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# Predictors of Survival in COPD: More than Just the FEV<sub>1</sub>

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## KEYWORDS

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**Summary** Chronic obstructive pulmonary disease (COPD) ranks fourth as a cause of death in the United States, behind heart disease, cancer, and stroke. Additionally, since serious co-morbidities are often present in patients with COPD, many die from other diseases such as cardiac disease or cancer. Not surprisingly, multiple factors, reflective of both respiratory disease process and the substantial co-morbidity, predict survival in the disease. As might be expected, physiologic derangements such as airflow obstruction, hypoxemia, lung hyperinflation, and exercise capacity predict survival in COPD. Anemia, cachexia and reductions in lean body mass also relate to prognosis. Perhaps less recognized is the more recent documentation that more subjective assessments, such as dyspnea and health related quality of life, are also important predictors of survival. The integration of some of the most important of these variables may provide a more comprehensive evaluation of disease severity. For example, a validated multi-dimensional disease rating that includes the body mass index (B), degree of airflow obstruction (O), dyspnea (D), and exercise capacity (E) (BODE Index) is capable of predicting COPD-related hospitalization and mortality more than its individual components. © 2008 Elsevier Ltd. All rights reserved.

## Mortality in COPD

Since individuals with COPD are at substantial risk for serious co-morbidity such as cardiovascular disease and cancer, it is perhaps not surprising they frequently die with their disease, not from it. De-

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pending on the characteristics of the samples studied, about 1/3 to 1/2 or more of deaths are due to causes other than COPD. These findings undoubtedly point toward co-morbidity, which is pervasive in this population. Some of the factors related to survival in COPD are discussed below.

## Markers for Mortality in COPD

### Forced expiratory volume in 1 second (FEV<sub>1</sub>)

Although no single physiologic measure can capture the multiple factors that elevate the risk for mortality in patients with COPD, the diminished FEV<sub>1</sub> has a long-established association with increased mortality in this disease. For example, in the Intermittent Positive Pressure Breathing (IPPB) trial, the patient's age and initial FEV<sub>1</sub> values were the most accurate predictors of mortality in 985 patients with COPD who were followed for 3 years.<sup>1</sup> FEV<sub>1</sub> has long been used in COPD as the principal variable determining the presence of disease, its severity, and the response to different modalities of treatment.<sup>2</sup>

Cigarette smoking is without doubt the primary etiologic factor for COPD. Therefore, lifestyle changes, principally, smoking cessation, can reduce the accelerated decline in FEV<sub>1</sub> seen in susceptible patients, to the average to age-adjusted normal decline.<sup>3,4</sup> Nonetheless, in some susceptible smokers who quit, FEV<sub>1</sub> levels still decline after smoking cessation at an accelerated rate for reasons that remain obscure.

Pharmacologic intervention with long-acting inhaled bronchodilators, either alone<sup>5</sup> or combined with inhaled corticosteroids<sup>6</sup> can result in sustained improvements in FEV<sub>1</sub> by more than 15% for up to 1 year. Such findings have prompted large pharmacological trials with outcomes such as survival that have provided us with very valuable information<sup>7</sup>.

Bilateral lung volume reduction (LVR), a surgical technique reserved for patients with severe heterogeneous emphysema, may improve FEV<sub>1</sub> by almost 79% 6 months after the procedure.<sup>8</sup> Further in some selected patients with upper lobe emphysema and poor exercise capacity after rehabilitation, LVR can also improve survival.<sup>9</sup> The improvement in FEV<sub>1</sub> observed with single-lung transplantation can be as high as 231% and for bilateral-lung transplantation is 498%. It is thus possible to improve the degree of airflow limitation associated with this disease and concomitantly observe an improvement in survival. In those studies, the association of changes in survival as an outcome is loosely related to the change in FEV<sub>1</sub>.

