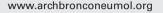# ARCHIVOS DE BRONCONEUMOLOGIA

Original Article

Causes of Death and Risk Factors for Mortality in Patients With Severe Chronic Obstructive Pulmonary Disease

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ABSTRACT

Objective: The objective of this study was to assess the causes of death and risk factors for mortality in a cohort of patients with severe chronic obstructive pulmonary disease (COPD).

Patients and methods: We studied 203 patients with severe COPD (forced expiratory volume in 1 second [FEV$_1$] <50%), who were attended in our respiratory department day hospital (2001-2006). Clinical variables were recorded on inclusion, and clinical course and causes of death were retrospectively reviewed.

Results: The mean (SD) age of patients was 69 (8) years and the mean FEV$_1$ was 30.8% (8.2%). One-hundred and nine patients died (53.7%); death was attributed to respiratory causes in 72 (80.9%), with COPD exacerbation being the most frequent specific cause within this category (48.3%). During follow-up, 18.7% required admission to the intensive care unit (ICU). Survival at 1, 3, and 5 years was 80%, 53%, and 26%, respectively. The multivariate analysis showed that mortality was associated with age, stage IV classification according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), cor pulmonale, and hospital admission during the year prior to inclusion. Need for admission to the ICU during follow-up was a factor independently associated with higher mortality.

Conclusions: Mortality in patients with severe COPD was high and exacerbation of the disease was one of the most frequent causes of death. Age, GOLD stage, cor pulmonale, prior admission to hospital, and need for admission to the ICU during follow-up were independent predictors of mortality.

Causas de muerte en pacientes con EPOC grave. Factores pronósticos

RESUMEN

Objetivo: El objetivo del estudio es evaluar las causas de muerte y los factores pronósticos de mortalidad en una cohorte de pacientes con enfermedad pulmonar obstructiva crónica (EPOC) grave.

Pacientes y métodos: Se incluyó a 203 pacientes con EPOC grave (volumen espiratorio forzado en el primer segundo < 50%) controlados en el Hospital de Día de Neumología (2001-2006). Se registraron diversas variables clínicas en el momento de la inclusión, y se revisaron retrospectivamente la evolución y las causas de muerte.

Resultados: La edad media (± desviación estándar) de los pacientes fue de 69 ± 8 años, y el volumen espiratorio forzado en el primer segundo del 30,8 ± 8,2%. Fallecieron 109 pacientes (53,7%). De éstos, 72 murieron de causas respiratorias (80,9%), de las cuales la exacerbación de la EPOC fue la más frecuente (48,3%). Durante el seguimiento, el 18,7% precisó ingreso en la Unidad de Cuidados Intensivos (UCI). La supervivencia al año, a los 3 y 5 años fue del 80, el 53 y el 26%, respectivamente. El análisis multivariante mostró que la mortalidad se asociaba a la edad, al estadio IV de la clasificación de la Global Initiative for Chronic Obstructive Lung Disease (GOLD), al cor pulmonale y a la estancia hospitalaria durante el año previo a la inclusión. La necesidad de ingreso en la UCI durante el seguimiento constituyó un factor independiente asociado a mayor mortalidad.

Conclusiones: La mortalidad en la EPOC grave es elevada y la exacerbación de la enfermedad constituye la causa más frecuente. La edad, el estadio GOLD, el cor pulmonale, los ingresos hospitalarios previos y la necesidad de ingreso en la UCI durante el seguimiento son factores pronósticos independientes de mortalidad

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Introduction

Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of death in the world.[1] According to the numerous studies that have investigated the specific causes of death in patients with COPD, respiratory failure is the leading cause among patients with most severe disease, whereas those with mild-moderate disease are more likely to die of associated diseases such as lung cancer or cardiovascular disease. However, it is often difficult to establish the actual cause of death in patients with COPD, particularly if mortality is assessed solely from death certificates or death registers.[2]

In addition, although several studies have attempted to assess the risk factors for mortality in COPD, the findings have been inconsistent in studies of patients with stable COPD,[3-5] those of patients after hospitalization for exacerbation,[6-8] and even those of patients after admission to an intensive care unit (ICU).[9,10] The objectives of this study were to assess mean survival and causes of death in a cohort of patients with severe COPD and to retrospectively analyze the risk factors for mortality (baseline characteristics of the population) as well as the influence on mortality of admission to the ICU during follow-up.

