ORIGINAL ARTICLE

Risk Factors for Mortality in Chronic Obstructive Pulmonary Disease

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OBJECTIVE: Although the factors predictive of survival in patients with chronic obstructive pulmonary disease (COPD) have been widely studied, full consensus has yet to be reached. The objective of this study was to further clarify how lung function parameters, exercise tolerance, and quality of life influence survival in patients with COPD.

PATIENTS AND METHODS: This prospective study included 60 patients diagnosed with COPD. At the start of the study, patients underwent respiratory function tests, exercise testing, and 6-minute walk test. They also answered a chronic respiratory disease questionnaire to measure health-related quality of life. Follow-up lasted 7 years.

RESULTS: Five of the 60 patients withdrew from the study. Twenty-six of the remaining 55 patients (47%) died during the study. Univariate Cox regression analysis showed a correlation between survival and age, degree of obstruction, inspiratory capacity, carbon monoxide diffusing capacity, and peak exercise tolerance. No correlation was found between survival and body mass index, PaO2, PaCO2, total lung capacity, residual volume, maximal respiratory pressures, 6-minute walk test distance, or health-related quality of life.

CONCLUSIONS: Our findings show that peak exercise tolerance is the best predictor of survival in patients with COPD.

Key words: COPD. Exercise tolerance. Mortality. Survival.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a major public health problem throughout the world. The prevalence and incidence of the disease are increasing continuously.1 Survival in patients with COPD has been linked with age,2 abnormal findings in lung function tests,3 airway hyperresponsiveness,4 body mass index (BMI),14 dyspnea,6 and presence of cor pulmonale or associated...
comorbidity. Although some authors have analyzed groups of factors, it has been impossible to draw firm conclusions or establish associations, and the prognostic factors for COPD are still the subject of debate.

To help determine which of the following factors was associated with survival and which was best able to predict survival: age, BMI, smoking habit (both current and past, with pack-years), lung function variables, exercise test results, and CRQ score. One variable for every 8 events (deaths) was chosen to be introduced into a multivariate Cox regression model. The Kaplan–Meier method was used to analyze the factor on survival of the variable—stratified into quartiles—that was found to be the most relevant in the regression analysis.

**Patients and Methods**

**Patients and Design**

Sixty patients with COPD were selected according to the following inclusion criteria: age 75 years or less, forced expiratory volume in 1 second (FEV1) equal to or less than 70% of predicted; ratio of FEV1 to forced vital capacity (FVC) equal to or less than 65%; PaO2 greater than 55 mm Hg at rest; and no indication for home oxygen therapy on enrollment. Patients were excluded if they had been admitted to hospital in the preceding month or had documented clinically relevant heart disease or osteoarticular disease that might have prevented study procedures from being performed. Enrollment lasted from February 1992 to January 1995. The ethics committee of our hospital approved the study and patients gave their informed consent.

**Variables**

The primary outcome measure was survival at 7 years. The following series of tests were performed to collect information on independent variables possibly associated with survival: lung function tests, including spirometry under baseline conditions and spirometry after bronchodilation (FVC, FEV1/FVC, maximum voluntary ventilation (MVV), and inspiratory capacity (IC); total lung capacity (TLC) and residual volume (RV) by the helium dilution technique; carbon monoxide transfer coefficient (KCO) by the inhalation method (SensorMedics, Yorba Linda, California, USA); and resting arterial blood gas analysis (pH, PaO2, and PaCO2) (ABL-500, Radiometer, Copenhagen, Denmark).

Exercise testing to determine peak exercise capacity was done with a cycle ergometer, with breath-by-breath monitoring. The technicians instructed and encouraged the patients during the test, which was concluded when the symptoms became unbearable or on the physician’s indication. The 6-minute walk test was performed in a 25-meter hospital corridor. Patients were instructed on how to perform the test and received standard encouragement while walking from one end of the corridor to the other, covering as many meters as possible for 6 minutes without running. The encouragement was given to ensure that optimum test results were obtained, although the test itself was performed only once.