### Lung hyperinflation

Severe hyperinflation is a recognizable characteristic of COPD expressed on the physical exam by the barrel-shaped chest seen in patients with emphysema.<sup>10</sup> In normal individuals, exercise produces tidal volume increases secondary to both increased end-inspiratory lung volume and reductions in end-expiratory lung volume or functional residual capacity. In COPD, by contrast, patients display *increases* in end-expiratory lung volume with exercise, therefore reducing inspiratory capacity and causing end-inspiratory lung volume to approach total lung capacity. Static hyperinflation represents a permanent elevation in end-expiratory lung volume, caused by changes in the elastic or recoil properties of the lungs that trigger increasing lung volumes. Some evidence supports the use of hyperinflation as a surrogate marker for mortality in COPD. For example, the relationship between lung hyperinflation, measured as the ratio of inspiratory capacity to total lung capacity or IC/TLC, and mortality in 689 patients (95% males) with COPD, was an important independent predictor of mortality after 34 months of follow-up. The increase in mortality became critical for an IC/TLC ratio below 25% (critical hyperinflation).<sup>11</sup> There is now accumulating evidence that hyperinflation can be effectively treated with pharmacotherapeutic agents<sup>12</sup> and even more effectively with lung volume reduction surgery.<sup>8</sup>

### Pulmonary cachexia

Weight loss is prevalent among patients with COPD, and has emerged as an independent risk factor for its mortality.<sup>13,14</sup> The impact of weight change on outcomes in COPD was examined retrospectively in 400 COPD patients who had not received nutritional therapy, and in a prospective post hoc analysis of 203 COPD patients who received nutritional support alone or in combination with anabolic steroids.<sup>15</sup> In the retrospective portion of the study, low body mass index (BMI) (<25 kg/m<sup>2</sup>) was associated with a significant increase in the risk for mortality ( $P < 0.001$ ). In a multivariate analysis of the prospective data, weight gain (>2 kg/8 wks) was a significant predictor of survival.<sup>15</sup> Although more evidence is needed before universal recommendations may be made, weight change can be considered an independent and modifiable risk factor for mortality in patients with COPD that also deserves surveillance.<sup>15</sup>

### Anemia

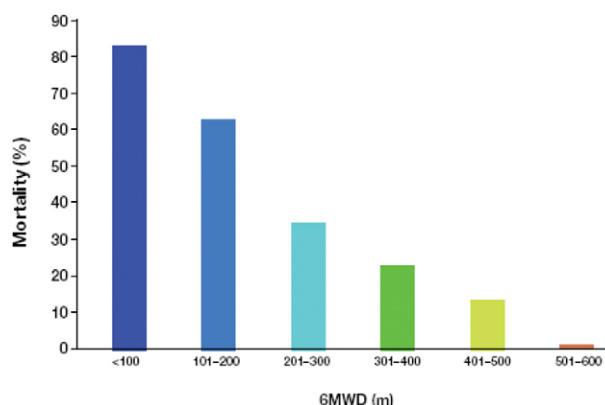
Anemia in COPD patients may be more prevalent than expected, affecting 10% to 15% of patients

suffering from severe forms of the disease.<sup>16</sup> In a study of 2,524 COPD patients who were prescribed long-term oxygen therapy, 12.6% of males and 8.2% of females were identified as anemic.<sup>17</sup> Recently, a linear correlation was identified between hemoglobin levels and mortality in a cohort that included 700 patients with COPD.<sup>18</sup> Anemia – hemoglobin < 12.9 g/dl – was present in 116 (17%) patients. Anemic patients had a significantly higher Medical Research Council (MRC) score, a lower 6-minute walk distance (6MWD) and a higher mortality than non anemic patients. These differences remained significant when controlling for the relevant demographic, physiologic, and disease covariates in regression analyses, where anemia was an independent predictor of the above outcomes. Other investigators have found anemia to be associated with poor outcomes in COPD.<sup>17,19</sup> Anemia may accompany disease chronicity and inflammation in COPD and contribute to poor exercise performance because of its association with worsening dyspnea, possibly due to a decrease in oxygen delivery. It is intuitive although remains unknown whether alleviating anemia in patients with COPD will lead to improved outcomes and reduced mortality.

