

Comorbidities and Risk of Mortality in Patients with Chronic Obstructive Pulmonary Disease

Miguel Divo¹, Claudia Cote^{2†}, Juan P. de Torres³, Ciro Casanova⁴, Jose M. Marin⁵, Victor Pinto-Plata³, Javier Zulueta³, Carlos Cabrera⁶, Jorge Zagaceta³, Gary Hunninghake¹, and Bartolome Celli¹; for the BODE Collaborative Group

¹Pulmonary and Critical Care Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; ²Division of Pulmonary and Critical Care Medicine, The Bay Pines Veterans Affairs Healthcare System, University of South Florida, Tampa, Florida; ³Department of Pulmonology, University Clinic of Navarra, Pamplona, Spain; ⁴Pulmonary Department, Hospital Universitario La Candelaria, Universidad de La Laguna, Santa Cruz de Tenerife, Spain; ⁵Respiratory Service, Hospital Universitario Miguel Servet, Zaragoza, Spain; and ⁶Pulmonary Department, Hospital Universitario de Gran Canaria Dr Negrin, Las Palmas de Gran Canarias, Spain

Rationale: Patients with chronic obstructive pulmonary disease (COPD) are afflicted by comorbidities. Few studies have prospectively evaluated COPD comorbidities and mortality risk.

Objectives: To prospectively evaluate COPD comorbidities and mortality risk.

Methods: We followed 1,664 patients with COPD in five centers for a median of 51 months. Systematically, 79 comorbidities were recorded. We calculated mortality risk using Cox proportional hazard, and developed a graphic representation of the prevalence and strength of association to mortality in the form of a "comorbidome." A COPD comorbidity index (COPD specific comorbidity test [COTE]) was constructed based on the comorbidities that increase mortality risk using a multivariate analysis. We tested the COTE index as predictor of mortality and explored whether the COTE index added predictive information when used with the validated BODE index.

Measurements and Main Results: Fifteen of 79 comorbidities differed in prevalence between survivors and nonsurvivors. Of those, 12 predicted mortality and were integrated into the COTE index. Increases in the COTE index were associated with an increased risk of death from COPD-related (hazard ratio [HR], 1.13; 95% confidence interval, 1.08–1.18; $P < 0.001$) and non-COPD-related causes (HR, 1.18; 95% confidence interval, 1.15–1.21; $P < 0.001$). Further, increases in the BODE and COTE were independently associated with increased risk of death. A COTE score of greater than or equal to 4 points increased by 2.2-fold the risk of death (HR, 2.26–2.68; $P < 0.001$) in all BODE quartile.

Conclusions: Comorbidities are frequent in COPD and 12 of them negatively influence survival. A simple disease-specific comorbidities index (COTE) helps assess mortality risk in patients with COPD.

Keywords: pulmonary disease; chronic obstructive; comorbidity; mortality

Chronic obstructive pulmonary disease (COPD) is an important cause of morbidity and mortality around the world (1, 2). Patients with COPD frequently suffer from concurrent comorbidities, such as cardiovascular (3) and cerebrovascular disease (4), lung cancer (5), and diabetes (6). Those comorbidities were

(Received in original form January 6, 2012; accepted in final form April 19, 2012)

† Deceased.

Author Contributions: The authors attest that they made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; and final approval of the version to be submitted for revision.

Correspondence and requests for reprints should be addressed to Miguel Divo, M.D., Pulmonary and Critical Care Division, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115. E-mail: mdivo@partners.org

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 186, Iss. 2, pp 155–161, Jul 15, 2012

Copyright © 2012 by the American Thoracic Society

Originally Published in Press as DOI: 10.1164/rccm.201201-00340C on May 3, 2012

Internet address: www.atsjournals.org

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Patients with chronic obstructive pulmonary disease frequently suffer from concurrent comorbidities, yet their nature, prevalence, and impact on mortality is poorly understood.

What This Study Adds to the Field

This study evaluates the spectrum and prevalence of comorbidities affecting patients with chronic obstructive pulmonary disease attending pulmonary clinics. It establishes the relationship between these comorbidities and the risk of death over a median of 51 months. The prevalence and mortality risk are expressed using an orbital bubble chart (the comorbidome) and a quantitative risk stratification comorbidity tool (the COTE index) that is simpler than the Charlson score.

adjudicated as the primary causes of death in more than 60% of nonsurvivors in two large randomized controlled pharmacologic trials (7, 8); however, limited data exist on the prognostic value of capturing the effects of these comorbidities in patients with COPD.

Determining the risk of death in COPD has been better ascertained using multidimensional indices, such as the BODE (body mass index, FEV₁, dyspnea, and exercise capacity) (9), the ADO (age, dyspnea, and FEV₁) (10), and the DOSE indexes (dyspnea, FEV₁, smoking status, and, exacerbation frequency) (11) rather than using the classic unidimensional information provided by the FEV₁. However, those indices do not systematically include the presence or impact of coexisting diseases. The few studies that have explored COPD-related comorbidities (12–16) suggest that compared with age-matched controls some comorbidities are more likely to coexist with COPD (16), and that they impact on relevant outcomes, such as health-related quality of life (12, 13), use of healthcare resources (15), response to intervention (12), and mortality (14, 15). However, these studies were not planned to systematically evaluate the prevalence and role of comorbidity in COPD, several were performed in single centers with small number of patients (12, 14), used retrospective administrative databases (6, 17, 18), or enrolled patients admitted in the acute care hospital after an acute exacerbation (14, 15) limiting the applicability of their findings.