The health-related quality of life was investigated with the validated Spanish translation of the Chronic Respiratory Questionnaire (CRQ). The date and cause of death were recorded for patients who died during the study. In the case of patients who were lost to follow-up, the date of the last visit was recorded.

**Statistical Analysis**

The baseline data were presented as mean (SD), with the range also shown in parentheses. A univariate and multivariate Cox regression analysis was done to determine which of the following factors was associated with survival and which was best able to predict survival: age, BMI, smoking habit (in pack-years), lung function variables, exercise test results, and CRQ score. One variable for every 8 events (deaths) was chosen to be introduced into a multivariate Cox regression model. The Kaplan–Meier method was used to analyze the factor on survival of the variable—stratified into quartiles—that was found to be the most relevant in the regression analysis.

**Results**

The study included 60 patients—all men. The mean (SD) age was 65 (7) years (range, 46-74 years), and the BMI was 26 (3.6) kg/m2 (range, 18-34 kg/m2). The following mean values were obtained in the lung function tests: FVC, 63% (15%) of predicted (range, 33%-94%); FEV1, 35% (14%) of predicted (range, 15%-68%); FEV1/FVC, 40% (11%) (range, 23%-64%); RV, 179% (45%) of predicted (range, 87%-278%); inspiratory capacity, 1.9 (0.4) L (range, 1.06-2.89 L); TLC, 112% (20%) of predicted (range, 82%-100%); PaO2, 70 (9) mm Hg (range, 56-89 mm Hg); PaCO2, 44 (5) mm Hg (range, 34-54 mm Hg). The mean value of peak exercise capacity in the exercise testing was 525 (168) kilopond meters (kpm) per minute (range, 200-1000 kpm/min). The mean maximum minute ventilation (VEmax) was 39 (12) L/min (range, 19-65 L/min), and peak oxygen uptake (VO2max) was 1.1 (0.3) L/min (range, 0.6-1.9 L/min). The mean distance covered in the 6-minute walk test was 306 (57) m (range, 200-450 m), and the mean scores on the CRQ were 17.5 (3.8) (range, 10.1-26.8) for the overall scale; 3.2 (1) (range, 1.0-6.6) for the dyspnea subscale; 4.5 (1.2) (range, 1.5-6.8) for the fatigue subscale; 4.8 (1.3) (range, 2.6-7) for the emotional subscale; and 5.1 (1.6) (range, 1-7) for the disease management subscale. There were no statistically significant differences between the 2 groups for the variables analyzed. Five of the patients withdrew from the study for personal reasons. The overall survival after 7 years of follow-up was 53%. In this period, 26 of the 55 patients died (47%), 11 (20%) due to respiratory insufficiency, 7 (27%) due to lung cancer and 1 (4%) due to nonlung cancer, 2 (8%) due to acute myocardial infarction, and 5 (19%) due to other reasons.

**TABLE 1**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Δ Risk/Unit %</th>
<th>P</th>
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<tbody>
<tr>
<td>Age, y</td>
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</tr>
<tr>
<td>FEV1, % pred</td>
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<tr>
<td>FEV1/FVC % pred</td>
<td>0.9</td>
<td>.016</td>
</tr>
<tr>
<td>IC, % pred</td>
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<td>.048</td>
</tr>
<tr>
<td>RV, % pred</td>
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<td>.024</td>
</tr>
<tr>
<td>MVV, kpm/min</td>
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<td>.001</td>
</tr>
<tr>
<td>Winex, kpm/min/min</td>
<td>0.1</td>
<td>.04</td>
</tr>
<tr>
<td>VO2max L/min</td>
<td>0.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>VEmax L/min</td>
<td>0.4</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; IC: inspiratory capacity; KCO: carbon monoxide transfer coefficient; abd: after bronchodilation; pred: predicted values; kpm: kilopond meters; VEmax: maximum voluntary ventilation; VO2max: peak oxygen uptake; MVV: maximum voluntary ventilation; Wmax: maximum work load.
In the univariate Cox regression analysis, an association was found between survival and age, degree of obstruction (FEV₁ and FEV₁/FVC after bronchodilation), inspiratory capacity (percentage of predicted), KCO (percentage of predicted), MVV (percentage of predicted), and peak exercise capacity assessed as peak workload (Wmax), VEmax, and VO₂max (Table 1).

