ORIGINAL ARTICLE

The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index in Chronic Obstructive Pulmonary Disease

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ABSTRACT

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is characterized by an incompletely reversible limitation in airflow. A physiological variable — the forced expiratory volume in one second (FEV_1) — is often used to grade the severity of COPD. However, patients with COPD have systemic manifestations that are not reflected by the FEV_1. We hypothesized that a multidimensional grading system that assessed the respiratory and systemic expressions of COPD would better categorize and predict outcome in these patients.

METHODS

We first evaluated 207 patients and found that four factors predicted the risk of death in this cohort: the body-mass index (B), the degree of airflow obstruction (O) and dyspnea (D), and exercise capacity (E), measured by the six-minute–walk test. We used these variables to construct the BODE index, a multidimensional 10-point scale in which higher scores indicate a higher risk of death. We then prospectively validated the index in a cohort of 625 patients, with death from any cause and from respiratory causes as the outcome variables.

RESULTS

There were 25 deaths among the first 207 patients and 162 deaths (26 percent) in the validation cohort. Sixty-one percent of the deaths in the validation cohort were due to respiratory insufficiency, 14 percent to myocardial infarction, 12 percent to lung cancer, and 13 percent to other causes. Patients with higher BODE scores were at higher risk for death; the hazard ratio for death from any cause per one-point increase in the BODE score was 1.34 (95 percent confidence interval, 1.26 to 1.42; P<0.001), and the hazard ratio for death from respiratory causes was 1.62 (95 percent confidence interval, 1.48 to 1.77; P<0.001). The C statistic for the ability of the BODE index to predict the risk of death was larger than that for the FEV_1 (0.74 vs. 0.65).

CONCLUSIONS

The BODE index, a simple multidimensional grading system, is better than the FEV_1 at predicting the risk of death from any cause and from respiratory causes among patients with COPD.

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CHRONIC OBSTRUCTIVE PULMONARY disease (COPD), a common disease characterized by a poorly reversible limitation in airflow,[1] is predicted to be the third most frequent cause of death in the world by 2020.[2] The risk of death in patients with COPD is often graded with the use of a single physiological variable, the forced expiratory volume in one second (FEV_1).[1,3,4] However, other risk factors, such as the presence of hypoxemia or hypercapnia,[5,6] a short distance walked in a fixed time,[7] a high degree of functional breathlessness,[8] and a low body-mass index (the weight in kilograms divided by the square of the height in meters),[9,10] are also associated with an increased risk of death. We hypothesized that a multidimensional grading system that assessed the respiratory, perceptive, and systemic aspects of COPD would better categorize the illness and predict the outcome than does the FEV_1 alone. We used data from an initial cohort of 207 patients to identify four factors that predicted the risk of death: the body-mass index (B), the degree of airflow obstruction (O) and functional dyspnea (D), and exercise capacity (E) as assessed by the six-minute–walk test. We then integrated these variables into a multidimensional index — the BODE index — and validated the index in a second cohort of 625 patients, with death from any cause and death from respiratory causes as the outcome variables.

METHODS

Between January 1997 and June 2002, a total of 859 outpatients with a wide range in the severity of COPD were recruited from clinics in the United States, Spain, and Venezuela. The study was approved by the human-research review board at each site, and all patients provided written informed consent. COPD was defined by a history of smoking that exceeded 20 pack-years and a ratio of FEV_1 to forced vital capacity (FVC) of less than 0.7 measured 20 minutes after the administration of albuterol.[1] All patients were in clinically stable condition and receiving appropriate therapy. Patients who were receiving inhaled oxygen had to have been taking a stable dose for at least six months before study entry. The exclusion criteria were an illness other than COPD that was likely to result in death within three years; asthma, defined as an increase in the FEV_1 of more than 15 percent above the base-line value or of 200 ml after the administration of a bronchodilator; an inability to take the lung-function

and six-minute–walk tests; a myocardial infarction within the preceding four months; unstable angina; or congestive heart failure (New York Heart Association class III or IV).

