Original Article

Two-year mortality in survivors of acute exacerbations of chronic obstructive pulmonary disease: A North Indian study

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ABSTRACT

Objectives: Data about long-term mortality of Indian patients following acute exacerbation of chronic obstructive pulmonary disease (AECOPD) are scant. We set out to study the 2-year mortality in north Indian patients following discharge after AECOPD. **Materials and Methods:** One hundred and fifty-one (96 male) patients admitted for AECOPD and discharged were followed for 2 years at 3, 6, 12, 18, and 24 months for mortality. Statistical analysis was performed to identify risk factors associated with mortality. **Results:** Sixty (39.7%) of the 151 recruited died during the 24 months of follow-up, 30 (19.8%) at 3-month, 43 (28.5%) at 6-month, 49 (32.4%) at 1-year, 55 (36.4%) at 18-month, and 60 (39.7%) at 2 years. There was no mortality in Global Initiative for Chronic Obstructive Lung Disease (GOLD) Stage I (0 of 6 cases), whereas it was 12.3% (*n* = 8 of 65 patients) in GOLD Stage II, 41.7% (*n* = 15 of 36 cases), in GOLD Stage III, and 84.1% (*n* = 37 of 4 cases), of patients with GOLD Stage IV. Mortality was associated with 6-min walk distance, oxygen saturation, low body mass index, history of congestive heart failure, and St. George Respiratory Questionnaire score. **Conclusion:** Indian patients discharged after AECOPD have a high 2-year mortality. Measures to reduce the frequency of exacerbations need to be routinely adopted in patients with COPD.

KEY WORDS: Acute exacerbation, chronic obstructive pulmonary disease, GOLD, mortality

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INTRODUCTION

An acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is an acute worsening of dyspnea, cough, and/or sputum production/change in the quality that is beyond normal day-to-day variation and sufficient to warrant a change of medications.[1] Although adequate drugs and therapeutic interventions are available to control the clinical symptoms of chronic obstructive pulmonary disease (COPD) and reduce airway inflammation, exacerbations in COPD lead to an accelerated decline in lung functions[2,3] reduced health status and quality of life,[4] and increased risk of death. Apart from in-hospital mortality during an acute exacerbation, studies on long-term mortality after hospitalization have shown a 1-year mortality from 22%[5] to 43%[6] and a 2-year mortality of 36%[7] to 49%,[6] thus being one of the worst clinical outcomes in a chronic disorder regardless of the organ involvement.

COPD is a frequently encountered clinical problem in India with AECOPD as a common cause for hospitalization. Recently, a high prevalence was reported in Northern India by the Burden of Lung Disease investigators,[8,9] and thus it is expected that there is a high frequency of

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hospitalizations as a result of AECOPD with considerable morbidity and mortality. A recent study from South India recorded an in-hospital mortality of 12% in AECOPD.[10] While long-term mortality following exacerbations has been well described in the developed countries, there is a paucity of literature from the developing countries and no data are available from India. The present study was designed against this backdrop to prospectively examine the postdischarge mortality of patients surviving an AECOPD and analyze the factors associated with increased mortality.

MATERIALS AND METHODS

A prospective observational study was conducted at Sher-I-Kashmir Institute of Medical Sciences, Srinagar, 750-bedded tertiary care hospital. One hundred and fifty-one patients of AECOPD (COPD defined as postbronchodialtor forced expiratory volume 1 s (FEV1/forced vital capacity) ratio of <0.7) who were discharged after a hospital stay of at least 24 h were recruited for the study.