Since the inception of the BODE cohort, an ongoing prospective observational multinational study of outpatients with COPD attending pulmonary clinics, we have systematically recorded the

presence or subsequent development of comorbidities. We hypothesized that we could determine the prevalence of individual comorbidities and the strength of the association between the number and nature of the comorbidity and risk of death over time. With this information, we developed a point scale index, the COPD specific CO-morbidity TEst (COTE). Finally, we explored whether the COTE index provided additional prognostic information to that provided by the BODE index.

Some of the results of this study have been previously presented in the form of an abstract during the 2011 European Respiratory Society meeting (19).

METHODS

Study Design and Population

The BODE cohort is an ongoing prospective, multicenter, observational study of subjects with COPD, recruited from pulmonary clinics in the United States and Spain, with repeated examinations at least every year. The ethics committee at each of the participating centers approved the study and all patients signed informed consent before enrollment.

Between November 1997 and March 2009, a total of 1,664 subjects from all five sites were enrolled in the study and followed until either the time of death or to March 2010. The consort diagram for the cohort is shown in Figure E1 in the online supplement.

The details of the BODE cohort inclusion and exclusion criteria have been previously described (9). In brief, COPD was defined on the basis of a history of smoking (>10 pack-years) and on lung function test results following the American Thoracic Society/European Respiratory Society standards (20). All patients were in clinically stable condition and receiving standard therapy. Subject were excluded if they had primary asthma, inability to take the lung function and 6-minute walk tests, or any condition that could unacceptably increase the subject's risk of performing any of the testing.

Measurements

We recorded age, sex, post-bronchodilator spirometry, and the BODE index (9) at baseline and after each visit.

Comorbidities

Comorbidities were systematically recorded through direct questioning for the following conditions: (1) those diseases included in the Charlson comorbidity index (21) (19 comorbidities); (2) all comorbidities listed in the subject's medical record; or (3) those expressed during enrollment interview and subsequent visits. The diagnosis of a comorbidity was confirmed by either reviewing the patient's medication list, or when feasible by confirmatory tests available from their medical records. Conditions that had completely resolved were excluded (i.e., pneumonia).

Survival

The follow-up time for each subject was determined from the date of enrollment to the date of the last visit or attempt to verify subject status. Death or lost in follow-up was verified by calling each subject or their family if they failed to return for appointments, and if we were unable to reach them, by checking the social security death index (United States). Cause-specific mortality was ascertained by each site investigator to the highest detail possible and then categorized in a systematic and masked fashion by four of the investigators (B.C., C.C., J.Z., and M.D.) as either death related to (1) COPD, (2) non-COPD respiratory cause, (3) cardiovascular, (4) cancer, (5) other causes, or (6) unknown, as previously described (8).

Development of the Comorbidity and COTE Index

To evaluate the strength of the association of the comorbidities with the risk of death, we performed multivariate analyses using Cox proportional hazards regression including all 79 recorded comorbidities. We integrated this information with the prevalence of the disease to construct the "comorbidity," which is the graphical expression of the

comorbidity prevalence and risk of death in the form of an orbital bubble chart.

The COTE index was constructed by scoring those same comorbidities that were associated with a statistically significant hazard of death. The sum of the points intends to capture the individual or combination of diseases affecting each patient.

Statistical Analysis

When appropriate, data for continuous variables are presented as means \pm SD or median and 25–75 interquartile range (IQR). Group comparison was conducted using Fisher exact test (for categorical variables) and two-tailed *t* tests or the Wilcoxon rank-sum test (for continuous variables). Prevalence is expressed as percentage of the population at risk.

To calculate the effect of the COTE and BODE indexes on the risk of death we fitted stratified Cox models to account for violations of the proportional hazards assumption. Stratified Cox models were fit with a stratification term indicating follow-up times of less than 18 months and greater than or equal to 18 months. To assess the predictive value of the COTE index alone and in comparison with the BODE index we used C statistics and the Net Reclassification index (22). The probability of death at 5 years was grouped similarly to those described previously (0 to <5%, 5% to <10%, 10% to <20%, and \geq 20%) (22). A *P* value of less than 0.05 was considered statistically significance. All analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, NC). The study data were collected and managed using REDCap (Research Electronic Data Capture) a secure, web-based data capture application hosted at the Brigham and Women's Hospital-Partners Healthcare System (23).

RESULTS

Characteristics of the Cohort

The demographic and baseline characteristics of the 1,659 patients included in the analysis are summarized in Table 1. The cohort consisted primarily of white males with a mean FEV₁ %predicted of 47% with a wide range of airflow obstruction (Global Initiative for Chronic Obstructive Lung Disease stages). The mean BODE index was 3.7 and all BODE quartiles were represented (Table 1) (9). The median follow-up for this cohort was 51 months (IQR, 28–78 months). During the observation period, 40% of the subjects died, and the median follow-up for nonsurvivors was 36 months (IQR, 17–55) compared with 62 months (IQR, 40–91) for survivors (*P* < 0.001) (see Figure E1 in the online supplement). Of the 671 subjects who died

TABLE 1. SUBJECTS' CHARACTERISTICS

Demographic	
N	1,659
Age, mean \pm SD	66 \pm 9
Male, n (%)	1,477 (89)
Spirometry	
FEV ₁ % (mean \pm SD)	49 \pm 20
GOLD I (%)	135 (8)
GOLD II (%)	593 (36)
GOLD III (%)	639 (39)
GOLD IV (%)	292 (17)
BODE	
BODE (mean \pm SD)	3.7 \pm 2.6
BODE 0, 1, 2 (%)	595 (36)
BODE 3, 4 (%)	470 (28)
BODE 5, 6 (%)	312 (19)
BODE 7, 8, 9, 10 (%)	282 (17)
Number of comorbidities	
Average \pm SD	6 \pm 3
Range	0–21

Definition of abbreviation: GOLD = Global Initiative for Chronic Obstructive Lung Disease.

during the observation period the primary cause of death could be determined in 551 subjects (82%). Respiratory cause of death was the primary cause in 328 subjects (49%), with COPD representing 268 cases (40%). In 283 patients (42%), death was caused by nonrespiratory causes; 144 subjects died from cancer (21%) and 51 died from cardiovascular diseases (8%) (see Figure E2).

