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ORIGINAL RESEARCH

Predictors of Mortality in Patients with COPD and Chronic Respiratory Failure: The Quality-of-Life Evaluation and Survival Study (QuESS): A Three-Year Study

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Abstract

Previous studies sought to identify survival or outcome predictors in patients with COPD and chronic respiratory failure, but their findings are inconsistent. We identified mortality-associated factors in a prospective study in 21 centers in 7 countries. Follow-up data were available in 221 patients on home mechanical ventilation and/or long-term oxygen therapy. Measurements: diagnosis, co-morbidities, medication, oxygen therapy, mechanical ventilation, pulmonary function, arterial blood gases, exercise performance were recorded. Health status was assessed using the COPD-specific SGRQ and the respiratory-failure-specific MRF26 questionnaires. Date and cause of death were recorded in those who died. Overall mortality was 19.5%. The commonest causes of death were related to the underlying respiratory diseases. At baseline, patients who subsequently died were older than survivors ($p = 0.03$), had a lower forced vital capacity ($p = 0.03$), a higher use of oxygen at rest ($p = 0.003$) and a worse health status (SGRQ and MRF26, both $p = 0.02$). Longitudinal analyses over a follow-up period of 3 years showed higher median survival times in patients with use of oxygen at rest less than 1.75 l/min and with a better health status. In contrast, an increase from baseline levels of 1 liter in O_2 flow at rest, 1 unit in SGRQ or MRF26, or 1 year increase in age resulted in an increase of mortality of 68%, 2.4%, 1.3%, and 6%, respectively. In conclusion, the need for oxygen at rest, and health status assessment seems to be the strongest predictors of mortality in COPD patients with chronic respiratory failure.

Introduction

Chronic respiratory diseases, whether obstructive or restrictive in their lung function impairment, frequently result in chronic respiratory failure (CRF). In these patients, life expectancy is approximately 4 years when the forced expiratory volume in 1 second (FEV_1) is 1.0 L and little more than 2 years when the FEV_1 is about 0.5 L (1).

Survival is improved by long-term oxygen therapy (LTOT) (2, 3). LTOT has also been shown to improve survival by about 3.5 years in patients with hypoxemic chronic obstructive pulmonary disease (COPD), but survival is worse if more severe airflow limitation is present when oxygen therapy is started (4). A number of studies have sought to identify survival or outcome predictors in patients with severe hypoxemia but their findings are inconsistent (5–7). For example, measurements from lung spirometry are not clear and consistent predictors of mortality.

Keywords: chronic, COPD, health status, mortality determinants, quality of life, respiratory failure

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It is not clear if non-invasive positive pressure ventilation is able to improve survival in COPD patients with stable severe COPD (8). However, in a 2-year study performed in 140 patients with severe hypercapnic COPD two year survival rates were higher in ventilated compared to non-ventilated patients (1 year, 87.7% versus 56.7%; 2 years, 71.8% versus 42%, p = 0.001) (9).

Health status is impaired in patients with severe hypoxia and the degree of impairment is correlated with the level of hypoxia (9, 10). Health status has previously been tested as a predictor of mortality of death in hypoxic COPD, but mainly using general health measures (11, 12), which are now known to be insensitive in COPD. More recently scores of disease-specific questionnaires such as SGRQ were found to predict mortality (13), and poor health status measured using COPD-specific questionnaires has been shown to be associated with a greater likelihood of death or hospitalization (14, 15). Looking specifically at mortality, there have now been three studies that have examined predictive factors in patients with moderate COPD (16–18).

The first is a retrospective analysis of patients participating in a pulmonary rehabilitation program in which functional status was shown to be a more powerful predictor of mortality than the FEV_1 (16). Two prospective studies have been performed in patients with non-hypoxic COPD; these were confined almost exclusively to male patients. One showed that age, FEV_1, body mass index and health status measured using the SGRQ were all significant independent predictors of mortality (17), but exercise capacity was not measured in that study. The other study measured peak oxygen uptake (VO_2max) during ergometer exercise and found that age, FEV_1, VO_2max and disease-specific health status (SGRQ) were predictors of mortality (18). Few studies have followed patients for longer periods of time COPD or included patients with CRF and LTOT (5).

