REVIEW ARTICLE

Prognostic Factors in Chronic Obstructive Pulmonary Disease

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Efforts over the last few decades to extend the life expectancy of patients with chronic obstructive pulmonary disease (COPD) have faced difficulties, but our perception of the problems involved is now starting to change. Improvements in our understanding of the pathogenic and etiological mechanisms of the disease, analysis of the causes of death, and, in particular, identification of the relevant prognostic factors have resulted in firm advances that allow us to face the future with greater optimism. The aim of this review is to provide a detailed analysis of the chief prognostic factors described in the literature and to evaluate the therapeutic implications of these findings. The traditional view maintained that the accelerated decline over time in forced expiratory volume in 1 second was one of the best predictors of mortality, and this belief has for decades determined the strategies used to treat COPD. However, we now know COPD to be a multidimensional disease and are aware that some of its other manifestations have important prognostic implications. Lung hyperinflation, exercise tolerance, exacerbations, comorbidity, and systemic manifestations—in particular those related to the cardiovascular system—have all been shown in recent years to be strong predictors of mortality. The inflammatory substrate, whether local or systemic, merits special consideration because it appears to be the cause of many of these manifestations. These newly identified prognostic factors are of great interest in that it may be possible to moderate their influence, a circumstance that highlights the need to change the traditional treatment approach and devise therapeutic interventions oriented towards reversing the effects of these factors.

Key words: *COPD. Prognostic factors. Predictors of mortality.*

Factores pronósticos en la EPOC

Prolongar la supervivencia de los pacientes con enfermedad pulmonar obstructiva crónica (EPOC) es, y ha sido durante décadas, un objetivo complicado. Sin embargo, poco a poco esta percepción empieza a cambiar. De la mano de un mejor conocimiento etiopatogénico de la enfermedad, del análisis de las causas de muerte y sobre todo de la identificación de diversos factores pronósticos, se van dando pasos firmes que permiten afrontar el futuro con mayor optimismo. La presente revisión pretende analizar de forma pormenorizada los principales determinantes pronósticos que se han descrito en la literatura médica y valorar sus posibles implicaciones terapéuticas. Tradicionalmente se ha aceptado que el volumen espiratorio forzado en el primer segundo y su descenso acelerado a lo largo del tiempo era uno de los mejores predictores de mortalidad. Este hecho condicionó durante décadas el objetivo terapéutico en la EPOC. Sin embargo, hoy sabemos que la EPOC es una enfermedad con múltiples dimensiones, algunas de las cuales tienen importantes consecuencias pronósticas. La hiperinsuflación pulmonar, la tolerancia al esfuerzo, las exacerbaciones, la comorbilidad y las manifestaciones sistémicas, especialmente las resultantes de la esfera cardiovascular, son dimensiones que en los últimos años se han revelado como potentes predictores de muerte. El sustrato inflamatorio, tanto local como sistémico, parece estar detrás de muchas de estas manifestaciones y por ello merece especial consideración. Estos nuevos factores pronósticos tienen la virtud de ser potencialmente modificables, lo que subraya la necesidad de planificar intervenciones terapéuticas orientadas a revertir sus efectos cambiando de alguna forma la estrategia tradicional.

Palabras clave: *EPOC. Factores pronósticos. Predictores de mortalidad.*

Introduction

For decades we have been resigned to the idea that little or nothing could be done to slow down disease progression and reduce mortality in patients with chronic obstructive pulmonary disease (COPD), but fortunately this attitude is now starting to change. Improvements in our understanding of the pathogenic and etiological mechanisms of the disease, analysis of the main causes of death, and, in particular, identification of the relevant prognostic factors have resulted in firm advances that allow us to face the future with greater optimism. The circumstance that may have most influenced this change of perspective has been the realization that, apart from lung function and the most important parameter used to test this aspect of the disease (forced expiratory volume in 1 second [FEV_1]), COPD also comprises other, potentially modifiable, components that exercise considerable prognostic influence. The discovery that COPD is a chronic inflammatory disease with systemic implications, the identification of its relationship with the cardiovascular system, the consideration of the importance