Comorbidities

A total of 79 comorbidities were observed in this cohort including some that are sex predominant (breast cancer, benign prostate hypertrophy, prostate cancer, hypogonadism). The average number of comorbidities (± SD) was 6 ± 3.5 per subject for the whole cohort; 4.6 ± 3.2 for females; and 6.2 ± 3.5 for males (P < 0.001). The average number of comorbidities was higher for the nonsurvivors compared with survivors (6.5 ± 3.8 and 5.8 ± 3.3, respectively; P < 0.001).

The distribution of the most prevalent (>5%) and significant comorbidities is shown in Figure 1, and expanded to include all of them in Figure E3 and Table E1. There is a heavy tailed distribution, ranging from 52% to less than 1%. Fifteen comorbidities had a significantly higher prevalence in nonsurvivors compared with survivors (shown by the presence of asterisks in Figure 1). Using multivariate analysis, only 12 of them increased the risk of death over the study time and were selected to construct the COTE index (Tables 2 and 3).

The COPD Comorbidome

The prevalence of the 12 comorbidities associated with increased risk of death, those with an overall prevalence higher than 10%, and the strength of their association with mortality are presented in Figure 2 as an orbital bubble chart. Mortality is fixed at the center, and each comorbidity is represented as a bubble or “planet” with their diameter proportional to the prevalence. Each planet is positioned in a radial “orbit” with the distance to the center scaled from the inverse of the hazard ratio (HR) (1/HR). The closer the comorbidity is to the center, the higher the conferred risk. All bubbles associated with a statistically

significant increase in mortality are fully inside the dotted orbit (1/HR <1).

COTE Index

The comorbidities included in the COTE index are shown in Table 3. Similar to the Charlson index (24), a scale value points in the range of one to six points was assigned to each selected comorbidity in proportion to its HR (1–1.5 = 1, >1.5–2 = 2, and >2 = 6 points with the exception other cancers, which were assigned two points).

The effect of the COTE index on the risk of death varied over time. There was minimal evidence that an increased COTE index was associated with an increase in the hazard of death in patients with COPD followed for less than 18 months (HR, 1.04; 95% confidence interval [CI], 0.98–1.10; P = 0.18). In contrast, an increased COTE index was associated with death in patients with COPD followed for greater than or equal to 18 months (HR, 1.16; 95% CI, 1.13–1.19; P < 0.001). Therefore, the remaining models were fit with a stratification term accounting for this time difference. Overall, the HR for death conferred by an increase of one point in the COTE index was 1.14 (95% CI, 1.10–1.16; P < 0.001). Increases in the COTE index were associated with an increased risk of death from COPD-related (HR, 1.13; 95% CI, 1.08–1.18; P < 0.001) and non-COPD-related causes (HR, 1.18; 95% CI, 1.15–1.21; P < 0.001). The same association was observed at each of the study sites and between Spain and the United States. Using C statistics, the performance of COTE to predict mortality (C = 0.66; P < 0.0001) was similar to that of the Charlson Comorbidity Index (C = 0.65; P < 0.0001).

COTE, BODE, and Mortality

In models adjusting for age, sex, race, and the BODE index, an increased COTE index remained a significant predictor of death (HR, 1.10; 95% CI, 1.08–1.13; P < 0.001). To identify the level of the COTE index with the greatest predictive value for death in patients with COPD we used receiver operating characteristic curves. A COTE index greater than or equal to four resulted in the greatest area under the curve (C = 0.63) and was associated