VARIABLES SELECTED FOR THE BODE INDEX

We determined the following variables in the first 207 patients who were recruited between 1995 and 1997: age; sex; pack-years of smoking; FVC; FEV_1, measured in liters and as a percentage of the predicted value according to the guidelines of the American Thoracic Society[11]; the best of two six-minute–walk tests performed at least 30 minutes apart[12]; the degree of dyspnea, measured with the use of the modified Medical Research Council (MMRC) dyspnea scale[13]; the body-mass index[9,10]; the functional residual capacity and inspiratory capacity[11]; the hematocrit; and the albumin level. The validated Charlson index was used to determine the degree of comorbidity. This index has been shown to predict mortality.[14] The differences in these values between survivors and nonsurvivors are shown in Table 1.

Each of these possible explanatory variables was independently evaluated to determine its association with one-year mortality in a stepwise forward logistic-regression analysis. A subgroup of four variables had the strongest association — the body-mass index, FEV_1 as a percentage of the predicted value, score on the MMRC dyspnea scale, and the distance walked in six minutes (generalized $r^2=0.21$, P<0.001) — and these were included in the BODE index (Table 2). All these variables predict important outcomes, are easily measured, and may change over time. We chose the post-bronchodilator FEV_1 as a percent of the predicted value, classified according to the three stages identified by the American Thoracic Society, because it can be used to predict health status,[15] the rate of exacerbation of COPD,[16] the pharmacoeconomic costs of the disease,[17] and the risk of death.[18,19] We chose the MMRC dyspnea scale because it predicts the likelihood of survival among patients with COPD[8] and correlates well with other scales and health-status scores.[20,21] We chose the six-minute–walk test because it predicts the risk of death in patients with COPD,[7] patients who have undergone lung-reduction surgery,[22] patients with cardiomyopathy,[23] and those with pulmonary hypertension.[24] In addition, the test has been standardized,[12] the clinically significant thresholds have been determined,[25] and it can be used to predict resource uti-

lization.[26] Finally, there is an inverse relation between body-mass index and survival[9,10] that is not linear but that has an inflection point, which was 21 in our cohort and in another study.[10]

VALIDATION OF THE BODE INDEX

The BODE index was validated prospectively in two ways in a different cohort of 625 patients who were recruited between January 1997 and January 2003. First, we used the empirical model: for each threshold value of FEV_1, distance walked in six minutes, and score on the MMRC dyspnea scale shown in Table 2, the patients received points ranging from 0 (lowest value) to 3 (maximal value). For body-mass index the values were 0 or 1, because of the unique relation between body-mass index and survival described above. The points for each variable were added, so that the BODE index ranged from 0 to 10 points, with higher scores indicating a greater risk of death. In an exploratory analysis, the various components of the BODE index were assigned different weights, with no corresponding increase in predictive value.

STUDY PROTOCOL

In the cohort, patients were evaluated with the use of the BODE index within six weeks after enrollment and were seen every three to six months for at least two years or until death. The patient and family were contacted if the patient failed to return for appointments. Death from any cause and from specific respiratory causes was recorded. The cause of death was determined by the investigators at each site after reviewing the medical record and death certificate.

STATISTICAL ANALYSIS

Data for continuous variables are presented as means ±SD. Comparison among the three countries was completed with the use of one-way analysis of variance. The differences between survivors and nonsurvivors in pulmonary-function variables and other pertinent characteristics were established with the use of t-tests for independent samples. To evaluate the capacity of the BODE index to predict the risk of death, we performed Cox proportional-hazards regression analyses.[27] We estimated the hazard ratio, 95 percent confidence interval, and P value for the BODE score, before and after adjustment for coexisting conditions as measured by the Charlson index. We repeated these analyses using the BODE index as the predictor of interest in

Table 1. Characteristics of the First 207 Patients, According to Whether They Survived.*

Characteristic	Survived (N=182)	Died (N=25)	P Value
	mean ±SD		
Age (yr)	66±9	70±7	0.03
FVC (liters)	2.78±0.89	2.27±0.57	0.04
FEV_1			
Liters	1.31±0.63	0.84±0.33	0.002
Percent of predicted	43±19	28±12	0.001
FRC (%)	150±43	170±52	0.12
Inspiratory capacity (liters)	2.0±0.7	1.6±0.5	0.007
MMRC dyspnea scale†	2.7±0.89	3.3±0.87	0.001
Distance walked in 6 min (m)	264±113	175±86	0.001
Body-mass index‡	26±5	23±5	0.002
Hematocrit (%)	42±5	39±5	0.01
Albumin (g/ml)	4.0±0.3	3.8±0.4	0.08
Smoking history (pack-yr)	88±48	77±48	0.36
Charlson index§	2.9±1.3	5.9±1.9	0.02

* FVC denotes forced vital capacity, FEV_1 forced expiratory volume in one second, and FRC functional residual capacity.
† Scores on the modified Medical Research Council (MMRC) dyspnea scale can range from 0 to 4, with a score of 4 indicating that the patient is too breathless to leave the house or becomes breathless when dressing or undressing.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Scores on the Charlson index can range from 0 to 33, with higher scores indicating more coexisting conditions.