Demographic data, clinical history, and clinical examination were recorded in all patients on a predefined proforma. The patients were investigated as per the protocol that included routine blood chemistry, hemogram, blood gas analysis, radiograph of the chest, echocardiography, sputum and blood cultures, etc. Computed tomography scan of the chest was performed when indicated. Patients were managed with bronchodilators, steroids, oxygen (delivered through nasal prongs, nasal or venturi masks as necessitated), antibiotics and noninvasive or invasive ventilation. Information regarding a number of prior hospital admissions if any, history of smoking was collected. At discharge, arterial blood gas determinations were repeated and a spirometry performed. All comorbidites were recorded and a 6-min walk test performed for walking distance. St. George's Respiratory Questionnaire (SGRQ) was administered after standardization and validation in a locally understandable vernacular for the three components scores: symptoms, activities, and impact. A total score was calculated from all three components, with zero indicating no health impairment and 100 representing maximum impairment. A 6-min walk test was done at discharge to determine the 6-min walking distance (6MWD).

All the patients were followed after discharge for 2 years with a follow up every 2 months and a telephonic enquiry in the case of a missed follow-up. The primary study end points was death.

Patients were excluded from the study if death occurred during the hospital stay, or there was pulmonary edema at hospital admission or the patients hospitalized for a cause other than the acute exacerbation of COPD.

Analysis of the data was performed using Stata 8.0 (Stata Corporation, College Station, Texas, USA). Chi-square test and the unpaired *t*-test as appropriate were used when comparing patients who died during the study. The relationship between survival time and patients' characteristics was determined using Kaplan–Meire survival analysis and Cox regression. Multivariate analysis was also performed with the Cox model after adjustment for global initiative for chronic obstructive lung disease (GOLD) stages. The analyzed independent variables were chosen based on statistical significance in the bivariate analysis and on clinical relevance. Health status, 6MWD, SaO_2 at discharge, and age were entered as continuous variables, whereas gender, co-morbidities, and treatment were entered as categorical variables. The proportional hazard assumption was tested for all the independent variables in the models, and no violation was detected ($P > 0.1$). The study protocol was reviewed and approved by the hospital research and ethics committee. Values have been expressed as mean ± standard deviation (SD) and a value of $P < 0.05$ was considered statistically significant.

RESULTS

The 151 patients comprised 96 males and 55 females with median age of 65 years (mean + SD= 65.4 ± 9.0 years). One hundred and four patients were tobacco smokers, with hookah smoking being the most common form of smoking ($n = 55$), whereas 43 smoked only cigarettes. The distribution of cases as per GOLD stages included Stage I ($n = 6$), Stage II ($n = 65$), Stage III ($n = 36$), and Stage IV ($n = 44$). The patients presented with various symptoms that included symptoms included breathlessness (88.1%), cough (69.5%), altered sensorium (17.9%), and hemoptysis (7.3%). Associated comorbidites in the patients included hypertension ($n = 77$), diabetes ($n = 13$), congestive heart failure ($n = 56$), ischemic heart disease ($n = 25$), and muscle wasting (body mass index [BMI] <18 kg/m^2) ($n = 19$). Electrocardiographic evidence of right ventricular dominance was seen in 91 patients. Frequent exacerbations (defined as two or more exacerbation per year) occurred in 31.8% of COPD patients. During the course of the study, about 40.6% of males and 40% of female patients were readmitted again. Frequent exacerbations were related to the severity of COPD according to GOLD stage ($P = 0.005$).

The at-discharge 6MWD ranged from 82 to 498 meters (mean ± SD 241.2 ± 97.1 m), being 245.2 ± 97.7 (82, 496) in male patients and 234.2 ± 96.6 (98, 498) in females ($P = 0.505$). Oxygen saturation ranged from 78 to 96.5% (mean ± SD 90.2 ± 3.6%).

