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REVIEW

Predictors of mortality in COPD

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Summary
Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality in adults. Although FEV_1 remains the most important physiologic indicator of the severity of airflow obstruction in COPD, its predictive value for mortality is weak when it is higher than 50% of predicted. Furthermore, other easily obtainable clinical variables predict mortality better than the FEV_1 in COPD patients with a wide range of airflow limitation. Chief among these predictors are functional dyspnea, exercise capacity, and the body mass index (BMI), although emerging research suggests a potential role for biomarker profiles in outcome predictions. The validated multidimensional BMI (B), degree of airflow obstruction as expressed by the FEV_1 (O), dyspnea with the modified medical research council (D), and exercise (E) measured with the 6 min walk or BODE index encompasses the predictive validity of the best of these variables into a single surrogate measure of disease severity and survival. This article reviews these predictors of mortality in COPD.

Contents

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Chronic obstructive pulmonary disease (COPD) is now the fourth leading cause of death worldwide[1] and it will become the third leading cause of death worldwide by 2020.[2,3] This increasing mortality is attributed to the smoking epidemic and the aging of the world population. The prevalence of COPD has increased as mortality from heart attacks and strokes, both of which share a common risk factor with COPD (ie, cigarette smoking), has decreased.[4] In 2004, the United States ranked third highest among 18 industrialized countries in COPD mortality for females and fourth highest for males.[5]

Although the hallmark feature of COPD is airflow limitation resulting from chronic bronchitis or emphysema, COPD is often accompanied by multiple comorbidities that lead to a spiral of decline, with an increased risk for mortality. The extent to which specific comorbidities and symptoms may be used to predict COPD mortality is unclear. This article reviews potential predictors of mortality in COPD.

Forced expiratory volume in 1 second

COPD is a complex disease with many inflammatory pathways that initiate and potentiate the disease process (Fig. 1). Neutrophils, macrophages and CD8 + T-lymphocytes are the key inflammatory cell types involved in COPD.

These cells release the reactive oxygen species (ROS), chemokines (e.g. interleukin [IL]-8), cytokines (e.g. tumor necrosis factor [TNF]-α) and proteases (e.g. neutrophil elastase and matrix metalloproteinase) that are instrumental in producing a chronic inflammatory state.[6,7]

The ongoing inflammatory process leads to enlargement of the alveolar spaces, fibrosis, destruction of the lung parenchyma, loss of elasticity and small airways obstruction (obstructive bronchiolitis). Mucus hypersecretion is a prominent feature of COPD. In contrast to asthma, airway hyper-responsiveness is not a commonly prevalent feature of COPD.[6,7] Notably, histological studies reveal that even