To identify the factors that determine mortality in end-stage patients with CRF of various causes including COPD, we designed a 3-year prospective study that recruited male and female patients from centers in a number of countries (the Quality of Life Evaluation and Survival Study – QuESS) (19). To ensure that we explored all possible factors, we examined a very wide range of possible determinants of mortality, including demographic, clinical, physiological, and health status measurements. Results described in this article are limited to the population of COPD patients.

Methods

Study design

Twenty-one study centers in 7 countries (Canada, Czech Republic, Italy, Japan, Spain, UK, and USA) contributed patients. All participated on a voluntary basis, and none received financial support. Patients were enrolled from January 1999 to December 2000 and followed for three years. The patients were seen at baseline and at 6, 12, 24 and 36 months from baseline (19). All subjects were outpatients with COPD and CRF, ex-smokers, requiring the use of overnight home mechanical ventilation (HMV) and/or LTOT at the time of enrollment and clinically stable at the time of entry. Inpatients, unstable patients, those with a history of allergic rhinitis, asthma, drug abuse, lung cancer, neuromuscular disorders, sleep apnea, poor motivation or major psychiatric disorders were excluded. The Maugeri Foundation Ethical Committee reviewed the study and approved its conduct.

Measurements

At baseline, data on diagnosis, co-morbidities, medications, long-term oxygen therapy (years of use before enrolment, source, flow rates, hours/day), mechanical ventilation (years of use before enrolment, hours/night), pulmonary function tests (PFTs), arterial blood gases on room air (ABGs), exercise performance, and health status were recorded. At follow-up, all measurements were repeated and data concerning exacerbations, hospitalizations, antibiotics and corticosteroid courses were recorded. The date and cause of death were recorded in those who died (19).

Spirometry was performed in accordance to the American Thoracic Society criteria (20) PFTs were measured at least 15 minutes after the administration of salbutamol 200 mcg. Arterial blood gases were measured while breathing room air. Exercise performance was measured using the shuttle walking test (SWT) (21), chosen because it could be standardized across all study centers.

Dyspnea was evaluated by the Medical Research Council Dyspnoea Questionnaire (22). Health status was assessed with a generic questionnaire, the Medical Outcomes Study Short-Form Health Survey (SF-36) (23) and two disease-specific instruments, i.e., the St George's Respiratory Questionnaire (SGRQ) (24) and the Maugeri Foundation Respiratory Failure Questionnaire (MRF26) (25). The SF-36, originally validated in 11,186 subjects, has been found to be a valid measure of health in both asthmatic and COPD patients. The SGRQ is a disease-specific questionnaire for chronic lung disease with a total and three components scores for: Symptoms, Activity and Impacts (which addresses social and psychological effects of the disease). The Maugeri Foundation Respiratory Failure Questionnaire (MRF26) is a measure developed specifically for chronic respiratory failure (9). In contrast to SGRQ, its items were selected to be applicable to patients with obstructive or restrictive diseases with chronic respiratory failure and it defines two areas of health impairment due to CRF not identified by SGRQ. It has two components: Activity and Perceived Invalidity. Mood status was assessed using the Hospital Anxiety and Depression Scale (HAD) (26).

Statistical analyses

Unpaired *t*-tests were used for univariate analyses comparing LTOT vs. LTOT+HMV groups, and patients who subsequently died or survived. Receiver-operating

characteristics (ROC) analysis (27) was applied to define cut-off points for the baseline variables that were found in the univariate analyses to be statistically different between 'survivors' and 'subsequently died.' The ROC curve allowed identification of a cut-off value with the highest sensitivity and specificity for predicting mortality. Using this cut-off value, patients were categorized into 'more impaired' (values above the ROC threshold for age, oxygen flow, SGRQ and MRF-26; values below the ROC threshold for FEV_1 and FVC) and 'less impaired' (values below the ROC threshold for age, oxygen flow, SGRQ and MRF-26; values above the ROC threshold for FVC). Longitudinal analysis using Kaplan–Meier estimates and log-rank test was used to compare survival curves of 'more' and 'less impaired' subjects, as defined above. Cox's semi-parametric hazards model was used to test the association between the baseline variables and mortality and to estimate the risks of mortality.

Variables included in the Cox models were age, FVC%, LTOT/rest, SGRQ score (Total and Impact), MRF26 score (Total and Activity) and sex. A backward elimination approach (Likelihood Ratio) was used to select the variables associated with mortality; entry and removal criteria for the procedure were set at 0.05 and 0.10, respectively. Only results of the final models are shown in this article.