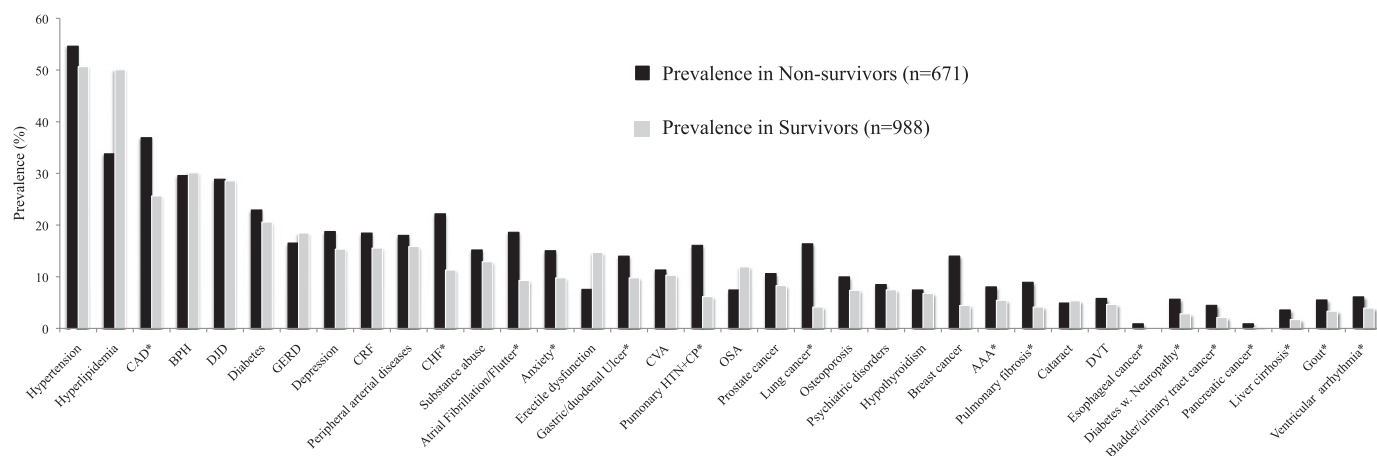


Figure 1. Comorbidities with more than 5% prevalence in survivors (green bars) and nonsurvivors (red bars). The figure also includes those comorbidities with a significantly (asterisk) higher prevalence in nonsurvivors compared with survivors regardless of their absolute prevalence (see Figure E2 and Table E1 for details). AAA = abdominal aortic aneurysm; BPH = benign prostatic hypertrophy; CAD = coronary artery disease; CHF = congestive heart failure; CRF = chronic renal failure; CVA = cerebrovascular accident; DJD = degenerative joint disease; DVT = deep venous thrombosis; GERD = gastroesophageal reflux disease; OSA = obstructive sleep apnea; pulmonary HTN+RHF = pulmonary hypertension and right heart failure.

TABLE 2. COMORBIDITIES WITH THE STRONGEST ASSOCIATION WITH INCREASED RISK FOR DEATH

Comorbidity	Prevalence (%)	Hazard Ratio		P Value
			(95% confidence interval)	
Oncologic				
Lung cancer	9.1	2.02	(1.63–2.51)	<0.001
Pancreatic cancer	0.4	2.72	(1.18–6.30)	0.02
Esophageal cancer	0.4	2.79	(1.15–2.79)	0.02
Breast cancer*	7	6.18	(1.07–35.68)	0.04
Pulmonary				
Pulmonary fibrosis	6.1	1.51	(1.13–2.03)	0.006
Cardiac				
Atrial fibrillation/flutter	13	1.56	(1.25–1.96)	<0.001
Congestive heart failure	15.7	1.33	(1.06–1.68)	0.02
Coronary artery disease	30.2	1.27	(1.06–1.54)	0.01
Gastrointestinal				
Gastric/duodenal ulcers	11.5	1.32	(1.05–1.66)	0.02
Liver cirrhosis	2.5	1.68	(1.07–2.65)	0.02
Endocrine				
Diabetes with neuropathy	4	1.54	(1.05–2.27)	0.03
Psychiatric				
Anxiety*	13.8	13.76	(2.13–88.63)	0.006

* Calculated on the female cohort and excluding male-specific comorbidities from the multivariate analysis.

with a 2.3-fold increased risk of death (HR, 2.3; 95% CI, 2.00–2.75; $P < 0.001$). Comparable with previous studies (9) the BODE index was a significant predictor of death in patients with COPD ($C = 0.74$); however, there was evidence that COTE index added to the predictive value of the BODE index

($C = 0.79$ for the COTE and BODE index; $P < 0.001$ for the addition of the COTE index). Similarly, the COTE index improved the net reclassification of subjects with COPD when added to the BODE index (net reclassification improvement 23%; SE 3%; $P < 0.001$).

In each BODE quartile those patients with a COTE index of four or above had over a 2.2-fold increase in their risk of death (HR, 2.26–2.68; $P < 0.001$ for all groups). This is shown in Figure 3 in the form of Kaplan-Meier survival curves stratified by each BODE quartile.

DISCUSSION

This longitudinal observational multicentric study of patients with COPD attending pulmonary clinics, in which comorbidities were systematically identified, had three main findings. First, although a large number of comorbidities may be present in patients with COPD, a limited number of easily identifiable ones are independently associated with COPD and non-COPD mortality. Second, from the resulting HR for death and prevalence data of the more frequent comorbidities, a new expression of the relationship of comorbidities and COPD is presented, the COPD comorbidome. Third, a new comorbidity risk index (COTE) was developed. This simple index, which provides complementary information to the BODE index, can help predict which patients with COPD are at increased risk of death regardless of their baseline physiologic state.

COPD is a complex respiratory disease frequently associated with systemic manifestations (25, 26). Indeed, a low body mass