### Exercise capacity

Exercise capacity, measured by the 6MWD test, has been significantly correlated with mortality in patients with COPD.<sup>20</sup> The 6MWD test has established reliability and validity in predicting survival in a variety of settings, including post-pulmonary rehabilitation and after lung-volume–reduction surgery (LVRS).<sup>20</sup> In 198 predominantly male patients (83%) with severe COPD who were followed for 2 years, survival increased progressively with increases in the 6MWD, when distances were divided into discrete 100-meter increments (Figure 1). Furthermore, the 6MWD test was a better predictor of mortality than FEV<sub>1</sub> and BMI. Importantly, the decline in 6MWD occurred independently of changes in FEV<sub>1</sub> indicating that both are possibly measuring different domains of the disease and could be considered complementary.

Several treatment approaches improve exercise capacity in patients with COPD. In 1,218 patients with severe emphysema, LVRS resulted in significantly greater improvements in exercise capacity after 24 months, compared with standard medical care.<sup>9</sup> Further, in patients with predominantly upper-lobe emphysema and diminished exercise capacity, significant reductions in mortality were seen in those who underwent LVRS. In contrast, patients with non–upper-lobe emphysema and high exercise



**Figure 1** Mortality progressively decreases as the 6-minute walk distance (6MWD) test score increases ( $P < 0.0001$ , by Chi-squared analysis). For distances < 100 m,  $n = 19$ ; for 101–200 m,  $n = 61$ ; for 201–300 m,  $n = 57$ ; for 301–400 m,  $n = 46$ ; and for > 400 m,  $n = 15$ .<sup>18</sup> Reprinted with permission from *Eur Respir J*. Copyright 2004, European Respiratory Society.

capacity experienced an increase in mortality in association with surgery.

Although less consistent than for the 6MWD, pharmacological treatments have also been shown to improve exercise endurance measured using a constant load exercise protocol during a formal cardiopulmonary exercise test.<sup>21,22</sup>

### Dyspnea

Dyspnea, the most fundamental and debilitating symptom of COPD should be routinely evaluated and considered in conjunction with pulmonary function when evaluating COPD. Pharmacological treatment with different agents and using different dyspnea scales have consistently shown to improve breathlessness in patients with COPD.<sup>21,23</sup> Pulmonary rehabilitation also is highly effective at decreasing dyspnea among COPD patients.<sup>24</sup>

Dyspnea has also been found to be predictive of survival in COPD. In a 5-year, prospective, multicenter trial of 227 patients with COPD,<sup>25</sup> survival rate was not significantly linked to COPD staging based on FEV<sub>1</sub>. Rather, dyspnea as measured using the Medical Research Council dyspnea questionnaire did predict survival ( $P < 0.001$ ).

### Quality of life, functional status, and activity level

Quality of life is a personal, subjective entity that it difficult to fully portray. However, health-related quality of life (HRQL), focusing on those aspects of quality of life affected by the disease and its treatment, is easier to quantify. The measurement of HRQL allows us to obtain a better picture of how

patients are affected by their illness. Assessment in subjective areas such as dyspnea and HRQL provides complementary information to physiologic measurements. For example, there is only a weak association between the level of dyspnea and degree of airway obstruction in COPD, and changes in dyspnea can occur without documented changes in the FEV<sub>1</sub>. While there is an association between physiologic measures and HRQL, other factors influence the individual's perception of this subjective variable. In COPD, these include symptoms, activity levels, social factors, emotional state, recreational factors and sleep.

There is frequently confusion over terminology in the measurement of dyspnea, HRQL, and functional status in COPD. For example, some dyspnea measures rate the symptom of breathlessness through its limitation on activity. Furthermore, activity level (also referred to as functional status) is an important component of questionnaire-rated HRQL measurement: it is generally either a major component or one of several domains of the instrument. Finally, walk tests or tests of exercise endurance have often been used as surrogate measures of overall activity levels.

Lower HRQL has been associated with mortality and morbidity in COPD. However, the considerable overlap (and confusion) among dyspnea, functional status, activity levels, and HRQL makes it difficult to determine just what components of this complex variable influence survival.

