.-May	1.01 (0.91-1.12)	0.850
	Season at admission, Jun.-Aug.	1.08 (0.96-1.22)	0.176
	Season at admission, Sep.-Nov.	0.98 (0.88-1.09)	0.752
	O3, per 10 ug/m^3	1.00 (0.995-1.01)	0.573
	PM2.5, per 10 ug/m^3	1.00 (0.998-1.01)	0.217

[a] $P<0.05$

Table 3. Parsimonious analysis for factors associated with hospital stay at index admission

Variable	RR 95%CI	P value
Age, per 5 years	1.01 (0.997-1.03)	0.126
Pre-FEV1	0.97 (0.95-1.00)	0.055
VTE	1.40 (1.09-1.78)	0.007*
Pulmonary encephalopathy	1.53 (1.07-2.18)	0.020*
Respiratory infection	1.11 (1.01-1.23)	0.040*
Osteoporosis	1.42 (1.05-1.91)	0.021*
Emergency admission	1.06 (0.98-1.14)	0.147

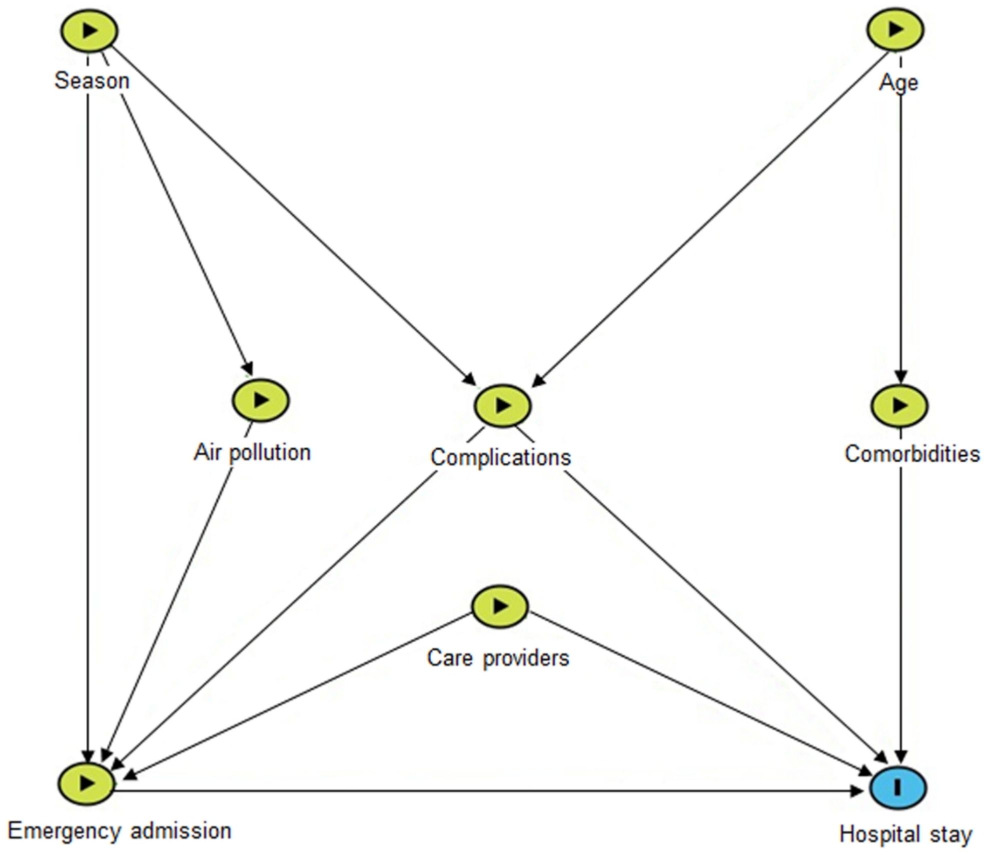
[a] $P<0.05$

Figure 1. Conceptual model using directed acyclic graph (DAG) for factors associated with hospital stay

Based on current knowledge on COPD risk factors, we developed a conceptual model using DAG. Potential covariates at baseline were grouped into five blocks: patient demographic characteristics (age, gender, marital status, residence), COPD complications, comorbidities, hospital factors (emergency admission, weekday of admission) and environmental factors (season, ozone and $PM_{2.5}$ at admission).

Figure 2. COPD costs during hospitalization

During hospitalization, total cost and the out-of-pocket cost were compared among patients with LOS ≤8 days, 9-14 days, and >14 days according to quartiles of LOS. The costs increased with longer LOS (P_{trend} <0.0001 for both total cost and the out-of-pocket cost).



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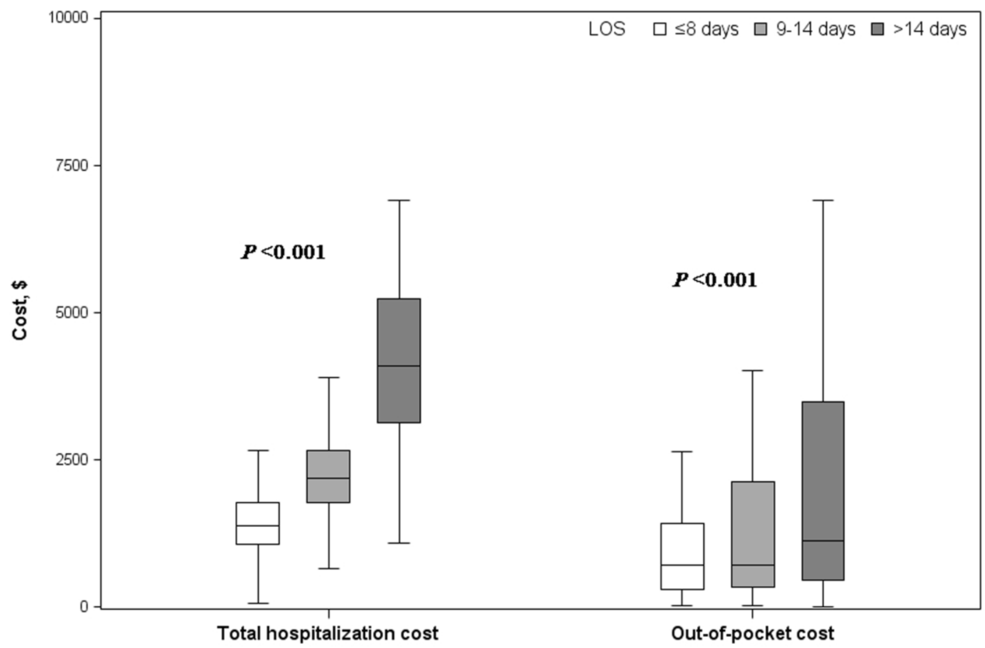
122x104mm (600 x 600 DPI)



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228x152mm (300 x 300 DPI)

SUPPLEMENTARY INFORMATION

Factors Associated with Inpatient Length of Stay among Hospitalized Patients with Chronic Obstructive Pulmonary Disease, China, 2016-2017: a retrospective study