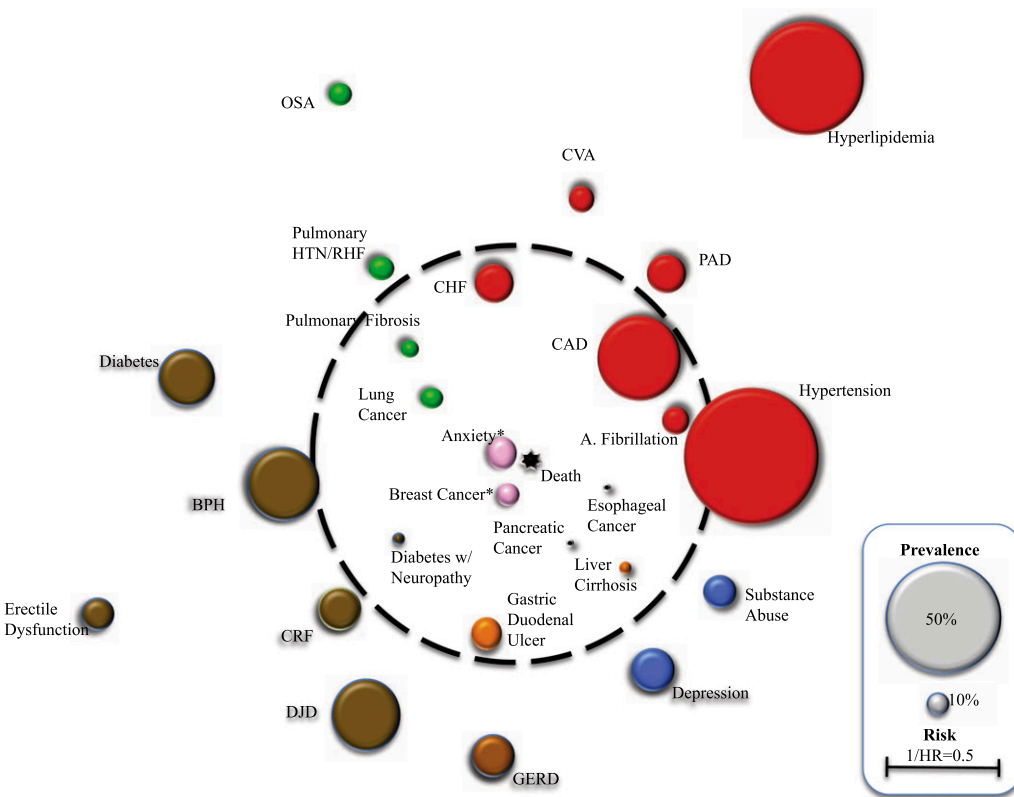


Figure 2. The “comorbidome” is a graphic expression of comorbidities with more than 10% prevalence in the entire cohort, and those comorbidities with the strongest association with mortality (hazard ratio [HR], >1; 95% confidence interval, >1; $P \leq 0.05$). The area of the circle relates to the prevalence of the disease. The proximity to the center (mortality) expresses the strength of the association between the disease and risk of death. This was scaled from the inverse of the HR (1/HR). All bubbles associated with a statistically significant increase in mortality are fully inside the dotted orbit (1/HR < 1). Bubble colors represent organ systems or disease clusters (cardiovascular = red, female-specific comorbidities = pink, pulmonary = green, psychiatric = blue, others = brown and orange). A. fibrillation = atrial fibrillation/flutter; BPH = benign prostatic hypertrophy; CAD = coronary artery disease; CHF = congestive heart failure; CRF = chronic renal failure; CVA = cerebrovascular accident; DJD = degenerative joint disease; GERD = gastroesophageal reflux disease; OSA = obstructive sleep apnea; PAD = peripheral artery disease; pulmonary HTN+RHF = pulmonary hypertension and right heart failure.

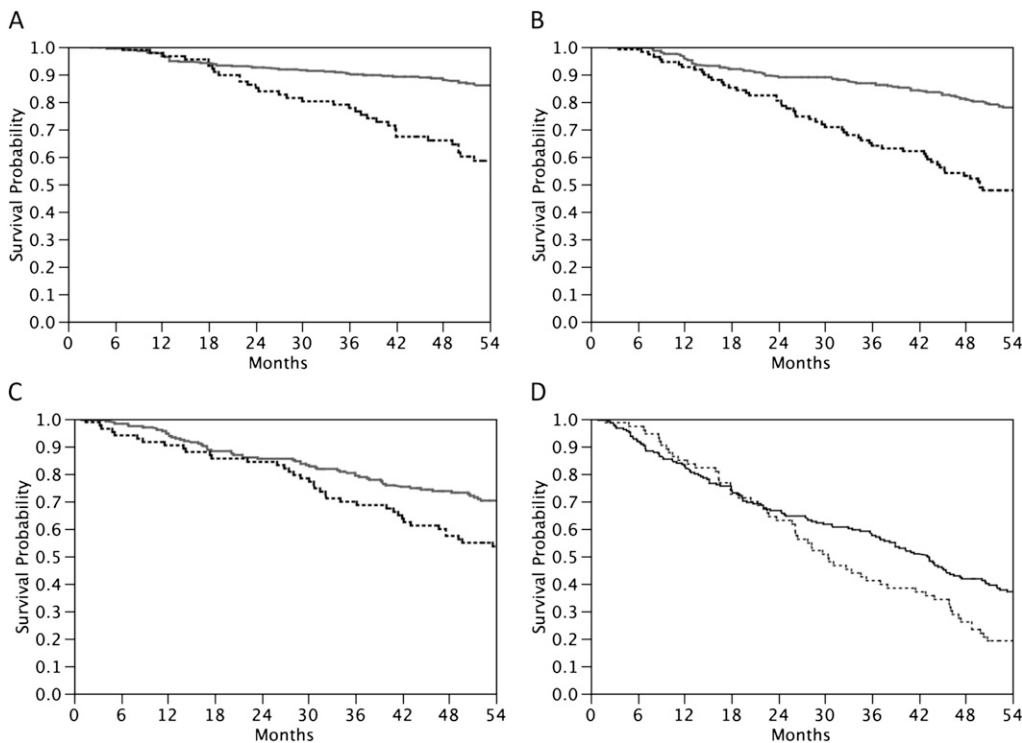


Figure 3. Kaplan-Meier survival curve representing survival probability at 54 months. To demonstrate the predictive contribution of the COTE to the BODE index, the survival curves were represented for each BODE score quartile (9). (A) BODE Q1 (scores = 0, 1, 2). (B) BODE Q2 (scores = 3, 4). (C) BODE Q3 (scores = 5, 6). (D) BODE Q4 (scores = 7, 8, 9, 10). In each panel, patients were categorized as COTE score of 0–3 (solid line) or those greater than or equal to 4 points (dotted line). See Table E2 for further details.

index, higher dyspnea scores, and impaired exercise capacity confer a poor prognosis that is independent of the degree of airflow limitation (9). In addition, there is accumulating evidence that patients with COPD are prone to develop other important diseases, such as coronary artery disease (6), lung cancer (5), osteoporosis (27), anemia (28), depression (29), and dysfunctional skeletal myopathy (30). Because the association with these other diseases seems to be stronger in patients with COPD than in patients without the disease (16), Fabbri and coworkers (31) proposed that perhaps COPD was just one more manifestation of a systemic inflammatory syndrome. This concept has received great attention; however, the associations have been explored in databases not specifically designed to evaluate comorbidities or reported in studies where only a selected number of comorbidities were evaluated.