Oga *et al.*<sup>26</sup> studied 144 male COPD patients for 5 years. Most (64.5%) of the mortality over this period was due to respiratory related causes, yet the HRQL scores on two respiratory-specific instruments, the Saint George's Respiratory Questionnaire (SGRQ) and the Chronic Respiratory Disease Questionnaire (CRQ) were not different at baseline among those who survived from those who died.

Domingo-Salvany *et al.*<sup>27</sup> evaluated survival (using Cox multivariate hazard analysis) in 321 male COPD patients for over 7 years. Less than 50% of the 106 deaths were from respiratory causes. They determined that worse lung function, greater age, lower BMI and poorer HRQL (measured by the SGRQ) or poor physical function levels (physical component of SF-36) were predictive of respiratory-related mortality.

Martinez *et al.*<sup>28</sup> reported on mortality in 609 COPD patients enrolled in the medical arm of the National Emphysema Treatment Trial-NETT, 64.2% of whom were male. Median follow up was 3.9 years with a total mortality rate of 12.7%. Using multivariate hazard ratio, the modified BODE, followed by exercise test stress test and 6 MWD were highest predictors of mortality (HR  $\geq$  2). A multivariate

analysis was also undertaken using two models, one with the individual components of the BODE (model 1) and one (model 2) with a modified BODE index (substituting the MRC with the UCSD SOBQ). In the first model, age, oxygen use, RV (% pred), exercise workload, difference in percent of emphysema upper lung:lower lung (UL:LL), and perfusion ratio were significant. The SGRQ was not predictive of mortality and the SOBQ was not significantly related to mortality. In model 2, the model remained essentially the same with the only additional variable contributing being diffusion capacity, hemoglobin and the modified BODE. The greatest ratios (HR  $\geq$  1.74) in both cases was the difference in percentage of emphysema (UL:LL) and age (HR  $\geq$  1.64).

Fan *et al.*<sup>29</sup> followed 3,282 males with COPD over one year; their mortality rate was 5.1% (n = 106). HRQL was measured using the Seattle Obstructive Lung Disease Questionnaire (SOLDQ),<sup>30</sup> and the physical (PCS) and mental health (MCS) components of the Short-Form-36 questionnaire (SF-36). Overall, the odds ratio was highest for the lowest quartiles, with the physical domain of the SOLDQ demonstrating the highest (OR > 6) risk for mortality than the other measures (OR < 4.5). The multivariate logistic regression model included other variables (age, steroid use, comorbidities, and prior hospitalization). In this model, only the physical component of the SOLDQ was a risk factor for mortality (OR from highest 2.9 to 5.7 lowest quartile).

In summary, the evaluation of HRQL in COPD patients following treatment or in predicting mortality, the area which has seemed to be overlooked as a predictor, is the activity level of the patient. Whether measured by exercise stress test, walk distance or as a major or minor component of a HRQL measure, the activity level of the patient is an important factor in understanding COPD patients.

How should we measure activity levels in the future? We have shown that when a functional status measure or subscore of functional status in a HRQL measure is included in the analysis, the activity component contributes to mortality. In some cases this contribution exceeds many other domains, including well accepted physiologic measures (DLCO), or co morbidities (BMI). Evaluation of the specific contribution of functional status in either domains of HRQL measures, or disease specific functional status measures should be an important area of measurement focus in future studies. It should no longer be sufficient to report a total score as these minimize the potential contribution of the domains, such as functional status, of these questionnaires.

## Methodological problems in predicting survival in COPD

Many of the variables predicting survival in univariate analyses are inter-related. For example, the relationships between age and degree of airway obstruction with mortality are strong. This should come as no surprise as both advancing age and the degree of airway obstruction are associated with mortality. Because of this, analysis of factors predicting survival should consider controlling for age and FEV<sub>1</sub>. Additionally, most studies of mortality in COPD patients were of male subjects, which historically, has been the major gender affected by COPD. Given the increase in numbers of females diagnosed with COPD, an effort should be made to include female subjects in studies.