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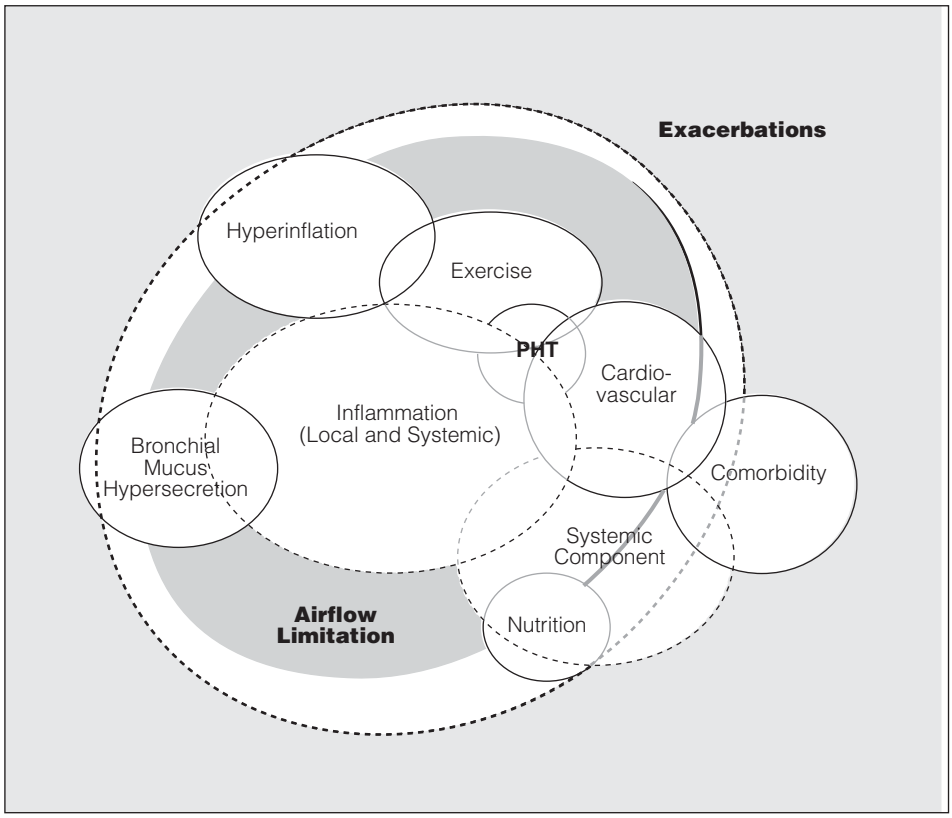

Figure 1. Schematic representation of the chief prognostic dimensions in COPD. Airflow limitation is one of the mechanisms with the greatest influence on survival. This central mechanism is surrounded by various disease components that have prognostic implications, many of which are interrelated. Inflammation, both local and systemic, may be the pathogenic substrate that links these different dimensions. PHT indicates pulmonary hypertension.

of comorbidity, and recognition of the important role played by exacerbations are some of the factors that, in our opinion, form part of this conceptual shift. The aim of this review is to provide a detailed analysis of the chief prognostic factors described in the literature and to evaluate the therapeutic implications of these findings. For practical purposes, we have divided these prognostic factors into those that are not modifiable and those—much more interesting from a therapeutic standpoint—that can be modified. The modifiable factors are grouped according to their relationship to the different dimensions of the disease (Figure 1).

Nonmodifiable Prognostic Factors

Age

Studies both of patients with stable COPD[1-4] and exacerbations[5-7] have found that older age is inevitably associated with an increase in mortality, a logical correlation not only in COPD but also in any disease. From the point of view of therapy, this association is perhaps of scant clinical importance. From a methodological standpoint, however, it means that all analytical models should be stratified and adjusted by age. The fact that comorbidity usually increases with age could, for example, be interpreted as evidence of some degree of interaction. However, even after adjustment for age, comorbidity remains an adverse prognostic factor.[7]

Recently, several authors have indicated that other, potentially modifiable, age-related factors, such as social support, physical disability, depression, and quality-of-life, could be responsible for the adverse prognostic effect attributed to age.[8] In a study undertaken to identify predictors of mortality following hospitalization, Almagro et al[9] observed that age had prognostic value in the univariate analysis, but that this effect disappeared in the multivariate analysis when other dimensions, such as social support, physical disability, depression, and quality of life, were included.

Sex

COPD has always been more common among men than women. However, in recent years we have witnessed a steady increase in the prevalence of this disease among women, particularly in Western countries, a development directly linked to the increase in the prevalence of smoking in this group. However, some of the data reported in the literature indicate that women may actually be more susceptible to developing COPD,[10-12] and to greater severity and higher mortality when they do.[13] While women live longer than men in population-based studies,[14] the situation may be different among patients with COPD. The authors of a recent study of COPD patients receiving long-term oxygen therapy (LTOT) in the home observed that the women were, in general, younger and that their cigarette consumption tended to be lower than that of

the men.[13] After adjustment for potential confounding variables, the relative risk of death among women in that study was 54% compared to the men. While other researchers have reported similar findings,[15] not all the data in the literature are consistent on this point.[16-18] Although the debate is still open, the author of a recent opinion article discussing the origins of possible sex differences in this context suggested that these may be linked to differences relating to certain systemic complications of COPD, such as muscle dysfunction and depression.[19] The evidence shows that women with COPD are almost 3 times more likely to suffer depression than men who have the disease (38% compared to 13%)[20] and lose twice as much fat-free mass (40% as compared to 20%).[21]

Potentially Modifiable Prognostic Factors

Smoking

Smoking is by far the most important risk factor for developing COPD,[22] and it gives rise to respiratory symptoms, lung function abnormalities, and higher mortality.[23-25] Exposure to smoke from biomass fuel combustion (for example, wood smoke) has also been identified as a factor in the pathogenesis of COPD in developing countries,[26] and a recent study found mortality among patients exposed to biomass smoke to be similar to that among smokers.[27] Despite this evidence, few studies have found smoking or wood smoke exposure to play a direct role as a predictor of mortality. Oga et al[2] observed a relationship between cumulative tobacco consumption (pack-years) and mortality in a univariate analysis. However, they observed no association between smoking status at baseline and mortality, a finding consistent with the results of other studies.[3] The observed lack of effect may possibly be the result of a statistical bias because baseline smoking status is a parameter that can change at any time and many smokers quit precisely when the disease reaches its most critical phase.