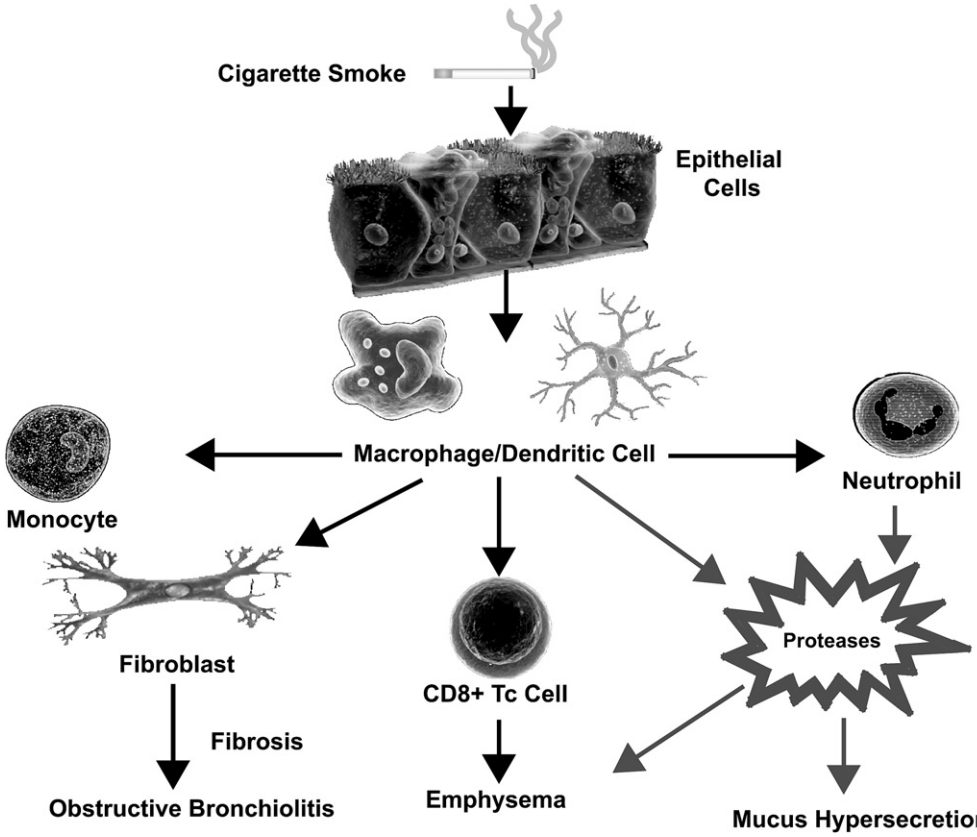

Figure 1 COPD Results from Inflammation. Legend: Airway inflammation in COPD is characterized by a neutrophilic inflammation with increased numbers of macrophages and CD8 + T-lymphocytes. These cells release the reactive oxygen species (ROS), chemokines (e.g. interleukin [IL]-8), cytokines (e.g. tumor necrosis factor [TNF]-α) and proteases (e.g. neutrophil elastase and matrix metalloproteinase) that are instrumental in producing a chronic inflammatory state.[6,7] Source: Barnes, Hansel. Lancet 2004;364:985.[6] (no permissions required).

patients who stop smoking will maintain some degree of COPD which will obstruct the airways as long as 20 years after smoking cessation.[8]

Fletcher and Peto's landmark 1977 study[9] reported a relationship between airflow obstruction and survival in a study of more than 2700 men who were followed for 20 to 25 years. This study reported that in patients who had COPD, the risk of death was strongly correlated with the degree of measured FEV_1 at the initial study survey. Longitudinal data, however, revealed overlap in the rate of decline of FEV_1 between patients with COPD and control subjects so that individual values of FEV_1 are not good predictors of outcome. Since this early spirometry research, several studies have confirmed the statistically significant but not strong relationship between FEV_1 and mortality.[10–13] In spite of this weak relationship, the risk of death in patients with COPD is still graded with the use of this single physiological variable.[9] There are several other problems with using the FEV_1 as an outcome measure in clinical trials of COPD. First and foremost, FEV_1 cannot change in patients whose disease is characterized as poorly reversible. Indeed, it is going to be very difficult to alter the rate of decline of FEV_1 in studies that select patients who are unresponsive to bronchodilators. Yet most studies have focused on this largely unachievable physiological outcome. Second, FEV_1 values do not fully express the complexity of COPD and all of its manifestations. Other easily obtainable clinical variables predict mortality better than FEV_1 in COPD patients.

An appreciation of the mechanisms contributing to the progression of COPD will help to illuminate outcome predictors. We have learned over the past 15 years that people with COPD have an increased prevalence of lung cancer, myopathy, osteoporosis, anemia, coronary artery disease, anxiety, and depression.[14] Whether these common comorbidities are part of a spillage of disease from the lungs to other body systems or whether they are separate components of a systemic inflammation is a matter of ongoing debate. Many different studies performed over the past decade suggest that COPD is associated with low-grade systemic inflammation. A meta-analysis of these studies[15] confirms that patients with stable COPD maintain increased numbers of leukocytes (some of them with an activated phenotype) and increased levels of acute phase response proteins (C-reactive protein [CRP] and fibrinogen) and cytokines like IL-6 and TNF.[15]