Many studies did not analyze separately those subjects dying from respiratory related deaths from those dying from other causes (e.g., lung cancer, myocardial infarction). To understand the effects of COPD on mortality, greater control should be made in analyzing respiratory causes of mortality from non respiratory causes. To make progress in care of patients with COPD, we must be cautious in our research methods, to clearly identify new directions.

In multivariate analyses to date, relatively few factors have withstood the rigor of predicting mortality in COPD patients. For instance, using a univariate hazards analysis involving 149 COPD patients followed by a multi-center consortium of pulmonary rehabilitation programs,<sup>31</sup> variables most related to survival were the functional status scores on the Pulmonary Functional Status Scale, and improvement in the six minute walk distance. Significant, but less strongly predictive of survival was a higher FEV<sub>1</sub>. We have reviewed similar published studies and a summary of the findings from these studies are presented in Table 1.

## Multidimensional staging of COPD and mortality

COPD is now recognized as a disease with not only respiratory impairment but one that also has significant systemic consequences. In this context, it becomes increasingly important to identify respiratory and systemic manifestations of COPD that can effectively signal an increased risk for mortality. Similarly, it would be important to identify which of these variables may serve as surrogates for outcomes. The recognition and modification of likely surrogates for mortality may provide an early opportunity to ameliorate morbidity and improve survival. If several variables predict mortality independently,

it is logical that a multidimensional tool that incorporates several of these variables should be able to provide a more comprehensive evaluation of a patient's compromise and hence it's clinical staging.

As accumulating evidence suggests that multiple factors can be associated with mortality in COPD, it is reasonable that a composite index may provide a practical way to more comprehensively evaluate patients with COPD. Celli and colleagues evaluated 207 patients with COPD and identified 4 easily measured variables that predicted an elevated risk for death: BMI (B), degree of airflow obstruction (O), dyspnea as measured by the MRC dyspnea scale (D), and exercise capacity (E) as measured by the 6MWD test.<sup>32</sup> These variables were used to construct a multidimensional scale, the BODE index, that ranged from 0 (least risk) to 10 (highest risk) (Table 2).

The BODE index was prospectively validated in a separate cohort of 625 predominantly male patients with COPD who were evaluated every 3 to 6 months for at least 2 years, or until death.<sup>32</sup> The results indicated that each quartile increase in the BODE Index score yielded an increase in the risk for mortality (Figure 2). In fact, quartile 4 (BODE Index score of 7 to 10) was associated with a mortality rate of 80% at 52 months. The BODE Index predicted mortality more accurately than the FEV<sub>1</sub> (Figure 2).

In a preliminary study that included 720 patients (93% male) with COPD, the BODE Index has also been shown to correlate well with measures of quality of life, as assessed by the St. George's Respiratory Questionnaire (SGRQ). The highest correlation was seen between BODE total scores and the activity component of the SGRQ. The overall correlation between BODE and SGRQ was  $r = 0.58$ ;  $P < 0.0001$ . The SGRQ scores increased as BODE quartiles increased. In univariate analysis both tools predicted survival in COPD.<sup>33</sup>

Furthermore, in clinical studies comparing the BODE Index with FEV<sub>1</sub>, the BODE Index was shown to better assess progression of disease secondary to COPD exacerbation,<sup>34</sup> and to be a significantly better predictor than the FEV<sub>1</sub> for the risk for hospitalization due to exacerbations.<sup>35</sup>

Pulmonary rehabilitation has become an integral component of the standard of care in the comprehensive management of COPD<sup>36,37,7</sup>. Pulmonary rehabilitation is known to improve several of the surrogate markers for mortality in COPD, namely dyspnea and exercise capacity. Based on this, Cote et al explored the hypothesis that pulmonary rehabilitation would lessen the severity of COPD and the risk for mortality, as measured by the BODE Index.<sup>39</sup> In this study, of the 246 patients who qualified for and were offered rehabilitation, 116 accepted