Sixty (39.7%) of the 151 recruited died during 24 months of follow-up. The number of patients who died at various periods of follow-up was 30 (19.8%) at 3-month, 43 (28.5%) at 6-month, 49 (32.4%) at 1-year, 55 (36.4%) at 18-month, and 60 (39.7%) at 2 years of follow-up. There was no mortality in GOLD Stage I (0 of 6 cases) while it was 12.3% ($n = 8$

of 65 patients) in GOLD Stage II (n = 15 of 36 cases) and 41.7% (n = 37 of 44 cases) in GOLD Stage III [Figure 1]. About 84.1% of patients in GOLD Stage IV died during the 2-year of follow-up. Patients with a total SGRQ score of >60 had a much higher mortality (82.5%) compared to those with a SGRQ score of < 60 (9.1%) (Figure 2). Patients with frequent exacerbation (32% of the patients) had increased mortality with respect to those who had <2 exacerbations per year.

On multilogistic regression, factors associated with increased mortality included lower health status as assessed using SGRQ [Figure 2], a lower SaO_2 at discharge (≤90%) [Figure 3] and a lower 6MWD [Figure 4]; mortality being high when 6MWD was between 150–250 M. In addition, a lower arterial pH (<7.35) and a higher pCO_2 >45 mmHg) at presentation were associated with increased 2-year mortality. Higher mortality also occurred in patients with history of heart failure (P = 0.000), those with a body mass index <18 Kg/m^2 (P = 0.000) and [Figure 5]. The use of long-acting β^2 agonists alone or in combination with inhaled corticosteroids was associated with decreased mortality when compared to those patients who received neither of these medications (P = 0.000).

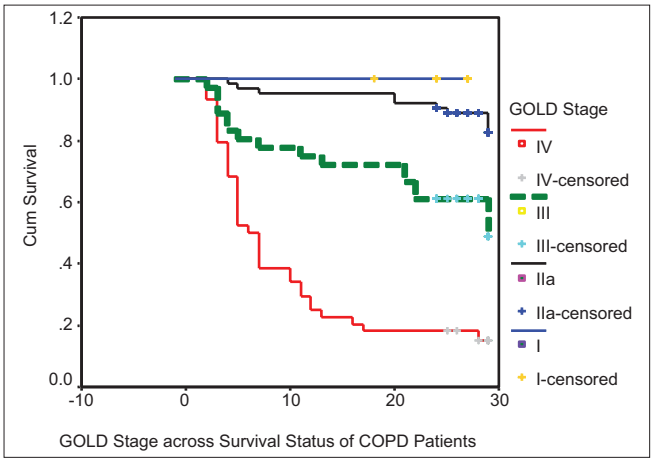

Figure 1: Kaplan–Meire survival curve in acute exacerbations of chronic obstructive pulmonary disease patients with respect to the stage of chronic obstructive pulmonary disease

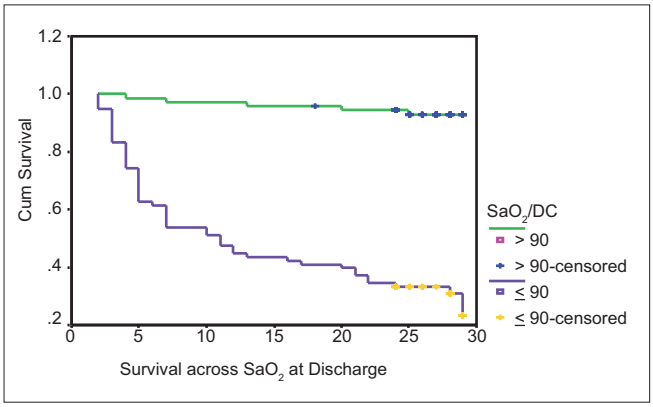

Figure 3: Kaplan–Meire survival curve with relation to SaO_2 at discharge

DISCUSSION

Our study demonstrates that mortality rates after an exacerbation are high in North-Indian patients with COPD, the 2-year mortality rates being 39.7% while that at 1-year of discharge being 32.4%. The study, to the best of our knowledge, is the only study performed in India even as other researchers from elsewhere have reported mortality rates in this subset of patients to vary between 23% and 49% [Table 1].

