



Editorial

Causes of Death and Prediction of Mortality in COPD

Causas de muerte y predicción de mortalidad en la EPOC

Ingrid Solanes García^{a,*} and Pere Casan Clarà^b

^aHospital de la Santa Creu i de Sant Pau, Universidad Autónoma de Barcelona, Barcelona, Spain

^bInstituto Nacional de Silicosis (INS), Hospital Universitario Central de Asturias, Oviedo, Spain

Chronic Obstructive Pulmonary Disease (COPD) is a disease with high prevalence and that produces great morbidity and mortality worldwide.¹⁻⁴ The IBERPOC epidemiological study⁵ found that the prevalence of COPD in Spain was 9.1% in subjects aged 40-69 years (with differences by region). However, the diagnostic criteria used 10 years ago were not those established in the current GOLD guidelines.⁶ COPD, which in 1990 was the fifth leading cause of death in the world, became the fourth leading cause in 2000, and is estimated to rank third in 2020.⁷ It is also important to remember that it is an underdiagnosed disease⁵ and there were very few therapeutic options until the last few years.

Although the target organ is the lung, its impact can be multiorganic^{6,8,9} meaning that it can affect any tissue, either by hypoxia and/or hypercapnia, systemic inflammation or physical inactivity secondary to the dyspnea these patients suffer. In advanced stages of their disease patients show impairment in general physical condition, their health-related quality of life, and their ability to perform activities of daily living. Furthermore, survival is clearly reduced as compared to the general population.

Global mortality at 4-7 years in COPD patients at a mean age of 65-70 years, ranges from 30-48%¹⁰⁻¹³ and mostly depends on the severity of the disease at the time of diagnosis. Domingo-Salvany et al.¹⁰ found a mortality of 33% in a group of 303 patients diagnosed with COPD [forced expiratory volume in one second (FEV₁) (± SD) of 45 (± 18)%], and followed up for an average period of 4.8 years. Solanes et al.¹¹ found a mortality of 47% in a 7-year follow up of 60 COPD patients (FEV₁ 35 [± 14]%). Recently, Moreno et al.¹⁴ found that mortality at 1, 3 and 5 years was 20%, 47% and 74% respectively in a retrospective analysis of 203 COPD patients (FEV₁ 31 [± 8]%), with a median follow-up period of 38 months. Other authors have detected greater mortality but have analysed patients with more advanced disease. Martinez et al.¹² followed a group of patients with emphysema and severe airflow limitation (FEV₁ 27 [± 7]%) for a mean of 3.9 years and found a mortality of 48%.

The main cause of death is evolution of the disease. Between 50-80% of COPD patients in our area¹⁰⁻¹⁴ die from respiratory causes either due to exacerbation (30-50%) of COPD itself, lung neoplasm (8.5 to 27%) or other causes of respiratory origin. In initial stages of the disease, a greater proportion of the causes of death are of non-respiratory origin, although the majority are related with tobacco consumption, above all cancer and vascular diseases (ischemic heart disease and stroke).

The prognosis of this disease has been widely studied and is related to multiple factors. Identifying a prognostic factor is important so that it can be acted upon, either through prevention or therapeutic management. For this reason, we classify them into two groups: those which belong to the individual and those which can be modified using therapeutic interventions.

Most studies for the first group have detected an increase in the relative risk of death based on age: Anthonisen et al.,¹⁵ Nishimura et al.,¹⁶ Domingo-Salvany et al.,¹⁰ Oga et al.¹⁷ and Solanes et al.¹¹ described a statistically significant relative risk of death of 1.058, 1.12, 1.06, 1.09 and 1.108, respectively, for each successive year of age. Martinez et al.¹² detected an increase in relative risk of 1.56 (95% CI: 1.23-2.32) among those older than 70, in comparison to those who had not reached that age (p<0.0001). In contrast, the Ries et al.¹⁷ group did not detect an age-related increased risk, although that study calculated risk in 5-year blocks. Bowen et al.¹⁸ detected a tendency towards age-related death but failed to reach statistical significance (p = 0.08). In any case, age is not a modifiable factor, so identifying it as a prognostic factor probably has little relevance in clinical practice.

The degree of functional alteration and, especially, the degree of airflow obstruction, have also been widely studied and most cases have been related with mortality.¹¹⁻¹⁷ In different studies, the relative risk of death for each 1% increase in FEV₁ varies between 0.94-0.97%. In the study by Ries et al.,¹³ risk was calculated per 100ml increase in FEV₁, finding a relative risk of 0.84. Schols et al.¹⁹ found no increased relative risk of death by changing FEV₁, having adjusted the analysis for age, BMI and arterial partial pressure of oxygen (PaO₂). The Anthonisen group¹⁴ analysed baseline and postbronchodilator FEV₁ and although both were able to predict survival, the postbronchodilator test was more significant. Other lung function variables have been

*Corresponding author.