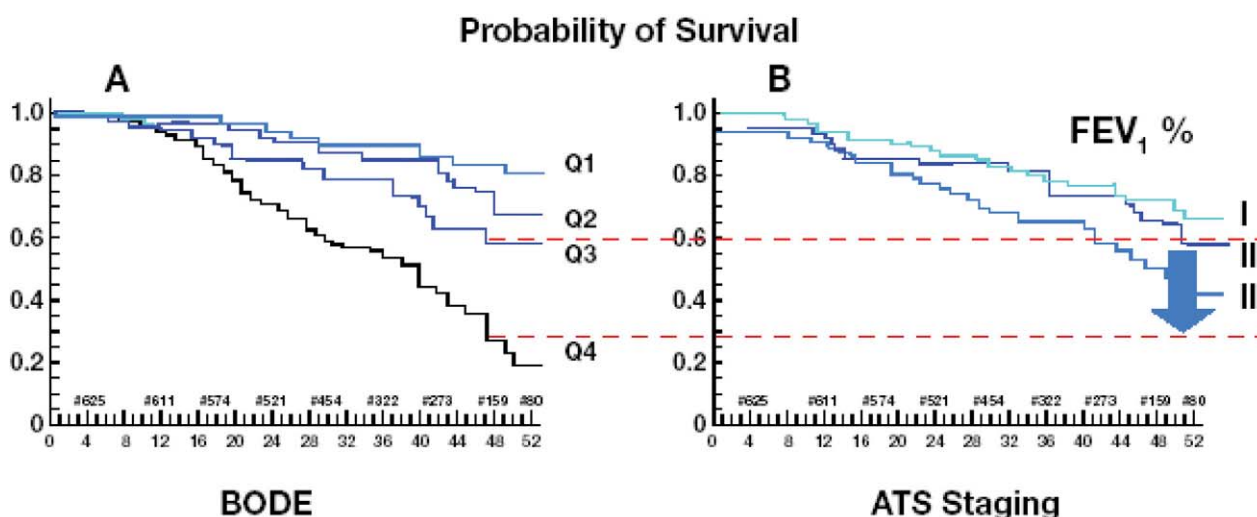
**Table 1** Predictors of survival in COPD patients using multivariate analysis

	Cox Hazard Analysis (HR)				Logistic Regression (OR)	
	Oga <i>et al</i> n = 144	Domingo-Salvany <i>et al</i> n = 312 n = 609	Martinez <i>et al</i> n = 3,282	NA	Fan <i>et al</i> NA 96.3%	
Subjects	64.5%	*45.3%	64.2%	NA	NA	
Respir. COD (%)	100%	100%				
Males(%)						
Variables		SGRQ	SF-36	w/o BODE	BODE	
Age	1.13	1.59	1.65	1.64	1.72	1.50
FEV <sub>1</sub>	0.94	2.32	2.38	NS		⊙
RV % pred.	⊙	⊙	⊙	1.57	1.56	⊙
Diff % emphysema	⊙	⊙	⊙	1.74	1.80	⊙
TLC % pred.	⊙	⊙	⊙	0.68	NS	⊙
CPET	⊙	⊙	⊙	1.54	1.48	⊙
Perfusion ratio	⊙	⊙	⊙	1.57	1.53	⊙
DLCO	NS	⊙	⊙	NS	1.36	⊙
Hemoglobin	⊙	⊙	⊙	NS	1.38	⊙
↓PaO <sub>2</sub>	⊙	⊙	⊙	NS	NS	⊙
↑PaCO <sub>2</sub>	⊙	⊙	⊙	NS	NS	⊙
O <sub>2</sub> use	⊙	⊙	⊙	1.46	NS	⊙
Peak VO <sub>2</sub>	NS	⊙	⊙	⊙	⊙	⊙
Co-morbidity	⊙	⊙	⊙	⊙	⊙	2.00
Smoking Hx	NS	⊙	⊙	NS	NS	adj
Steroid use	NS	⊙	⊙	⊙	⊙	1.80
BMI	NS	0.69	0.68	NS		⊙
6MWT	⊙	⊙	⊙	NS		⊙
BODE	⊙	⊙	⊙	⊙	1.48	⊙
Self-report tools						
SF-36 PCS	⊙		1.40	⊙	⊙	NS
SGRQ total	1.035	1.36		NS	NS	⊙
CRQ total	NS	⊙	⊙	⊙	⊙	⊙
CRQ dyspnea	NS	⊙	⊙	⊙	⊙	⊙
CRQ fatigue	NS	⊙	⊙	⊙	⊙	⊙
UCSD SOBQ	⊙	⊙	⊙	NS		⊙
SOLDQ-Physical	⊙	⊙	⊙	⊙	⊙	⊙
51–75 <sup>th</sup>	⊙	⊙	⊙	⊙	⊙	2.90
26–50 <sup>th</sup>	⊙	⊙	⊙	⊙	⊙	3.20
0–26 <sup>th</sup>	⊙	⊙	⊙	⊙	⊙	5.70