Patients and Methods

Patients

Consecutive patients diagnosed with severe COPD (forced expiratory volume in 1 second <50%)[11,12] who were attending the respiratory department day hospital of the Corporació Parc Taulí, Barcelona, Spain, were consecutively included between January 2001 and June 2006. The day hospital of our department is mainly responsible for monitoring patients with severe COPD who are admitted to hospital and/or who attend the emergency room 2 or more times a year. These patients attend regular scheduled follow-up visits every 3 months and can call the unit or be treated on an emergency basis in the event of exacerbation. Other interventions are also undertaken; these include smoking cessation programs, respiratory rehabilitation/physiotherapy, and education by the nursing staff with regard to inhalation techniques.

Patients with obstructive respiratory complaints of other origins such as bronchiectasis, asthma, and sequelae of tuberculosis were excluded from the analysis.

Methods

The following variables were collected at baseline: smoking habit and cumulative dose (pack-years), dyspnea severity,[13] number of hospitalizations and visits to the emergency department in the previous year and number of days in hospital, forced spirometry (Datospir, Sibelmed, Barcelona, Spain), resting arterial gas analysis (ABL-500, Radiometer, Copenhagen, Denmark), body mass index (BMI), COPD stage according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria,[14] corticosteroid use, diagnosis of cor pulmonale, and chronic home oxygen therapy. Cor pulmonale was considered to be present when diagnosed in the medical history using clinical, electrocardiographic, and/or echocardiographic criteria. A detailed list of concurrent disease of each patient was drawn up, and the Charslon index combining age and comorbidity was calculated.[15]

During follow-up, the number of admissions to the ICU, need for invasive or noninvasive mechanical ventilation, length of hospital stay, and reason for admission were recorded. Finally, the cause of death was noted, specifying place, date, and precise diagnosis. The cause of death was determined by an exhaustive review of the medical records (reason for admission, intercurrent processes, final cause of death), given that most patients died in a hospital setting. The cause of death in patients who died at home was recorded as unknown. The causes of death were classified in 3 groups as *a)* respiratory, which included COPD exacerbation, community-acquired or nosocomial pneumonia, lung cancer, and pulmonary embolism; *b)* cardiac, which included ischemic heart disease, heart failure, and arrhythmia; or *c)* stroke (ischemic or hemorrhagic). The remaining causes were included in a miscellaneous group.

Statistical Analysis

All the information was entered into a database and processed with the SPSS statistical package version 15 (SPSS, Chicago, Illinois, USA). The statistical analysis consisted of an initial descriptive analysis of the baseline and follow-up variables. Quantitative variables were expressed as mean (SD) and median (range). Categoric variables were expressed as frequency and percentage. To determine the variables associated with mortality at the end of the study, a univariate analysis was done using the χ^2 test for categoric variables and the test for comparison of means for quantitative ones. The Kaplan-Meier method was used to estimate survival times and curves, and the logrank test was used to compare curves. Finally, to determine factors associated with survival in the multivariate analysis, a Cox regression model was constructed in which the variables that had been statistically significant in the univariate survival analysis that improved the fit (conditional stepwise method) were included.

Results

Between January 2001 and June 2006, 210 patients were included. Seven were excluded during follow-up to leave a final number of patients analyzed in December 2006 of 203 (all with at least 6 months of follow-up). Almost all these patients were men (n=202, 99.6%). Table 1 shows the main characteristics of the study sample, and Table 2 presents the most common comorbidities. Of note is that COPD was the only chronic disease in 19.2% of the patients.

Follow-up lasted for a mean of 28 months (range, 6-60 months). In this period, 2 patients received a double-lung transplant and 1 underwent lung volume reduction surgery.

At the end of follow-up, 109 patients had died (53.7%). The mean estimated survival time in the total sample was 38 months, and estimated survival at 1, 3, and 5 years was 80%, 53%, and 26%, respectively (Figure 1). The causes of death are presented in Table 3. In total, 20 patients (18.3%) died outside the hospital setting, and so were recorded as dying of unknown cause. Of the known causes, the most frequent were respiratory (80.9%), with COPD exacerbation being the most common specific cause within this category (48.44%). Nonrespiratory causes were varied, with relatively few deaths attributed to ischemic heart disease (3.4%) and a relatively high rate associated with acute abdomen (6.7%) of varied origins (intestinal occlusion, intestinal ischemia, etc).