Pulmonary Factors

Forced expiratory volume in 1 second. COPD is defined as "a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases."[22,28] Since FEV_1 is the parameter that best reflects airflow limitation it is not surprising that many studies have shown both baseline FEV_1 values and the annual decline in lung function to be strong predictors of mortality and morbidity in COPD.[1,29-32] These findings have strengthened the concept of a natural history characterized by an accelerated decline in lung function over time—a model first proposed by Fletcher et al[33] and later expanded on by Burrows and Earle.[29] For decades, the treatment of COPD has been guided by this model, and the chief aim of therapy has been to modify disease progression and mortality by way of approaches devised solely with the aim of limiting functional decline. Of all these interventions, smoking cessation is the only one that has been shown to attenuate lung function decline and reduce mortality; in the Lung Health Study, Anthonisen et al[25,34] confirmed that smoking cessation slowed down annual decline in FEV_1[34] and had a favorable effect on survival.[25] In a large cohort of patients with mild COPD followed for almost 15 years, they observed that those who received conventional treatment had a relative risk of death of 1.18 (95% confidence interval [CI], 1.02-1.37) compared to those who took part in a tobacco cessation program. Mortality was also lower in the intervention group when the results were analyzed by specific cause of death, but the difference was only significant in the case of respiratory death unrelated to lung cancer (1.08 compared to 0.56 per 1000 population and year, P=.01).

The fact that COPD is considered to be a chronic inflammatory disease and the existence of an association between this local inflammation and the degree of functional impairment[35] led in the 1990s to a number of clinical trials that evaluated the influence of inhaled corticosteroids on the annual decline in FEV_1.[36-39] None of these trials demonstrated a statistically significant effect, although a later meta-analysis found a scant, but nonetheless significant, reduction of 7.7 mL/year (95% CI, 1.3-14.2; P=.02).[40]

Lung function is, unquestionably, a key component in our overall understanding of the mechanisms and progression of COPD. However, since very little has been achieved by research into this aspect of the disease, a new analysis of the situation is required. In this respect, it is interesting to note that morbidity and mortality differ in patients with a similar degree of functional impairment[41] and that a whole series of previously unexplored variables have now been shown to predict mortality independently of lung function. These include the body mass index (BMI),[18,42] dyspnea,[4] exercise capacity,[2,43] hyperinflation,[44] quality of life,[45] exacerbations,[3] systemic inflammation,[46] and several multidimensional indexes.[47] Moreover, it is interesting to note that some of these variables have even greater predictive capacity than FEV_1.[2,3,44,47] This new line of investigation has changed our expectations and obliges us to reinterpret our concept of the natural history of COPD.

Bronchial hyperresponsiveness. Few studies have studied the possible association between nonspecific bronchial hyperresponsiveness and mortality in patients with COPD. Hospers et al[48] monitored a population-based cohort of 2008 participants in 3 towns in the Netherlands for almost 20 years. During this period, 526 participants died. Mortality due to COPD was higher among patients with severe histamine airway hyperresponsiveness, and this risk was independent of sex, age, smoking status, lung function, and BMI, among other variables of interest. The strong association between bronchial hyperresponsiveness and lumen diameter makes lung function a confounding variable in these studies. In the opinion of Vestbo and Hansen,[49] the Dutch study failed to adequately adjust histamine

hyperresponsiveness for lung function because the authors used only 3 categories to stratify by FEV_1: greater than 100%, 80% to 100%, and under 80%. This third category appears very broad, and undoubtedly bronchial hyperresponsiveness may vary within this group depending on lumen diameter.

Lung hyperinflation. The loss of elastic recoil and the onset of expiratory airflow limitation give rise to progressive air trapping evidenced by an increase in end-expiratory lung volume and a reduction in inspiratory capacity (IC). This static lung hyperinflation and its increase during exercise (dynamic hyperinflation) have been associated with dyspnea, exercise intolerance, and limitations in the functional capacity of these patients.[50,51] However, it was not until very recently that the prognostic implications of this parameter were recognized. In a recent study of 689 outpatients with COPD, Casanova et al[44] observed that the presence of static hyperinflation—expressed as the ratio of IC to total lung capacity (IC/TLC)—was an independent predictor of mortality in COPD. On follow-up at 5 years, mortality in the group with an IC/TLC of 25% or less was 71%, as compared to 29% in the group of patients with a higher IC/TLC. Martínez et al[41] also observed that mortality was higher among patients with a higher residual volume and they found a similar tendency among patients with a lower IC/TLC. Other authors have found hyperinflation expressed as the ratio of residual volume to TLC to have predictive value.[4] However, the results are inconsistent when absolute IC values are used. In a longitudinal study, Schols et al[52] found no prognostic significance when they analyzed the prognostic value of resting IC as a percentage of predicted. In another study, Celli et al[47] did not find absolute values of IC or any other lung volume measurement to have predictive value.

