Predictors of Mortality in Patients with Stable COPD

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OBJECTIVES: To determine which easily available clinical factors are associated with mortality in patients with stable COPD and if health-related quality of life (HRQoL) provides additional information.

DESIGN: Five-year prospective cohort study.

SETTING: Five outpatient clinics of a teaching hospital.

PARTICIPANTS: Six hundred stable COPD patients recruited consecutively.

MEASUREMENTS: The variables were age, $FEV_{1\%}$, dyspnea, previous hospital admissions and emergency department visits for COPD, pack-years of smoking, comorbidities, body mass index, and HRQoL measured by Saint George's Respiratory Questionnaire (SGRQ), Chronic Respiratory Questionnaire (CRQ), and Short-Form 36 (SF-36). Logistic and Cox regression models were used to assess the influence of these variables on mortality and survival.

RESULTS: $FEV_{1\%}$(OR: 0.62, 95% CI 0.5 to 0.75), dyspnea (OR 1.92, 95% CI 1.2 to 3), age (OR 2.41, 95% CI 1.6 to 3.6), previous hospitalization due to COPD exacerbations (OR 1.53, 1.2 to 2) and lifetime pack-years (OR 1.15, 95% CI 1.1 to 1.2) were independently related to respiratory mortality. Similarly, these factors were independently related to all-cause mortality with dyspnea having the strongest association (OR 1.54, 95% CI 1.1 to 2.2). HRQoL was an independent predictor of respiratory and all-cause mortality only when dyspnea was excluded from the models, except scores on the SGRQ were associated with all-cause mortality with dyspnea in the model.

CONCLUSIONS: Among patients with stable COPD, $FEV_{1\%}$ was the main predictor of respiratory mortality and dyspnea of all-cause mortality. In general, HRQoL was not related to mortality when dyspnea was taken into account, and CRQ and SGRQ behaved in similar ways regarding mortality.

KEY WORDS: chronic obstructive pulmonary disease; mortality; health-related quality of life.
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INTRODUCTION

Forced expiratory volume in the first second (FEV_1) is a cornerstone for the management of chronic obstructive pulmonary disease (COPD). It is essential not only for diagnosing the disease but also for establishing its severity, as reflected in guidelines for the management of COPD.[1,2] Several studies have also demonstrated that FEV_1 is related to disease prognosis.[3,4] Other variables such as dyspnea,[5] body mass index (BMI),[6] previous hospitalization,[7] or exercise capacity[8] have emerged as prognostic factors. Recently, Cote and Celli summarized the literature on currently known predictors of mortality in COPD.[9] Grouping some of these factors into indices, such as the BODE index, appears to offer better prognostic power than FEV_1,[10] but relevant predictors may be missing. Moreover, to improve the use of these predictive models, they need to include variables that are easily gathered in busy clinical practices.

Although health-related quality of life (HRQoL) has been shown to be an independent predictor of mortality in patients with COPD,[11] not all HRQoL measurement instruments appear to behave in the same way.[12] Few studies have compared St. George's Respiratory Questionnaire (SGRQ) and the Chronic Respiratory Questionnaire (CRQ) for assessing prognosis in COPD patients.

The objectives of this study were to determine which factors used in daily clinical practice were predictive of mortality among patients with stable COPD and the relative importance of each, with the final goal being the future development of a multidimensional measure based on these clinical factors. We also aimed to determine whether HRQoL predicted mortality in this population and whether the two instruments for measuring HRQoL in patients with COPD behaved differently from each other.

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METHODS

Study Design and Sample

Between February 1998 and February 1999, we recruited all patients previously diagnosed with COPD who were under the age of 80 and who regularly visited outpatient clinics affiliated with a teaching hospital that has a catchment area of 300,000 inhabitants. All patients with COPD have to be seen by their pulmonary specialist between 1 to 4 times per year. Those who fulfilled the selection criteria were interviewed in-person when attending their pulmonary visit. All patients were followed for a period of three years by telephone and were interviewed in-person 5 years after the start of the study. The study was approved by the Research Committee of the Hospital Galdakao-Usansolo, and all patients provided verbal informed consent as required.