During follow-up, 38 patients required admission to the ICU (18.7%), of whom 19 (9.3%) needed invasive mechanical ventilation with orotracheal intubation. Only 7 patients died in the ICU (3.4%), but survival in these patients was clearly lower than in the rest of the study sample (Figure 2), with a mean survival in patients requiring admission to the ICU of 29 months (2.5 years) compared to 41 months (3.5 years) in those who were not admitted to the ICU during follow-up (*P*=.002).

The univariate analysis is shown in Table 1. The multivariate Cox regression analysis (Table 4) indicated that the predictors of mortality in the study sample were age, chronic cor pulmonale, stage IV disease according to the GOLD classification, and larger number of days in hospital in the year prior to inclusion (essentially when days of hospitalization exceeded 60). Need for admission to the ICU during

Table 1
Characteristics of the Patients at the Time of Inclusion and Comparison Between Those Who Died During Follow-up and Those Who Survived[a]

	Total (n=203)	Alive (n=94)	Dead (n=109)	P
Mean age, y	69.2 (8.2)	66.7 (8.2)	71.4 (7.6)	<.001
Active smokers	22 (10.8%)	9 (9.6%)	13 (11.9%)	.59
Pack-years	65.3 (33.5)	64.8 (31.3)	65.8 (35.4)	.82
Charslon comorbidity index				
≤3	38 (18.7%)	25 (26.6%)	13 (11.9%)	.004[b]
4-6	139 (68.5%)	61 (64.9%)	78 (71.6%)	
≥7	26 (12.8%)	8 (8.5%)	18 (16.5%)	
Dyspnea				.01
Grade 0-2	135 (66.5%)	71 (75.5%)	64 (58.7%)	
Grade 3-4	68 (33.5%)	23 (24.5%)	45 (41.3%)	
BMI, kg/m²	26.5 (4.7)	26.9 (4.9)	26.1 (4.6)	.22
≤21		8 (8.5%)	11 (10.3%)	
>21		86 (91.5%)	96 (89.7%)	.67
FVC, L	2.30 (0.6)	2.46 (0.55)	2.22 (0.61)	.005
FVC, %	58.9 (14.7)	60.4 (14.1)	57.8 (15.3)	.21
FEV₁, L	0.86 (0.2)	0.93 (0.27)	0.81 (0.24)	.001
FEV₁, %	30.8 (8.2)	31.8 (8.4)	29.9 (7.9)	.10
FEV₁/FVC	37.8 (10.2)	38.4 (9.3)	37.3 (10.9)	.42
PaO₂, mm Hg	62.3 (10.3)	64 (10.1)	60.7 (10.2)	.21
PaCO₂, mm Hg	47.5 (8.0)	45.8 (7.7)	48.9 (8)	.007
Hemoglobin	14.3 (2.1)	14.7 (2.27)	13.9 (1.9)	.025
≤12		8 (8.5%)	18 (16.7%)	
12-18		78 (83%)	86 (79.6%)	
>18		8 (8.5%)	4 (3.7%)	
Chronic HOT	91 (44.8%)	31 (33%)	60 (55%)	.002
Corticosteroid use	17 (8.4%)	10 (10.6%)	7 (6.4%) .28	
CPC	59 (29.1%)	15 (16%)	44 (40.4%)	<.001
GOLD stage III	59 (29.1%)	38 (40.4%)	21 (19.3%)	.001
GOLD stage IV	144 (70.9%)	56 (59.6%)	88 (80.7%)	.001
Hospitalizations in previous year				
0	26 (12.8%)	16 (17%)	10 (9.2%)	.049[b]
1	41 (20.2%)	21 (22.3%)	20 (18.3%)	
≥2	136 (67%)	57 (60.6%)	79 (72.5%)	
Visits to the emergency department in previous year				
0	20 (9.8%)	13 (13.8%)	7 (6.4%)	.06[b]
1	26 (12.8%)	13 (13.8%)	13 (11.9%)	
≥2	157 (77.4%)	68 (72.3%)	89 (81.7%)	
Days in hospital in previous year	26.8 (27.4)	22 (23.6)	32.2 (29.5)	.009
Admission to ICU during follow-up	38 (18.8%)	7 (7.4%)	31 (28.4%)	<.001

