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Original Article

Predictors of outcome in patients admitted with acute exacerbation of chronic obstructive pulmonary disease in a rural Tertiary Care Center

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is associated with a high degree of mortality and morbidity around the world with the burden of the disease being more in the developing countries. In the Indian context data is limited. This study was carried out to determine the predictors of outcome in patients admitted with acute exacerbation of COPD in a rural Tertiary Care Center in the state of Kerala. **Materials and Methods:** This was a prospective cohort study. Patients admitted with acute exacerbation of COPD in the Intensive Care Unit between August 2013 and July 2014 was included in the study. Sociodemographic data, clinical variables, and investigations were collected. Mortality with respect to relevant risk factors was compared using Kaplan–Meier method and Cox proportional hazard model. **Results:** Seventy patients were enrolled in the study of whom 58 (82.9%) were above the age of 60 years. Majority of the patients (87.1%) were males. Tobacco smoking was the main risk factor in them. All the females had a history of exposure to biomass fuel in the form of firewood; none of them were smokers. Majority of patients (80.0%) had a history of one or more co-existing illnesses. Anemia was found to be an independent risk factor for mortality (adjusted hazard ratio: 3.167, 95% confidence interval: 1.516–6.616). Risk factors for poor outcome in COPD patients reported from other centers in India were not found to be relevant in this study. **Conclusions:** Anemia could be an independent risk factor for mortality in COPD patients. India already has a high prevalence of iron deficiency anemia especially in the rural area and in the geriatric population. Henceforth, family practitioners and primary care physicians may remain vigilant regarding the development of anemia in their COPD patients and institute remedial measures without delay. Futhermore, the wide variation reported in the predictors of outcome of COPD along with the finding of this study calls for an urgent need for more studies.

Keywords: Acute exacerbation, chronic obstructive pulmonary disease, predictors of outcome, rural area

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of death and disability around the world.[1] The age-adjusted death rate of this disease is highest in low-income areas of the world including South Asia and sub-Saharan Africa.[2] Even in high-income countries, there is a definite trend in socioeconomic related outcome with those in the lower socioeconomic status faring worse.[3] The high economic burden this disease imposes on the individual, and the health care delivery system of a nation needs to be emphasized.[4]

In the Indian context, there is limited data regarding prevalence of COPD. The estimated prevalence is between 6.5% and 7.7%;

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but this is by no means accurate.[5] The nationwide prevalence of chronic bronchitis alone has been estimated to be 3.49%[6] but this data do not include emphysema which is the other major determinant of COPD. The predictors of poor outcome in Indian patients admitted with acute exacerbation have variously been estimated to be hypotension,[7] need for invasive ventilation, presence of co-morbid illness, and hypercapnia.[8] Owing to the heterogenecity of present studies[5] and large populations in the country being out of the scope of available studies, even this data is far from complete. In the setting of Kerala where this study was done, also, there is a significant dearth of information regarding COPD in indexed literature.

Materials and Methods

This prospective cohort study was done to determine the predictors of outcome in patients admitted with acute exacerbation of COPD in a Tertiary Care Center in the state of Kerala, India. The hospital where this study was done is situated in a rural setting not far from the Western Ghats. The climate in the region is humid and the vegetation green throughout without any significant air pollution.

A total of 70 patients admitted with acute exacerbation of COPD in the Intensive Care Unit (ICU) between August 2013 and July 2014 were included in the study. There were no set criteria to define ICU admission and was left best to the clinical judgment of the admitting physician who first saw the patient in the emergency. The only other inclusion criteria was a known clinician made diagnosis of COPD with supporting spirometry or a high probability of the disease (on the basis of clinical history, history of chronic exposure to respiratory irritants, smoking history, physical examination, and chest radiograph).

Type II respiratory failure was defined as hypercarbia ($PaCO_2$ > 45 mm Hg) (*N*: 35–45 mm of Hg) with a co-existing hypoxia (PaO_2 < 80 mm Hg) (*N*: 80–100 mm of Hg).

