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Original Research Article

A Prospective Hospital-Based Research on Acute Exacerbations of COPD

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Abstract

Aim: To evaluate the acute exacerbations of COPD in Bihar region

Methods: This prospective study was done the Department of Medicine, Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar, India for 1 year. The outcomes of interest were in-hospital mortality and one-year mortality after discharge. The demographics, comorbid diseases, concomitant medications and COPD medications. The COPD-related medications, including short-acting and long-acting b_2 agonists, anticholinergics, inhaled corticosteroids and theophyllines, were measured in the 6 months before the index hospitalization.

Result: 100 patients were included in this study. the mean age of the entire population was 74 years and 70% of them were male. The majority of the patients had comorbidities and the average score on the Charlson comorbidity index was 3.7. The most commonly observed comorbidities were hypertension (64%), coronary artery disease (37%) and stroke (30%). About three-fourths of the patients were placed on #2 COPD medications and the number of emergency visits for COPD was #2 in 79% of patients. The length of stay in hospitals was 13±20 days. 11% of patients had been admitted to the ICU with an average stay of 8.5days. Mechanical ventilation was required in 8% patients and the median duration of ventilatory support was 7.5days. 4% patients were placed on non-invasive ventilation. During the index hospitalization, 10 (10%) of patients died. 11% of patients had been admitted to the ICU with an average stay of 8.5days. Mechanical ventilation was required in 8% patients and the median duration of ventilatory support was 7.5days. 4% patients were placed on non-invasive ventilation.

Conclusion: In conclusion, an exacerbation requiring hospitalization denotes a poor long-term outcome in COPD patients; even it is the first-ever one. The burden of comorbidities has a significant role in determining mortality risks, and should be carefully evaluated and managed.

Keywords: COPD, Exacerbation

Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gasses. An acute exacerbation of COPD refers to a flare up or episode where a person breathing becomes worse than normal.[1] acute exacerbation in COPD (AECOPD) is frequent in the course of the illness and is the most common reason for medical visits, hospital admissions, and mortality among these patients. Exacerbations of COPD are associated with increased morbidity and mortality.[2] The prevalence of COPD disease about 251 million cases in 2016 and the deaths estimated were 3.17 million in 2015 globally and the percentage is about 5% deaths in a year were estimated globally.[3] The incidence rates were higher in men than in women above the age of 60 years people.[4,5] As of 2016, COPD is the second big- gest cause of death in India. The prevalence ranged between 2 and 22% among the men and 1.2 to 19% among women in different population-based studies across India.[6] Cigarette smoking is the most common cause of COPD that accounts for about 85 to 90% of cases. The other causes for COPD include exposure to environmental smoke, passive smoke, occupational exposure, and genetic predisposition.[7] The common symptoms of COPD are shortness of breath, cough (with or with-out expectoration), fever, chest tightness, and hemoptysis.[8] The main goals involved in the treatment of COPD are to provide symptomatic relief and reduce the risk of future prevention of exacerbation, reduce disease progression, and reduce mortality.[2] The primary goals of pharmacotherapy are to decrease the severity of symptoms, improve the overall health status and reduce the disease frequency, complications, and severity of the exacerbations.[9]

Material and methods

This prospective study was done the Department of MEDICINE, Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar, India for 1 year, after taking the approval of the protocol review committee and institutional ethics committee.

The study cohort consisted of all patients who had been hospitalized for COPD exacerbations between October 2020 to November 2021, were included in this study. we defined hospitalizations for COPD exacerbations as patients admitted with a primary diagnosis of COPD or those with a primary diagnosis of pneumonia and a secondary diagnosis of COPD in this study.[10-13] We included the pneumonia codes because it is often difficult to decide if COPD exacerbations are accompanied with pneumonia or not, and co- existence of COPD exacerbations and pneumonia is common.[14] The study population also had to have at least two outpatient visits for COPD and to be dispensed at least two COPD-related medications within one year. During the study period, the first admission for COPD exacerbations was defined as the index hospitalization.