We found no association between survival and the following variables: BMI, PaO₂, PaCO₂, FVC after bronchodilation (%), TLC (percentage of predicted), RV (percentage of predicted), maximum respiratory pressures (percentage of predicted), distance covered in the 6-minute walk test, and quality of life according to the score on the CRQ for any of the subscales. The association between survival and pack–years was on the borderline of statistical significance (relative risk [RR], 1.01; \( P = .054 \)). The variables entered were age, FEV₁/FVC ratio after bronchodilation, and VEmax. In the Cox regression analysis with a forward stepwise approach, only VEmax was included in the final model (RR, 0.926; \( P = .001 \)). In the backwards stepwise analysis, both VEmax (RR, 0.936; \( P = .001 \)) and age (RR, 1.075; \( P = .054 \)) were included in the model (Table 2). The models were run using the same procedure, that is, each of the other variables that measure peak exercise capacity (Wmax or VO₂max) were entered instead of VEmax (Table 2). Of the 6 models obtained, the most parsimonious was the one that included just VEmax.

Once VEmax had been chosen as the variable that best predicted survival, the patients were divided into quartiles according to this variable, and a Kaplan–Meier analysis was done with the 4 groups obtained (Figure). More than 75% of the patients with VEmax greater than or equal to 42 L/min survived the 7 years of follow-up, whereas fewer than 55% of the patients with VEmax below that value survived for 7 years (\( P = .0002 \), log-rank test).

Discussion
The most important finding of this study was that the risk factors for mortality in patients with COPD were associated with peak exercise capacity. The peak exercise capacity, assessed by exercise testing, was the best predictor of survival in these patients (all of whom were men with substantially deteriorated lung function). Many studies have analyzed predictors of survival in COPD, but few have assessed variables that reflect peak exercise capacity. Oga et al15 studied a cohort of 144 patients with COPD for 5 years and, like us, came to the conclusion that peak exercise capacity—assessed with VO₂max in that particular study—predicted survival even better than the degree of airway obstruction or age. Those authors assumed that VO₂max was the principal measure of peak exercise capacity. In our study, however, not only VO₂max but also Wmax and VEmax, were useful for predicting survival, and VEmax was a slightly stronger predictor than the other two.

COPD is a multisystem disease.16 Peak exercise capacity depends on many factors that could be related to survival, such as age, degree of obstruction, cardiovascular response, and...
nutritional status,27 and muscle characteristics.8-20 All of these are related to the functional reserve, and together they condition the specific response of a patient at peak exercise capacity. At the same time, any measure of peak exercise capacity is a good indicator of state of health and a predictor of survival.

Submaximal exercise capacity has been studied for its predictive value. In a 3-year follow-up of 138 patients with chronic respiratory disease (87% with COPD) who were participating in a respiratory rehabilitation program, Gerardi et al12 found that if peak exercise capacity was below 20 kg/m², and the mean BMI was 26 kg/m². The mean BMI in the study of Bowen et al22 was 25 kg/m² and in that of Domingo-Salvany et al27 it was 27 kg/m², values slightly above those reported in other studies. Neither of those studies showed an increased risk associated with low BMI. Furthermore, Marquis et al25 observed that loss of muscle mass measured by computed tomography was a better predictor of mortality than BMI alone.

It is not surprising that age is associated with survival, and indeed this agrees with previous findings.8-12 The risk of death in our study increased with age and decreased with degree of obstruction as assessed by FEV₁, and the FEV₁/FVC ratio after bronchodilatation, inspiratory capacity, KCO, MVV, and variables derived from the exercise testing. No association was found between survival and body mass index, pack-years smoked, quality of life, or distance covered in the 6-minute walk test.

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SOLANES ET AL. RISK FACTORS FOR MORTALITY IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

In conclusion, for all variables analyzed, peak exercise capacity alone was most useful for predicting survival, more so than other variables such as the degree of obstruction, quality of life, BMI, or age, in patients with COPD.

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REFERENCES