The mortality in our patients was directly proportional to the stage of the COPD among the patients with a demonstrable increase in mortality in direct relation to the higher stages of COPD, ranging from 12.3% in stage 2 to 84% in GOLD Stage IV. Mortality rates in COPD have been found to correlate with the reducing lung function,[19-21] with a step-wise increase and a pronounced increase in risk at a level of FEV1 below 50% predicted, suggesting a threshold effect in mortality risk at this level. Reduced baseline lung function has been reported to be a predictor of mortality by other investigators as well [Table 1]. Thus the data suggest that exacerbation is an added insult to the inexorable increase in morbidity and

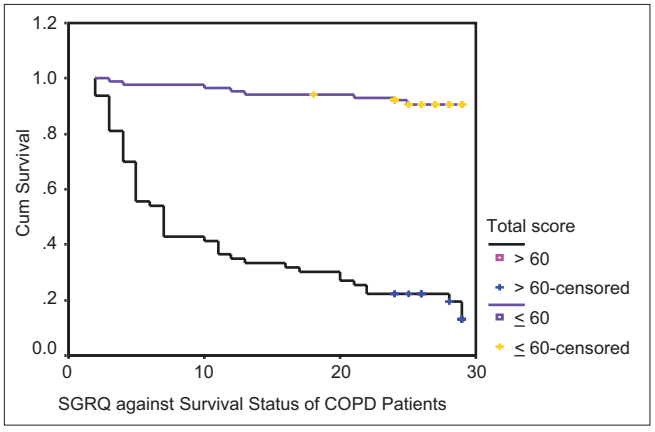

Figure 2: Kaplan–Meire survival curve in patients with higher (total St. George's Respiratory Questionnaire score ≤60) and lower health status (total St. George's Respiratory Questionnaire score >60)

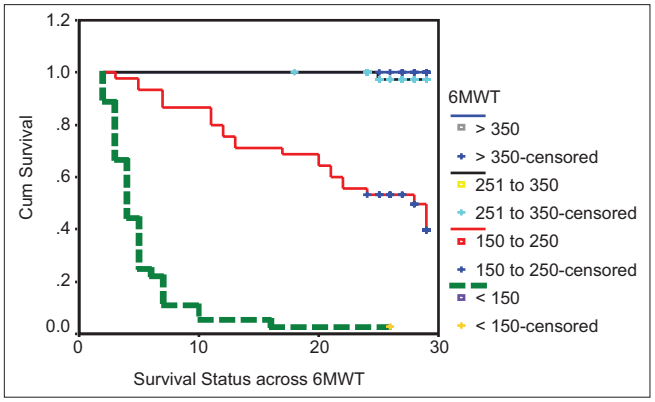

Figure 4: Kaplan–Meire survival curves in relation to 6-min walking distance at discharge

Table 1: Comparison of the mortality rates following exacerbations of chronic obstructive pulmonary disease and identified risk factors

Authors (year)	Patients	1-year mortality	2-year mortality	Risk factors
Connors *et al*.[6]	1016 patients with severe exacerbation	43%	49%	FEV_1, BMI, age, PaO_2
Almagro *et al*.[5]	135 patients after severe exacerbation	22%	35.6%	Age, women, SGRQ, previous severe exacerbations, $PaCO_2$
Groenewegen *et al*.[7]	171 patients with severe exacerbation	23%	23%	$PaCO_2$, age
Kim *et al*.[10]	482 patients after ED visit	23%	-	Age, comorbidities, previous severe exacerbations
Gudmundsson *et al*.[11]	416 patients	-	29.3%	Age, SGRQ score, lower pulmonary function, diabetes
Coleta *et al*.[12]	78 patients using LTOT	15.4%	-	BDI, PaO_2, $PaCO_2$, SGRQ
Fan *et al*.[13]	603 patients	7.5%	-	-
Gershon *et al*.[14]	>30,000 patients from Canadian registry	4.3%–5.7%	-	-
Piquet *et al*.[15]	1824 patients with severe exacerbation	16.8%	-	Age, lower BMI, lung cancer, cardiovascular comorbidity, previous severe exacerbations, LTOT
Ho *et al*.[16]	4029 patients with severe exacerbations	22%	-	Age, comorbidity
Müllerova *et al*.[17]	2138 patients	5.1% in patients without severe exacerbation and 14.6% in patients with severe exacerbation	-	Severe exacerbations, longer hospital stay
Mekov *et al*.[18]	152 patients	7.2%	-	Age, FEV_1 value, severe exacerbation in previous year and reduced quality of life
Present study (Koul *et al*.)	151 patients	32.4%	39.7%	GOLD stage, heart failure, health status, 6MWD, BMI, hypoxia