The outcomes of interest were in-hospital mortality and one-year mortality after discharge. The demographics, comorbid diseases, concomitant medications and COPD medications . The COPD-related medications, including short-acting and long-acting b_2 agonists, anticholinergics, inhaled corticosteroids and theophyllines, were measured in the 6 months before the index hospitalization. Comorbidities as detailed in S1 Table were noted if they were present prior to the index hospitalization. The Charlson comorbidity index was calculated as previously described.[15] We also collected

information about the index hospitalization, including the duration of hospital stay, frequency and length of intensive care unit (ICU) admission, acute cardiovascular events, use of non-invasive ventilatory support, and use of mechanical ventilation and ventilator days. The cardiovascular events of interests included acute myocardial infarction, unstable angina, acute heart failure, transient ischemic attack, and ischemic stroke.

Statistical Analysis

Data analyses were performed using SPSS software (Version 25.0, SPSS Inc., Chicago, IL, USA). A 2-sided P value of <0.05 was considered statistically significant.

Results

Characteristics of Patients and Index Hospitalizations

100 patients were included in this study. The baseline characteristics of the patients are reported in Table 1. On cohort entry, the mean age of the entire population was 74 years and 70% of them were male. The majority of the patients had comorbidities and the average score on the Charlson comorbidity index was 3.7. The most commonly observed comorbidities were hypertension (64%), coronary artery disease (37%) and stroke (30%). About three-fourths of the patients were placed on #2 COPD medications and the number of emergency visits for COPD was #2 in 79% of patients. The length of stay in hospitals was 13±20 days (Table 2). 11% of patients had been admitted to the ICU with an average stay of 8.5days. Mechanical ventilation was required in 8% patients and the median duration of ventilatory support was 7.5days. 4% patients were placed on non-invasive ventilation.

In-hospital Outcome

During the index hospitalization, 10 (10%) of patients died (Table 1). The non survivors were older and had a higher Charlson comorbidity index score than survivors. Comorbidities, including heart failure, malignancy and stroke, were more commonly seen in non survivors; instead, a higher proportion of survivors had hyperlipidemia. Angiotensin II receptor blockers, b blockers and statins were more commonly prescribed in patients surviving the index hospitalization. As expected, non survivors had a longer hospital length of stay and were more likely to require ICU admission and ventilatory support (Table 2). In addition, more cardiovascular events occurred during the hospital stay among the non survivors. Multivariate logistic regression analysis showed that a higher age and Charlson comorbidity index score independently predicted in-hospital mortality (Table 3). In addition, the use of angiotensin II receptor blockers or b blockers was associated with lower in-hospital mortality.

Table 1. Baseline characteristics of the study population with chronic obstructive pulmonary disease with regard to the in-hospital outcome

Characteristics		In-hospital outcome		
	Total	Survivor	Non survivor	
	100	90	10	P value
Age, years	74± 11	74± 11	79± 9	0.001
Male sex	70	65	5	0.13
Charlson comorbidity index	3.7± 2.7	3.67± 2.7	4.5± 2.9	0.001
Comorbidities				
Coronary artery disease	37	35	2	0.40
Depressive disorder	10	9	1	0.45

Diabetes mellitus	27	25	2	0.46
End-stage renal disease	6	5	1	0.30
Heart failure	21	19	2	0.01
Hyperlipidemia	20	19	1	0.04
Hypertension	64	60	4	0.83
Liver cirrhosis	2	1	1	0.26
Malignancy	11	10	1	0.01
Stroke	30	28	2	0.02
Co-medications				
ACEI	22	20	2	0.20
ARB	18	17	1	0.01
Antiplatelet	38	35	3	0.36
b blocker	25	24	1	0.005
Statin	7	6	1	0.005
COPD medications				
SABA	43	39	4	0.59
LABA	13	12	1	0.97
Anticholinergic	30	27	3	0.43
ICS	15	14	1	0.86
Theophylline	58	53	5	0.11
COPD severity proxy indicators				
COPD medications				
#2	75	68	7	0.89
.2	25	22	3	
COPD-related emergency visits				
#2	79	70	9	0.69
.2	21	20	1	

Table 2. Major events during the index hospitalization regarding the in-hospital outcome

Events		In-hospital outcome		
	Total	Survivor	Non survivor	
	100	90	10	P value
Length of hospital stay, days	13± 20	12± 15	32± 63	0.001
ICU admission	11	8	3	0.001
Length of ICU stay, days	8.5± 9	7.5± 8	11.5± 12	0.005
MV	8	5	3	0.001
Duration of MV, days	8 (2–19)	7 (3–16)	11 (1–28)	0.55
Non-invasive ventilation	4	2	2	0.001
Cardiovascular events	4	3	1	0.01