COD = cause of death; RV = residual volume; BMI = body mass index; CPET = cardio pulmonary exercise testing; 6MWD = six minute walk distance; SGRQ = Saint George Respiratory Questionnaire; UCSD SOBQ = UC San Diego shortness of breath questionnaire; SOLDQ = Seattle Obstructive Lung Disease Questionnaire; Adj = analysis adjusted for that variable; \*analysis reported in those who died due to a respiratory cause; ⊙ = not used in study; shaded cells = variable a component of BODE; TLC = total lung capacity; Dlco = diffusion capacity; Diff %emphysema = difference in emphysema upper lung : lower lung; SF-36 = Medical Outcomes Study short form 36; CRQ = Chronic Respiratory Questionnaire; BODE = BODE index (BMI, airflow obstruction [FEV<sub>1</sub>], dyspnea [UCSD SOBQ], exercise capacity [6 minute walk]); NS = non significant; NA = not addressed.

and completed the 8-week, 3-times weekly rehabilitation program; 130 declined for reasons that remain unclear. The change in BODE scores were compared between rehabilitation program participants and non participants.

At baseline, BODE Index scores were in the 3rd and 4th quartiles for 75% (n = 83) of the patients in this cohort (98% male). Patients were followed for more than 2 years or until death. During that time, approximately 30% of the patients who partic-

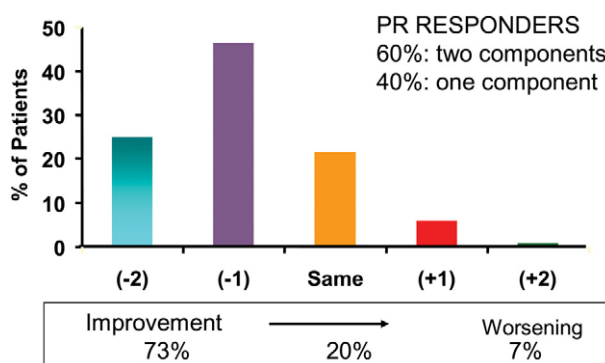


**Figure 2** Kaplan–Meier Survival Curves for the Four Quartiles of the body mass index, degree of airflow obstruction, dyspnea, and Exercise Capacity Index (BODE; Panel A) and the Three Stages of Severity of Chronic Obstructive Pulmonary Disease as defined by the American Thoracic Society (ATS; Panel 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 4 groups ( $P < 0.001$  by the log-rank test). In Panel B, Stage I is defined by a forced expiratory volume in 1 second ( $FEV_1$ ) that is more than 50% of the predicted value, Stage II by an  $FEV_1$  that is 36% to 50% of the predicted value, and Stage III by an  $FEV_1$  that is no more than 35% of the predicted value. Survival differed significantly among the 3 groups ( $P < 0.001$  by the log-rank test).<sup>28</sup> # = number at risk. Reprinted with permission from *N Engl J Med*. Copyright 2004, Massachusetts Medical Society.

