

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 distance, or health-related quality of life.

Age, degree of obstruction (measured as the ratio of forced expiratory volume in 1 second to forced vital capacity after administration of bronchodilator), and maximum minute ventilation in the exercise test were introduced initially in the multivariate Cox stepwise regression analysis, but only maximum minute ventilation remained in the final model (relative risk, 0.926; $P < .001$).

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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Factores de riesgo de mortalidad en la EPOC

OBJETIVO: Aunque los factores que predicen la supervivencia en pacientes con enfermedad pulmonar obstructiva crónica (EPOC) han sido ampliamente estudiados, no disponemos de un consenso establecido. El objetivo de este estudio ha sido contribuir a clarificar el papel que desempeñan los parámetros de función pulmonar, tolerancia al esfuerzo y calidad de vida en la supervivencia en la EPOC.

PACIENTES Y MÉTODOS: Se diseñó un estudio prospectivo en el que se incluyó a 60 pacientes diagnosticados de EPOC. Al inicio del estudio realizaron pruebas funcionales respiratorias, prueba de esfuerzo máximo y prueba de la marcha de 6 min, y respondieron un cuestionario de enfermedad respiratoria crónica para determinar la calidad de vida relacionada con la salud. El seguimiento de los pacientes fue de 7 años.

RESULTADOS: Se retiraron del estudio 5 de los 60 pacientes. De los 55 restantes, 26 (47%) murieron durante el estudio. El análisis univariante con regresión de Cox mostró que existía relación entre la supervivencia y la edad, el grado de obstrucción, la capacidad inspiratoria, la capacidad de difusión del monóxido de carbono y la tolerancia al ejercicio máximo; no se observó dicha relación entre la supervivencia y el índice de masa corporal, la presión arterial de oxígeno y anhídrido carbónico, la capacidad pulmonar total, el volumen residual, las presiones máximas respiratorias, la prueba de la marcha de 6 min ni la calidad de vida relacionada con la salud.

En el análisis multivariante con regresión de Cox con pasos hacia adelante, en el que se introdujeron la edad, el grado de obstrucción (medido con la relación volumen espiratorio forzado en el primer segundo/capacidad vital forzada tras la administración de broncodilatador) y la ventilación minuto máxima en la prueba de esfuerzo, sólo esta última entró en el modelo final (riesgo relativo = 0,926; $p < 0,001$).

CONCLUSIONES: Nuestros hallazgos demuestran que la tolerancia al ejercicio máximo es el mejor predictor de supervivencia en los pacientes con EPOC.

Palabras clave: EPOC. Tolerancia al ejercicio. Mortalidad. Supervivencia.

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,² airway hyperresponsiveness,^{3,4} body mass index (BMI),^{4,5} dyspnea,⁶ and presence of cor pulmonale or associated

comorbidity.⁷ 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 clarify the factors predictive of survival in patients with COPD, we prospectively monitored a cohort of patients with COPD for 7 years.

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 [Datospir-92, Sibelmed, Barcelona, Spain]⁸) and lung volumes (total lung capacity [TLC] and residual volume [RV] by the helium dilution technique); carbon monoxide transfer coefficient (KCO) by the inhalation method (Sensormedis, Yorba Linda, California, USA)⁹; 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,¹⁰ 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.¹¹ 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).¹²

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 analysis¹³ 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.¹³ The Kaplan-Meier method¹⁴ was used to analyze the effect 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%-190%); 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), maximal minute ventilation (VE_{max}) was 39 (12) L/min (range, 19-65 L/min), and peak oxygen uptake (VO_{2max}) 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, 0.8-6) 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 (42%) 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
Increase in Risk per Unit Change in the Risk Factor*

Variable	Δ Risk/Unit, %		P
	Minimum	Maximum	
Age, y	2	20	.015
FEV ₁ , abd, % pred	0.4	6.9	.029
FEV ₁ /FVC abd, %	0.9	9.3	.016
IC, % pred	0	4.8	.048
KCO, % pred	0.3	3.3	.024
MVV, % pred	0.6	7.3	.021
W _{max} , kpm/min	0.3	0.9	<.001
VO _{2max} , L/min	0.1	0.4	<.001
VE _{max} , L/min	0.4	12.4	<.001

*FEV₁, indicates forced expiratory volume in 1 second; FVC, forced vital capacity; IC, inspiratory capacity; KCO, carbon monoxide transfer coefficient; abd, after bronchodilation; pred, predicted value; kpm, kilopond meters; VE_{max}, maximum minute ventilation; VO_{2max}, peak oxygen uptake; MVV, maximum voluntary ventilation; W_{max}, 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 (W_{max}), VE_{max}, and VO_{2max} (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 VE_{max}. In the Cox regression analysis with a forward stepwise approach, only VE_{max} was included in the final model (RR, 0.926; P<.001). In the backwards stepwise analysis, both VE_{max} (RR, 0.936; P=.001) and age (RR, 1.075; P=.097) 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 (W_{max} or VO_{2max}) were entered instead of VE_{max} (Table 2). Of the 6 models obtained, the most parsimonious was the one that included just VE_{max}.