Fen Dong[1], Ke Huang[2], Xiaoxia Ren[2], Shiwei Qumu[2], Hongtao Niu[2], Yanyan Wang[3], Yong Li[2], Minya Lu[4], Xinshan Lin[2,5], Ting Yang[2*], Jianjun Jiao[6*], Chen Wang[2,7]

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Supplementary Figure S1- Flow chart of data cleaning process

Supplementary Table S1- Observational studies on LOS and risk factors in patients admitted for COPD

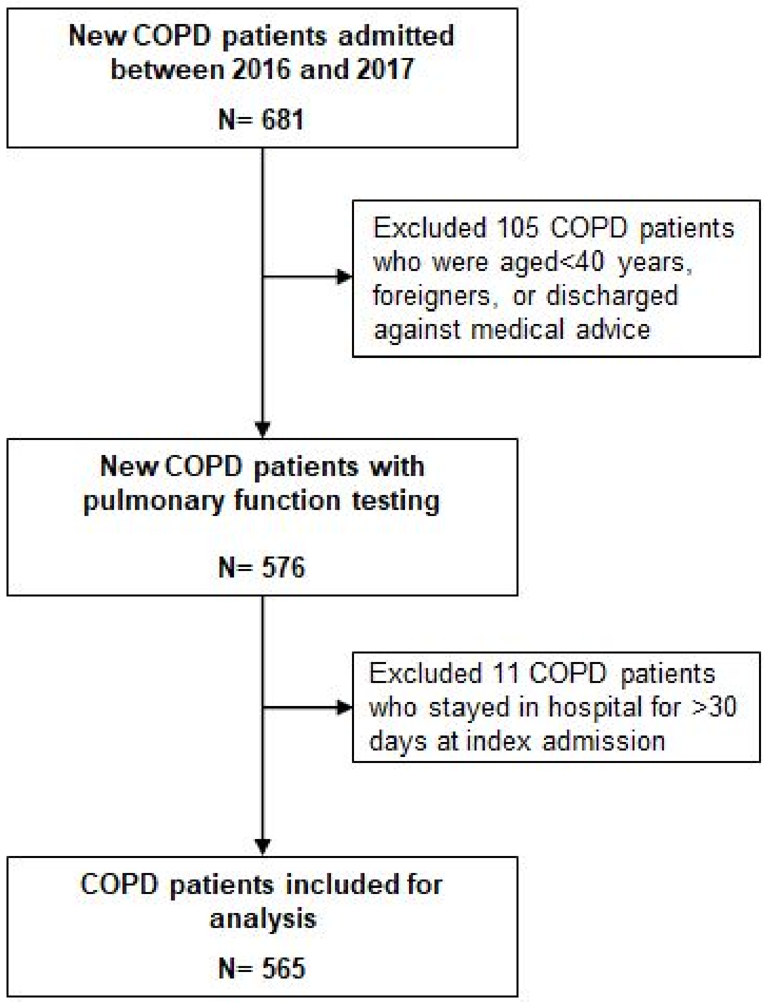

Figure S1- Flow chart of data cleaning process

Table S1. Observational studies on LOS and risk factors in patients admitted for COPD [a]

Countries/regions	Years for LOS	Study patients	LOS	Risk factors for longer LOS
Thirteen European counties[1]	Oct.-Dec.2010; Jan.-Feb. 2011	Exacerbated COPD patients in Europe	Median (IQR): 7 (4-11) days	Clinical severity, treatment
UK[2-5]	2006-2010	COPD patients registered with London general practitioners aged ≥45 years	Mean: 8.2 days in 2006 and 7 days in 2010	Age, hospital and community factors
	Apr.1st, 2005- Mar.31st, 2010	COPD patients aged ≥40 years in Blackpool, UK	Median: 6 days Mean: 9.8 days	Age, deprivation, Charlson index, specialty of admission, and cause of exacerbations
	Mar. 2007- Apr. 2008	65 AECOPD patients	Median: 5 (1-27) in normal eosinophils and 8 (2-61) in eosinopenia	Eosinopenia
	Mar. 2015-Mar. 2016	99 COPD patients admitted to department of pulmonary medicine at Landspitali National University hospital	9 days	No clear association between energy or protein intake and LOS
Norway[6]	March 2006-December 2008	Patients discharged after COPD at Oslo University hospital in Norway	Median: 6 (3.5-11) days	Admission between Thursday and Saturday, heart failure, diabetes, stroke, high arterial PCO2, and low serum albumin level were associated with LOS>11 days.[b]

Countries/regions	Years for LOS	Study patients	LOS	Risk factors for longer LOS
Italy[7]	2010	269 COPD patients in a respiratory rehabilitation unit in Italy	Mean ±SD: 31±17 days	Comorbidity, age, invasive procedure, disability, admission provenance predicted longer stay (≥ 30 days)[b]
Portugal[8]	Jan-Jun., 2016	242 diabetic patients with AECOPD or community acquired pneumonia	Median: 10 days (min-max, 1-66)	LOS was positively correlated with glycemic variability
Spain[9]	Jun. 2008-Sep. 2010	AECOPD patients visiting emergency department in Spain	-	Baseline dyspnea, physical activity level, and hospital variability
US[10,11]	Jan. 1st, -Dec. 31st, 2016	3399 COPD patients with LOS ≤60 days in Premier healthcare database	Mean ± SD: 11.64±9.40 days	Comorbidity (congestive heart failure, fluid and electrolyte disorders, renal failure) were associated with longer stay
	Oct. 1st, 2008- Sep. 30th, 2010	25301 COPD patients admitted to veteran affairs health care system	Mean ± SD: 4.2±2.7 days for weekend discharged patients, 5.4±4.9 days for weekday discharged patients	Fewer weekend discharges was associated with longer stay.
Australia[12]	2007	172 AECOPD patients	7.8 days in patients with diabetes, 6.5 days in patients without diabetes	Patients with diabetes had increased LOS, but differences were not statistically significant after adjustment for covariates.
China[13,14]	Mar. 2013-Aug.2016	346 AECOPD patients in a tertiary hospital in Hongkong, China	Median (IQR): 5 (7) days	An eosinophil value of <0.144 × 109/L on admission or <2% was associated with

Countries/regions	Years for LOS	Study patients	LOS	Risk factors for longer LOS
				longer hospital LOS (≥ 5 days) for AECOPD [b]
	January-June, 2014	81 exacerbated COPD patients in a hospital in Anhui, China	Mean ± SD: 9.6±4.1 days	Respiratory infection was associated with LOS

[a] we conducted a literature review by searching literatures in the following database: Medline, Embase, Pubmed and Web of Science. We searched observational studies that focused on risk factors of longer hospital stay at index admission in COPD inpatients. Terms used in search were: "Chronic obstructive pulmonary disease", "COPD", "hospitalization", "length of stay", "LOS", and "hospital stay". Published years ranged from 2000 to 2019. Study types included prospective study, retrospective study, cohort analysis or observational study. We also searched the references in retrieved papers for supplement studies that may be missed during the search