The mechanisms underpinning the association between air trapping and mortality are currently poorly understood. However, we might at least speculate that a certain beneficial effect could be expected following a therapeutic intervention. Hyperinflation, whether static or dynamic, can be influenced by both surgery and pharmacotherapy. The National Emphysema Treatment Trial was a multicenter study undertaken to evaluate the impact of lung-volume-reduction surgery on survival among patients with very severe COPD.[53] In general terms, the study failed to demonstrate the superiority of the surgical intervention over conservative treatment. However, a significant reduction in mortality was observed after surgery in the group of patients with upper-lobe emphysema and low exercise capacity.[53] Various drugs have been shown to reduce air trapping to a greater or lesser degree,[54,55] but it not known whether this outcome is associated with any beneficial effect on prognosis. The Understanding the Potential Long-Term Impact on Function with Tiotropium (UPLIFT) study is currently monitoring almost 8000 patients for 3 years.[56] Although lung function is still the primary outcome measure of that study, the protocol does envisage an analysis of survival and the results are awaited with great interest.

Gas exchange. It has been accepted for decades that LTOT prolongs survival in patients with advanced COPD and severe hypoxemia (baseline PaO_2<55 mm Hg). The evidence supporting this view comes from the results of 2 large controlled trials carried out in the early 1980s: the Medical Research Council trial[16] in Britain and the Nocturnal Oxygen Therapy Trial in the United States of America.[17] In both of these trials, survival was better among patients who received LTOT for at least 15 hours a day, and it has been suggested that this improvement could be related to the prevention or stabilization of pulmonary hypertension.[57-59] However, the life expectancy of patients with COPD receiving supplemental oxygen was low, with a 5-year survival rate of approximately 40%,[17] and this treatment was not shown to have any beneficial effect among patients with moderate hypoxemia.[60] The fact that LTOT improves survival could, on the basis of logic, indicate that mortality is higher among patients with severe hypoxemia, but the results in the literature are inconsistent on this point. In studies that took place before LTOT was in general use, hypoxemia and hypercapnia were reported to be strong prognostic indicators,[30,61,62] but more recent studies have not found this association.[15,41,63,64] While it would initially seem logical to attribute this change to the beneficial effect of oxygen therapy, the emergence of new confounding variables, such as comorbidity and exercise capacity, may also have influenced these results. Surprisingly, the administration of LTOT is predictive of a poor prognosis in some case series.[3,41] This may be because it is an epimarker of severity, but this finding perhaps merits greater attention. Most patients who receive LTOT are very inactive, and the authors of a recently published study found a low level of physical activity to be associated with the worst prognosis.[65]

The presence of hypercapnia is also generally considered to be indicative of a poor prognosis in chronic respiratory diseases, especially COPD,[3,16,29,66,67] but this point is still the subject of debate.[15,63,64,68] Some researchers have suggested that hypercapnia could, in certain patients, be an adaptive mechanism that facilitates a reduction in the energy expended on ventilatory work at the expense of high resting $PaCO_2$.[69] A distinction should perhaps be made between progressive hypercapnia caused by respiratory insufficiency and adaptive hypercapnia.

Chronic pulmonary hypertension and cor pulmonale. In patients with COPD, the presence of pulmonary arterial hypertension has traditionally been associated with a lower survival rate,[30,70] to the point that an increase in mean pulmonary artery pressure of 10 mm Hg is associated with a fourfold increase in the risk of death.[71] Most of the prognostic studies that have evaluated the role of pulmonary hypertension were carried out before the introduction of LTOT. LTOT could potentially stabilize pulmonary artery pressure and even slow down the progression of pulmonary hypertension,[57-59] in which case a beneficial effect would be expected. However, in a study of 84 patients receiving supplemental oxygen, Oswald-Mammosser et al[72] found

a 5-year survival rate of 15% in the group of patients with pulmonary artery pressure above 30 mm Hg and 63.9% among those with lower pulmonary artery pressure. It is interesting to note that FEV_1, hypoxemia, and hypercapnia had no predictive value in this study. More recently, Burgess et al[73] also demonstrated the importance of pulmonary hypertension and ventricular dysfunction in determining prognosis when they found a worse prognosis among patients with echocardiographic markers indicative of right ventricular dysfunction. Incalzi et al[74] found similar results in patients with electrocardiographic signs of right ventricular hypertrophy or right atrial overload. An S_1-S_2-S_3 pattern was the sign of chronic cor pulmonale most predictive of mortality. This pattern is associated with the presence of acute pulmonary embolism, and it has been suggested that it is indicative of, but not specific to, chronic cor pulmonale. It is, however, also associated with hyperinflation.[74]