Irrespective of the debate surrounding the origins of COPD comorbidities, their role in the clinical course of COPD is receiving increasing attention. A recent prospective study of 955 patients with COPD for approximately 5 years documented comorbid conditions for which patients had received treatment. There were 84 comorbidities requiring treatment. Logistic regression analysis using mortality as the dependent variable identified lung cancer, nicotine addiction, depression, obesity, coronary artery disease, congestive heart failure, atrial fibrillation, peripheral vascular disease, diabetes mellitus, gastroesophageal reflux disease, prostate cancer, obstructive sleep apnea, and pulmonary hypertension as the variables with independent association with hospitalization and survival. The total number of comorbidities correlated with hospitalizations ($r = 0.28$, $p < 0.001$).[16]

Causes of mortality in COPD

Findings surrounding causes of mortality in COPD vary, depending on the population studied. The Lung Health Study[17] was a randomized clinical trial of smoking cessation and inhaled bronchodilator therapy (ipratropium) in 5887 smokers 35 to 60 years of age who did not consider themselves ill, had little evidence of other disease, but had mild to moderate airway obstruction. During 14 years of follow-up, mortality was relatively low at approximately 12%. The most common causes of mortality in this cohort were cancer (33%) and cardiovascular disease (22%); respiratory disease accounted for only 8% of deaths. These findings led to the widespread assumption that the primary cause of death in patients with COPD is heart disease.

In patients with more severe COPD, however, a very different mortality profile emerges. A pooled analysis[18] of individual patient data from seven randomized trials involving 5085 patients with stable COPD was performed, comparing the effects of inhaled corticosteroids and placebo. Among the 4% of patients who died during 26 months of follow-up, the leading cause of mortality was respiratory disease, as opposed to cardiovascular causes (34% and 30%, respectively). Cancer and other causes accounted for 21% and 15% of mortalities, respectively. These findings were confirmed by the TORCH study,[19] which also reported respiratory illness as the leading cause of mortality (35%), followed by cardiovascular disease (27%), cancer (21%), other (10%), and unknown (7%).[19]

Exercise capacity as a predictor of mortality

Several systemic manifestations that accompany COPD can signal an increased risk for mortality. Recognizing these manifestations allows for a more comprehensive assessment of disease severity and helps clinicians to make informed prognoses in patients with a wide range of airflow limitation.

Exercise capacity is one of the most important prognostic predictors. The spiral of decline in COPD is characterized by progressively decreased exercise capacity and impaired physical functioning. Exercise capacity reflects both respiratory and non-respiratory manifestations of COPD and also indicates the extent to which the pulmonary and cardiovascular systems can coordinate to supply oxygen to the rest of the body. COPD patients have been shown to have an accelerated loss of aerobic capacity ($V_{O_2}max$) which impacts on overall physical functioning. Whether exercise capacity can predict mortality has been the subject of several studies. A long-term study of 6213 men revealed that after adjustment for age, the peak exercise capacity was the strongest predictor of the risk of death among both normal subjects and those with cardiovascular disease.[20] In the setting of COPD specifically, a study of 144 patients who were followed for 5 years reported 31 deaths. $V_{O_2}max$ was shown to be the best predictor of mortality, independent of FEV_1 and patient age.[21] In a study by Pinto-Plata and colleagues,[22] the 6 minute walk distance test (6MWD) was determined in 198 patients with severe COPD. Over a 2-year period, survival increased progressively with increases in the 6MWD. Patients unable to walk 100 m had a mortality rate approaching 90% at

1 year. Yet those with similarly impaired airflow (as measured by their FEV_1) who were able to walk more than 400 m had significantly higher survival ($p < 0.0001$). The study demonstrated that exercise capacity was a better predictor of mortality than both FEV_1 and body mass index (BMI).[22] From a clinical standpoint, a quick exercise capacity test for a variety of medical problems, be it pulmonary hypertension, congestive heart failure, or interstitial pulmonary fibrosis, will help the physician to assess patient status and adopt appropriate interventions.