[b] In risk factor analysis, LOS was categorized into a binary variable.[6,7,13]

AECOPD=acute exacerbation of COPD; UK=United Kingdom; US=United States

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Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and	3

		balanced summary of what was done and what was found	
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	#3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources /	#8	For each variable of interest give sources of	6-8

measurement		data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	
Bias	#9	Describe any efforts to address potential sources of bias	6
Study size	#10	Explain how the study size was arrived at	n/a. In this retrospectively cohort, patients were consecutively admitted
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7-9
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	8-9
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	n/a. In this study, we studied potential factors related to length of

			stay in COPD patients
Statistical methods	#12c	Explain how missing data were addressed	23 Table 1
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	
Statistical methods	#12e	Describe any sensitivity analyses	
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	9 Figure S1
Participants	#13b	Give reasons for non-participation at each stage	9 Figure S1
Participants	#13c	Consider use of a flow diagram	9 Figure S1
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	9, 23 Table 1

Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	23 Table 1
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	7, hospital stay at the initial admission was the follow-up time
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	9, 23 Table 1
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10, 24-26 Table 2-3
Main results	#16b	Report category boundaries when continuous variables were categorized	10 Figure 2
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a. Relative risk was the main indicator for length of stay in this

			paper
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	n/a. This study focused on the potential factors associated with prolonged hospital stay in COPD patients

Discussion

Key results	#18	Summarise key results with reference to study objectives	10-11
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	14
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	14
Generalisability	#21	Discuss the generalisability (external validity) of	14

		the study results	
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

None This checklist can be completed online using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

Factors Associated with Inpatient Length of Stay among Hospitalized Patients with Chronic Obstructive Pulmonary Disease, China, 2016-2017: a retrospective study

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Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Epidemiology, Respiratory medicine
Keywords:	Chronic airways disease < THORACIC MEDICINE, Epidemiology <

	THORACIC MEDICINE, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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Factors Associated with Inpatient Length of Stay among Hospitalized Patients with Chronic Obstructive Pulmonary Disease, China, 2016-2017: a retrospective study

Fen Dong[1], Ke Huang[2], Xiaoxia Ren[2], Shiwei Qumu[2], Hongtao Niu[2], Yanyan Wang[3], Yong Li[2], Minya Lu[4], Xinshan Lin[2,5], Ting Yang[2*], Jianjun Jiao[6*], Chen Wang[2,7]

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ABSTRACT

Objectives: To identify factors associated with length of stay (LOS) in Chronic obstructive pulmonary disease (COPD) hospitalized patients, which may help shorten LOS and reduce economic burden accrued over hospital stay.

Design: A retrospective cohort study

Setting: This study was performed in a tertiary hospital in China.

Participants: COPD patients who were aged ≥40 years and newly admitted between 2016 and 2017.

Primary and secondary outcome measures: LOS at initial admission was the primary outcome and health expenditures were the secondary outcome. To identify factors associated with LOS, we collected information at index hospitalization and constructed a conceptual model using directed acyclic graph. Potential factors were classified into five groups: demographic information, disease severity, comorbidities, hospital admission, and environmental factors. Negative binomial regression model was fitted for each block of factors and a parsimonious analysis was performed.

Results: Totally, we analyzed 565 COPD patients. The mean age was 69±11 years old and 69.4% were male. The median LOS was 10 (IQR 8-14) days. LOS was significantly longer in patients with venous thromboembolism (VTE) (16 vs 10 days, p=0.0002) or with osteoporosis (15 vs 10 days, p=0.0228). VTE (RR 1.38, 95% CI 1.07-1.76), hypoxic-hypercarbic encephalopathy (RR 1.53, 95%CI 1.06-2.20), respiratory infection (RR 1.12, 95%CI 1.01-1.24), osteoporosis (RR 1.45, 95%CI 1.07-1.96), and emergence admission (RR 1.08, 95%CI 1.01-1.16) were associated with longer LOS. In parsimonious analysis, all these factors remained significant except emergency admission, highlighting the important role of concomitant morbidities in patients' hospital stay. Total hospitalization cost and patients' out-of-pocket cost increased monotonically with LOS (both p_{trend} <0.0001).

Conclusion: Patients' concomitant morbidities predicted excessive LOS in COPD patients. Healthcare cost increased over the length of stay. Quality improvement initiatives may need to identify patients at high risk for lengthy stay and implement early interventions to reduce COPD economic burden.

Keywords: Pulmonary disease, Chronic obstructive; Length of Stay; Risk Factors; DAG

Article Summary

Strengths and limitations of this study

- LOS and economic burden were analyzed in newly admitted COPD patients in developing countries.
- The primary data analysis was based on conceptual model and theoretical model driven
- Real experiences of hospitalized patients in the real-world clinical setting were analyzed
- Analysis in this single center study may not reflect the comprehensive profile of LOS in Chinese patients.
- Indirect hospitalization costs were not analyzed due to unavailability of data on patients' indirect costs.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a burdensome chronic respiratory disease. It's estimated to cause 2.6% Disability-Adjusted Life Years (DALYs) globally and ranked as the third top cause of DALYs in China.[1] The prevalence of COPD in Chinese adults is 8.6%, with approximately 100 million COPD patients.[2] People aged over 40 years are particularly at high risk due to its onset in later life. During COPD progress, acute worsening respiratory symptoms can be easily triggered,[3,4] leading to hospitalizations and increased use of health service.[5] Spending on hospital-based care constitute the major healthcare cost in COPD patients, accounting for 65.9%-77% of medical costs in China.[6,7] The direct medical cost of COPD was estimated at $1732.24 per patient annually in 2006[8,9] and hospitalization cost per admission increased to $3669.33 in 2016.[10] COPD is also a costly disease in developed countries. In US, it consumes $72 billion in direct healthcare cost each year[11] and the tremendous cost is projected to be on the rise.[11,12] Given the large prevalent population and substantial economic burden, interventions targeted to COPD hospitalization are needed. Hospital stay is an important outcome for health care systems[13] and indicates the acute impact of exacerbation on patients.[14] Length of stay (LOS) correlates with hospitalization cost.[15] Shortening LOS might be one way to slow down the escalating healthcare cost.

Owing to disparities in healthcare systems or service use, there exists a high heterogeneity of LOS across countries.[12,16,17] In China, some patients stay longer under certain circumstances, eg, discharged and readmitted on the same day due to complicated conditions, prolonging their actual stay for the same hospitalization. Two prior studies in Chinese COPD patients demonstrated that respiratory coinfection and eosinopenia were associated with longer stay.[14,18] However, these studies focused more on single exposure-outcome relationship between one risk factor and LOS. The lengthy stay is multifactorial and a diversity of factors can contribute to prolonged LOS, such as poor patients' health status, complicated disease conditions, and organization operation et al.[17,19-22] Some of these factors are related to health system and some are patient-level factors. To effectively reduce LOS and COPD disease burden, it's of paramount importance to identify important factors associated with LOS.