Abbreviations: BMI, body mass index; CPC, chronic cor pulmonale; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease classification; HOT, home oxygen therapy; ICU, intensive care unit.
[a] Data are shown as mean (SD) or number of patients (%).
[b] χ² test for comparison of linear correlation

Table 2
Study of Comorbidities

Comorbidity	
Hypertension	30.5% (62/203)
Diabetes mellitus	16.7% (34/203)
Ischemic heart disease	14.7% (30/203)
Sleep apnea syndrome	13.3% (27/203)
Atrial fibrillation	12.8% (26/203)
Previous neoplastic disease	8.9% (18/203)
Chronic liver disease	3.4% (7/203)
Left heart failure	1.9% (6/203)
Others	15.7% (32/203)

follow-up was also an independent factor associated with greater mortality.

Discussion

The patients in this study had severe COPD, substantial comorbidity, and high mortality. Death was most often attributed to respiratory causes, of which COPD exacerbation was the most frequent. Another finding of note was that the main risk factors for mortality were age, COPD severity (GOLD stage IV, chronic cor
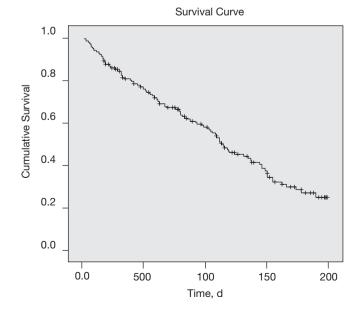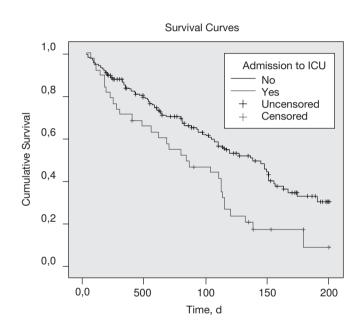

Figure 1. Kaplan-Meier survival curves.

Table 3
Causes of Death in the Patients Studied

Cause	Patients
Respiratory	80.9% (72/89)
COPD exacerbation	48.44% (43/89)
Community-acquired pneumonia	7.9% (7/89)
Nosocomial pneumonia	14.6% (13/89)
Lung cancer	8.9% (8/89)
Invasive aspergillosis	1.1% (1/89)
Cardiac	5.6% (5/89)
Ischemic heart disease	3.4% (3/89)
Heart failure	1.1% (1/89)
Arrhythmia	1.1% (1/89)
Stroke	1.2% (1/89)
Others	12.4% (11/89)
Acute abdomen	6.7% (6/89)
Septic shock	2.3% (2/89)
Extrapulmonary cancer	2.38% (2/89)
Opiate intoxication	1.1% (1/89)
Unknown	18.3% (20/109)

Table 4
Risk Factors for Mortality According to Multivariate Cox Regression Model

Variable	OR (95% CI)	P
Age, y	1.07 (1.04-1.10)	<.001
Chronic cor pulmonale	1.69 (1.13-2.55)	.011
GOLD stage IV	1.66 (1.02-2.69)	.04
Days in hospital in previous year		
1-30	1.4 (0.71-2.78)	.32
30-60	1.60 (0.76-3.37)	.22
>60	3.56 (1.62-7.81)	.002
Admission to ICU during follow-up	2.21 (1.41-3.46)	.001

Abbreviations: CI, confidence interval; ICU, intensive care unit; OR, odds ratio.

Figure 2. Survival analysis comparing patients admitted to the intensive care unit (ICU) with those not admitted.

pulmonale), and previous hospitalization. Need for admission to the ICU during follow-up was also a factor independently associated with higher mortality.