Table 2. Variables and Point Values Used for the Computation of the Body-Mass Index, Degree of Airflow Obstruction and Dyspnea, and Exercise Capacity (BODE) Index.*

Variable	Points on BODE Index			
	0	1	2	3
FEV_1 (% of predicted)†	≥65	50–64	36–49	≤35
Distance walked in 6 min (m)	≥350	250–349	150–249	≤149
MMRC dyspnea scale‡	0–1	2	3	4
Body-mass index§	>21	≤21		

* The cutoff values for the assignment of points are shown for each variable. The total possible values range from 0 to 10. FEV_1 denotes forced expiratory volume in one second.
† The FEV_1 categories are based on stages identified by the American Thoracic Society.
‡ Scores on the modified Medical Research Council (MMRC) dyspnea scale can range from 0 to 4, with a score of 4 indicating that the patient is too breathless to leave the house or becomes breathless when dressing or undressing.
§ The values for body-mass index were 0 or 1 because of the inflection point in the inverse relation between survival and body-mass index at a value of 21.

dummy-variable form, using the first quartile as the reference group. These analyses yielded estimates of risk similar to those obtained from analyses using the BODE score as a continuous variable. Thus, we focus our presentation on the predictive characteristics of the BODE index and present only bivariate results for survival according to quartiles of the BODE index in a Kaplan–Meier analysis. The statistical significance was evaluated with the use of the log-rank test. We also performed bivariate analysis on the stage of COPD according to the validated staging system of the American Thoracic Society.[3]

In the Cox regression analysis, we assessed the reliability of the model with the body-mass index, degree of airflow obstruction and dyspnea, and exercise capacity score as the predictor of the time to death by computing bootstrap estimates using the full sample for the hazard ratio and its 95 percent confidence interval (according to the percentile method). This approach has the advantage of not requiring that the data be split into subgroups and is more precise than alternative methods, such as cross-validation.[28]

Finally, in order to determine how much more precise the BODE index is than the FEV_1 alone, we computed the C statistics[29] for a model containing FEV_1 or the BODE score as the sole independent variable. We compared the survival times and estimated the probabilities of death up to 52 months. In these analyses, the C statistic is a mathematical function of the sensitivity and specificity of the BODE index in classifying patients by means of the Cox model as either dying or surviving. The null value for the C statistic is 0.5, with a maximum of 1.0 (with higher values being better).[29]

RESULTS

The validation cohort consisted primarily of elderly patients (Tables 3 and 4) with all degrees of severity of COPD. The FEV_1 was slightly lower among patients in the United States than among those in Venezuela or Spain. The U.S. patients also had more functional impairment, more severe dyspnea, and more coexisting conditions. The 27 patients (4 percent) lost to follow-up were evenly distributed according to the severity of COPD and did not differ significantly from the rest of the cohort with respect to any measured characteristic. There were 162 deaths (26 percent) over a median follow-up of 28 months (range, 4 to 68). The majority of patients (61 percent) died of respiratory insufficiency, 14

Table 3. Characteristics of the Patients in the Validation Cohort.

Characteristic	No. of Patients (%) (N=625)
Severity of COPD*	
Stage I (FEV_1 >50% of predicted)	186 (30)
Stage II (FEV_1, 36–50% of predicted)	204 (33)
Stage III (FEV_1 ≤35 percent of predicted)	235 (38)
BODE index score†	
0	33 (5)
1	55 (9)
2	81 (13)
3	95 (15)
4	92 (15)
5	75 (12)
6	55 (9)
7	60 (10)
8	43 (7)
9	24 (4)
10	12 (2)

* Because of rounding, percentages do not total 100. The three stages of chronic obstructive pulmonary disease (COPD) were defined by the American Thoracic Society. FEV_1 denotes forced expiratory volume in one second.
† Higher scores on the body-mass index, degree of airflow obstruction and dyspnea, and exercise capacity (BODE) index indicate a greater risk of death. Quartile 1 was defined by a score of 0 to 2, quartile 2 by a score of 3 to 4, quartile 3 by a score of 5 to 6, and quartile 4 by a score of 7 to 10.

percent died of myocardial infarction, 12 percent of lung cancer, and the rest of miscellaneous causes. The BODE score was lower among survivors than among those who died from any cause (3.7±2.2 vs. 5.9±2.6, P<0.005). The score was also lower among survivors than among those who died of respiratory causes, and the difference between the scores was larger (3.6±2.2 vs. 6.7±2.3, P<0.001).