Thus, we conducted a retrospective longitudinal study to analyze factors associated with hospital stay. Study population were COPD patients who were newly admitted to National Clinical Research Center for Respiratory Diseases (NCRCRD), a 354-bed, medical and clinical research center in a tertiary hospital in Beijing, China.

METHODS

We retrospectively analyzed patients consecutively admitted between Jan.1st 2016 to Dec.31st 2017. The eligible patients were Chinese inpatients with primary diagnosis of COPD at initial admission in respiratory units, who were aged ≥40 years and had pulmonary function testing. Considering the aim to identify patients at high risk of prolonged hospital stay, patients discharged against medical advice were excluded. Patients who had been hospitalized for COPD in 2015 were also excluded to remove the influence of COPD admissions within prior 12 months on the first admission during the study period.[20] Patients with LOS longer than 30 days at the first admission were excluded as well.

All diagnoses, including primary and five secondary diagnoses, were determined by International Classification of Diseases, 10th Revision (ICD10) coding system. COPD was defined as J40-J44 in ICD-10 codes. Unique individuals with primary diagnosis of COPD at index admission were identified. To guarantee accuracy of ICD10 coding, diagnoses were ascertained by checking details in medical records.

Hospital stays

LOS was calculated as days by subtracting the admission date from discharge date at the index admission, which was the initial hospital stay. For patients readmitted frequently during study period, their initial hospital stays were included for analyses. If patients were discharged and readmitted on the same day, the readmissions were recorded as the same hospitalization as the initial one. LOS for the same-day discharge and readmission were calculated as the summed days of hospital stay in each consecutive admission.

Direct economic burden

Given the unavailability of data about days off from work due to COPD disabling effect, we only analysed direct health care expenditures during hospitalization. Information on total costs and patients' out-of-pocket costs were obtained and converted to U.S. dollars using annual currency exchange rate in 2017 (1 dollar=6.7518 yuan).[23]

Potential factors

COPD is a complex disease involving airflow obstruction and multisystem diseases,[24] We combined secondary diagnoses to characterize COPD's concomitant diseases, including comorbidities and complications according to guidelines[25] and researches.[24,26-28] Comorbidities were cardio/cerebro-vascular diseases, diabetes, respiratory infection, bronchiectasis, gastroesophageal reflux, obstructive sleep apnea syndrome (OSAS), lung cancer, depression or anxiety, and osteoporosis. Complications included respiratory failure, pulmonary heart diseases, hypoxemia, venous thromboembolism (VTE), pneumothorax and hypoxic-hypercarbic encephalopathy. As particulates in the air can trigger respiratory symptoms and lead to emergency visiting or hospitalization,[29-31] we analyzed ambient air pollutants on admission. Data on daily concentrations of particulate matter with a diameter of <2.5 μm ($PM_{2.5}$) and ozone were obtained from the Environment Monitoring Station nearest to the study site. Air pollutant concentrations change across seasons. Given the potential impact of seasonal changes (temperatures, humidity),[32] we also took seasons into consideration. Emergency admission and day of week of admission were analyzed as hospital factors. The weekday of admission was dichotomized into Thursday-Sunday and Monday-Wednesday.

Patient and public involvement

Patients were not involved in this retrospective study.

Statistics

Data were summarized as number (percentage) for categorical variables and mean±SD or median (interquartile ranges [IQR]) for continuous variables as appropriate. The Wilcoxon rank sum test was adopted to compare LOS between patients with co-existing morbidities and those without the morbid condition. To comprehensively analyze important risk factors for longer LOS, we first developed a conceptual model using directed acyclic graph (DAG). According to the model, baseline covariates were grouped into five blocks: patient demographic characteristics, COPD complications, comorbidities, hospital and environmental factors. Given the overdispersion in distribution of LOS, negative binomial regression was modelled to estimate the effect of potential covariates on hospital stay in each block. Rate ratios (RR, also known as relative risk) with 95% confidence interval (CI) were reported for the changes in percent of association between covariates and LOS. Then we fitted a final parsimonious model with significant variables obtained in aforementioned models. Hospitalization costs among patients with different LOS were compared using Kruskal-Wallis test. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, North Carolina, USA) with two-tailed $p<0.05$.

This study was approved by China-Japan Friendship Hospital Clinical Research Ethics Committee (approval no. 2018-163-K119). Privacy and confidentiality of all patient's information were maintained. Patient informed consent was not required.

RESULTS

Altogether, 565 new COPD patients were analyzed (Figure S1). The cohort had a mean age of 69±11 years and 69.4% were male. Table 1 summarized the general information of eligible patients. Respiratory failure (11.4%) and pulmonary heart diseases (10.7%) were the top complications of COPD while cardiovascular or cerebrovascular diseases (61.7%) was the most common comorbidity. Among the index admissions, 252 (44.6%) admissions occurred on Thursday-Sunday. Outpatient departments were the main source for COPD admissions, with 30.7% admissions from emergency. Inpatient numbers were similar across seasons. Median exposure to ambient O_3 and $PM_{2.5}$ were 92 ug/m^3 and 52 ug/m^3, respectively. LOS was 10 (IQR: 8-14) days and total hospitalization cost was $2080.7 (1501.6, 2877.17).

Conceptual model for LOS

A conceptual model was developed based on existing knowledge about COPD and its LOS (Table S1).[17,19,20,29-35] Figure 1 presented the links from individual-level characteristics, health system-related factors, and environmental factors to LOS.

Factors associated with LOS

Based on the conceptual model, we grouped potential factors into five blocks: patient demographic characteristics (age, gender), lung function and COPD complications, comorbidities, hospital factors (emergency admission, weekday) and environmental factors (season, ozone and $PM_{2.5}$ at admission).

In single model with each block of factors, concomitant VTE (RR 1.38, 95% CI 1.07-1.76) and hypoxic-hypercarbic encephalopathy (RR 1.53, 95% CI 1.06-2.20) were associated with an increased risk of longer stay. Lung function was negatively associated with LOS with marginal insignificance. Respiratory infection (RR 1.12, 95% CI: 1.01-1.24), osteoporosis (RR 1.45, 95% CI: 1.07-1.96), and emergence admission (RR 1.08, 95% CI: 1.01-1.16) emerged as significant risk factors for longer LOS. No significant associations were observed regarding demographic and environmental factors (Table 2).

When comparing LOS in COPD patients with co-existing morbidities and those without the morbid conditions, longer LOS was observed in patients with VTE than those without VTE (16 vs 10 days, p=0.0002). In patients with osteoporosis, LOS was longer compared to those without osteoporosis (15 vs 10 days, p=0.0228).