E-mail address: isolanes@santpau.cat (I. Solanes Garcia).

related to survival. Inspiratory capacity²⁰ and the inspiratory capacity-to-total lung capacity have proven to be independent prognostic factors for predicting survival in COPD patients.^{12,21}

Furthermore, bronchial hyperreactivity seems to be a poor prognosis factor. Hospers et al.²² followed 2,008 individuals who had had a bronchial challenge test with histamine for 30 years. Mortality in the COPD patient group was related to the degree of bronchial hyperreactivity, i.e. the relative risk of death increased when a lower concentration of histamine was needed to trigger a positive bronchial provocation test response, for those patients which had negative test responses. In either case, the group of patients with a positive histamine test would benefit most from treatment with inhaled corticoids and, therefore a pharmacological intervention on this group of patients could improve their prognosis.

COPD is associated with an inflammatory response of the lungs to noxious agents⁶ and is a disease that usually involves frequent exacerbations and hospital re-admissions. Exacerbations and re-admissions are independent factors for predicting mortality, and as such, mortality increases when the severity and frequency of these exacerbations increases.^{23,24} This inflammation occurs not only locally but there appear to be systemic manifestations that play an important role in the pathogenesis of the disease.⁸ The most widely used biomarker to evaluate systemic inflammation is increased PCR found in some COPD patients,²⁵ and this has also proven to be an independent mortality predictor for this disease.²⁶

Some studies have shown a poorer prognosis for patients that started with a low BMI.^{15,17,27} Landbo et al.²⁸ showed a poorer prognosis in patients with a low BMI when associated with a marked degree of functional alteration. On the other hand, Bowen et al.,¹⁸ Domingo-Salvany et al.¹⁰ and Solanes et al.¹¹ found no increased relative risk associated with BMI, but in these three studies, the mean BMI was significantly higher than those in previous studies. Marquis et al.²⁹ and Schols et al.³⁰ found that muscle mass loss or fat-free mass loss worsened the prognosis of the disease even more so than weight loss.

We measured health-related quality of life and dyspnea, and we quantified them with various questionnaires and not all seemed to predict survival equally. The Chronic Respiratory Disease Questionnaire did not seem to be sensitive enough to predict survival,¹¹ although the area of dyspnea is the best that could be used for this purpose.¹⁶ Other questionnaires, such as the St. George's Respiratory Questionnaire,^{10,12,17} the Breathing Problems Questionnaire,¹⁷ or the modified Fletcher 5-point dyspnea scale¹⁶ have shown to be better at predicting mortality.

Submaximal and maximal exercise tolerance have been shown to have power in predicting survival. There is controversy regarding which of the various tests is the most ideal for this purpose. Bowen et al.¹⁸ detected that submaximal exercise tolerance, evaluated with a 6-minute walk test (6-MWT) after a breathing rehabilitation program, was better at predicting survival than before such a program had been performed. Casanova et al.³¹ also detected that in addition to desaturation during the test, the risk of death increased even more. Oga et al.¹⁷ and Solanes et al.¹¹ detected that the variables related with the maximum stress test were the best for predicting survival. Cote et al.³² specifically compared the 6-MWT test with minute ventilation during stress testing and found that the 6-MWT test had greater predictive power of mortality than the minute ventilation during maximal testing.

Given that various parameters have been proven to be able to predict survival, some authors have worked to find an index that combines the various factors. Celli et al.³³ described the BODE index which includes: BMI, the degree of airflow obstruction measured using FEV₁, degree of dyspnea using the Medical Research Council scale, and exercise capacity measured with the 6-MWT test. The score obtained showed that this index would be better at predicting prognosis for the disease than each factor separately. Furthermore, in

the case of equal scores on this index between men and women, survival in women is greater.³⁴ Once this index was described, small modifications were proposed to ensure that they are at least as good at predicting survival. Cote et al.³⁵ replaced the 6-MWT test with peak oxygen consumption during the maximal stress test (mBODE). The value for predicting mortality using the new index was not greater than the BODE index, but it was more difficult to obtain. In an attempt to simplify the BODE index, Soler-Cataluña et al.³⁶ replaced the 6-MWT test (difficult to achieve in primary care patients) with recording the frequency of exacerbations and described the BODEX, which is able to predict mortality as well as the classic BODE index. There are also other indices that are good predictors. The "COPD Prognostic Index" is a 100-point scale that is not only able to predict mortality but also exacerbations and hospital admissions.³⁷ Puhan et al.³⁸ recently described and analysed the ADO index which includes age, dyspnea and airflow obstruction. This index appears to be useful as a prognostic factor in COPD patients and is easier to obtain than the earlier indices.