Exercise. Exercise capacity can be affected by a series of complex and important factors, including ventilation, gas exchange, circulation, muscle function, nutritional status, and disease symptoms.[75] As most of these factors have been reported to be prognostic variables, a logical inference would be that exercise capacity itself could be one of the most powerful prognostic indicators.[4,16,17,42,44,72,73] In a study of 150 patients with moderate-to-severe COPD, Oga et al[2] found that exercise capacity—measured by determining maximum oxygen uptake—was not only significantly associated with mortality independently of lung function, but was also the best predictor of mortality in their cohort. Moreover, those authors observed that exercise capacity, like lung function, deteriorated over time in these patients, a finding that contributes new information to the traditional concept of the natural history of COPD.[76]

The 6-minute walk test—probably a test of submaximal effort and a more accurate reflection of daily physical activity—has also been shown to be a good predictor of mortality.[43,47,77] In fact, a close correlation has been reported between maximum oxygen uptake and 6-minute walk distance.[78] Pinto-Plata et al[43] observed a 1-year mortality rate of over 80% among patients with a 6-minute walk distance under 100 meters. This test has recently been incorporated into a multidimensional prognostic scale together with lung function, dyspnea, and nutritional status,[47] and in that study 6-minute walk distance was the variable with the greatest predictive value. It has been reported that 6-minute walk distance, like maximum oxygen uptake, declines over time in these patients, and that this decline is particularly marked among those with severe disease.[79]

Symptoms

Chronic bronchial hypersecretion. The importance of chronic mucus hypersecretion as a predictor of survival has been the subject of some debate. While some studies found no association,[33,80,81] others have reported an adverse effect on both all-cause mortality[82,83] and COPD mortality.[84,85] Of all these studies, perhaps the one that has provided most information is the Copenhagen City Heart Study. The original cohort included in that study comprised some 90 000 inhabitants of the city, of whom 3677 were over 65 years of age.[85] The prevalence of chronic mucus hypersecretion reported for the whole cohort was 8.2% among women and 12.5% among men. In the group over 65 years of age, chronic mucus hypersecretion was found to be an independent predictor of death from obstructive lung disease and lung cancer (with a relative risk of 2.5 and 2.0, respectively). Among the patients in whom it was possible to measure FEV_1 repeatedly during the 15-year observation period, no association was found between chronic mucus hypersecretion and accelerated decline of lung function in this older cohort. However, in an earlier study of a sample group of younger individuals from the Copenhagen City Heart Study, this variable was found to predict rapid decline in FEV_1.[86] By contrast, a strong association was observed between chronic mucus hypersecretion and the incidence of respiratory infections. Using data from the same cohort, Prescott et al[87] established an association between chronic mucus hypersecretion, pulmonary infection, and mortality. Those authors suggest that hypersecretion may only play a significant role in patients with severe or terminal COPD.

Dyspnea. Dyspnea is a subjective sensation of difficulty in breathing caused by a complex set of multifactorial mechanisms. These derangements usually involve the respiratory control system, neuromechanical receptors, ventilation, the respiratory musculature, and abnormalities in gas exchange, among other mechanisms.[88] Since dyspnea is a multifactorial clinical manifestation, it can perhaps provide prognostic information. In a study of 227 patients with COPD followed prospectively for 5 years, Nishimura et al[4] demonstrated that grade of dyspnea—measured using the Medical Research Council scale—was a stronger predictor of mortality than staging of disease severity on the basis of lung function. Compared to grade II dyspnea, the relative risk of death was 2.21 (95% CI, 0.93-5.27) for grade III, 8.31 (95% CI, 3.41-20.27) for grade IV, and 61.3 (95% CI, 13.2-285.4) for grade V. Other authors have reported similar findings, although only in the univariate analysis.[41]

Health-Related Quality of Life

The use of generic and specific questionnaires to measure health-related quality of life is a practice that has become much more widespread in recent years. Several studies have related measures of health status with disease severity,[89-91] exacerbations,[92,93] and survival[2,45,94] in these patients. In a cohort of 321 men with COPD, Domingo-Salvany et al[45] found that both the 36-item Short Form Survey, a generic instrument for evaluating health status, and the St George's Respiratory Questionnaire (SGRQ), a disease-specific questionnaire for evaluating health-related quality of life in patients with COPD, were

independently associated with both overall and respiratory mortality. For each 4-point increase on the total SGRQ score, they observed that the risk of death from all causes increased by 5.1% (95% CI, 0.97%-9.4%) while respiratory mortality increased by 12.9% (95% CI, 4.5%-22%). Other authors have reported similar results.[2,94] By contrast, the usefulness of the total score on the Chronic Respiratory Disease Questionnaire as a predictive variable is less clear,[2,95] with some authors reporting no evidence of a prognostic relationship and others finding an association.[96]