**Table 2** Calculation of the BODE index. Points from each variable are added according to the threshold value measured for each one. The value ranges from 0 to a maximum of 10

Variable	BODE Score			
	0	1	2	3
$FEV_1$ , % predicted	>65	50–65	35–49	<35
Dyspnea: MRC	0–1	2	3	4
6MWD meters	>350	250–349	150–249	<149
BMI	>21	<21		

$FEV_1$  = forced expiratory volume in 1 second; MRC = Medical Research Council; 6MWD = 6-minute walk distance test; BMI = body mass index.



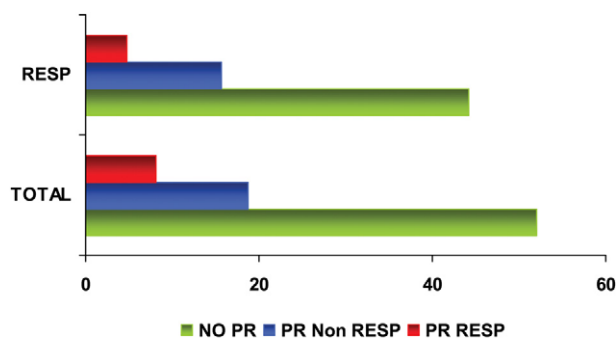
**Figure 3** Distribution of the change in BODE Index in all patients completing pulmonary rehabilitation (3 months). Improvement in the BODE score is manifested by decreases in the index, whereas an increase in the value implies worsening in the prognosis. More than 70% of the patients had an improvement of at least 1 unit in the BODE Index.<sup>35</sup> Reprinted with permission from *Eur Respir J*. Copyright 2005, European Respiratory Society.

ipated in rehabilitation continued exercise training 3 times weekly for the entire 2-year period. After pulmonary rehabilitation, 71% of those participating in the 2 year PR program had improved their BODE Index scores by at least 1 point, with 25% improving by 2 points (Figure 3).

The patients in the PR group had an initial BODE Index of 5.07, which decreased significantly to 4.18 after PR (month 3). Patients in this group shifted from the 3rd quartile to 2nd quartile, and their initially predicted mortality of 20% to 30% changed to an observed mortality of 11.2%. Patients in the non-PR group had a BODE Index entry of 6.94 (approaching BODE 4th quartile), and in this group there was

almost a 20% worsening of BODE Index over time. This group of patients had the highest mortality rate (50%) (Figure 4).

These data suggest that the BODE Index changes not only reflect the global changes due to PR, but may also imply a change in outcome, suggesting that the BODE Index can be considered a surrogate marker for mortality.<sup>39</sup> For patients who responded to pulmonary rehabilitation, defined as an improve-



**Figure 4** All-cause and respiratory mortality at 2 years in patients with no pulmonary rehabilitation (PR; purple bars), PR nonresponder patients (blue bars), and PR responder patients (red bars).<sup>35</sup> Reprinted with permission from *Eur Respir J*. Copyright 2005, European Respiratory Society.

ment in the BODE Index score of at least 1 point, BODE Index scores improved by a statistically significant 25% at 3 months, compared with the patients who did not respond to rehabilitation. These improvements in BODE Index scores were maintained for a full 2 years after the start of pulmonary rehabilitation, while patients who did not participate in pulmonary rehabilitation displayed an 18% deterioration in BODE Index scores.<sup>39</sup> Thus, the BODE Index may be a useful tool in predicting survival in patients with severe COPD who participate in pulmonary rehabilitation programs.

Finally, a recent study by Imfeld and colleagues explored the change in the BODE index after lung volume reduction in 186 patients that had the procedure and were followed for a period of close to 60 months.<sup>40</sup> LVRS resulted in improvement in BODE scores with the mean value decreasing from 7.1 to 4 units 6 months after surgery, thus proving that BODE does respond to intervention. More importantly, the change in BODE at 6 months was a predictor of subsequent survival, thus suggesting that the change in BODE can be used as an outcome measure.

### Conflict of interest statement

B Celli, CG Cote, SC Lareau and PM Meek have no conflict of interest to declare.

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