Results

Patients

A total of 319 COPD patients were recruited. Ten patients were lost to follow-up due to the withdrawal of two centers. At one year, complete follow-up data were available for 221 patients (Table 1). At baseline, 18% of patients had one co-morbid condition, 13% had two, and 23% had three or more co-morbidities. All subjects were on LTOT, 23 also received overnight HMV. LTOT had been started on average 2.8 ± 2.5 years before the study. The number of years of mechanical ventilation before the study was 2.5 ± 2.5 years. Principal baseline characteristics of subjects at enrollment are shown in Table 1. We did not find any statistical difference between the two groups of subjects, ventilated vs. not ventilated, apart from age (ventilated patients were younger) and FEV_1/FVC (ventilated patients had a higher ratio).

Three years after enrollment, 178 participants were still alive and 43 had died (19% mortality). Males had a mortality rate higher than women, almost double, although not statistically significant (22.5% vs 11.7%, p = 0.064). The commonest cause of death was respiratory-related in 33 patients (85% acute on chronic respiratory failure). Non-respiratory diseases caused death in 10 patients (60% cardiac disease).

Univariate analysis – all cause mortality

The patients who died over three years of follow-up were 3 years older at baseline than the survivors (p = 0.03) (Table 2). They had a more impaired FVC (p = 0.03) and required a slightly higher resting oxygen flow prescription (p = 0.003). Baseline health status scores for SGRQ were significantly worse in the patients who subsequently died (Total and Impact scores; both p = 0.02), similarly with the MRF26 (Total score, p = 0.02; and Activity score, p = 0.004).

Table 1. Principal baseline characteristics of the 221 subjects at enrollment; 198 were on LTOT and 23 on LTOT+ HMV

	All patients N = 221	LTOT N = 198	LTOT + HMV N = 23	p-value
Age (yr)	67.8 ± 8.2	68.4 ± 7.8	63.0 ± 9.6	**0.003**
Male sex (%)	72,4	72,2	73,9	0.893
BMI	26.2 ± 5.5	26.1 ± 5.3	27.3 ± 6.5	0.512
FVC (% predicted)	59.6 ± 19.9	60.1 ± 20.0	55.3 ± 19.5	0.302
FEV_1 (% predicted)	34.4 ± 15.2	34.4 ± 15.0	34.2 ± 18.0	0.765
FEV_1/FVC	46.5 ± 16.3	45.4 ± 15.0	56.7 ± 23.0	**0.020**
SWT (meters)	179 ± 120	180 ± 123	174 ± 99	0.234
pH	7.398 ± 0.034	7.399 ± 0.003	7.386 ± 0.053	0.352
PaO_2 (mmHg)	56.0 ± 9.2	55.6 ± 8.9	59.5 ± 11.4	0.434
$PaCO_2$, (mmHg)	47.3 ± 9.1	47.1 ± 9.1	49.5 ± 8.7	0.876
O_2-rest (L/min)	1.7 ± 0.7	1.7 ± 0.7	1.6 ± 0.9	0.887
MRC-Dyspnea	3.2 ± 1.3	3.2 ± 1.3	3.2 ± 1.4	0.899
HAD-Anxiety	6.4 ± 4.5	6.4 ± 4.6	6.8 ± 3.9	0.567
HAD-Depression	6.5 ± 4.0	6.4 ± 4.1	7.3 ± 3.9	0.346
SF36-MCS	47.4 ± 11.5	47.4 ± 11.4	47.8 ± 12.6	0.787
SF36-PCS	34.3 ± 9.5	34.2 ± 9.7	35.4 ± 7.0	0.668
SGRQ-Total	53.1 ± 17.3	53.5 ± 17.2	49.6 ± 17.7	0.305
SGRQ Symptoms	51.6 ± 23.4	52.4 ± 23.4	45.0 ± 22.9	0.212
SGRQ Activity	69.0 ± 20.7	69.8 ± 20.0	62.9 ± 25.3	0.253
SGRQ Impact	44.4 ± 19.3	44.6 ± 19.5	43.0 ± 18.2	0.717
MRF26-Total	43.8 ± 25.4	44.0 ± 25.5	42.8 ± 25.1	0.838
MRF26 Activity	42.7 ± 28.9	43.2 ± 28.9	37.8 ± 28.6	0.393
MRF26 Impairment	45.0 ± 27.0	44.7 ± 27.1	47.8 ± 26.5	0.301

*Data are summarized as mean and standard deviations.
p-values are related to the unpaired *t*-test comparing LTOT and LTOT+HMV.
Bolded values indicate statistically significant p-values.