Exacerbations

Exacerbations were for decades regarded as mere epiphenomena in the natural history of COPD. However, recent evidence indicates that, quite to the contrary, exacerbations have a negative effect on disease progression and mortality.[97] Several studies have reported a marked increase in mortality after hospitalization.[5,6,9,98] In a study of 1016 patients hospitalized for hypercapnic respiratory insufficiency, Connors et al[5] observed a mortality rate at 1 year of 43%. Other later studies enrolling patients with less severe disease found mortality rates at 1 year of 22% to 23%.[6,9] Traditionally, this excess mortality has been attributed to baseline disease severity; that is, the more severe the case of COPD, the greater the likelihood the patient will be hospitalized, and the greater the risk of death. However, our group recently observed that severe exacerbations (those requiring emergency department visits or hospitalization) are independent predictors of death.[3] In a 5-year follow-up of 304 men with COPD, we observed a correlation between mortality and the frequency and severity of exacerbations in that the risk of death in patients who had 1 or 2 exacerbations a year was double that of those who had no exacerbations, and the risk among patients who had 3 or more exacerbations a year was 4 times higher. Exacerbation severity was also related to mortality in that mortality was higher among patients requiring hospitalization than among those treated in the emergency department. If these results are confirmed by future studies, treatments capable of reducing the severity or frequency of severe exacerbations could potentially reduce the mortality associated with such episodes. Noninvasive mechanical ventilation has been shown to reduce in-hospital mortality, a finding that further highlights the need to reduce the severity of exacerbations,[99] although long-term results in this respect are inconclusive.[100] With respect to prevention, there are fortunately a number of treatment options that can, to a greater or lesser degree, reduce the frequency of exacerbations; these include inhaled corticosteroids, long-acting bronchodilators, influenza vaccinations, rehabilitation, physical activity, and antioxidants. Inhaled corticosteroid therapy is the treatment option that has been most studied, probably because of its anti-inflammatory action. In several studies, the use of inhaled corticosteroid therapy was associated with both a reduction of around 25% in the number of exacerbations and a significant improvement in quality of life.[101] A meta-analysis of a database of 5000 patients who took part in various clinical trials indicated that such treatment may have a beneficial effect on survival in spite of its limited effect on lung function.[102] The preliminary results of the Towards a Revolution in COPD Health (TORCH) Study have been published very recently.[103] The primary objective of this 3-year clinical trial enrolling over 6200 patients with moderate-to-severe COPD was to evaluate the effect on mortality of a combined treatment comprising an inhaled corticosteroid and a long-acting adrenergic β_2 agonist. Mortality was reduced by 17.5% in the group of patients receiving combined salmeterol/fluticasone therapy as compared to a control group receiving placebo (*P*=.052). These results indicate that this treatment option could improve survival in at least a large number of patients with COPD. If this proves to be the case, it would be the first pharmacological treatment capable of modifying the natural history of the disease. The precise mechanisms underlying this improvement in survival have not as yet been studied. It is, however, possible that a reduction in the number of exacerbations may be a contributing factor since the group receiving the combined treatment had 25% fewer exacerbations than the controls,[103] an effect that had already been documented in the literature.[104,105] Since other drugs, such as tiotropium, have also been shown to significantly reduce the number of exacerbations, these treatments could also be expected to have a beneficial effect on survival.[106] Among the nonpharmacological approaches, regular physical activity has also recently been associated with lower mortality in COPD, perhaps because it significantly reduces the number of hospitalizations.[65]

The pathogenic mechanisms leading to death in patients with severe exacerbations are poorly understood at this time. It has been suggested that inflammation, both local and systemic, and cardiovascular abnormalities may play an important role.[3] It has recently been reported that almost 25% of exacerbations with an unclear etiology may be caused by a pulmonary embolism.[107] In general, the estimated annual mortality from pulmonary embolism is around 25%.[108] Carson et al[109] observed that 53.3% of patients with COPD and pulmonary embolism died within 1 year, a much higher mortality rate than that observed in COPD patients without an embolism. In a randomized prospective study of the role of home prophylaxis with heparin in a group of 87 patients with severe COPD, Modesto-Alapont et al[110] observed no significant reduction in the development of thromboembolic disease or overall mortality rates. However, the sample size in this study was small and perhaps insufficient for the detection of statistically significant differences. The annual mortality rate in the group receiving low-molecular-weight heparin was 9.1% as compared to 20.4% in the control group (*P*=.23).

Systemic Manifestations of COPD

Nutritional abnormalities. It has been reported that 20% to 30% of patients with advanced COPD have a low body weight (BMI≤20 kg/m^2),[18,111] and this variable has been shown to be a predictor of mortality, independent of lung function, in both epidemiologic studies and studies of patients with severe COPD on LTOT.[18,42,52,111,112] Progressive weight loss has also been

identified as a prognostic marker. Prescott et al[113] found that patients who lost more than 1 unit BMI (approximately 3.8 kg) had a relative risk of death of 2.14 (95% CI, 1.18-3.89) after adjustment for other variables. In Spain, the prevalence of low body weight in these patients is appreciably lower than in other developed countries, with reported figures varying between 4% and 7%.[114,115] However, analysis of body composition has revealed muscle wasting in 62% of those with normal body weight and 20.7% of overweight patients.[114] Muscle wasting has been associated with greater deterioration in skeletal muscle function,[116] lower exercise tolerance,[117] increased dyspnea,[118] poorer health-related quality of life,[119] and, more recently, also a worse prognosis.[114,120-122] It has a greater predictive value than BMI.[120,121] Marquis et al[120] demonstrated, using computed tomography, that a midthigh cross-sectional area of 70 cm^2 or less was associated with a fourfold increase in risk of death, independently of any other prognostic factors. Using anthropometric measurements, we also observed a worse prognosis in patients with a midarm muscle area at or below 25% of the reference value, even when they had normal body weight or were overweight.[114] More recently, Schols et al,[121] who assessed body composition in a series of 412 patients with moderate-to-severe COPD using bioelectrical impedance, also found a higher mortality rate among patients with a lower fat-free mass, independent of other confounding variables, and these results have been confirmed by other authors.[122]