A peer reviewed, pilot tested, structured questionnaire was used to collect data which included sociodemographic variables, clinical variables, and investigations. Data entry was done using Epidata software, version 3.1 (developed by "The Epidata Association", Odense, Denmark) and analysis was done using R software, version 3.1.1 (developed by "The R Foundation for Statistical Computing", Vienna, Austria). Event in the study was defined as death occurred while in hospital. All the discharges from hospital were right censored. Continuous variables were categorized by relevant clinical cut-off values. Overall mortality and mortality within each group of patients were expressed as number of deaths per 100 person days. Survival curve was plotted using Kaplan–Meier method and median survival period with its 95% confidence interval (CI) was calculated. The log-rank test was done for statistical association of relevant risk factors with mortality. The effect size of risk factors on mortality was calculated as hazard ratios (HRs). Univariate and multivariate analysis to derive HR was done using Cox proportional hazard model. $P < 0.05$ was considered statistically significant association.

The study was approved by the Institutional Ethics Committee of the hospital and has been registered with the "Clinical Trials Registry of India": CTRI/2013/12/004210.

Results

The total number of patients enrolled in the study was 70 of whom 58 (82.9%) were designated as elderly (above 60 years of age). Sixty-one (87.1%) were males. History of tobacco smoking was given by all the male participants. There was a general mix of both cigarette and bidi and hence an attempt was not made to differentiate between them. All the females (*n* = 9, 12.9%) had a history of exposure to biomass fuel in the form of firewood. None of them were smokers. Majority of patients (80.0%) had history of one or more co-existing illnesses; 19 (27.1%) had diabetes mellitus, 20 patients (28.6%) had hypertension, 29 (41.4%) had ischemic heart disease, four patients (5.7%) had past history of tuberculosis, and 32 (45.7%) had history of other significant co-morbidities (cerebrovascular accident, renal failure, leukemia, chronic liver disease, hypothyroidism, seizure disorder, and benign prostatic hypertrophy).

Three participants were admitted for exacerbation of breathlessness for the first time. All the other participants had previous history of hospital admissions. Nine patients (12.9%) were already on home oxygen therapy.

On initial admission analysis of the primary parameters reflecting gas exchange/oxygen supply (arterial blood gas analysis and hemoglobin) 49 patients (70.0%) were in type II respiratory failure and 35 (50.0%) had anemia (males <13 g % and females <12 g %).[9,10] The mean PaO_2 was 70 mm of Hg with standard deviation (SD) of 17.54 and mean $PaCO_2$ was 67.93 with SD of 27.92.

The major X-ray finding was hyperinflated lung fields (emphysema) (*n* = 51, 72.9%). Signs of pneumonia were seen in 29 patients (41.4%); 4 (5.7%) had pneumothorax, 3 (4.3%) had bronchiectasis, 3 (4.3%) had some degree of lung fibrosis, 2 (2.8%) had a cavitatory lesion, 1 (1.4%) had a lobar collapse, and 1 (1.4%) had effusion on the chest X-ray.

Regarding causes of exacerbation, infection was suspected to be culprit in majority of the patients (*n* = 51, 72.9%). This was corroborated by clinical findings (fever/increase in purulence of sputum) and investigations (increased white cell count/positive sputum culture/chest X-ray).

The mean duration of hospital stay was 6.55 days (SD of 4.29) and mean duration of ICU stay was 3.67 days (SD of 3.38). The cohort constituted 459 person-days of observation, and the mortality rate was 8 per 100 person-days; 37 (52.9%) died in hospital. Median follow-up period for the entire cohort as well as for the censored was 6 days. A Kaplan–Meier survival curve