In final parsimonious analysis, concomitant VTE, hypoxic-hypercarbic encephalopathy, respiratory infection, and osteoporosis remained significant for increased risk in lengthy stay (all P<0.05) (Table 3).

COPD economic burden

Patients having prolonged LOS were supposed to consume greater health resources. We further analyzed the changes in COPD healthcare cost over LOS and observed an upward trend in both total hospitalization cost and patients' out-of-pocket cost (both P_{trend} <0.0001). Figure 2 depicted the increase in costs among patients with LOS ≤8 days, 9-14 days, and >14 days divided by quantiles. Total costs in the three subgroups were $1385.72 (1066.28, 1781.46), $2177.73 (1779.58, 2650.42) and $4104.61 (3124.56, 5233.09), respectively (p<0.0001). The corresponding figures for patients' out-of-pocket cost were $701.16 (291.69, 1426.55), $708.13 (329.97, 2130.87) and $1124.53 (461.49, 3491.55) (p<0.0001).

DISCUSSION

COPD is costly and shortening hospital stay is one way to reduce its high economic burden. In this retrospective study involving nearly 600 COPD patients admitted between 2016 and 2017, we analyzed factors associated with LOS from multiple aspects, aiming to identify risk factors that could characterize high-risk population or determine early interventions that should be promptly delivered. COPD complications (VTE, hypoxic-hypercarbic encephalopathy) and comorbidities (respiratory infection and osteoporosis) were identified as important factors for prolonged LOS. Direct healthcare cost was in a graded increase with longer LOS.

Existing evidence on LOS in COPD patients showed a high heterogeneity and geographical variation.[17,19,20,36-40] The analysis of COPD audit data across 13 European countries demonstrated an average LOS of 7 days in COPD patients.[17] In a study of COPD comorbidity and LOS in US, mean LOS exceeded one week.[40] A real-life study in Norway showed a much longer LOS among patients admitted to rehabilitation unit, which were longer than 30 days.[39] In our study, the median LOS was 11 days. Risk factors for longer LOS also varied across different studies. Such variance are probably due to disparities in health systems in which patients are managed,[17] diverse study population defined by different in/exclusion criteria, and various ways to deal with data, e.g., outcome definitions.[19,39] In this study, there was a subgroup of patients who were discharged and readmitted immediately on the same day for the same cause of hospitalization. To reflect their real-life experience, we took the same-day discharge and readmission into consideration.

Co-existing morbidities have been mentioned as predictors of LOS.[20,21] As shown in our data, VTE predicted longer LOS. It can be provoked by immobilization, heightened systemic inflammation, venous stasis or other factors that place COPD patients at risk of thrombosis.[40] Patients presenting lower limb swelling, dyspnea or other symptoms usually undergo ultrasound or CT pulmonary angiogram for diagnosis. The additional examinations and antithrombotic therapy can prolong their LOS. Likewise, hypoxic-hypercarbic encephalopathy may contribute to the prolonged stay. It occurs when neuronal damage is induced by oxygen and CO2 retention and acidosis[41], resulting in physical impairment and coma, subsequently prolonging hospital stay. Respiratory infections are a common trigger for COPD exacerbation. In our study, it was significantly associated with LOS. The greater bacterial load and inflammation could delay patients' recovery, which, in return, placed patients at greater likelihood of lengthy stay. In an AECOPD study on infectious phenotypes,[14] COPD patients with virus and/or bacteria infection had longer LOS than non-infectious patients. Osteoporosis was another contributor to lengthy stay. In GOLD 2020, osteoporosis is mentioned as a concomitant chronic disease that influences COPD patients' hospitalizations.[42] Some COPD-related factors precipitate osteoporosis development, e.g., long-term inhaled corticosteroids use for maintenance therapy[40,43,44], and lung function deterioration in disease progress.[45] Systematic inflammation and oxidative stress through sarcopenia in COPD can lead to bone metabolic abnormalities and COPD-associated osteoporosis[45], placing COPD patients at risk of fractures and longer stay.[46] The prolonged LOS in patients with aforementioned concomitant diseases underscore the need for effective management of COPD comorbidities and early prevention.

Additionally, we observed a monotonically increasing trend in both total hospitalization cost and out-of-pocket cost over LOS, indicating longer hospital stay cost more in COPD patients. The domestic and international studies concordantly showed that COPD is a highly expensive disease and hospital-based care cost represents the major cost driver.[7,12] In 2016, COPD hospitalization cost was $3669.33 per Chinese patient per admission.[10] In US, the cost accounted for over 70% of total COPD healthcare costs.[19] The direct cost is estimated at $72 billion annually[11] and is projected to be on the rise.[11,12]

The substantial economic burden may be addressed through shortening hospital stay with tailored interventions taken.

As shown in our study, COPD complications, (venous thromboembolism and hypoxic-hypercarbic encephalopathy) and comorbidities (respiratory infection and osteoporosis) increased risk of prolonged hospital stay. These comorbid conditions are potentially preventable and treatable. For instance, early thromboprophylaxis like anticoagulation or mechanical prophylaxis are adopted when COPD patients are admitted to prevent thrombotic events during hospitalization; provide respiratory support promptly when patients present hypoxic-hypercarbic syndrome; and recommend patients pneumococcal and influenza vaccination to avoid respiratory infection. These tailored interventions are expected to shorten LOS and save healthcare cost of COPD patients.

There were several strengths in our study. First, we provided clinical epidemiological data on LOS and its risk factors in newly admitted patients for COPD. Currently, studies on hospital stay are mainly restricted to developed countries.[14,17-20,22,36,47,48] Our study demonstrated health care for Chinese COPD patients, including a comprehensive risk factor analysis for LOS and an increase of economic burden along with longer stay. Our study, together with the few prior studies in Chinese people,[14,18] would help fill the gap in knowledge of COPD inpatients' LOS in developing countries. Second, we took the same-day discharge and readmission into consideration when analyzing the collected routinely data in daily clinical practice, which reflected real experiences of hospitalized patients in the real-world clinical setting. The identified risk factors could help determine early interventions to prevent excessive stay, which further reduce economic burden accrued over hospital stay. Hence, the findings are clinically relevant and have clinical implications. In addition, as the analyzed data were from electronic medical records, data collection process was standardized and all data were under scrutiny before entering into electronic system in hospital. Diagnoses of COPD and other diseases were ascertained by reviewing medical records to ensure reliable data. Fourth, the primary data analysis was based on conceptual model by the use of DAG, which visually represented models in a graph with unidirectional arrows and made assumptions about exposures' effects on LOS transparent and explicit[49]. Thus, the findings were theoretical model driven.

Hospital stay is a complex issue that is subject to patient, hospital and heath system factors. The underlying mechanisms have not been completely disentangled and merit further investigations. The monotonically increasing hospitalization cost with LOS underscores the great importance of shortening hospital stay in reducing COPD economic burden, which may keep rising with the growing and aging population.