Cardiovascular manifestations of COPD. Among patients with mild COPD, cardiovascular diseases and lung cancer account for two thirds of deaths.[25] As the disease progresses, the role of respiratory insufficiency becomes increasingly more important. Nonetheless, cardiovascular mortality is also common among patients with moderate-to-severe COPD. The authors of the TORCH study reported that 25% of deaths among patients with moderate-to-severe COPD were related to cardiovascular disease, a finding that highlights the need for a better understanding of the relationship between COPD and cardiovascular disease.[123] COPD is an important risk factor for atherosclerosis, such that even small reductions in FEV_1 are associated with a twofold to threefold increase in the risk of ischemic heart disease, ictus, and sudden cardiac death.[124,125] The mechanism responsible for this association has not yet been clarified, but it has been suggested that systemic inflammation may play a key role. Sin and Man[126] observed that the presence, in patients with moderate-to-severe obstruction, of high concentrations of C-reactive protein—a marker of systemic inflammation—substantially increases the risk of cardiac damage. This finding could potentially have 2 therapeutic implications: in the first place, reducing systemic inflammation could, at least hypothetically, reduce cardiovascular risk; and secondly, working in the opposite direction, improvements in both the prevention and treatment of the various cardiovascular risk factors could help prolong the life of patients with COPD.

Although research on the subject is scant, inhaled corticosteroids have been shown to reduce systemic inflammation. In a placebo-controlled trial enrolling 41 patients with COPD, inhaled fluticasone reduced C-reactive protein values in peripheral blood by almost 50% and also reduced plasma concentrations of interleukin 6.[127] Along the same lines, a pharmacoepidemiologic study with a number of methodological limitations reported that low doses of inhaled corticosteroids may reduce the incidence of myocardial infarction in patients with COPD.[128] It has recently been reported that treatment with statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers appears to improve survival in patients with COPD.[129,130] However, since the evidence for this assertion comes from observational and retrospective studies, further research is needed.

Anemia. Compensatory erythrocytosis caused by an increase in erythropoietin secretion triggered by hypoxemia has traditionally been observed in patients with arterial hypoxemia. However, COPD also has a systemic inflammatory component which, in some patients, can affect erythropoiesis as happens with other chronic inflammatory processes. Consequently, hemoglobin levels in patients with COPD could be the result of a balance between the stimulation of erythropoiesis caused by hypoxia and its depression by inflammation. The authors of a recent retrospective and observational study of a large cohort of 2524 patients with COPD who were about to start LTOT found that 12.6% of the men and 18.5% of the women were anemic.[131] In this particular population, the authors reported a strong association between hematocrit level and survival. Cumulative survival on follow-up at 3 years was 24% among patients with a hematocrit value under 35% as compared to 70% in the group of patients whose hematocrit was 55% or higher.[131]

Systemic inflammation. As we have seen earlier, systemic inflammation has been associated with various manifestations of COPD, many of which have prognostic implications. Nutritional abnormalities,[132] cardiovascular manifestations,[126] anemia,[131] and, more recently, even pulmonary hypertension[133] have all been linked to a greater or lesser degree with the presence of systemic inflammation, and especially with high concentrations of C-reactive protein. All of these associations provide evidence in support of the hypothesis that the systemic inflammation observed in patients with COPD may have prognostic consequences. In a recent study, Man et al[46] measured C-reactive protein values in 4803 patients with mild-to-moderate COPD who took part in the Lung Health Study. C-reactive protein was associated with all-cause mortality, cardiovascular mortality, and cancer mortality. Comparing the upper and lower quintiles of C-reactive protein concentration, the relative risk of death was 4.03 (95% CI, 1.23-13.21) at 1 year, 3.30 (95% CI, 1.38-7.86) at 2 years, and 1.82 (95% CI, 1.22-2.68) after 5 years of follow-up.