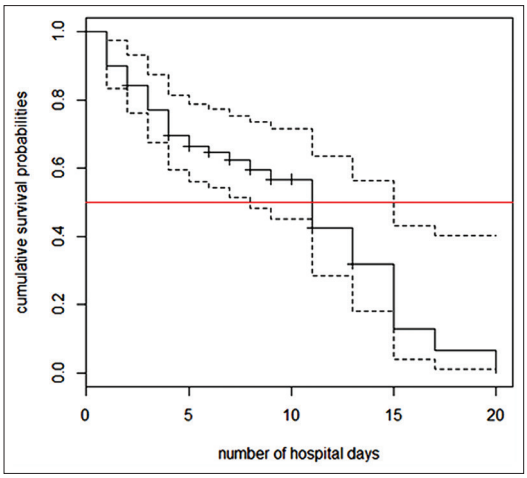

Figure 1: Kaplan–Meier survival curve with 95% confidence interval for the cohort of chronic obstructive pulmonary disease patients

was plotted [Figure 1]; the median survival time was found to be 11 days (95% CI: 8–15).

Forty-seven patients (67.14%) needed noninvasive ventilation, 32 (45.71%) needed invasive ventilation and 21 (30.0%) needed both noninvasive and invasive ventilation; 12 patients (17.14%) did not require any source of assisted ventilation.

Mortality in relation to the different characteristics of the cohort was tabulated [Table 1]. Among the different characteristics, only hemoglobin status had a significant association with mortality by Kaplan–Meier survival analysis ($P = 0.001$). Furthermore, HR of mortality for anemia with reference to normal hemoglobin status was 2.829 (95% CI: 1.404–5.702) by Cox proportional hazard method. Other lab parameters (liver function, renal function, electrolytes, etc.) did not have any significant association with mortality. In regression model involving clinical and laboratory parameters at the time of admission, again anemia emerged as an independent risk factor for mortality [Table 2]. A dose-response relationship of hemoglobin with mortality could not be studied because the numbers of patients with moderate and severe grades of anemia were small. Historical and demographic variables were not associated with mortality [Table 3]. Association of gender with mortality could not be studied due to very small numbers ($n = 9$) in female category.

Table 1: Mortality in the cohort in the different risk groups

Risk factors	Number of deaths	Person days of observation (hospital stay)	Mortality per 100-person-days
Age (in years)			
Above 60	32	376	8.5
Up to 60	5	83	6.0
Sex			
Male	32	406	7.9
Female	5	53	9.4
Home oxygen therapy			
Absent	32	366	8.7
Present	5	93	5.4
Significant co-morbidities			
Present	32	373	8.6
None	5	86	5.8
$PaCO_2$ (mm Hg)			
Above 45	33	355	9.3
Up to 45	4	104	3.8
PaO_2 (mm Hg)			
Below 80	30	331	9.1
80 and above	7	128	5.5
SaO_2 (%)			
Below 80	9	109	8.3
80 and above	28	350	8
Hemoglobin status (WHO criteria)			
Anemia	24	191	12.6
Normal	13	268	4.9

Table 2: Cox proportional hazard model predicting risk factors of mortality by clinical and laboratory parameters at the time of admission

Risk factors	Univariate analysis		Multivariate analysis	
	Hazard ratio with 95% CI	*P*	Hazard ratio with 95% CI	*P*
$PaCO_2$ (mm Hg)				
Above 45	2.176 (0.750-6.313)	0.152	1.796 (0.607-5.310)	0.289
Up to 45 (reference)	1		1	
PaO_2 (mm Hg)				
Below 80	1.957 (0.808-4.742)	0.137	1.826 (0.738-4.519)	0.193
≥80 (reference)	1		1	
SaO_2 (%)				
Below 80	1.269 (0.584-2.757)	0.547	1.409 (0.609-3.263)	0.423
≥80 (reference)	1		1	
Hemoglobin status (WHO criteria)				
Anemia	2.829 (1.404-5.702)	0.004	3.167 (1.516-6.616)	0.002
≥80 (reference)	1		1	