There were several limitations. First, the study was performed in NCRCRD, one of top hospitals in respiratory field in China. LOS may differ in patients admitted to secondary hospitals or other health institutes that provide suboptimal care for respiratory disease. This single-center study may not reflect the overall scenario of COPD hospitalized patients. We could not analyze the average LOS among patients with multiple rehospitalizations, which could reflect long-term disease burden of COPD. To obtain a more comprehensive profile of hospital stay in Chinese COPD patients, it is necessary to conduct a multi-center study with hospitals across different grades and regions involved. A nation-wide network of health information system is recommended to capture all hospitalizations and track the real-time dynamic admissions in COPD patients. Second, we used hospitalization costs as a proxy for COPD economic burden because information about patients' indirect costs were not available in this study. To perform a profound analysis of COPD economic burden, indirect costs also need to be evaluated. Further study on COPD economic burden should take both direct and indirect costs into consideration in the future.

CONCLUSION

This study underscores the significance of concomitant morbidities and disease severity in predicting COPD hospital stay. Healthcare cost increased over hospital stay. Identification of high-risk patients for excess stay and delivery of early interventions such as thromboprophylaxis may offer one way to shorten LOS in COPD patients, which would help reduce the economic burden accrued over the stay.

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Competing interests None declared

Patient consent for publication Not required

Ethics approval We obtained approval from the China-Japan Friendship Hospital Clinical Research Ethics Committee (approval no. 2018-163-K119). Privacy and confidentiality of all patient's information were maintained. Patient informed consent was not required.

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Availability of data and material: Not applicable

Code availability: Not applicable

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Table 1. Characteristics of patients hospitalized for COPD

Study patients N=565		Values [a]
Demographic characteristics	Age, years	69±11
	Men	392 (69.4)
	Married	544 (96.3)
	Local resident	361 (63.9)
Lung function and complications [b]	Pre-FEV1	1.16 (0.84, 1.73)
	Respiratory failure	63 (11.4)
	Pulmonary heart diseases	59 (10.7)
	Hypoxemia	10 (1.8)
	VTE	9 (1.6)
	Pneumothorax	2 (0.4)
	Hypxic-hypercarbic encephalopathy	4 (0.7)
Comorbidities [b]	Cardio/Cerebrovascular Diseases	340 (61.7)
	Diabetes	102 (18.5)
	Respiratory infection	67 (12.2)
	Bronchiectasis	47 (8.5)
	Reflux esophagitis	38 (6.9)
	OSAS	18 (3.3)
	Lung cancer	5 (0.9)
	Anxiety depression	12 (2.2)
	Osteoporosis	6 (1.1)
	Obesity	56 (9.9)
Admission	Admitted on Thursday-Sunday	252 (44.6)
	Admitted from emergency	173 (30.7)

Study patients N=565		Values [a]
Seasons at admission	March-May	164 (29.0)
	June-August	145 (25.7)
	Sep.-Nov.	94 (16.6)
	Dec.-Feb.	162 (28.7)
Air pollution at admission	O_3, ug/m^3	92 (63, 150)
	$PM_{2.5}$, ug/m^3	52 (25, 88)
Hospital stay and healthcare cost	Length of stay, days	10 (8, 14)
	Direct cost of hospitalization, $	2080.7 (1501.6, 2877.17)

[a] Data were represented as mean ± SD or median (Interquartile) for continuous variables where appropriate and n (%) for categorical variables.

[b] Fourteen patients' complications and comorbidities were missing due to their unavailable data on secondary diagnoses.

Table 2. Single model analysis for factors associated with hospital stay at index admission based on DAG

Block	Variable	RR 95%CI	P value
Demographic characteristics	Age, per 5 years	1.02 (1.00-1.03)	0.032
	Male	1.04 (0.96-1.12)	0.312
Lung function and complications	FEV1	0.97 (0.95-1.00)	0.055
	Respiratory failure	1.05 (0.94-1.18)	0.396
	Pulmonary heart diseases	1.03 (0.92-1.16)	0.624
	Hypoxemia	0.96 (0.74-1.24)	0.757
	VTE	1.38 (1.07-1.76)	0.012*
	Pneumothorax	1.63 (0.98-2.70)	0.057
	Hypoxic-hypercarbic encephalopathy	1.53 (1.06-2.20)	0.023*
COPD comorbidities	Cardio/Cerebrovascular Diseases	1.05 (0.98-1.13)	0.184
	Diabetes	0.98 (0.90-1.07)	0.648
	Respiratory infection	1.12 (1.01-1.24)	0.035*
	Bronchiectasis	1.00 (0.88-1.13)	0.967
	Reflux esophagitis	1.00 (0.88-1.15)	0.959
	OSAS	1.17 (0.97-1.42)	0.094
	Lung cancer	1.09 (0.77-1.57)	0.620
	Anxiety depression	0.89 (0.69-1.13)	0.324
	Osteoporosis	1.45 (1.07-1.96)	0.018*
	Obesity	0.97 (0.86-1.08)	0.559
Hospital factors	Admitted on Thursday-Sunday	1.04 (0.97-1.11)	0.319
	Admitted from emergency	1.08 (1.01-1.16)	0.033*
Environmental factors	Season at admission, Mar.-May	1.01 (0.91-1.12)	0.850
	Season at admission, Jun.-Aug.	1.08 (0.96-1.22)	0.176

Block	Variable	RR 95%CI	P value
	Season at admission, Sep.-Nov.	0.98 (0.88-1.09)	0.752
	O3, per 10 ug/m^3	1.00 (0.995-1.01)	0.573
	PM2.5, per 10 ug/m^3	1.00 (0.998-1.01)	0.217

[a] *P*<0.05

Table 3. Parsimonious analysis for factors associated with hospital stay at index admission

Variable	RR 95%CI	P value
Age, per 5 years	1.01 (0.997-1.03)	0.126
Pre-FEV1	0.97 (0.95-1.00)	0.055
VTE	1.40 (1.09-1.78)	0.007*
Hypoxic-hypercarbic encephalopathy	1.53 (1.07-2.18)	0.020*
Respiratory infection	1.11 (1.01-1.23)	0.040*
Osteoporosis	1.42 (1.05-1.91)	0.021*
Emergency admission	1.06 (0.98-1.14)	0.147