Table 3. Logistic regression analysis of variables predictive of in-hospital mortality in patients admitted with chronic obstructive pulmonary disease

Variables	Odds ratio	95% CI	P value
Age, per year	1.06	1.03–1.06	0.001

CCI, per point	1.09	1.01–1.15	0.01
Heart failure	1.35	0.94–1.92	0.10
Hyperlipidemia	0.83	0.52–1.30	0.39
Malignancy	1.38	0.89–2.19	0.15
Stroke	1.18	0.85–1.66	0.32
Use of ARB	0.62	0.38–0.98	0.04
Use of b blocker	0.64	0.41–0.95	0.02
Use of statin	0.41	0.14–1.14	0.08

11% of patients had been admitted to the ICU with an average stay of 8.5days. Mechanical ventilation was required in 8% patients and the median duration of ventilatory support was 7.5days. 4% patients were placed on non-invasive ventilation

Discussion

In this population-based cohort study, we provide information about the first- ever hospitalizations for a COPD exacerbation. The main findings are summarized as follows: (i) During the index hospital stay, 11% of the patients required ICU admission, 8% had been placed on mechanical ventilation and the in-hospital mortality rate was 4%. (ii) The age and comorbidity index were independent in-hospital mortality predictors; the use of angiotensin II receptor blockers and b blockers was found to be associated with a reduction in the risk of in-hospital mortality. (iii) Among patients surviving the index hospitalization, 10% of them died within one year of discharge. (iv) Increased age, a higher comorbidity index, the presence of chronic comorbid conditions, such as liver cirrhosis and malignancy, and a longer hospital stay and ICU admission during the index hospitalization were associated with a higher mortality risk at one year. Statin or b blocker use may be beneficial in COPD patients with respect to the one-year outcome following discharge.

Although COPD exacerbations have been widely studied, the exacerbation under study is seldom the first in the patient's disease course. Recently, a study on first-ever hospitalizations for COPD demonstrated the risk of subsequent severe exacerbations and long-term mortality of these patients.[16] Our study further provides insight into short-term and long-term mortality risk factors for a first- ever hospitalization for COPD exacerbations and describes major events, namely in-hospital mortality, and need for ICU care and ventilatory support, during the index hospital stay. Both studies had similar patient age and one-year mortality rates. In addition, both found that higher age and comorbidity indexes were significant mortality predictors. Thus, the two studies collaborated to produce more comprehensive picture of a first-ever severe exacerbation for physicians taking care of COPD patients.

Our study shows the high prevalence of comorbidities in patients hospitalized for COPD exacerbations and their importance in relation to in-hospital and one- year prognosis in this population. In stable COPD patients, the comorbidity severity, measured by the Charlson comorbidity index, is a well-established mortality predictor.[17,18] However, the evidence is less consistent for hospitalized COPD exacerbations. A number of studies showed no independent association between the comorbidity burden and in-hospital [19] or longer-term mortality [20, 21] although various comorbidity indexes have been shown to be independently predictive of in-hospital death [22-24] and

post-discharge mortality.[25] The discrepancies may be explained by differences in the study design, source population and scoring system for comorbidities. In reality, over the past decade, the GOLD has put more and more emphasis on recognition and management of comorbid illnesses in COPD because of their potential impact on patient prognosis. Our findings consolidate the idea that an individual patient's health status plays a significant role in determining mortality risk in COPD patients.