Comorbidity

Comorbidity is a standard exclusion criterion in many prognostic studies,[1,17,18,62,67] and in others no information is provided on this subject or it is simply not evaluated.[61,63,64,66] Moreover, most studies exclude elderly patients and it is precisely in these cohorts that concurrent diseases usually develop. Finally, as discussed earlier, it is sometimes difficult to determine whether the presence of a comorbid condition is a random circumstance or a direct consequence of the COPD.[134] For all these reasons, it is difficult to interpret the data on the prognostic value of comorbidity in COPD. Antonelli-Incalzi et al[7] studied this question in a cohort of 270 patients discharged following hospitalization for COPD. Renal failure and ischemic heart disease were the strongest prognostic factors in the multivariate analysis. The authors also assessed comorbidity using the Charlson Index.[135] This index, which is used to quantify comorbidity in order to assess risk of death in hospitalized patients, has been shown to have predictive value in a geriatric population with chronic diseases.[136] However, in the original study the Charlson Index did not show predictive capacity in the multivariate analysis. Gronewegen et al[6] also analyzed this prognostic index in patients hospitalized for exacerbation of COPD. More than two thirds of the patients had at least 1 comorbidity, and the mean (SD) score on the Charlson Index was 1.55 (0.90). Although relative risk of death was significantly associated with the Charlson Index (relative risk, 1.38; 95% CI, 1.06-1.80; *P*=.016), multivariate analysis did not demonstrate an independent association. Some authors[137] have suggested that the inconsistent results may be due to the fact that these studies assumed a linear relationship between the Charlson Index and mortality when the relationship is more likely to be exponential. In fact, in a Spanish study of 135 patients admitted to hospital for COPD, greater comorbidity as measured by the Charlson Index was found to be significantly associated with higher mortality.[9] Those authors found chronic heart failure to be the comorbidity most often recorded in patients who died. After adjustment for different variables, multivariate analysis, revealed that in patients with a Charlson index of 3 or higher (corresponding to 2 chronic diseases or 1 severe disease apart from COPD) the risk of death was double that of patients with a lower index (odds ratio=2.2; 95% CI, 1.26-3.84; *P*=.005). Martí et al[112] also demonstrated that comorbidity, as measured by the Charlson Index, is a risk factor for mortality in patients on LTOT.

Multidimensional Scales

The evidence discussed in this review supports the current view that COPD is a disease characterized not only by the presence of airflow limitation and its consequences but also by the existence of important systemic manifestations that have also been shown to have predictive value. On the basis of this idea, Celli et al[47] developed a multidimensional index integrating the main prognostic factors and validated it in 625 patients. This scale, known as the BODE index, integrates data on BMI (B for body mass index), FEV_1 (O for airflow obstruction), dyspnea (D), and exercise capacity (E) assessed using the 6-minute walk test. They found that a 1-point increase on the BODE index was associated with a 34% increase in mortality from all causes (hazard ratio,1.34; 95% CI, 1.26-1.42; *P*<.001) and a 62% increase in respiratory mortality (hazard ratio=1.62; 95% CI, 1.48-1.77; *P*<.001). The BODE index proved to be a more effective prognostic variable than FEV_1,[47] and was also shown by the same research team to be a better predictor than IC/TLC.[44] The usefulness of this index in the context of various therapeutic interventions is currently being validated,[138,139] and new multidimensional scales that take into account other aspects of the disease (for example, exacerbations, hyperinflation, comorbidity, and systemic inflammation) are also being evaluated.

Apart from its predictive value, the BODE index represents, in our opinion, an important conceptual change. In contrast to the limited scope that exists for modifying lung function (the goal Celli referred to as the "Holy Grail" of the 20th century[140]), the components of the BODE index are variables that can be improved by a number of different interventions, and this change of direction will undoubtedly open up the possibility of improving prognosis. In a recent observational study of 246 patients who participated in a rehabilitation program, Cote and Celli[138] observed a corresponding improvement in survival among patients whose BODE index improved. Imfeld et al,[139] also showed the BODE index to be a predictor of mortality after lung volume reduction surgery, a finding that highlights the need for more research on this subject.

Conclusions

Since the identification of new risk factors may lead to changes in the therapeutic strategies used to treat COPD, this is an extremely important area of research. The present review discusses many different risk factors, but it is prudent to be both critical and cautious when making judgments about any prognostic factor. One of the chief limitations of this type of research is precisely the importance of the factors not considered in any given study (those not included in the predictive model). This may explain why, for example, numerous authors identify FEV_1 as one of the strongest predictors of mortality[1,29-33,61,62,67] while others, who are studying other, previously unexplored, dimensions, do not include lung function in their predictive model or attribute it less importance.[2,3,6,9,41,44,72] Future research in this field should consider the whole set of all the important dimensions of the disease, perhaps through the use of multidimensional scales. In our opinion, current evidence continues to support the view that lung function is one of the principal prognostic domains in COPD. However, other variables, such as lung hyperinflation and exercise tolerance, should be evaluated to complement the measurement of FEV_1. Exacerbations, comorbidity, and the systemic manifestations of the disease, especially those related to the cardiovascular system, have recently been shown to be strong predictors of mortality. Many of these manifestations appear to be related to the local and systemic

inflammatory substrate, an area that merits particular attention. These emerging prognostic dimensions have the virtue of being potentially modifiable and therefore highlight the need to consider therapeutic interventions aimed at improving survival by modulating the effect of these factors in patients with COPD, a goal that is fortunately coming closer and closer to becoming a reality.

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