Table 5 shows the BODE index as a predictor of death from any cause after correction for coexisting conditions. There were significantly more deaths in the United States (32 percent) than in Spain (15 percent) or Venezuela (13 percent) (P<0.001). However, when the analysis was done separately for each country, the predictive power of the BODE index was similar; therefore, the data are presented together. Table 5 shows that the BODE index was also a predictor of death from respiratory causes after correction for coexisting conditions (hazard ratio, 1.63; 95 percent confidence interval, 1.48 to 1.80; P<0.001). The Kaplan–Meier analysis of sur-

vival (Fig. 1A) shows that each quartile increase in the BODE score was associated with increased mortality (P<0.001). Thus, the highest quartile (a BODE score of 7 to 10) was associated with a mortality rate of 80 percent at 52 months. These same data are shown in Figure 1B in relation to the severity of COPD according to the staging system of the American Thoracic Society. The C statistic for 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 (expressed as a percentage of the predicted value). The computation of 2000 bootstrap samples for these data and estimation of the hazard ratios for death indicated that for each one-point increment in the BODE score the hazard ratio for death from any cause was 1.34 (95 percent confidence interval, 1.26 to 1.42) and the hazard ratio for death from a respiratory cause was 1.62 (95 percent confidence interval, 1.48 to 1.77).

DISCUSSION

We devised a simple grading system for COPD — the BODE index — and validated its use by showing that it is a better predictor of the risk of death from any cause and from respiratory causes than is the FEV_1 alone. We believe that the BODE index is useful because it includes one domain that quantifies the degree of pulmonary impairment (FEV_1), one that captures the patient's perception of symptoms (the MMRC dyspnea scale), and two independent domains (the distance walked in six minutes and the body-mass index) that express the systemic consequences of COPD. The FEV_1 is essential for the diagnosis and quantification of the respiratory impairment resulting from COPD.[1,3,4] In addition, the rate of decline in FEV_1 is a good marker of disease progression and mortality.[18,19] However, the FEV_1 does not adequately reflect all the systemic manifestations of the disease. For example, the FEV_1 correlates weakly with the degree of dyspnea,[20] and the change in FEV_1 does not reflect the rate of decline in patients' health.[30] More important, prospective observational studies of patients with COPD have found that the degree of dyspnea[8] and health-status scores[31] are more accurate predictors of the risk of death than is the FEV_1. Thus, although the FEV_1 is important to obtain and essential in the staging of disease in any patient with COPD, other variables provide useful information that can improve the comprehensibility of the evaluation of patients with COPD. Each variable should

Table 4. Characteristics of the Validation Cohort According to Country.*

Characteristic	Spain (N=223)	Venezuela (N=54)	United States (N=348)	P Value†
Age (yr)	66±8	64±10	67±9	0.02
Body-mass index	27.5±4.5	23.4±4.7	26.2±4.7	<0.001
FEV_1 (%)	47±17	47±19	39±15	<0.001
MMRC dyspnea scale‡	1.7±1.2	2.1±1.1	2.7±0.8	<0.001
Distance walked in 6 min (m)	446±99	225±40	311±121	<0.001
FEV_1 (liters)	1.29±0.52	1.4±0.64	1.20±0.57	0.01
FVC (liters)	2.92±0.98	2.8±0.94	2.72±0.8	0.09
Charlson index§	2.9±1.3	3.9±1.5	5.3±3.1	<0.001
BODE index¶	2.9±2.2	4.9±2.1	5.1±2.4	<0.001