ED: Emergency department, LTOT: Long-term oxygen therapy, BMI: Body mass index, FEV_1: Forced expiratory volume 1 s, SGRQ: St. George's Respiratory Questionnaire, BDI: Beck depression inventory, 6MWD: 6-min walking distance, GOLD: Global initiative for chronic obstructive lung disease

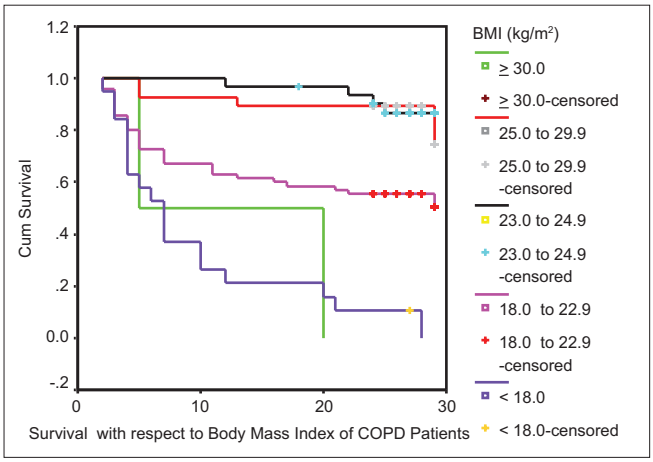

Figure 5: Kaplan–Meiere survival curves in relation to the body mass index

mortality of Indian patients with COPD with advancing stage of COPD, defined on the basis of previous GOLD guidelines.

The patients with heart failure had a higher mortality ($P < 0.001$) than those without heart failure. Congestive heart failure and cor pulmonale have been reported to shorten survival time,[6] whereas Gudmundsson *et al*.[11] reported that cardiovascular co-morbidity was a risk factor for increased mortality only in those patients with a lower health status. Coexistent cardiac disease has been shown to be a risk factor for mortality in patients with COPD exacerbation.[22] Furthermore, ischemic heart disease and/or congestive heart failure were reported to increase the rate of treatment failure, thus contributing to the worsening of the patients' condition. Our study also demonstrated that concomitant heart disease had a negative effect on survival and that cardiac co-morbidity is a risk factor of poor outcome, particularly in moderate–severe COPD patients ($P < 0.001$). Contrary to our results, no association between cardiac co-morbidity and the outcome was demonstrated previously in very severe COPD patients (FEV_1 <35% predictor and use of supplemental oxygen therapy).[23] The reason for this differing result may be the fact that when lung disease is severe, impairment in pulmonary function prevails over cardiac disease.

Health status (as assessed by SGRQ) had a direct relationship with the mortality in patients of COPD, with patients having SGRQ >60 having a higher mortality than those with SGRQ scores of ≤60 ($P < 0.001$). In the study by Gudmundsson *et al*.,[11] lower health status was related to higher mortality. This was true both for the total score on SGRQ as well as for the three subscales of activity, impact, and symptoms. Domingo-Salvany *et al*., in a study on male outpatients, reported that SGRQ and SF-36 total scores were independently associated with total mortality and respiratory mortality.[24]