Once VE_{max} 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 VE_{max} greater than or equal to 42 L/min survived the 7 years of follow-up, whereas fewer than 55% of the patients with VE_{max} 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

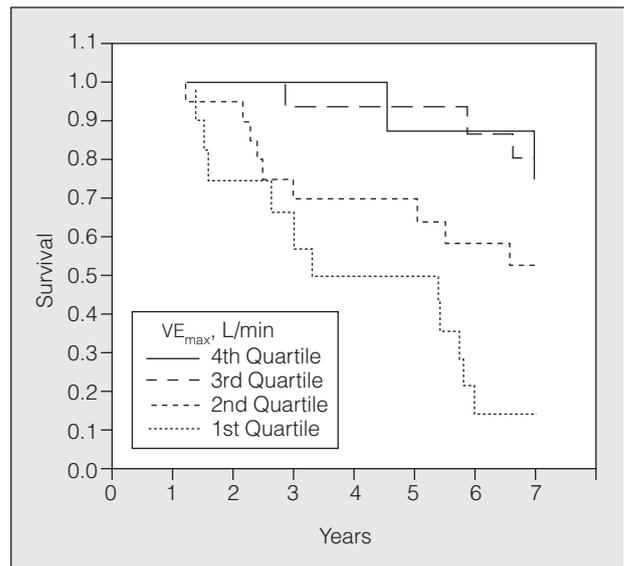


Figure. Kaplan–Meier curves by quartile group according to maximum minute ventilation (VE_{max}) in the exercise test. First quartile, VE_{max} <30.3 L/min; second quartile, 30.3 L/min ≤ VE_{max} ≤ 41.9 L/min; third quartile, 41.9 L/min < VE_{max} ≤ 53.7 L/min; fourth quartile, VE_{max} > 53.7 L/min. The difference between the 4 groups was statistically significant (P<.001, log-rank test).

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 VO_{2max} in that particular study—predicted survival even better than the degree of airway obstruction or age. Those authors assumed that VO_{2max} was the principal measure of peak exercise capacity. In our study, however, not only VO_{2max} but also W_{max} and VE_{max} were useful for predicting survival, and VE_{max} 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,

TABLE 2
Multivariate Cox Regression Analysis to Identify Factors Predictive of Survival in Chronic Obstructive Pulmonary Disease*

	Forward Stepwise			Backwards Stepwise		
	RR	95% CI	P	RR	95% CI	P
Age, y	—	—	—	1.075	0.987-1.172	.097
FEV ₁ /FVC abd	—	—	—	—	—	—
VE _{max} , L/min	0.926	0.890-0.964	<.001	0.936	0.900-0.975	.001
Age, y	—	—	—	1.078	0.981-1.184	.116
FEV ₁ /FVC abd	—	—	—	—	—	—
W _{max} (kpm/min)	0.994	0.991-0.997	<.001	0.995	0.992-0.998	.002
Age, y	—	—	—	1.090	0.994-1.194	.066
FEV ₁ /FVC pbd	—	—	—	—	—	—
VO _{2max} , L/min	0.998	0.025-0.347	<.001	0.998	0.031-0.494	.003

*FEV₁ indicates forced expiratory volume in 1 second; FVC, forced vital capacity; CI, confidence interval; abd, after bronchodilation; kpm, kilopond meters; RR, relative risk; VE_{max}, maximum minute ventilation; VO_{2max}, peak oxygen uptake; W_{max}, maximum work load.