* Plus–minus values are means ±SD.
† Analysis of variance was used to calculate the P values.
‡ Scores on the modified Medical Research Council (MMRC) dyspnea scale can range from 0 to 4, with a score of 4 indicating that the patient is too breathless to leave the house or becomes breathless when dressing or undressing.
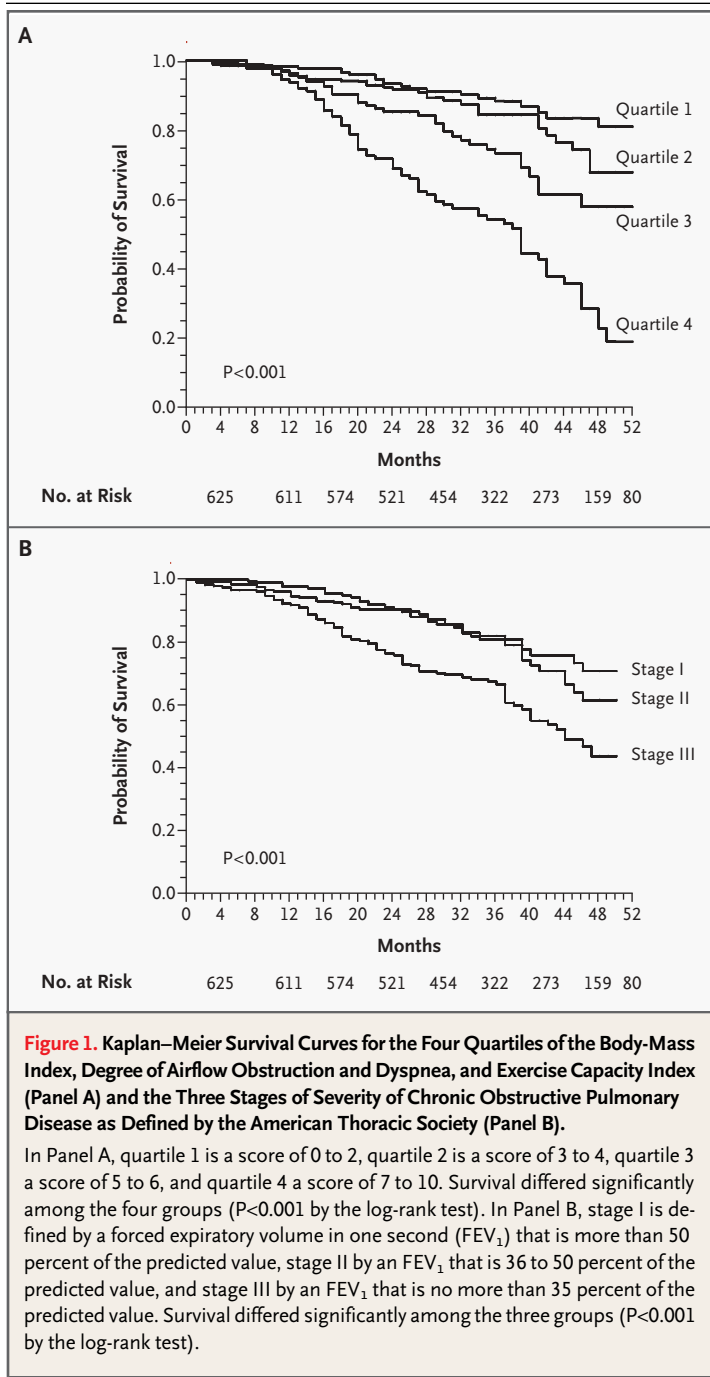§ Scores on the Charlson index can range from 0 to 33, with higher scores indicating more coexisting conditions.
¶ Scores on the body-mass index, degree of airflow obstruction and dyspnea, and exercise capacity (BODE) index can range from 0 to 10, with higher scores indicating a greater risk of death.

Table 5. Risk of Death from Any Cause and from Respiratory Failure, Pneumonia, or Pulmonary Embolism.*

Variable	Hazard Ratio (95% CI)	P Value
Risk of death from all causes		
Model I		
BODE score	1.34 (1.26–1.42)	<0.001
Model II		
BODE score	1.32 (1.23–1.40)	<0.001
Charlson index	1.05 (1.00–1.10)	0.06
Death from respiratory failure, pneumonia, or pulmonary embolism		
Model I		
BODE score	1.62 (1.48–1.77)	<0.001
Model II		
BODE score	1.63 (1.48–1.80)	<0.001
Charlson index	0.99 (0.93–1.07)	0.97

* The Cox proportional-hazards models for death from any cause include 162 deaths. The Cox proportional-hazards models for death from specific respiratory causes include 96 deaths. Model I includes the body-mass index, degree of airflow obstruction and dyspnea, and exercise capacity (BODE) index alone. The hazard ratio is for each one-point increase in the BODE score. Model II includes coexisting conditions as expressed by each one-point increase in the Charlson index. CI denotes confidence interval.