We found that the patients of COPD with BMI of <18 kg/m^2 had higher mortality ($P < 0.001$). Two of our two patients of COPD had BMI >30 kg/m^2 and both of them died during the study. However, due to a small sample size of COPD patients with BMI >30 kg/m^2, we cannot draw an inference regarding the relationship of a high BMI with mortality. The "Obesity paradox" described in heart failure[21] has been proposed to be operative in patients with COPD too, with overweight and obese having a decreased risk of death compared with those with normal weight (hazard ratio 0.9, 95% confidence interval 0.7–1.0).[25] However, caution has to observed in this oversimplification because increased BMI has not been found to be protective against fat-free mass depletion in COPD which is a feature of the preferential loss of muscle tissue in this disorder.[26] In addition, COPD is now a recognized risk factor for cardiovascular disease[23] and thus, further studies are needed to address this confounding factor in the mortality of patients with COPD.

Patients with increased effort tolerance in the current study as evidenced by 6MWD had a direct correlation with 2-year mortality, with a 97% mortality in patients with a 6MWD of <150 meters ($P < 0.001$), 53% mortality in patients with a 6MWD of 151–250 M and no mortality in patients with 6MWD of >350 m. Other studies carried out previously also have demonstrated that decreased distance walked during 6MWD is associated with increased mortality, being an independent predictor of mortality.[27] Since this is a simple measure to perform, we believe that 6MWD is an excellent prognostic marker for patients who survive a COPD exacerbation.[5]

Patients with hypoxia (PaO_2 <90%) at discharge had an increased mortality ($P < 0.001$) and mortality was higher among in those with a $PaCO_2$ >45. Costello *et al*. revealed in their study that PCO_2 at discharge was a better predictor of survival than PCO_2 on hospital admission in patients with respiratory failure and that reversible hypercapnia was associated with better prognosis. There was a lack of significance of low PO_2 at discharge which was explained by the use of long-term oxygen therapy (LTOT) at home after discharge in hypoxic patients.[28] When followed for prolonged periods the prognosis of hypoxic patients tends to improve and nearly becomes equal to nonhypoxic patients.[29] However, in the present study most of the patients with SaO_2 <90% at discharge were not using home oxygen therapy on a regular basis on recommended lines and those patients who were having the facility of home oxygen used it inadequately. This might explain the role of persistent hypoxia as a predictor of mortality in our patients as against earlier studies. Oxygen therapy in our patient population poses difficulties on account of financial reasons. An oxygen concentrator is ill afforded by a significant group of the population, and they resort to using refill cylinders and in an attempt to let the cylinder last for a greater period, they end up using oxygen for short intervals of time and with low flows so that in effect a significant percentage of patients receive inadequate LTOT. Additionally those with oxygen concentrators often face power shutdowns resulting in concentrators not working and the patients either resort to no oxygen or a low flow through a spare cylinder, if at all at hand.

While we did not demonstrate any correlation between the age and mortality in our patients, other investigators have reported higher mortality in patients with higher age.[30] The highest rate of mortality was seen in the 85-year-old and older age group 365 days after discharge while the lowest rate was the 30-day mortality of those aged 65–74 years.[30] Only 8.6% our of COPD patients were ≥80 years of age while the majority of the patients of COPD were ≤69 years of age. Hence, a significant impact of age as a co-variable was not manifest. Our study is limited by the fact that autopsies for causes of death were not available even as limited verbal autopsies attributed the mortality to progressive lung disease in majority of the participants.

CONCLUSION

We conclude that long term mortality in survivors of hospitalized AECOPD patients is high, being 32.4% at one year and 39.7% at 2 years was 32.4% after 1-year and 39.7% after 2-year of follow-up. The various factors associated with increased mortality ($P < 0.001$) were heart failure, lower health status (SGRQ total score >60), worse lung function (GOLD stage) 6MWD <150m and frequent exacerbations. Appropriate strategies aimed at reducing frequency and severity of exacerbations in COPD are warranted.

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Conflicts of interest
There are no conflicts of interest.

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