Survival curves – All cause mortality

We created survival curves using Kaplan–Meier estimates. For each of the continuous variables identified as predictors of mortality in the univariate analyses, ROC curves were used to establish cut-off points between patients who survive and those who did not. These were: Age 67 years; FVC 49.5% predicted; Oxygen flow at rest 1.75 L/min; SGRQ Total score 61.5%; SGRQ Impact score 51.5%; MRF26 Total score 40.4%; MRF26 Activity score 50.1%. Using these thresholds, patients were stratified into 'more impaired' and 'less impaired.' Kaplan–Meier survival curves were estimated and comparisons among subgroups were performed using log-rank tests. When categorized in this way, there was no effect of age and FVC on survival, but Oxygen flow at rest, and total scores for SGRQ and MRF26 were associated with different median time of survival (Figures 1–4).

Table 2. Baseline predictors of mortality: univariate approach

Parameter	Fatal cases *(mean ±SD)*	Non-fatal cases *(mean ±SD)*	p-value
Age (yr)	70.30 ± 5.40	67.21 ± 8.62	**0.030**
Male Sex (n,%)	36 (84%)	124 (70%)	0.064*
BMI	25.07 ± 5.32	25.70 ± 5.72	0.465
FVC (% pred)	53.76 ± 17.49	61.07 ± 20.27	**0.030**
FEV_1 (% pred)	31.51 ± 15.27	35.55 ± 15.55	0.086
FEV_1/FVC	51.38 ± 19.19	50.24 ± 20.63	0.701
SWT (meters)	147.77 ± 85.98	184.15 ± 118.24	0.200
LTOT/rest (L/min)	1.95 ± 0.56	1.59 ± 0.73	**0.003**
PaO_2 (mmHg)	55.35 ± 11.34	58.79 ± 10.57	0.067
$PaCO_2$ (mmHg)	49.86 ± 11.74	47.49 ± 8.59	0.096
MRC-dyspnea	3 (1–5)	3 (1–5)	0.170**
HAD-Anxiety	7.5 (0–18)	6 (0–19)	0.180**
HAD-Depression	8.5 (0–17)	6 (0–17)	0.070**
SF36-MCS	45.25 ± 12.16	47.06 ± 12.08	0.337
SF36-PCS	32.65 ± 9.81	34.82 ± 9.69	0.150
SGRQ-Total	58.79 ± 16.46	51.70 ± 17.20	**0.020**
SGRQ-Symptoms	58.14 ± 22.35	50.43 ± 24.46	0.110
SGRQ-Activity	73.72 ± 17.93	67.69 ± 20.37	0.094
SGRQ-Impact	50.58 ± 18.49	42.91 ± 19.31	**0.020**
MRF26-Total	52.24 ± 24.49	41.81 ± 25.26	**0.020**
MRF26-Activity	53.85 ± 30.35	39.97 ± 27.93	**0.004**
MRF26-Impairment	10.07 ± 3.35	5.48 ± 3.42	0.216

*Chi-square test.
**Median (min-max), Mann–Whitney test
Bolded values indicate statistically significant p-values..