The BODE cohort was recruited with the goal of methodically and longitudinally phenotyping patients with COPD as seen in pulmonary clinics. As part of that characterization, patients were systematically evaluated for the presence of comorbidities at baseline and at each subsequent visit. Besides the diseases included in the Charlson score that was used to quantify baseline comorbidity, patients were asked to state the development of any new disease or any new form of treatment provided for any ailment during the duration of follow-up. As seen in Figure 1, Figure E2, and Table E1, a total of 79 different comorbidities were identified over the median follow-up time of 51 months. As expected, not all of the comorbidities were equally prevalent, with some, such as hypertension and hyperlipidemia, affecting up to 50% of the patients, whereas others had a very low prevalence. Healthcare providers are faced by limitations in the time allotted to evaluate their patients, and therefore guidance that helps them select comorbidities likely to increase the risk of poor outcome could help optimize clinical interventions. The results here presented show that of the 79 comorbidities identified, 15 differed significantly between survivors and nonsurvivors. Of these, 12 were independently associated with increased risk of death (Table 2) and may constitute the core of comorbidities that

healthcare providers should pay increased attention to in guiding a targeted personalized screening and treatment or expanding the differential diagnosis in patients with a primary diagnosis of COPD (32). Some, such as coronary artery disease and lung cancer, are in agreement with previously reported literature (5, 33, 34). However, the increased risk provided by other cancers, such as esophageal and pancreatic, is less well known and breast cancer and anxiety in women somewhat surprising. Furthermore, the increased risk of death conferred by the presence of interstitial pulmonary fibrosis, peptic ulcer disease, liver cirrhosis, and atrial fibrillation and flutter has not been described. These findings raise the possibility of a close interaction among these diseases that may share common biologic pathways.

One novel finding of this study is the spatial expression of the prevalence of comorbidities and their strength of association with mortality in patients with COPD. This new expression shown in Figure 2, which we have termed “COPD comorbiodome,” visually conveys the prevalence of the disease (size of the circles) and the risk of death (proximity to the center).

TABLE 3. COMORBIDITIES AND POINT VALUES USED FOR THE COMPUTATION OF COTE INDEX

Comorbidity	Hazard Ratio	Point Assignment
Lung, esophageal, pancreatic, and breast* cancer	>2.00	6
Anxiety*	13.76	6
All other cancers		2
Liver cirrhosis	1.68	2
Atrial fibrillation/flutter	1.56	2
Diabetes with neuropathy	1.54	2
Pulmonary fibrosis	1.51	2
Congestive heart failure	1.33	1
Gastric/duodenal ulcers	1.32	1
Coronary artery disease	1.28	1

Hazard ratio <1.5 = 1, ≥1.5 = 2, and 6 for lung, pancreatic, esophageal, and breast cancer, similar to the value assigned in the Charlson Comorbidity.

* Valid on the female population only.

Although hypertension, hyperlipidemia, and obstructive sleep apnea are highly prevalent, the direct risk for death that these diseases confer is not significant. We believe the most likely reason is that they are all treatable or that they are risk factors for the development of more lethal disease, as is coronary artery disease. However, selected cancers conferred a great risk for death. Of these, lung cancer stands in a group by itself because it showed an aggregated prevalence of 9%, confirming the strong association between COPD and lung cancer (35). A novel finding in this study was the relatively high prevalence of interstitial pulmonary fibrosis (6%) and its independent strong association with risk of death. This observation provides support to the argument recently proposed by Washko and associates (36) that the combination of interstitial lung abnormalities and COPD, which they found in 8% of the COPD gene cohort, may bear an association mediated by the common risk factor of smoking. Liver cirrhosis and anxiety were also associated with increased risk for death and suggest some correlation with lifestyle and social behavior of this population that should be easily accessible with medical interview. The identification of anxiety as a risk factor for death, particularly in women, is intriguing from the perspective of its biologic relationship to COPD. However, our findings are consistent with previous studies, where anxiety is more prevalent in females (37) and impacts on important patient-related outcomes as is the case of rate of exacerbations and hospitalizations (38, 39). The nature of the association between anxiety, COPD, and risk of death should be explored in other cohorts because this condition is potentially treatable (40). The risk conferred by peptic ulcer disease is very interesting in light of the findings reported by the ECLIPSE (41) investigators, where one of the predictors of frequent COPD exacerbations was the presence of gastroesophageal reflux.

To fill the need for a simple specific tool of use to clinicians and researchers to quantify the comorbidities of patients with COPD, we developed the COTE index. Our data demonstrate that measurements of comorbidities as captured by the COTE index improve the prognostic accuracy for mortality in COPD when added to the BODE index. Using C statistic, the behavior of the COTE index to predict mortality was similar to that of the Charlson index but it is simpler to construct. The COTE index captures such diseases as atrial fibrillation, pulmonary fibrosis, and anxiety, which confer increased risk of death otherwise not included in the Charlson index. However, the Charlson index includes such comorbidities as renal and liver disease, categorized by a severity grading system that is not well defined, and it places very high values to diseases that are currently better controlled, such as AIDS (24).