Mortality was very high (53.7%), and 81.7% of deaths occurred in hospital, in line with findings from other published series.[3,5,7] Martí et al,[3] who analyzed 128 patients with disease of similar severity to the patients in our study in that they were receiving chronic home oxygen therapy, reported a slightly higher mortality rate (61%). Survival at 1 year in our series (80%) was also similar to that reported in the literature.[3,7,8] It is more difficult to compare survival at 3 and 5 years, as follow-up was shorter in most other studies; when longer follow-up periods were analyzed, the findings were however similar to ours.[3]

Mortality associated with nonrespiratory causes was low in this study sample. Such causes are more frequent in patients with mild-moderate COPD.[2,16] Mortality associated with respiratory causes—especially COPD exacerbation—was high in our study, in line with other studies.[2,3,17,18]

Unlike other studies,[3,7] in which information on the causes of death were collected from death registers and death certificates in

the reference areas, in our study, the information was derived from an exhaustive review of the medical records of the patients, thereby allowing more detailed data to be collected. Interestingly, the most frequent nonrespiratory cause of death was intercurrent abdominal complication (acute abdomen). It is likely that the severity of the underlying COPD played a part in limiting the therapeutic options available in such cases (surgery).

A noteworthy aspect of the study is the analysis of mortality in the subgroup of patients who required admission to the ICU during follow-up. Survival in this group was significantly shorter, and admission to the ICU was also an independent risk factor in the multivariate analysis, even though few patients actually died in the ICU. These results agree with those reported by other authors.[9,10] In a study in which long-term survival was assessed in 742 patients with COPD who had required admission to an ICU, survival at 6 years was 18.3% and the main factor that influenced mortality was quality of life before admission.[10]

The risk factors for mortality in the multivariate analysis included age[3,4,8,19,20] and chronic cor pulmonale,[3,21] as found in previous studies. A range of lung function variables that reflect COPD severity have also been associated with mortality in previous studies. These variables, which are included in classifications of COPD severity such as GOLD,[14] include forced expiratory volume in 1 second,[19] hypoxemia,[6] and hypercapnia.[4,8] GOLD stage IV disease continued to be a risk factor for mortality in the multivariate analysis in our study. Of note among the risk factors for mortality observed in the multivariate analysis of our cohort was hospitalization in the year prior to inclusion. Almagro et al[7] had already observed in a previous study that the need for readmission was an independent risk factor for death in a cohort of patients admitted for COPD exacerbation. In a study performed by Soler-Cataluña et al[4] in a cohort of patients with stable COPD, the authors concluded that severe COPD exacerbations (that is, those requiring medical attention or hospitalization) were an independent risk factor for death. Likewise, in our study, performed in a cohort of patients with severe COPD attended in the day hospital of our respiratory department in the year prior to inclusion, hospitalization in the previous year (especially when the stay exceeded 60 days) was an independent risk factor for death. However, we have no indication whether the results obtained can be extrapolated to patients with severe COPD and fewer annual exacerbations.

Another variable reported to be associated with mortality is BMI.[3,6,22,23] Although our study showed no increase in risk for patients with low BMI, we should point out that the overall mean BMI was 26.5 (4.7) kg/m² and that only 19 patients had a BMI below 21 kg/m². Like other authors,[8,21] we did not find the Charlson comorbidity index to be predictive of mortality in the multivariate analysis, although some authors have reported different findings on this point.[24]

With regard to the study limitations, we should first point out that men comprised 99.6% of the cohort, and so the results cannot be applied to women with severe COPD. Another limitation, which pertains to the analysis of causes of death, is that a relatively large percentage of patients died at home, and so the ultimate cause of

death could not be ascertained and was recorded as unknown. Likewise, we did not analyze microbiological data on the causative agent of COPD exacerbations and pneumonia which were the main causes of death. For the analysis of risk factors for death, it should be remembered that this is a retrospective study. Another limitation is that enrollment began in 2001, before the index comprising BMI, airflow obstruction, dyspnea, and exercise capacity (known as the BODE index) was published as a risk factor for death.[21] We therefore do not have the results of the 6-minute walk test for most patients and, therefore, it was not possible to analyze the influence of this variable or the BODE index on mortality in our cohort. Likewise, we did not measure static lung hyperinflation (inspiratory capacity/total lung capacity), which has proved an independent predictor of mortality in a recent study.[25]

In conclusion, mortality in patients with severe COPD is high and disease exacerbation is among the most frequent causes of death. Age, GOLD stage, cor pulmonale, prior admission to hospital, and need for admission to the ICU during follow-up were independent factors indicating poor prognosis and associated with higher mortality in these patients. Emphasis on reducing the number and degree of severe COPD exacerbations might be an effective approach to reducing mortality in these patients.

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