Patients were included in the study consecutively if they had been diagnosed with COPD at least six months previously and had been under treatment at the hospital's outpatient facilities for at least six months. Patients had to be stable (no increase in respiratory symptoms or changes in treatment) for six weeks prior to inclusion. Other inclusion criteria were FEV_1 <80% of the predicted value, with an FEV_1/FVC quotient <70%, and a negative bronchodilation test with FEV_1 change <200 ml and under 15% of the baseline value. The functional parameters used are those obtained following bronchodilation. Patients were not eligible for the study if they had been diagnosed with asthma, had extensive pulmonary tuberculosis or neoplastic processes, were suffering from psychiatric or neurological problems that might prevent effective collaboration, or had hearing or other problems that impeded accurate communication. Patients over the age of 80 were excluded given the potential difficulty of members of this age group to reliably provide the measurements required for this study.

Measures

Patients were asked about their level of dyspnea using a 5-point scale, adapted from Fletcher:[13] 1="dyspnea only with intense and strenuous exercise", 2="capable of walking at the same pace as other people of my age on the level", 3="capable of walking on the level at my own speed without dyspnea, but incapable of walking at the same pace as persons of my own age", 4="dyspnea after walking slowly for 100 meters" and 5="dyspnea when resting or after slight effort such as getting dressed". Dyspnea was also assessed using a 10-cm visual analogue scale (VAS) with values from 0 to 100 points, where 0 represented absence of dyspnea and 100 maximum dyspnea.

Number of pack-years was calculated by the product of years as a smoker and average number of cigarettes smoked per day, divided by 20, and body mass index (BMI) by dividing weight in kilograms by the square of height in meters. Comorbidities were determined by reviewing the patients' clinical histories. Spirometry was conducted following criteria from the American Thoracic Society (ATS)[14] and Spanish Pneumology and Thoracic Surgery Society),[15] (SEPAR) with a Master-Scope-PC spirometer (Erich Jaeger GmbH & Co, KG, Wuerzburg, Germany). Theoretical values were those prescribed by the European Community for Steel and Coal.[16] Global initiative for Chronic Obstructive Lung Disease (GOLD) criteria[17] were used to classify COPD into four stages based primarily on lung function impairment.

HRQoL was assessed using three instruments, one general and two disease specific, validated in Spanish populations. The SF-36[18,19] includes eight dimensions and two summary scales. Each dimension receives a score between 0 and 100 (100 representing the best health condition). The St. George's Respiratory Questionnaire (SGRQ)[20,21] comprises three dimensions (symptoms, impact, and activity) and a global score. Each dimension receives a score between 0 and 100, with 0 representing a complete lack of deterioration. The Chronic Respiratory Questionnaire (CRQ)[22,23] comprises four dimensions—dyspnea, fatigue, emotional function, and mastery.

Information on all patients' hospital admissions due to COPD exacerbation in the 2 years prior to their inclusion in the study was obtained by analyzing the database for our hospital, which is the benchmark hospital for these patients. In the unusual case of a patient having been admitted to another center, admission forms were used to establish the reason for admission. Vital status was determined initially by telephone interviews to all patients. All reported deaths and dates of deaths were confirmed by reviewing medical reports or examining of the hospital database and public death registries, or both. Deaths were considered confirmed if the record matched the subject on name, sex and date of birth. The cause of death was based on the hospital reports and public death registries. When death occurred out of hospital, researchers carried out a telephone survey of relatives and the primary care doctor. Later, the research team analyzed all data and established the causes of death.

Statistical Analysis

We present mean and standard deviations for continuous variables and frequencies and percentages for categorical variables. We used the Chi-Square and Fisher's exact tests to evaluate associations among categorical variables. To study the bivariate relationship between vital status at 5 years and potential predictor variables, we used Student's t-test and the Wilcoxon test for continuous variables and Chi-Square and Fisher exact tests for categorical variables.