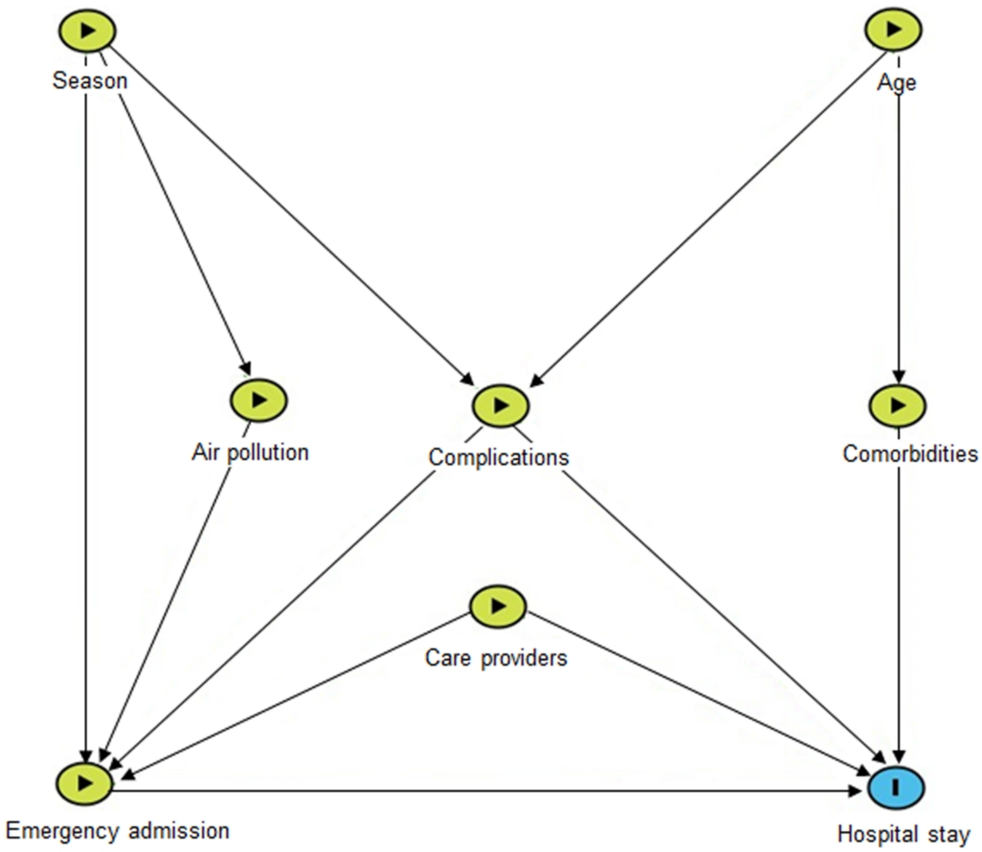
[a] P<0.05

Figure 1. Conceptual model using directed acyclic graph (DAG) for factors associated with hospital stay

Based on current knowledge on COPD risk factors, we developed a conceptual model using DAG. Potential covariates at baseline were grouped into five blocks: patient demographic characteristics (age, gender), COPD complications, comorbidities, hospital factors (emergency admission, weekday of admission) and environmental factors (season, ozone and $PM_{2.5}$ at admission).

Figure 2. COPD costs during hospitalization

During hospitalization, total cost and the out-of-pocket cost were compared among patients with LOS ≤8 days, 9-14 days, and >14 days according to quartiles of LOS. The costs increased with longer LOS (P_{trend} <0.0001 for both total cost and the out-of-pocket cost).



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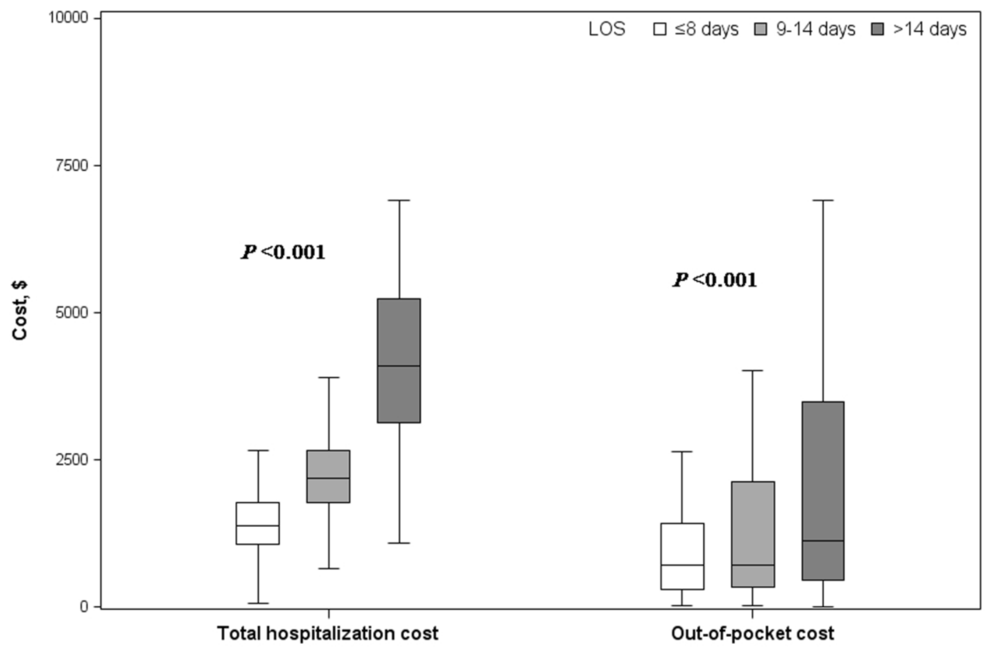
122x104mm (900 x 900 DPI)



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228x152mm (300 x 300 DPI)

SUPPLEMENTARY INFORMATION

Factors Associated with Inpatient Length of Stay among Hospitalized Patients with Chronic Obstructive Pulmonary Disease, China, 2016-2017: a retrospective study

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Supplementary Figure S1- Flow chart of data cleaning process

Supplementary Table S1- Observational studies on LOS and risk factors in patients admitted for COPD