To validate the usefulness of the COTE index, we split the cohort into those patients recruited in Spain and those in the United States. The same association was documented at each of the study sites. For Spain the HR was 1.12 (95% CI, 1.10–1.15; $P < 0.001$), whereas in the United States the HR was 1.13 (95% CI, 1.11–1.16; $P < 0.001$). The results of this study also show that a combination of BODE and COTE index provides healthcare workers and researchers with simple tools to better stratify patients and provide a platform for comparative effectiveness research (32).

This study has some limitations. First, there were few women included in the cohort. This was not by design, but it is the reality of the patients attending the clinics where the study is being conducted. However, there were 186 of them and with this number it was possible to identify breast cancer and anxiety as 2 of the 12 diseases that carried an independent increased risk of death. We find this relationship extremely interesting and worth studying in other cohorts. Second, at baseline some patients were excluded because of comorbidities that could cause early death and

difficulty in performing all of the tests. Specifically, patients with a recent myocardial infarction (4 mo), severe congestive heart failure, and untreated cancer were not recruited into the study. However, this should have worked against our findings by decreasing potential contributors to the diseases that have a high prevalence but that also conferred a poor prognosis to patients who developed them during the follow-up period, and provide a possible explanation of the better performance of the COTE index after 18 months of observation. Despite this exclusion at baseline, all three diseases when developed significantly increased the chance of death over the study time. Third, findings may not apply to all patients with COPD, because the patients were recruited from specialty clinics. However, as seen in Table 1, there were a large number of patients at all Global Initiative for Chronic Obstructive Lung Disease stages and BODE quartiles, and in addition, it is likely that patients such as the ones here studied represent most of those seen by practicing physicians in primary care (42).

In summary, we have confirmed that patients with COPD are frequently afflicted by comorbidities. A group of 12 easily identifiable comorbidities confer an independent risk of death and could form the core of diseases that could be screened by healthcare providers caring for these patients, because for some of them there are effective interventions that may help decrease the risk of death. We present the “comorbidome” as a novel expression of the prevalence of comorbidities and the strength of their association with risk of death in patients with COPD. Finally, the COTE index developed in this COPD cohort is a simple predictor of risk of death that complements the accepted BODE index and could be used to quantify the burden of comorbidity in the clinical and research setting.

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors dedicate this manuscript to honor the legacy of their dear coauthor and friend Claudia Cote, M.D. (1960–2010), for her outstanding contribution to chronic obstructive pulmonary disease research and her unconditional friendship. It is only appropriate that the proposed index, if accepted by the pulmonary community, may perpetuate her name in the field to which she devoted her life. The authors thank Michele Adrian (Wanted Design Studio) for her contribution to the graphic design of the comorbidome.

References

- Chen JC, Mannino DM. Worldwide epidemiology of chronic obstructive pulmonary disease. *Curr Opin Pulm Med* 1999;5:93–99.
- Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet* 2006;367:1747–1757.
- Anthonisen NR, Connett JE, Enright PL, Manfreda J. Hospitalizations and mortality in the lung health study. *Am J Respir Crit Care Med* 2002;166:333–339.
- Hansell AL, Walk JA, Soriano JB. What do chronic obstructive pulmonary disease patients die from? A multiple cause coding analysis. *Eur Respir J* 2003;22:809–814.
- Mannino DM, Aguayo SM, Petty TL, Redd SC. Low lung function and incident lung cancer in the United States: data from the first National Health and Nutrition Examination Survey follow-up. *Arch Intern Med* 2003;163:1475–1480.
- Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur Respir J* 2008;32:962–969.
- Berry CE, Wise RA. Mortality in COPD: causes, risk factors, and prevention. *COPD* 2010;7:375–382.
- McGarvey LP, John M, Anderson JA, Zvarich M, Wise RA. Ascertainment of cause-specific mortality in COPD: operations of the torch clinical endpoint committee. *Thorax* 2007;62:411–415.
- Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, Pinto Plata V, Cabral HJ. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004;350:1005–1012.