Logistic regression and Cox proportional hazard models were used in the multivariate analysis to assess the relationship between mortality and clinical and demographic variables. All-cause and respiratory-related mortality were used as dependent variables, in separate analyses. We selected independent variables that had a statistically significant association with vital status ($p<0.05$) and added each independent variable to the model separately. We then added the overall SGRQ and CRQ questionnaire scores separately to the above models. We also studied the significance of the SGRQ and CRQ questionnaire scores when the categorical dyspnea variable was removed from the models. For easier interpretation of the results, age, tobacco packs/year, $FEV_{1\%}$, total SGRQ and total CRQ were estimated as a 10-unit improvement. Finally, we evaluated the variables that measured dyspnea categorically (a four-level variable was created after collapsing level 4 and 5 of the 5-point rating scale) and continuously (using a VAS scale) to determine if they had different associations with mortality.

Bootstrapping methods were performed in order to evaluate the internal validity of the final multivariate models. The S-PLUS 2000 statistical program was used to perform these calculations.

We computed the C statistic using logistic regression models to study the contribution of each variable to the final predictive model. In these analyses, the C statistic is a mathematical function of the sensitivity and specificity of our score in classifying patients by means of a logistic regression model as either dying or surviving. The null value for the C statistic is 0.5, with a maximum value of 1.0 (higher values indicating better health). We started by performing a stepwise procedure; then estimated the C statistics for each variable by introducing them into the model, one by one.

All effects were considered significant at $p<0.05$, unless otherwise noted. All statistical analyses were performed using SAS for Windows statistical software, version 8.2. (SAS Institute, Inc., Carey, NC).

RESULTS

Of the 729 patients of the initial cohort, 63 were excluded because they were older than 80 years 27 patients had cancer, 11 patients had sensorial problems, six patients had dementia and 11 had diseases, which made it difficult to measure the different tests for the study. A total of 611 COPD patients (98% men) were included in the study. Their characteristics are presented in Table 1. After 5 years of follow-up, 166 (27%) patients had died—81 (13%) as a result of exacerbation of their baseline disease (COPD) and 16 (3%) of other respiratory causes. Forty (6.5%) died of cardiovascular or cerebrovascular causes, 26 (4%) of other causes, mainly neoplasms; no cause of death was recorded for 3 patients. The survival rates at 1, 3, and 5 years were 96%, 85%, and 73%, respectively.

Baseline Characteristics

Table 1 compares the baseline characteristics of those surviving and those who died over the five years of the study. Deceased patients were significantly older, had worse $FEV_{1\%}$, higher degree of dyspnea, hospitalized for COPD more often in the 2 years prior to the study, and smoked more. Health-related quality of life (HRQoL) results for patients who died during the study period were consistently poorer at baseline than for those who survived (Table 2).

Multivariate Analysis

In the logistic regression models, the variables that were independently related to both respiratory and all-cause mortality were $FEV_{1\%}$, dyspnea (5-point Fletcher scale with ratings of 4 and 5 collapsed to give 4 levels), age, hospitalizations in the 2 previous years, and lifetime pack-years of smoking (Table 3).

Baseline HRQoL, measured by either the disease specific or the SF-36 questionnaires, were not associated with mortality in the multivariate models. However, when dyspnea was excluded from the model, HRQoL measured by total SGRQ score (OR, 0.98; 95% CI, 0.96–0.99; p=0.002) and total CRQ score (OR 1.01; 95% CI, 1.01–1.02; p=0.03) proved to be independently associated with respiratory and all-cause mortality. When dyspnea was included in the logistic regression model using the VAS, it was not associated with respiratory (OR, 0.99; 95% CI, 0.98–1.01) or all-cause mortality (OR 1.00; 95% CI, 0.99–1.01). In these models, total SGRQ (OR, 0.98; 95% CI, 0.96–0.99) and total CRQ (OR, 1.01; 95% CI, 1.00–1.02) scores were related to respiratory mortality. BMI did not correlate with mortality in either the univariate or any of the multivariate analyses, nor did comorbidities when grouped or taken individually.