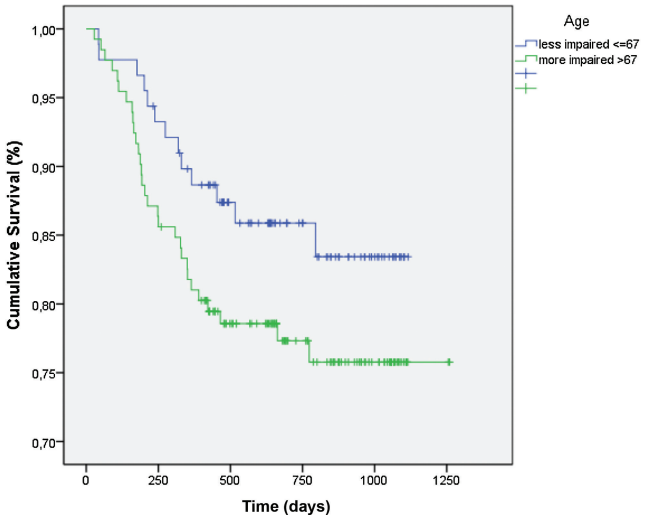

Figure 1. Survival curves of patients with chronic respiratory failure stratified for age; "More impaired" and "less impaired" subgroups were identified according to cut-off points of the ROC analysis. "More impaired" patients (dashed lines) presented a higher mortality than "less impaired" patients (continuous lines). P-value was calculated using the Log-Rank test. Older people (age > 67 yrs; n = 132) showed a trend in reduced survival; however, this was not statistically different with less older people (age ≤ 67 yr; n = 89), p = 0.178.

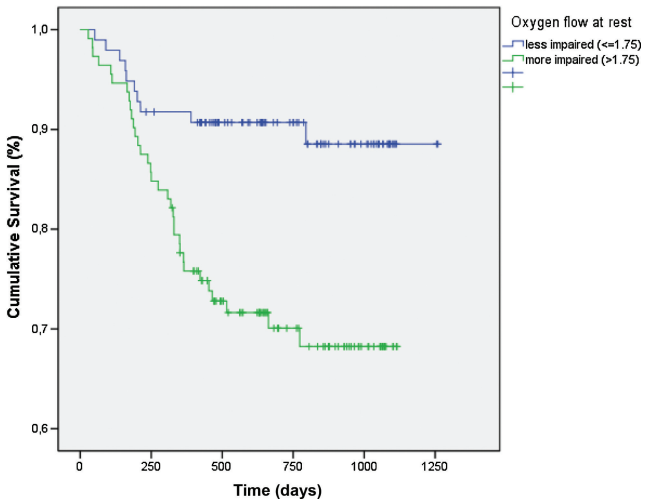

Figure 2. Survival curves of patients with chronic respiratory failure stratified for Oxygen flow at rest. "More impaired" and "less impaired" subgroups were identified according to cut-off points of the ROC analysis. "More impaired" patients (dashed lines) presented a higher mortality than "less impaired" patients (continuous lines). P-value was calculated using the Log-Rank test. Patients who used more than 1.75 L/min. of oxygen at rest (n = 112) had a higher mortality rate in comparison to patients who used less oxygen (≤1.75 L/min; n = 97), p = 0.001.

Seventy-eight percent of patients with a baseline oxygen flow at rest < 1.75 L/min survived 3 years in comparison to 59% survival in the more hypoxic group (p = 0.001). Patients with the poorest health status had a 3-year survival of 51% when categorized using the SGRQ total score, and 54% when categorized with the MRF26 total score. By contrast, patients with better health had better survival, 76% when categorized using SGRQ and 83% when using the MRF26 (p < 0.001 for all parameters except MRF26 Total score p < 0.019).

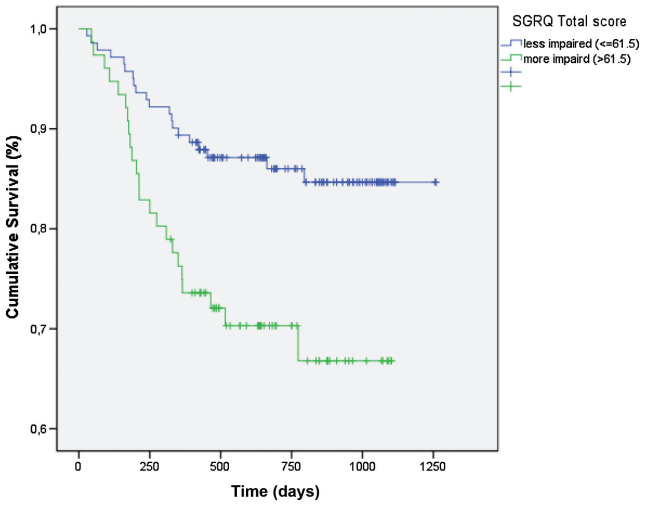

Figure 3. Survival curves of patients with chronic respiratory failure stratified for SGRQ total score. "More impaired" and "less impaired" subgroups were identified according to cut-off points of the ROC analysis. "More impaired" patients (dashed lines) presented a higher mortality than "less impaired" patients (continuous lines). P-value was calculated using the Log-Rank test. Patients with poorer health status (SGRQ Tot > 61.5; n = 76) had a higher mortality rate in comparison to patients who had a better health status (SGRQ Tot ≤ 61.5; n = 141), p = 0.001.