Figure 1. Kaplan–Meier Survival Curves for the Four Quartiles of the Body-Mass Index, Degree of Airflow Obstruction and Dyspnea, and Exercise Capacity Index (Panel A) and the Three Stages of Severity of Chronic Obstructive Pulmonary Disease as Defined by the American Thoracic Society (Panel B).

In Panel A, quartile 1 is a score of 0 to 2, quartile 2 is a score of 3 to 4, quartile 3 a score of 5 to 6, and quartile 4 a score of 7 to 10. Survival differed significantly among the four groups (P<0.001 by the log-rank test). In Panel B, stage I is defined by a forced expiratory volume in one second (FEV$_1$) that is more than 50 percent of the predicted value, stage II by an FEV$_1$ that is 36 to 50 percent of the predicted value, and stage III by an FEV$_1$ that is no more than 35 percent of the predicted value. Survival differed significantly among the three groups (P<0.001 by the log-rank test).

correlate independently with the prognosis of COPD, should be easily measurable, and should serve as a surrogate for other potentially important variables.

In the BODE index, we included two descriptors of systemic involvement in COPD: the body-mass index and the distance walked in six minutes. Both are simply obtained and independently predict the risk of death.[7,9,10] It is likely that they share some common underlying physiological determinants, but the distance walked in six minutes contains a degree of sensitivity not provided by the body-mass index. The six-minute–walk test is simple to perform and has been standardized.[12] Its use as a clinical tool has gained acceptance, since it is a good predictor of the risk of death among patients with other chronic diseases, including congestive heart failure[23] and pulmonary hypertension.[24] Indeed, the distance walked in six minutes has been accepted as a good outcome measure after interventions such as pulmonary rehabilitation.[32] The body-mass index was also an independent predictor of the risk of death and was therefore included in the BODE index. We evaluated the independent prognostic power of body-mass index in our cohort using different thresholds and found that values below 21 were associated with an increased risk of death, an observation similar to that reported by Landbo and coworkers in a large population study.[10]

The Global Initiative for Chronic Obstructive Lung Disease and the American Thoracic Society recommend that a patient's perception of dyspnea be included in any new staging system for COPD.[1,3] Dyspnea represents the most disabling symptom of COPD; the degree of dyspnea provides information regarding the patient's perception of illness and can be measured. The MMRC dyspnea scale is simple to administer and correlates with other dyspnea scales[20] and with scores of health status.[21] Furthermore, in a large cohort of prospectively followed patients with COPD, which used the threshold values included in the BODE index, the score on the MMRC dyspnea scale was a better predictor of the risk of death than was the FEV$_1$.[8]

The BODE index combines the four variables by means of a simple scale. We also explored whether weighting the variables included in the index improved the predictive power of the BODE index. Interestingly, it failed to do so, most likely because each variable included has already proved to be a good predictor of the outcome of COPD.

Our study had some limitations. First, relatively few women were recruited, even though enrollment was independent of sex. It probably reflects the problem of the underdiagnosis of COPD in women. Second, there were differences among the three countries. For example, patients in the United States had a higher mortality rate, more severe dyspnea, more functional limitations, and more co-

existing conditions than patients in Venezuela or Spain, even though the severity of airflow obstruction was relatively similar among the patients as a whole. The reasons for these differences are unknown, because there have been no systematic comparisons of the regional manifestations of COPD. In all three countries, the BODE index was the best predictor of survival, an observation that renders our findings widely applicable.

Three studies have reported the effects of the grouping of variables to express the various domains affected by COPD.[33-35] These studies did not include variables now known to be important predictors of outcome, such as the body-mass index. However, as we found in our study, they showed that the FEV_1, the degree of dyspnea, and exercise performance provide independent information regarding the degree of compromise in patients with COPD.

Besides its excellent predictive power with regard to outcome, the BODE index is simple to calculate and requires no special equipment. This makes it a practical tool of potentially widespread applicability. Although the BODE index is a predictor of the risk of death, we do not know whether it will be a useful indicator of the outcome in clinical trials, the degree of utilization of health care resources, or the clinical response to therapy.

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