CI: Confidence interval

Discussion

In this study, males formed the predominant gender with tobacco smoking being the main etiology in them. Studies from other centers in India also paint a similar picture regarding gender and etiology.[11-13] A definite delineation could not be made between cigarette and bidi in this study. Females though limited in number were united by a single cause, exposure to biomass fuel in the form of firewood; this mirrored studies across India and in other developing economies.[14-18]

Anemia was significantly associated with mortality (HR of 2.829). On the basis of human physiology polycythemia is what is expected of the long-standing hypoxia of COPD. Hypoxia increases erythropoietin (EPO) production in the proximal convoluted cell of the kidney which in turn enhances red blood cell (RBC) production. EPO also decreases apoptosis of the RBCs and increases their survival.[19] Though physiologically coherent, in actual practice anemia is more common than polycythemia.[20] The mechanisms of anemia in COPD are multifactorial.[21] Postulated mechanisms

Table 3: Cox proportional hazard model predicting risk factors of mortality from patient history

Risk factors	Univariate analysis		Multivariate analysis	
	HR with 95% CI	*P*	HR with 95% CI	*P*
Age (in years)				
Above 60	1.271 (0.492-3.283)	0.620	1.042 (0.390-2.785)	0.934
Up to 60 (reference)	1		1	
Home oxygen therapy				
Absent	2.122 (0.787-5.718)	0.137	2.057 (0.734-5.759)	0.170
Present (reference)	1		1	
Significant co-morbidities				
Present	1.235 (0.470-3.243)	0.669	1.091 (0.410-2.905)	0.862
None (reference)	1		1	

CI: Confidence interval; HR: Hazard ratio

include anemia of chronic disease (ACD), iron deficiency, vitamin deficiency, associated co-morbidities, hypogonadism, and treatment related.[22] Of these ACD is probably the predominant mechanism. ACD is an immune-mediated phenomenon where inflammation plays an important role in the pathogenesis.[23] Studies have demonstrated high levels of inflammatory parameters in anemic COPD patients.[24] The mechanisms incriminated in causing ACD are iron homeostasis dysregulation, blunted endogenous EPO production, impaired bone marrow erythropoietic response, and shortened RBC survival.[23]

Anemia being a risk factor for a poor outcome in COPD has far-reaching implications in a country like India. India already has a high prevalence of iron deficiency anemia, especially in the rural setting.[9,25] Moreover, this is further aggravated in the geriatric population.[26] Henceforth, health planners may have to consider COPD patients also as a risk group for anemia and target them for correction.

The postulated predictors of negative outcome in COPD patients reported from other centers in India are hypotension,[7] need for invasive ventilation, presence of co-morbid illness and the presence of hypercapnia.[8] The sample size in this study was inadequate to find an association of these risk factors and a negative outcome.

In a developing country like India frequent episodes of acute exacerbation of COPD puts a great strain on the meager health resources of the nation. The wide variation reported in the predictors of outcome[7,8] of COPD along with the finding of this study stand testimony to the fact that there is an urgent need for more studies. The vastness of the nation, rural-urban divide, cultural differences, poverty, and contrasting climate are all challenging aspects of doing a study that is representative of the population at large.

A small sample size has been a major limitation of this study. Never the less considering the dearth of data regarding COPD from Kerala and from India in general, it is hoped that the information generated will help to compute an adequately powered study in future. Meanwhile, family practitioners and primary care physicians may remain vigilant regarding the development of anemia in their COPD patients and institute remedial measures without delay.

Conclusions

Anemia could be an independent risk factor for mortality in COPD patients. India already has a high prevalence of iron deficiency anemia especially in the rural area, and this is compounded in the geriatric population. Henceforth, health planners may have to consider COPD patients also as a risk group for anemia and target them for correction. Meanwhile family practitioners and primary care physicians may remain vigilant regarding the development of anemia in their COPD patients and institute remedial measures without delay. In addition, the wide variation reported in the predictors of outcome of COPD along with the finding of this study calls for an urgent need for more studies.

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Conflicts of interest

There are no conflicts of interest.

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