COPD is commonly associated with cardiovascular diseases, such as coronary artery disease, heart failure, hypertension and stroke, because of shared risk factors or a causal relationship.[26]Angiotensin II receptor blockers, b blockers and statins are commonly used therapeutic drug classes in the management of cardiovascular patients and many trials have demonstrated their protective effects on cardiovascular outcomes.[27-29] We found here that these medications were also associated with favorable outcomes in patients with severe COPD exacerbations. Statins, as a class of lipid-lowering drugs, have an additional immunomodulatory effect that may reduce neutrophil infiltration, cytokine production and matrix remodeling in COPD;[30] thus, it is biologically plausible that statin use is associated with a decreased risk of COPD exacerbations and mortality.[31] Although a recent large-scale randomized controlled trial disapproved this concept,[33] it is still urged to dispense a statin for COPD patients with other indications for it. The use of b blockers has been traditionally considered a contraindication for COPD patients;[33] however, several studies have advocated that it is safe and even advantageous to initiate or continue b blocker therapy in COPD patients with or without an exacerbation.[34] Apart from cardiovascular protection of b blockers, they may theoretically exert beneficial effects in COPD patients by counteracting sympathetic tone or ameliorating ischemic burden.[35] Furthermore, as suggested in asthma, chronic dosing of b blockers in COPD patients could confer certain Broncho protective effects, such as reduced inflammation, mucous metaplasia and expression of various spasmogenic proteins, via the up regulation of b_2 adrenoceptors.[36] The renin-angiotensin system is potentially implicated in the COPD pathogenesis through its involvement in the regulation of pro-inflammatory mediators in the lung. Specifically, angiotensin II stimulates the release of interleukin-6, tumor necrosis factor-a and monocyte chemotactic protein-1, and has an immunomodulatory effect on T cell responses that mediate the lung injury in COPD.[37,37] A recent study has shown that angiotensin II receptor blockers inhibited the cytokine response of type I alveolar cells to lung injury.[39] Our findings and clinical observations support the beneficial role of angiotensin II receptor blockers in COPD patients.[31,40] Taken together, the favorable effects of these agents on COPD outcomes are worth particular attention. On one hand, they indicate the importance of comorbidity management in the care of COPD. On the other hand, these medications may, in theory, have direct pulmonary protective properties and alter the prognosis of COPD patients.

In line with prior studies,[41,42] the present study shows that patients with a longer hospital stay and ICU admission had a worse in-hospital outcome during an admission for COPD exacerbations. We also demonstrate that the two variables were independent mortality predictors at one year following discharge. Both longer hospital length of stay and ICU admission reflect the severity of acute illnesses, that has a negative impact on in-hospital prognosis and, to a lesser degree, the outcome after discharge.[43] Thus, the

findings in this study indicate that it may be helpful and important to commence post-discharge case management in patients experiencing ICU care or prolonged hospital stay during a COPD exacerbation in hope of improving long-term prognosis.

We found mortality in the first year after hospital discharge for COPD exacerbations to be 10%, a rate similar to that reported by another study.[16] However, our one-year mortality rate seemed not to be lower than those in other series that also included patients with prior severe COPD exacerbations.[25] Indeed, our study population had older age, an independent predictor of post- discharge mortality,[43] compared to other study subjects, but our results re- emphasize the impact of a hospitalized COPD exacerbation even it is the first-ever one. In short, other studies[44] and ours suggest that hospitalizations for a COPD exacerbation identify a COPD subpopulation with a poor outcome. Based on the present study, it is suggested that more intensive plans and follow-up may be required for these high-risk patients, particularly if they were older, comorbid or discharged after a COPD hospitalization involving long hospital stay or ICU treatment.

There were some limitations to this study. First, the accuracy of COPD diagnosis depends on proper ICD-9-CM coding. Although the lack of unique patient identifiers in the LHID prevented a validation study, the database has been widely used to study COPD.[45] In addition, we did not only rely on ICD-9 codes to identify COPD patients, but the use of COPD medications and an age of 40 or more years were mandatory elements. Second, the information on the severity of symptoms and exercise intolerance, and the data of pulmonary function testing were not available in the LHID; however, the proxy indicators for COPD severity and use of concomitant medications were controlled in the analysis. Third, cultural differences may hinder the generalization of our results. For example, rather than use inhaled drugs, Chinese people prefer to take oral medications. Thus, compared to studies conducted in western countries,[46] inhaled corticosteroids were less commonly prescribed and theophyllines were more frequently dispensed to our patients. In addition to clinical variables, several metabolic, physiological and hemodynamic factors were also found to have effects on the in-hospital mortality,[47] but these variables were not retrievable from the LHID. This is the inborn disadvantage of being a claims database study; however, this kind of study provides an unbiased population cohort for medical researches and offers a powerful means of generating evidence to devise healthcare strategies.[48]

Conclusion

In conclusion, an exacerbation requiring hospitalization denotes a poor long-term outcome in COPD patients; even it is the first-ever one. The burden of comorbidities has a significant role in determining mortality risks, and should be carefully evaluated and managed.

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