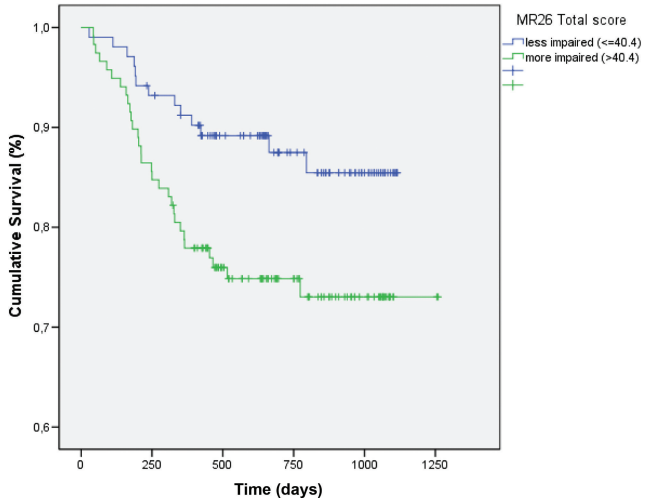

Figure 4. Survival curves of patients with chronic respiratory failure stratified for MRF26 total score. "More impaired" and "less impaired" subgroups were identified according to cut-off points of the ROC analysis. "More impaired" patients (dashed lines) presented a higher mortality than "less impaired" patients (continuous lines). P-value was calculated using the Log-Rank test. Patients with poorer health status (MRF-26 Tot > 40.4; n = 118) had a higher mortality rate in comparison to patients who had a better health status (MRF-26 Tot ≤ 40.4; n = 103), p = 0.019.

Cox models—All cause mortality

The proportional risk of mortality associated with the different predictors was evaluated using Cox models: an increase from baseline levels of 1 year of age, 1 L in oxygen flow at rest and 1 unit in SGRQ or MRF26 resulted in increased risk of mortality of 6%, 68%, 2.4% and 1.3% respectively (Table 3). Previous studies (28) have shown that a SGRQ score of 4 units is the threshold of clinical significance using this questionnaire. From the multivariate analysis, we calculated that, controlling for age and oxygen flow at rest, a 4-unit difference in SGRQ in our group of patients was associated with an 10% increased risk of mortality over the 1-year period. This association was independent of the baseline score.

Table 3. Hazard ratios and 95% confidence intervals from Cox models for all-cause mortality

	HR (95% CI)	p-value
Model 1*		
Age (years)	1.06 (1.01–1.10)	0.015
O_2 flow at rest (L/min)	1.68 (1.18–2.41)	0.004
SGRQ total (score)	1.024 (1.01–1.04)	0.011
Model 2†		
Age (years)	1.05 (1.01–1.10)	0.018
O_2 flow at rest (L/min)	1.56 (1.09–2.23)	0.015
MRF26 total (score)	1.013 (1.00–1.02)	0.018

*In model 1, the SGRQ was used as the measure of health status. Model 1 is based on 205 individuals and 43 deaths. Removed variables: SGRQ Impact, FVC%, Sex.
†In model 2 the MRF26 was used as the measure of health status. Model 2 is based on 207 individuals and 43 deaths. Removed variables: MRF26 Total score, FVC%, Sex.

Discussion

Predictors of mortality in patients with chronic respiratory failure and COPD have been analyzed in various studies but fewer studies considered a period of time more than 2 years. Furthermore, none of such studies considered health status among the predictors. This 3-year prospective study has shown that age, forced vital capacity, oxygen flow at rest and disease-specific health status are independent predictors of mortality in patients with COPD and chronic respiratory failure. Other physiological factors such as exercise performance were not related to three-year survival.

Age was a predictor of mortality, consistent with other studies involving less severe COPD patients (17, 18, 29), although in studies of patients with respiratory failure, age has been an inconsistent determinant of mortality (5, 7).

Resting hypoxemia was not identified as a mortality predictor in our sample of patients with CRF and COPD, and reduced PaO2 was claimed to predict mortality in hypoxemic COPD patients in one study (5), but not in some others (3, 17).