10. Puhan MA, Garcia-Aymerich J, Frey M, ter Riet G, Anto JM, Agusti AG, Gomez FP, Rodriguez-Roisin R, Moons KG, Kessels AG, et al. Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated BODE index and the ADO index. *Lancet* 2009;374:704–711.
11. Jones RC, Donaldson GC, Chavannes NH, Kida K, Dickson-Spillmann M, Harding S, Wedzicha JA, Price D, Hyland ME. Derivation and validation of a composite index of severity in chronic obstructive pulmonary disease: the DOSE index. *Am J Respir Crit Care Med* 2009;180:1189–1195.
12. Crisafulli E, Costi S, Luppi F, Cirelli G, Cilione C, Coletti O, Fabbri LM, Clini EM. Role of comorbidities in a cohort of patients with COPD undergoing pulmonary rehabilitation. *Thorax* 2008;63:487–492.
13. van Manen JG, Bindels PJ, Dekker FW, Bottema BJ, van der Zee JS, IJzermans CJ, Schade E. The influence of COPD on health-related quality of life independent of the influence of comorbidity. *J Clin Epidemiol* 2003;56:1177–1184.
14. Antonelli Incalzi R, Fuso L, De Rosa M, Forastiere F, Rapiti E, Nardecchia B, Pistelli R. Co-morbidity contributes to predict mortality of patients with chronic obstructive pulmonary disease. *Eur Respir J* 1997;10:2794–2800.
15. Terzano C, Conti V, Di Stefano F, Petroianni A, Ceccarelli D, Graziani E, Mariotta S, Ricci A, Vitarelli A, Puglisi G, et al. Comorbidity, hospitalization, and mortality in COPD: results from a longitudinal study. *Lung* 2010;188:321–329.
16. van Manen JG, Bindels PJ, IJzermans CJ, van der Zee JS, Bottema BJ, Schade E. Prevalence of comorbidity in patients with a chronic airway obstruction and controls over the age of 40. *J Clin Epidemiol* 2001;54:287–293.
17. Soriano JB, Visick GT, Muellerova H, Payvandi N, Hansell AL. Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. *Chest* 2005;128:2099–2107.
18. Sidney S, Sorel M, Quesenberry CP Jr, DeLuise C, Lanes S, Eisner MD. COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanente medical care program. *Chest* 2005;128:2068–2075.
19. Divo MJ, Cote C, De Torres JP, Casanova C, Marin JM, Pinto-Plata V, Zulueta J, Cabrera C, Zagaceta J, Celli B. Development and validation of a new comorbidity index for COPD. Presented at the European Respiratory Society Annual Congress. September 24–28, 2011, Amsterdam, The Netherlands. p. 253.
20. Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004;23:932–946.
21. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–383.
22. Cook NR, Ridker PM. Advances in measuring the effect of individual predictors of cardiovascular risk: the role of reclassification measures. *Ann Intern Med* 2009;150:795–802.
23. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (redcap): a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–381.
24. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol* 1994;47:1245–1251.
25. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. *Eur Respir J* 2009;33:1165–1185.
26. Agusti A, Sobradillo P, Celli B. Addressing the complexity of COPD. *Am J Respir Crit Care Med* 2011;183:1129–1137.
27. Jorgensen NR, Schwarz P, Holme I, Henriksen BM, Petersen LJ, Backer V. The prevalence of osteoporosis in patients with chronic obstructive pulmonary disease: a cross sectional study. *Respir Med* 2007;101:177–185.
28. Cote C, Zilberberg MD, Mody SH, Dordelly LJ, Celli B. Haemoglobin level and its clinical impact in a cohort of patients with COPD. *Eur Respir J* 2007;29:923–929.
29. Hill K, Geist R, Goldstein RS, Lacasse Y. Anxiety and depression in end-stage COPD. *Eur Respir J* 2008;31:667–677.
30. Couillard A, Prefaut C. From muscle disuse to myopathy in COPD: potential contribution of oxidative stress. *Eur Respir J* 2005;26:703–719.
31. Fabbri LM, Luppi F, Beghe B, Rabe KF. Complex chronic comorbidities of COPD. *Eur Respir J* 2008;31:204–212.
32. Tinetti ME, Studenski SA. Comparative effectiveness research and patients with multiple chronic conditions. *N Engl J Med* 2011;364:2478–2481.
33. Turner MC, Chen Y, Krewski D, Calle EE, Thun MJ. Chronic obstructive pulmonary disease is associated with lung cancer mortality in a prospective study of never smokers. *Am J Respir Crit Care Med* 2007;176:285–290.
34. Brody JS, Spira A. State of the art. Chronic obstructive pulmonary disease, inflammation, and lung cancer. *Proc Am Thorac Soc* 2006;3:535–537.
35. de Torres JP, Marín JM, Casanova C, Cote C, Carrizo S, Cordoba-Lanus E, Baz-Dávila R, Zulueta JJ, Aguirre-Jaime A, Saetta M, et al. Lung cancer in patients with COPD: incidence and predicting factors. *Am J Respir Crit Care Med* 2011;184:913–919.
36. Washko GR, Hunninghake GM, Fernandez IE, Nishino M, Okajima Y, Yamashiro T, Ross JC, Estepar RS, Lynch DA, Brehm JM, et al. Lung volumes and emphysema in smokers with interstitial lung abnormalities. *N Engl J Med* 2011;364:897–906.
37. Laurin C, Lavoie KL, Bacon SL, Dupuis G, Lacoste G, Cartier A, Labrecque M. Sex differences in the prevalence of psychiatric disorders and psychological distress in patients with COPD. *Chest* 2007;132:148–155.
38. Gudmundsson G, Gislason T, Janson C, Lindberg E, Suppli Ulrik C, Brondum E, Nieminen MM, Aine T, Hallin R, Bakke P. Depression, anxiety and health status after hospitalisation for COPD: a multi-centre study in the Nordic countries. *Respir Med* 2006;100:87–93.
39. Xu W, Collet JP, Shapiro S, Lin Y, Yang T, Platt RW, Wang C, Bourbeau J. Independent effect of depression and anxiety on chronic obstructive pulmonary disease exacerbations and hospitalizations. *Am J Respir Crit Care Med* 2008;178:913–920.
40. Paz-Diaz H, Montes de Oca M, Lopez JM, Celli BR. Pulmonary rehabilitation improves depression, anxiety, dyspnea and health status in patients with COPD. *Am J Phys Med Rehabil* 2007;86:30–36.
41. Agusti A, Calverley PM, Celli B, Coxson HO, Edwards LD, Lomas DA, MacNee W, Miller BE, Rennard S, Silverman EK, et al. Characterisation of COPD heterogeneity in the eclipse cohort. *Respir Res* 2010;11:122.
42. Steuten LM, Creutzberg EC, Vrijhoef HJ, Wouters EF. COPD as a multicomponent disease: inventory of dyspnoea, underweight, obesity and fat free mass depletion in primary care. *Prim Care Respir J* 2006;15:84–91.