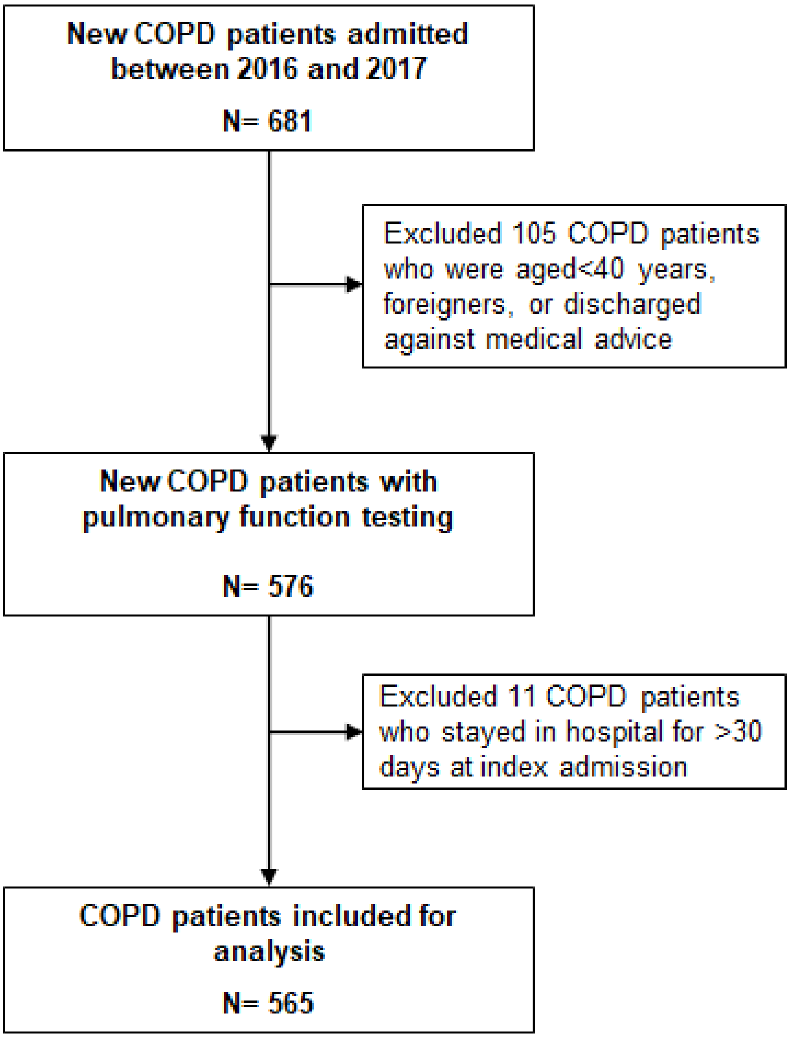

Figure S1- Flow chart of data cleaning process

Table S1. Observational studies on LOS and risk factors in patients admitted for COPD [a]

Countries/regions	Years for LOS	Study patients	LOS	Risk factors for longer LOS
Thirteen European counties[1]	Oct.-Dec.2010; Jan.-Feb. 2011	Exacerbated COPD patients in Europe	Median (IQR): 7 (4-11) days	Clinical severity, treatment
UK[2-5]	2006-2010	COPD patients registered with London general practitioners aged ≥45 years	Mean: 8.2 days in 2006 and 7 days in 2010	Age, hospital and community factors
	Apr.1st, 2005- Mar.31st, 2010	COPD patients aged ≥40 years in Blackpool, UK	Median: 6 days Mean: 9.8 days	Age, deprivation, Charlson index, specialty of admission, and cause of exacerbations
	Mar. 2007- Apr. 2008	65 AECOPD patients	Median: 5 (1-27) in normal eosinophils and 8 (2-61) in eosinopenia	Eosinopenia
	Mar. 2015-Mar. 2016	99 COPD patients admitted to department of pulmonary medicine at Landspitali National University hospital	9 days	No clear association between energy or protein intake and LOS
Norway[6]	March 2006-December 2008	Patients discharged after COPD at Oslo University hospital in Norway	Median: 6 (3.5-11) days	Admission between Thursday and Saturday, heart failure, diabetes, stroke, high arterial PCO2, and low serum albumin level were associated with LOS>11 days.[b]

Countries/regions	Years for LOS	Study patients	LOS	Risk factors for longer LOS
Italy[7]	2010	269 COPD patients in a respiratory rehabilitation unit in Italy	Mean ±SD: 31±17 days	Comorbidity, age, invasive procedure, disability, admission provenance predicted longer stay (≥ 30 days) [b]
Portugal[8]	Jan-Jun., 2016	242 diabetic patients with AECOPD or community acquired pneumonia	Median: 10 days (min-max, 1-66)	LOS was positively correlated with glycemic variability
Spain[9]	Jun. 2008-Sep. 2010	AECOPD patients visiting emergency department in Spain	-	Baseline dyspnea, physical activity level, and hospital variability
US[10,11]	Jan. 1st, -Dec. 31st, 2016	3399 COPD patients with LOS ≤60 days in Premier healthcare database	Mean ± SD: 11.64±9.40 days	Comorbidity (congestive heart failure, fluid and electrolyte disorders, renal failure) were associated with longer stay
	Oct. 1st, 2008- Sep. 30th, 2010	25301 COPD patients admitted to veteran affairs health care system	Mean ± SD: 4.2±2.7 days for weekend discharged patients, 5.4±4.9 days for weekday discharged patients	Fewer weekend discharges was associated with longer stay.
Australia[12]	2007	172 AECOPD patients	7.8 days in patients with diabetes, 6.5 days in patients without diabetes	Patients with diabetes had increased LOS, but differences were not statistically significant after adjustment for covariates.
China[13,14]	Mar. 2013-Aug.2016	346 AECOPD patients in a tertiary hospital in Hongkong, China	Median (IQR): 5 (7) days	An eosinophil value of <0.144 × 109/L on admission or <2% was associated with

Countries/regions	Years for LOS	Study patients	LOS	Risk factors for longer LOS
				longer hospital LOS (≥ 5 days) for AECOPD [b]
	January-June, 2014	81 exacerbated COPD patients in a hospital in Anhui, China	Mean ± SD: 9.6±4.1 days	Respiratory infection was associated with LOS

[a] we conducted a literature review by searching literatures in the following database: Medline, Embase, Pubmed and Web of Science. We searched observational studies that focused on risk factors of longer hospital stay at index admission in COPD inpatients. Terms used in search were: "Chronic obstructive pulmonary disease", "COPD", "hospitalization", "length of stay", "LOS", and "hospital stay". Published years ranged from 2000 to 2019. Study types included prospective study, retrospective study, cohort analysis or observational study. We also searched the references in retrieved papers for supplement studies that may be missed during the search

[b] In risk factor analysis, LOS was categorized into a binary variable.[6,7,13]

AECOPD=acute exacerbation of COPD; UK=United Kingdom; US=United States

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Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and	3

		balanced summary of what was done and what was found	
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	#3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources /	#8	For each variable of interest give sources of	6-8

measurement		data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	
Bias	#9	Describe any efforts to address potential sources of bias	6
Study size	#10	Explain how the study size was arrived at	n/a. In this retrospectively cohort, patients were consecutively admitted
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7-8
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	8
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	n/a. In this study, we studied potential factors related to length of stay in COPD patients

Statistical methods	#12c	Explain how missing data were addressed	23-24 Table 1
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	
Statistical methods	#12e	Describe any sensitivity analyses	
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	9 Figure S1
Participants	#13b	Give reasons for non-participation at each stage	9 Figure S1
Participants	#13c	Consider use of a flow diagram	9 Figure S1
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	9, 23-24 Table 1
Descriptive data	#14b	Indicate number of participants with missing	23-24 Table 1

		data for each variable of interest	
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	7, hospital stay at the initial admission was the follow-up time
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	9, 23-24 Table 1
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10, 25-27 Table 2-3
Main results	#16b	Report category boundaries when continuous variables were categorized	10 Figure 2
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a. Relative risk was the main indicator for length of stay in this paper
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity	n/a. This study focused on the

		analyses	potential factors associated with prolonged hospital stay in COPD patients
Discussion			
Key results	#18	Summarise key results with reference to study objectives	11
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	14
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	11-12, 14
Generalisability	#21	Discuss the generalisability (external validity) of the study results	13-14
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present	16

article is based

None