Hypercapnia was found to be a negative prognostic factor in other studies (2, 5), but in our large study, with a comparable evaluable sample of patients who were more severe, we did not confirm hypercapnia as a predictor of mortality. This might have been the result of a lower prevalence of patients with COPD and hypercapnic CRF in our sample, as well as the result of a less severe hypercapnia at baseline. Thus it appears that, between studies, PaO2 and PaCO2 vary in their predictive ability, but this may reflect the range of arterial blood gas changes in the different study populations rather than feature of the physiological disturbance.

Few studies have analyzed supplemental oxygen requirement at rest as a predictor of mortality. Ours is the first demonstration that oxygen requirement at rest, an indirect measure of disease severity for both COPD and CRF, predicts mortality and this effect was found to be independent of age or health status.

In our study as in the others, the FEV_1 was not a predictor of mortality (5, 7), although some studies reported that FEV_1/FVC ratio was an inconsistent or weak determinant of mortality (5, 7). This is quite unlike patients with less severe disease (17, 18, 29–31). Lung function (FEV_1) decline was evaluated as a predictor of mortality and lower or normal rates were found in long-term survivors in the Obstructive Lung Disease in Northern Sweden (OLIN) Study, with a 20-year follow-up period.

It also reported a survival rate of 19% in subjects with baseline severe and very severe COPD. That study also showed that age, male sex, disease severity and co-morbid ischemic heart disease or cardiac failure at entry are all predictors of mortality (32). The absence of an effect of FEV_1 on survival in severe patients may be explained by the fact that, in advanced COPD, secondary consequences of severe hypoxemia such

as cor pulmonale or pulmonary hypertension may be more important determinants of mortality. However, hemodynamic parameters such as right ventricular ejection fraction, pulmonary artery pressure were not constantly or consistently reported as being predictors of mortality in severe COPD patients (33, 34) and, consequently, were not considered as outcome measures in our study.

Another new and interesting finding of our study was the demonstration of FVC as a baseline predictor of mortality in the univariate analysis. This could mean that either persistent static over-inflation or severe emphysema can negatively impact disease prognosis in severe COPD: in fact both static hyperinflation (as assessed with IC to TLC ratio) and severe emphysema (assessed by HRCT) were demonstrated to be strong predictors of mortality in moderate-to very severe COPD patients (35, 36). In another study performed in patients with COPD and hypercapnic CRF undergoing noninvasive ventilation, static hyperinflation evaluated with residual volume/total lung capacity was identified as an independent predictor of mortality (37). Due to the methodological limitations of this study it was not possible to establish if hyperinflation or severe emphysema was associated with mortality in end-stage COPD patients, and therefore a more in depth analysis on these issues in subsequent studies is justified.

Recently, it has been demonstrated that gas transfer of carbon-dioxide provides prognostic information on survival of patients with COPD (38) compared to spirometry. In our study, as the QuESS was a multicenter study, it was not possible to obtain measurement of gas transfer from all the centers involved.

Tests of exercise capacity provide an integrative measure of overall cardiac, pulmonary and skeletal muscle function. In patients with moderate COPD, VO2max was the best predictor of mortality (18). In patients with hypoxia, data from the NOTT study show that patients with a baseline work capacity less than 35 watts had a higher mortality (42%) than those with better exercise capacity (24%), but no statistical test was reported (2). More recently 6MWT distance (39) and physical activity (40) were identified as being strong predictors of mortality in patients with severe (39) or moderate COPD (40).

By contrast, we did not find an association between exercise capacity and death, despite using an incremental maximum exercise test. We chose the shuttle test because it is simple, incremental and can be standardized easily between centers, unlike the 6-minute walk. Moreover, it has minimal 'learning effects' on repeated testing, and is able to produce results that are equivalent to those obtained from a conventional treadmill test in terms of peak oxygen uptake (41).

A more recent study (42) demonstrated that exercise capacity evaluated with the 6MWT and included in the composite index BODE was able to predict mortality in patients with stable COPD, but given the differences in the method of assessment of exercise capacity it was not possible to assess its predictor validity in hypoxemic COPD. Similarly, it was demonstrated that BODE is a valid indices to predict mortality in COPD (43).