nutritional status,¹⁷ and muscle characteristics.¹⁸⁻²⁰ 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 study of 158 patients with chronic respiratory disease (87% with COPD) who were participating in a respiratory rehabilitation program, Gerardi et al²¹ found that the distance covered in the walk test was a good predictor of survival. In another study of 149 patients with a 3-year follow-up, Bowen et al²² reported similar findings. In both cases, the distance covered after a rehabilitation program was a better predictor than the distance covered before the intervention. Recently, Pinto-Plata et al²³ also observed that submaximal exercise capacity predicted survival better than the traditional markers of disease severity, such as FEV₁ or BMI, and that the decrease in exercise capacity occurs regardless of the change in FEV₁. The findings of the aforementioned studies differ from those of our study in the predictive value of the initial walk test, an observation which can probably be explained by the different characteristics of the patients in terms of disease severity and age. Our patients had more severe disease but they were younger. Finally, Celli et al²⁴ proposed a multifactorial variable denominated BODE, which comprises BMI; degree of obstruction, determined by FEV₁ (percentage of predicted); dyspnea, as measured by the Medical Research Council scale from 0 to 4; and exercise capacity, measured with the 6-minute walk test. The authors did not assess peak exercise capacity and only compared the predictive value of BODE with that of FEV₁.

The univariate Cox regression showed that the risk of death increased with age and decreased with degree of obstruction as assessed by FEV₁ and the FEV₁/FVC ratio after bronchodilation, 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.

It is not surprising that age is associated with survival, and indeed this agrees with previous findings.^{2,6,15,25} Only Ries et al²⁶ and Bowen et al²² did not report such an association. In the study published by Ries et al,²⁶ risk was analyzed in 5-year increments, an arbitrary period that the authors considered clinically significant. Bowen et al²² observed a trend towards a correlation between age and mortality that was not statistically significant.

Our findings on the association between mortality in patients with COPD and the degree of obstruction agree with previous studies.^{2,6,15,25} The risk of death in our study increased with the degree of obstruction (RR=0.965 for FEV₁ and RR=0.952 for FEV₁/FVC, both after bronchodilation). This risk was similar to that reported in other studies,^{2,6,15} but it appears less marked than that calculated by Ries et al²⁶ (RR=0.84). However, in that study, risk was calculated for a clinically relevant unit change in FEV₁—taken to be 100 mL—whereas, in our analysis, the risk was calculated per milliliter change. On the other hand, Schols et al²⁷ did not report an increased

risk of death for FEV₁ if adjustment was made for age, BMI or change in BMI, and PaO₂. Recently, Martínez et al,²⁸ in a study of the factors predicting mortality in 609 patients diagnosed with COPD and with a mean follow-up of 3.9 years, found a mortality rate of 12.7 deaths per 100 persons per year of follow-up. In the multivariate analysis, it was observed that advanced age, oxygen therapy, decreased TLC, elevated RV, low peak exercise capacity, more emphysematous areas in the lower lung fields compared to the upper fields, and the modified BODE score were associated with increased mortality. FEV₁ was a significant predictor only in the univariate analysis and not the multivariate one.

Another variable reported to be associated with mortality is BMI.^{4,15,27} Landbo et al²⁹ reported that prognosis was worse in patients with low BMI only if this was associated with substantial deterioration in lung function. Although our study showed no increase in risk for patients with low BMI, we should point out that only 4 patients had a BMI 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 al²⁵ 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 al³⁰ observed that loss of muscle mass measured by computed tomography was a better predictor of mortality than BMI alone.

It appears that weight loss in patients with COPD depends essentially on loss of muscle mass.¹⁶ Mador³¹ reported that the association between muscle mass and mortality is not a causal one, but we cannot know whether loss of muscle mass is responsible for increased mortality or whether it is a marker of greater disease severity.

In our study, the association between the risk of dying and the number of pack-years smoked was almost significant ($P=.054$). Few studies have analyzed this variable, and the results are not conclusive. Nishimura et al⁶ found a relationship between pack-years and survival, whereas Oga et al¹⁵ did not. These contradictory results are surprising because both studies included a similar number of patients (183 in Nishimura et al⁶ and 150 in Oga et al¹⁵) and, in both cases, the mean number of pack-years was 58 and follow-up lasted 5 years.

Another variable studied in these patients was health-related quality of life. Not all questionnaires used to assess this parameter have shown good predictive value. We used the CRQ, which did not prove sensitive enough to predict survival for any of its subscales. Although other questionnaires such as the St George's Respiratory Questionnaire and the Breathing Problems Questionnaire are better predictors of survival than the CRQ, the dyspnea subscale of the CRQ seems to show an association with survival.¹⁵ Nishimura et al⁶ found that dyspnea measured on the modified Fletcher 5-point scale was an even better predictor ($P<.001$) than the stage of the disease ($P=.08$). Domingo-Salvany et al,²⁵ on the other hand, did not find that survival was associated with the mental component of the 36-item Short Form, although the physical component was predictive of survival. The score on the St George's Respiratory Questionnaire was also related to survival in that study.

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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