Table 1. Baseline Characteristics of Participants Who Survived and Those Who Died Over the Five-Year Study Period

	Total sample (n=611)	Survivors (n=445)	Non-survivors (n=166)	p value*
Mean age (SD), yr	67.2 (8.4)	65.5 (8.6)	70.1 (7.0)	<0.001
Mean pack/years smoked (SD)	47.7 (28.7)	44.9 (27.9)	55.6 (29.4)	<0.001
Mean BMI (SD)	27.8 (4.3)	27.9 (4.3)	27.5 (4.3)	0.28
Mean FEV_1 (SD), L	1.37 (0.46)	1.45 (0.46)	1.13 (0.38)	<0.001
Mean percent predicted FEV_1 (SD), %	49.7 (14.6)	52 (14)	43.6 (14)	<0.001
Mean FEV_1/VC (SD), %	50 (10.3)	51.1 (10.2)	47.3 (10.1)	<0.001
Current smokers, n (%)	130 (21)	101 (23)	29 (18)	0.26
Level of dyspnea, n (%)†				<0.001
1	44 (7)	43 (10)	1 (1)	
2	306 (50)	243 (55)	63 (38)	
3	233 (38)	147 (33)	86 (52)	
4–5	28 (4)	12 (3)	16 (10)	
Mean VAS dyspnea, (SD)	49.5 (20.5)	44.8 (20.5)	54.3 (20.5)	<0.001
COPD severity, n (%)				<0.001
GOLD stage I	304 (50)	249 (56)	55 (33)	
GOLD stage II	267 (44)	182 (41)	85 (51)	
GOLD stage III–IV	40 (6)	14 (3)	26(16)	
Previous hospitalizations‡, n (%)				<0.001
0	387 (63)	309 (69)	78 (47)	
1	131 (21)	91 (20)	40 (24)	
2	46 (8)	24 (5)	22 (13)	
3 or more	47 (8)	21 (5)	26 (16)	
Previous emergency department visits‡, n (%)				0.99
0	480 (79)	349 (78)	131 (79)	
1	79 (13)	58 (13)	21 (13)	
2 or more	52 (8)	38 (8)	14 (8)	
Mean number of comorbidities (SD) §	1.6 (1.2)	1.6 (1.2)	1.5 (1.2)	0.37

FEV_1 indicates forced expiratory volume in the first second; VC indicates vital capacity; BMI indicates body mass index; VAS indicates visual analogue scale and GOLD indicates Global Initiative for Chronic Obstructive Lung Disease

* *p-values refer to the comparison between survivors and non-survivors and are based on Student's t-test and Wilcoxon test for continuous variables and Chi-square and Fisher's exact tests for categorical variables*

† *Dyspnea was assessed using a modification of the Fletcher scale,[13] where 1=dyspnea only with intense and strenuous exercise, 2=capable of walking at the same pace as other people of my age on the level, 3= capable of walking on the level at my own speed without dyspnea, but incapable of walking at the same pace as persons of my own age, 4= dyspnea after walking slowly for 100 meters, and 5=dyspnea when resting or after slight effort such as getting dressed. Because of small numbers in level 4 and 5, these levels were collapsed to create four categories. VAS dyspnea values from 0 to 100 points, the greater the value, the worse the dyspnea*

‡ Over the prior two years

§ *Comorbidity was assessed as mean number of co morbidities/patient*

Table 2. Baseline Measures of Health-Related Quality of Life (HRQoL) for Survivors and Non-survivors*

	Survivors (n=445)	Non-survivors (n=166)	p value
St George's Respiratory Questionnaire (SGRQ) †			
Activity	50.4±21.1	62.0±18.6	<0.001
Impact	30.4±19.5	38.9±17.5	<0.001
Symptoms	40.5±20.9	47.0±20.7	<0.001
Total SGRQ	38.2±18.2	47.3±16.1	<0.001
Chronic Respiratory Questionnaire (CRQ) ‡			
Fatigue	20.6±5.9	19.0±5.2	0.002
Dyspnea	25.5±8.2	22.8±8.0	<0.001
Mastery	18.6±5.7	16.7±5.5	<0.001
Emotional function	35.8±9.5	34.5±8.8	0.13
Total CRQ	100.6±24.8	93.0±22.0	<0.001
Short Form 36 (SF-36) ‡			
PCSS	45.6±7.9	41.7±8.0	<0.001
MCSS	50.0±10.8	50.2±10.1	0.82
Physical functioning	65.1±21.5	50.0±23.6	<0.001
Role physical	78.5±35.8	72.1±37.1	0.05
Bodily pain	71.4±27.5	71.5±28.0	0.97
General health	48.2±22.3	40.9±19.2	<0.001
Vitality	62.4±23.6	54.4±21.7	<0.001
Social functioning	84.7±21.5	83.9±23.9	0.69
Emotional role	83.4±34.3	84.7±32.1	0.65
Mental health	76.8±21.3	73.5±21.5	0.08