Impaired health status at baseline was also found to be a predictor of mortality in patients with COPD and CRF. This study used questionnaires that were designed specifically to assess health status in chronic respiratory diseases, without or with CRF. Very similar results were obtained using the SGRQ and the MRF26, which are two disease-specific questionnaire that were developed using entirely different methodologies. Scores for these instruments, which address a broad range of effects of chronic lung disease and respiratory failure on daily functioning, were the powerful predictors of mortality in the univariate analyses in our study. In other studies, in less advanced COPD, disease-specific health status measured using the SGRQ (17, 18) was a predictor of mortality, but another disease specific measure for COPD (the Chronic Respiratory Questionnaire) did not predict death (18).

The predictive validity of health status questionnaires found in our study is compatible with the large body of evidence concerning the validity of these instruments which correlate with a range of physiological measures including exercise performance, arterial PaO2, respiratory symptoms, disability, exacerbation frequency and psychological status (44). They provide comprehensive coverage of numerous different effects of chronic respiratory disease, so it is not surprising that they also relate to mortality, which can be the end-result of a number of different patho-physiological processes. The determinants of mortality appear to differ, depending on the severity of the underlying disease, only FVC and disease-specific health status measurements appear to be consistent predictors across different levels of severity.

Health status measurements are now widely used in chronic respiratory diseases and there is a large body of data concerning their use. In our study, carried out in patients with a high risk of mortality, a 4-unit difference in baseline SGRQ score [the minimum clinically important difference (28)] was associated with a 8% difference in one-year mortality even after age and oxygen flow at rest were taken into account. In milder patients, with approximately half the mortality rate, a 4-unit difference score was associated with a 5.1% difference in risk of death (17). Thus the clinical significance of differences in SGRQ score, at least in terms of its relationship to mortality, may depend on the underlying severity of the disease.

In terms of mortality rate, in our cohort involving patients with chronic respiratory failure and COPD, the three year cumulative survival rate was 80.5%, which was higher than the 2-year survival rate of patients in other studies (45–49).

Limitations: the use of thresholds to identify subjects with higher or lower risk of mortality is promising but probably not enough. Therefore, we are planning a new study with a higher number of subjects in order to divide

patients into tertiles to identify a possible dose-response relationship.

Conclusion

This study has shown that in patients with respiratory failure, health status measurements predict mortality independently of age, supplemental oxygen requirements and vital capacity impairment. This study supports the use of an integrative multifaceted evaluation of CRF prognostic factors that should include health status along with the more conventional outcome measures such as physiological or clinical variables.

List of Abbreviations

ABGs	=	arterial blood gases
ANOVA	=	analysis of variance
BMI	=	body mass index
CI	=	confidence interval
COPD	=	Chronic Obstructive Pulmonary Disease
CRF	=	Chronic Respiratory Failure
FEV_1	=	forced expiratory volume in 1 second
FVC	=	forced vital capacity
HAD	=	Hospital Anxiety and Depression Scale
HR	=	hazard ratio
HMV	=	overnight home mechanical ventilation
LTOT	=	Long-Term Oxygen Therapy
MRC	=	Medical Research Council
MRC-dyspnea	=	Medical Research Council dyspnea scale
MRF26	=	Maugeri Foundation Respiratory Failure Questionnaire
MRF26-Total	=	Maugeri Foundation Respiratory Failure Questionnaire, total score
O_2-rest	=	oxygen flow rate required at rest
$PaCO_2$	=	arterial carbon dioxide tension
PaO_2	=	arterial oxygen tension
PFTs	=	pulmonary function tests
QuESS	=	Quality of Life Evaluation and Survival Study
ROC	=	Receiver-operating characteristics
SF36	=	Medical Outcome Study Questionnaire, short form 36 items
SF36-MCS and SF36-PCS	=	SF36 mental and physical component summary scores
SGRQ	=	St. George's Respiratory Questionnaire
SGRQ-Total	=	St George's Respiratory Questionnaire, total score
SWT	=	shuttle walking test
VO_2max	=	peak oxygen uptake

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Declaration of Interest Statement

None of the authors had involvement in any organization with direct financial interest in the subject of the manuscript.

Mauro Carone, conceived and designed the project and wrote the paper; Sabina Antoniu, partly analyzed and interpreted the data, partly wrote the paper and revised it; Paola Baiardi, performed statistical managing and analyzed the data, and partly wrote the paper; Vincenzo S. Digilio, partly interpreted the data, wrote the paper and revised it; Paul Wyatt Jones, conceived, designed and supervised the project, partly wrote the paper and revised it; Giorgio Bertolotti, conceived and designed the project, partly wrote the paper and revised it.

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