Multidimensional risk assessment

Given the systemic consequences of COPD, use of a composite index to assess prognosis may provide a more comprehensive way to evaluate COPD. The predictive value of numerous variables were evaluated in a prospective study of 207 patients with COPD.[4] The study assessed age, gender, smoking history in packs per year, functional vital capacity, FEV_1, dyspnea measured with the modified Medical Research Council dyspnea scale, BMI, functional residual capacity, inspiratory capacity, hematocrit, and albumin level. At 1 year, the investigators identified four variables that were most predictive of mortality risk: BMI, FEV_1, dyspnea, and exercise capacity. These variables were incorporated into the BODE index, a multifactorial 10-point staging scale that predicts risk of death in patients with COPD, a multidimensional assessment scale. Given the complex pathophysiology of COPD, the development of a multidimensional index — such as the BODE index — provides a means of classifying patients with COPD that also correlates with their prognosis. The individual components of the BODE index incorporate the pulmonary as well as the systemic effects seen in patients with COPD. The BODE index was then validated prospectively in 625 COPD patients who were evaluated every 6 months for at least 2 years. Each quartile increase in the BODE index score correlated to an increase in mortality risk. Patients with a BODE index in the quartile 4 (bode index score of 7—10) had a mortality rate of 80% at 52 months.[4] When shown in relation to the severity of COPD according to the staging system of the American Thoracic Society in place in 2004, the C statistic of the ability of the BODE index to predict the risk of death was 0.74, as compared with a value of 0.65 with the use of FEV_1 alone.[23] Ongoing follow-up of this initial study cohort and new patients continues to support the prognostic value of the BODE index.

Imfeld and colleagues[24] investigated whether the BODE index is able to predict survival after lung volume reduction surgery (LVRS) in a 40-month retrospective study of 186 patients with severe COPD. BMI, pulmonary function, 6MWD, and the modified Medical Research Council dyspnea score were assessed before and 3 months after LVRS, and the BODE index was calculated. The mean BODE index decreased from 7.2 ± 1.6 preoperatively to 4.0 ± 2.0 at 3 months after LVRS ($p < 0.001$). The postoperative BODE, but not the preoperative BODE, correlated with survival. A decrease to a lower BODE score class was associated with a reduced mortality (hazard ratio, 0.497, 95% confidence interval, 0.375—0.659; $p < 0.001$). Further, the BODE index was found to be more predictive of mortality than the FEV_1. These findings were confirmed by a comprehensive analysis of the data from the National Emphysema Therapy Trial (NETT).[25] This study randomized patients to medical treatment or to lung volume reduction surgery and followed them for over 5 years. A modified BODE score was calculated using the San Diego dyspnea scale instead of the original modified MRC scale and calculated in the same manner as the original BODE score. The change in BODE index measured at 6 months after randomization predicted survival at 2 and 5 years demonstrating the predictive power of BODE and equally important its possible role as a surrogate marker of response to therapy.

Inspiratory fraction

Static lung hyperinflation has important clinical consequences in patients with chronic obstructive pulmonary disease. A recent study[26] suggests a role for the inspiratory-to-total lung capacity ratio or ''inspiratory fraction'' (inspiratory capacity(IC)/total lung capacity (TLC)) as a measure of functional reserve and a predictor of mortality. In this study of 689 patients who had COPD, IC/TLC was found to be an important independent predictor of increased mortality. The IC/TLC also predicts exercise capacity[27] and has important influence on cardiac function during exercise.[28]

Exacerbations

Exacerbations of COPD are a major cause of morbidity, mortality and hospital admission, but there is currently no widely accepted definition of what constitutes an exacerbation of COPD.[29,30] In an attempt to correlate patient characteristics during acute exacerbation and length of survival, Connors and colleagues[31] conducted a prospective analysis of a cohort of 1,016 adult patients who were admitted to hospitals due to COPD exacerbations. Although only 11% of the patients died during the hospital stay, the 60-day, 180-day, 1-year, and 2-year mortality was high (20%, 33%, 43%, and 49%, respectively). Survival time was independently related to multiple factors, including illness severity, BMI, age, and other variables. Soler-Catalunya et al. have clearly shown in a cohort of patients with COPD that outcomes, including survival, are related to the presence, frequency and intensity of exacerbations with patients having no exacerbations manifesting better survival than those with more frequent visits to the emergency room or hospitalizations.[32] The same authors have demonstrated that the addition of exacerbations to the BODE may improve its predictive capacity.[33]

Biomarkers

The pathobiological processes that manifest in the lungs and elsewhere in patients with COPD could be associated with systemic biomarker levels detectable in the systemic circulation. There has been increasing interest in identifying pulmonary biomarkers of COPD to predict pathogenic processes and pharmacological responses. Potential biomarker sources include bronchial biopsies and bronchoalveolar lavage, which are highly invasive and thus

difficult to repeat. Exhaled gases and breath condensate are considerably less invasive, but results are highly variable. Induced sputum has provided useful information about inflammation and infection. Serum is easily obtainable, but predictive markers have yet to be substantiated. A comprehensive review of the literature on pulmonary biomarkers in COPD[34] concludes that though many have been described, none are in use, and more research is needed.