PCSS indicates physical component summary scale; MCSS indicates mental component summary scale
* *All data are presented as mean scores (SD)*
† *For the SGRQ, the higher score the worse the HRQoL*
‡ *For the CRQ and the SF-36, the higher the score the better the HRQoL*

When we evaluated survival using a proportional hazard model, we found the same results that have been described previously (Online-Appendix 1). To internally validate the final multivariate models we performed bootstrapping calculations of our estimates (Online-Appendix 2). The bootstrap results did not differ substantially from the original results.

The variables in order of importance to explain respiratory-related mortality were $FEV_{1\%}$ (C statistic 0.73), followed by dyspnea, age, previous hospitalization, and pack-years of smoking. For all-cause mortality, age (0.72) and dyspnea (0.65) occupied first and second place as mortality predictors, followed by $FEV_{1\%}$, previous hospitalization due to COPD exacerbation, and lifetime pack-years of smoking .

DISCUSSION

In patients with stable COPD, we found that several easily obtained clinical variables—$FEV_{1\%}$, dyspnea, age, prior hospitalizations for exacerbations of COPD, and pack-years of cigarette smoking—were associated with respiratory and all-cause and mortality. In contrast, HRQoL was not associated with respiratory or all-cause and mortality. Our study has several strengths compared to prior studies. We followed a larger number of patients (n=611) over a 5-year period and assessed key variables found to be associated with COPD-related mortality in smaller studies. We also used three measures of HRQoL and assessed the internal validity of our results using bootstrap methods.

The 5-year mortality rate in our population was 26%, which is comparable with mortality rates observed in studies of similar design.[5,8,11,24] The relatively low mortality rate is likely due to the fact that patients were recruited from outpatient clinics, not from hospitals settings[25] where mortality rates can be up to 49% at 2 years.[26]

$FEV_{1\%}$ had the strongest association with mortality in our study, a relationship that has been observed in other studies.[3,4] Dyspnea was the second most important factor independently related to respiratory mortality and was the most important factor associated with of all-cause mortality. This relationship has varied among prior studies. In one study, dyspnea was more predictive than $FEV_{1\%}$ in evaluating mortality after 5 years.[5] In other studies, however, dyspnea did not predict mortality.[11]

In our study, the number of severe COPD exacerbations requiring hospitalization and life time pack-years of smoking increased the risk of respiratory and all-cause mortality. Our results are congruent with recently published studies. [7,24,27,28] Whether co-morbidities are predictors of mortality among patients with COPD remains controversial. We did not observe an association between number of comorbidities, much as Domingo-Salvany et al. found.[11] However, Almagro et al., using the Charlson index, did observe comorbidities to be associated with mortality.[24] Soler et al.,[7] using the same index, showed no association between comorbidities and mortality. More importantly, although BMI <20 kg/m^2 has been associated with COPD-related mortality,[6] we did not find that it was associated with mortality. This may be due to the small number of patients with BMI <20 kg/m^2 in our study (n=26).

HRQoL, as measured by SGRQ and SF-36 questionnaires, has been linked both to respiratory and all-cause mortality.[8,11] In contrast, we did not find scores on these questionnaires to be independently related to mortality once they had been adjusted for other variables, particularly dyspnea as measured

Table 3. Adjusted Association between Univariate Predictors and 5-Year Mortality

	Respiratory mortality			All-cause mortality		
	OR*	95% CI	p value	OR*	95% CI	p value
Age	2.41	1.63–3.57	<0.001	2.27	1.69–3.06	<0.001
Dyspnea†	1.92	1.21–3.04	0.006	1.54	1.07–2.21	0.02
Pack/year	1.15	1.06–1.25	0.001	1.14	1.06–1.22	<0.001
Hospitalizations	1.53	1.18–1.98	0.001	1.48	1.20–1.83	<0.001
$FEV_{1\%}$	0.62	0.50–0.75	<0.001	0.74	0.63–0.86	<0.001
Total SGRQ	1.13	0.94–1.37	0.20	1.16	1.01–1.34	0.04
Total CRQ	0.92	0.81–1.03	0.16	0.93	0.84–1.02	0.12
Total SGRQ‡	1.30	1.11–1.54	0.002	1.26	1.11–1.43	<0.001
Total CRQ‡	0.85	0.76–0.95	0.006	0.88	0.81–0.96	<0.01