Since the BODE index was published in 2004,³³ professionals who treat and research the disease are in search of the index that best predicts survival, by combining several variables. However, they fail to consider that the maximal stress test alone gives us a great deal of information. The result of this test is influenced by all the remaining variables: age, BMI, dyspnea, exercise tolerance, the degree of training, the degree of muscle atrophy, cardiovascular fitness, the degree of airway obstruction, air trapping and, ultimately, the degree of functional reserve. However, this test is not used very often, which has been justified by the fact that it is not available in many health centres, but isn't it true a cardiologist's work could never be understood without stress testing? Why do we pulmonologists accept this and not give stress testing the importance it has to our patients?

Modifiable factors through therapeutic interventions is also found in literature. There are two classic studies that showed that oxygen therapy improved COPD patient survival in terms of respiratory failure and other certain characteristics.^{39,40} The first³⁹ showed that continuous oxygen, 24 hours a day, improved survival more than 12h overnight use. The second⁴⁰ established a minimum of 15h of oxygen per day in patients with intense hypoxemia and cor pulmonale. In patients with moderate hypoxemia (PaO₂ 56-65mmHg), home oxygen therapy has been shown to improve survival.⁴¹ Respiratory rehabilitation in the stable phase has been shown to improve certain survival-related parameters,⁴² especially in relation to the quality of life, dyspnea, exercise tolerance and therefore also the BODE index.⁴³ Nonetheless, there are no conclusive studies that show that respiratory rehabilitation in the stable phase improves survival.⁴² This is probably because studies with this aim do not have a large enough sample of patients and because there is lack of continuity in these programs, meaning that when the program is not completed, the effect is lost. Respiratory rehabilitation programs after exacerbations may have a beneficial effect on mortality. Puhan et al.,⁴⁴ in a meta-analysis, included six studies with a total of 230 patients after an acute exacerbation of their disease, and found a decrease in mortality in those who had entered a rehabilitation program, with an extrapolated relative risk of 0.45 (95%CI 0.22 to 0.91).

Most of the studies carried out to determine the effect of the various drug treatments on mortality are financed by the pharmaceutical industry. The TORCH study⁴⁵ evaluated treatment with salmeterol and fluticasone propionate in COPD patients and included a 3-year follow-up showed a reduction in lung function decline in the group treated with the two drugs compared to a placebo group. Although there was a tendency for the combination group to have a better survival rate, it failed to reach statistical significance ($p = 0.052$).⁴⁶ Subsequently, the UPLIFT study⁴⁶ evaluated COPD survival in patients treated with tiotropium versus placebo and included a follow-up of 4 years. At 4 years, at which time

information was obtained from more than 95% of participants, there was better survival among the tiotropium-treated group in comparison with the control group (Relative risk 0.87, 95% CI 0.76-0.99). However, at 4 years and 30 days (although information had been lost regarding a good many of the patients), the difference between both groups in terms of mortality failed to reach statistical significance. The INSPIRE study⁴⁷ looked at COPD patients who were followed for 2 years and compared tiotropium bromide treatment with salmeterol/fluticasone propionate treatment. Although the study was not designed specifically to evaluate differences in mortality and therefore the results should be interpreted with caution, it showed a small, statistically significant difference in survival for those treated with salmeterol-fluticasone.

When considering drug treatments, special attention should be given to the study of the effect that statins have on prognosis of the disease, due to their systemic immunomodulatory and anti-inflammatory effects. A recent meta-analysis⁴⁸ showed that statins may reduce morbidity and/or mortality in COPD patients. In any case, more controlled studies are needed to verify this claim.

Survival (amount), as with other illnesses, is very important in COPD and all variables that allow us to predict and quantify survival are of great interest. Those with the greatest predictive power are probably those that include exercise capacity (maximal or submaximal), measuring the functional reserve of the organism (respiratory, cardiac, or metabolic). Although survival, as we have seen, has been widely studied, it probably should not be the only concept that should be considered when evaluating COPD. The way patients live from diagnosis and the limitations that the disease introduces into daily life (quality of life) are elements that can and should be quantified and should also be part of COPD research. Just as the ancient Greeks had two words to define "time", we should add to the merely chronicle of survival (*chronos*), the quality of life lived (*kairos*). *Chronos* and *kairos*, always at both extremes of the ever-present *Chronos*.

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