Limited data are available from histologic data from a study of the antiinflammatory effects of salmeterol/fluticasone propionate in COPD.[35] Study subjects underwent bronchial biopsies and sputum analysis at baseline and at the end of the study to determine change in the numbers of CD8+ and CD68+ cells/mm^2 in biopsy specimens and sputum neutrophils. Treatment was shown to reduce CD8+ cells and sputum neutrophils. Another study profiled gene expression of human lung tissue from smokers with severe emphysema and identified 102 genes that accurately distinguished severe emphysema from other lung tissue.[36] However, the clinical value of these findings has not yet been demonstrated. There is little information about how these and other biomarkers relate to disease progression, severity, or response to therapy. Nor is there any evidence to support a relationship between biomarkers and the extrapulmonary manifestations of COPD.

Histological analysis within the setting of oncology has been more conclusive. A study of gene expression in tissue from lung cancer specimens[37] revealed 16 genes that correlated with survival among patients. When five genes were selected for further analysis, they were found to independently predict relapse-free and overall survival. Further, response to chemotherapy was associated with the presence of the 5 genes. The study clearly links biomarkers to both disease outcome and therapeutic response in lung cancer; unfortunately, there are no comparable findings in the COPD literature.

A systematic review[15] of studies reporting on the relationship between FEV_1 or forced vital capacity (FVC) and levels of various systemic inflammatory markers revealed an association between CRP and reduced lung function. A subsequent editorial[38] commented on three additional studies that demonstrated an inverse linear relationship between FEV_1 and CRP. The clinical utility of these findings, however, is questionable. An elevated CRP is nonspecific since it suggests any number of health problems. Why use CRP as a marker of impaired lung function when FEV_1 is easily and non-invasively obtainable and is more specific to the pulmonary system? Markers are of clinical significance only when their change predicts a change in health outcomes.

Recent research has attempted to bridge this gap. An 8-year follow-up of 1302 participants from the Copenhagen City Heart Study who were identified as having airway obstruction (defined as FEV_1/FVC less than 0.7) revealed higher baseline serum levels of CRP in participants who were subsequently diagnosed with COPD.[39] A baseline CRP value of more than 3 mg/L in this population of patients with airway obstruction was predictive of COPD hospitalization and death. A multifactorial analysis including sex, age, FEV_1% predicted, tobacco consumption, and ischemic heart disease showed an increase of equivalent hazard ratios for COPD hospitalization and COPD death of 1.4 (1.0—2.0) and 2.2 (1.2—3.9), respectively. However, a separate analysis of our own BODE study cohort ($N = 218$) did not duplicate these findings. Mortality rates were comparable among patients with CRP levels higher than 3 mg/L and those with levels lower than 3 mg/L.[40] From