* *Logistic regression controlled for all other variables in the table except as noted below*
† *Dyspnea was measured using the Fletcher scale[13] modified by collapsing ratings of 4 and 5 to create four levels. The greater the level, the worse the dyspnea*
‡ *These models do not include dyspnea*

by Fletcher's[13] 5-point rating scale. In the study by Oga et al.[8] dyspnea was not included in the Cox analysis. In the study by Domingo-Salvany et al.,[11] dyspnea was measured by a visual analogue scale (VAS) and HRQoL measured by SGRQ and PCSS.

The use of different measures for dyspnea may explain the difference between our results and those of Domingo-Salvany et al.[11] Several studies discuss the usefulness of instruments such as VAS for measuring dyspnea during exercise.[29] However, to the best of our knowledge, no study compares VAS with other dyspnea scales such as Fletcher's scale[13] or the MRC scale[30] in clinically stable patients. Dyspnea scales such as the MRC scale, which is similar to the one used in our study, have been shown to be useful in COPD severity classification and in establishing prognosis.[5,31] The VAS may not have the same utility, base on our study results. This may be due to the fact that the VAS method, measuring from 0 to 100, may be more difficult to be understand by patients than specific descriptions of dyspnea chosen from a rating scale. In fact, when we used a VAS to measure dyspnea, dyspnea was no longer independently related with mortality, but HRQoL was as independently associated with mortality.

No published studies have directly compared the two disease specific HRQoL measures, St. George's Respiratory Questionnaire and Chronic Respiratory Questionnaire, as predictors of respiratory mortality. One study found that CRQ did not successfully predict mortality in a cohort of COPD patients.[12] In our study, neither of the two questionnaires was independently associated with respiratory mortality. However, when we excluded dyspnea from the model or included it as VAS, both questionnaires were independently associated with respiratory and all-cause mortality and their capacity as a predictor of mortality was quite similar. This is largely driven by the fact that dyspnea is a key determinant of HRQoL, as has been demonstrated in other studies.[32,33]

Our study adds to previous prognostic studies of COPD patients. From the clinical perspective, busy clinicians, especially in primary care settings, are not likely to measure exercise capacity and calculate the BODE index. They need easy methods for predicting mortality. All of our variables are readily available to clinicians caring for COPD patients. From the research perspective, our study contributes to the literature in several ways. First, we directly assessed the added value of measuring HRQOL, using three different tools, to see if any of them adds anything beyond the clinical factors. When dyspnea is included, HRQoL appears to be less important as a predictor of mortality. Second, we assess dyspnea by using two different measurement methods, rating and visual analog (VAS) scales. From our data, it seems that rating scales are the preferred method.

Our study has several limitations. We did not assess for changes in any of the main independent variables (e.g., dyspnea, FEV1, HRQoL) to determine if changes in these variables were associated with mortality. Second, the patient population was almost entirely comprised of men. This reflects the current distribution of COPD in Spain,[7,11] where women did not begin to smoke until late in the 20th century. Although the high percentage of men does not reflect a selection bias or affect the validity of the results, it does limit their generalizability to women. Finally, we focused on variables that are easy to obtain in daily clinical practice. We did not include others, such as the exercise capacity or the presence of pulmonary hypertension, that without any doubt have prognostic ability but are more difficult to obtain

Several clinical variables including $FEV_{1\%}$ and dyspnea are strongly associated with respiratory and all-cause mortality among patients with stable COPD. Age, previous hospitalizations due to COPD exacerbation, and lifetime pack-years of smoking are also important in establishing the prognosis of COPD. Subsequent studies of new multifactorial predictive modes using these simple measures should be developed. In contrast, two respiratory-specific HRQoL measures, the SGRQ and CRQ, were not independently related to mortality, or survival, when dyspnea was taken into account.

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