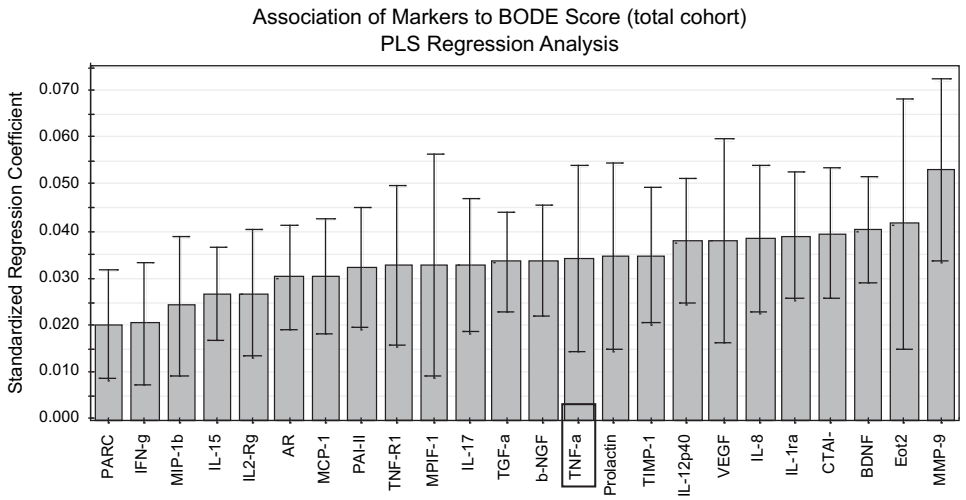

Figure 2 Association of Biomarkers to BODE Score. Correlation of the selected biomarker panel with the BODE index in patients with COPD. The size of the bar in the graph indicates the magnitude of the regression coefficients and the 95% confidence interval is also indicated for each bar. If the confidence interval includes zero, the associated biomarker is ''not significant.'' The overall regression model was significant by a permutation test ($p < 0.01$). AR, amphiregulin; BDNF, brain-derived neurotrophic factor; bNGF, b-nerve growth factor; IFNc, interferon c; IL, interleukin; IL-1ra, interleukin 1 receptor antagonist; IL-2Rc, interleukin 2 receptor gamma; I-TAC, interferon c-inducible T cell a chemoattractant; MCP-1, monocyte chemotactic protein 1; MIP-1b, macrophage inflammatory protein 1b; MMP-9, matrix metalloproteinase 9; MPIF-1, myeloid progenitor inhibitory factor 1; PAI-II, plasminogen activator inhibitor II; TGFa, transforming growth factor a; TIMP-1, tissue inhibitors of metalloproteinases 1; TNFa, tumor necrosis factor a; TNF R1, tumor necrosis factor receptor I; VEGF, vascular endothelial growth factor. Source: reproduced in its entirety from Pinto-Plaza et al.[42] (permission to reproduce required).

a clinical perspective, therefore, CRP appears to be less useful than FEV_1, BMI, and 6-minute walking distance.

Recently, there has been some use of high-density microarray technology to systematically define the serum protein expression profile in patients with COPD.[41,42] The most recent of these studies[42] explored the relationship between a selected subset of 24 biomarkers with clinically important outcome variables in COPD, including lung function, the BODE index and its components, and the frequency of exacerbations. The biomarkers were selected from clusters statistically associated with the diagnosis of COPD and thought to have known or potential significance in the pathobiology of COPD.

The study identified a biomarker profile (Fig. 2) characteristic of patients with COPD. The study further demonstrated an association between the level of selected biomarkers and lung function, the degree of airflow limitation and DLCO, a marker of lung tissue destruction. The study also showed a correlation between the expression of the serum biomarkers and clinical manifestations of COPD represented by functional capacity, the BODE index, and exacerbation rates.

Conclusions

Intriguing as these findings are, I concur with the words of one of the esteemed forefathers of modern medicine, Sir William Osler, who said ''If it were not for the great variability among individuals, medicine might as well be a science and not an art.'' The predictive value of specific biomarker profiles in individuals with COPD, in my opinion, remains uncertain. Although biological marker discovery is an intriguing research topic and may help us identify novel therapeutic approaches, it is complex and challenged by technological problems and biological noise which still need to be addressed. Clinical physiological markers, incorporated into the BODE index and other multidimensional staging tools, may be valuable not only in the assessment of severity and progression of disease, but also in evaluating the response to medical interventions.

Conflict of interest

Bartolome R. Celli, MD, reports having received honoraria as a consultant from Almirall, AstraZeneca, Boehringer-Ingelheim Pharmaceuticals, Inc, Dey Pharmaceutical, Esteve, GlaxoSmithKline, and Pfizer Inc. He has also received speaking fees from the same companies. The division he heads has had grants from Aeris, AstraZeneca, Boehringer-Ingelheim Pharmaceuticals, Inc, Forrest Laboratories, and GlaxoSmithKline.

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