

The Modified BODE Index: Validation with Mortality in COPD

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ABSTRACT

Introduction: The peak oxygen uptake (VO_2) remains the gold standard measurement of exercise capacity and has been associated with survival. A modified BODE index replacing the 6MWD with peak VO_2 as % of predicted (mBODE %) has been developed and found to have excellent correlation with the conventional BODE index. **Objectives:** To compare the ability of the conventional BODE and the mBODE% to predict mortality in 444 patients with COPD followed over 71 ± 34 months. Anthropometrics, spirometry, lung volumes, co-morbidity, cardiopulmonary cyclo-ergometry test, and 6MWD were determined at entry. **Results:** The mean BODE indexes for the cohort were: BODE = 4.1 ± 2 and mBODE % = 5.5 ± 2 , $p < 0.0001$. Both indexes correlated with mortality; BODE ($r = 0.32$, $p < 0.0001$) and mBODE % ($r = 0.31$, $p < 0.0001$). Logistic regression analysis with COPD survival as the dependent variable identified the BODE index, Charlson's and watts as variables associated with this outcome (% deviance = 17.1, $p = 0.00001$). **Conclusion:** the conventional BODE index which uses 6MWD predicts mortality in COPD as well as the modified index using peak $VO_2\%$. These results support the use of the simpler index which includes the 6MWD in the comprehensive evaluation of patients with COPD.

Introduction:

The oxygen uptake measured at peak exercise (peak VO_2) during incremental cardiopulmonary exercise test (CPET), is considered the gold standard to evaluate exercise capacity. Peak VO_2 helps predict survival in patients undergoing lung resection (1, 2), lung volume reduction surgery (LVRS) (3), and in patients with COPD (4) and heart failure (5). The six-minute walk test (6MWD) is easy to perform, has been standardized (6) and also predicts mortality in COPD (7, 8) and in pulmonary hypertension (9).

The 6MWD is considered a sub-maximal test, however, Casas and colleagues (10) have shown that patients with COPD walk at a pace close to their maximally exercise capacity while the peak VO_2 measured at the end of an incremental protocol in COPD is not a true maximal oxygen uptake (11, 12). This indicates that the differences between tests in the patients with COPD may not be as large as otherwise suspected. There is a modest but significant correlation between the peak VO_2 and 6MWD (13, 14) implying that the tests are not equal, however, as it relates to their capacity to predict survival in COPD, we have recently shown that the 6MWD is equal if no better than peak VO_2 at predicting this outcome (15).

The BODE index, which incorporates measurements of nutrition (BMI or Body Mass Index), air flow obstruction (FEV_1), dyspnea (The Modified Medical Research Council Dyspnea Scale or MMRC) and exercise capacity as measured by the 6MWD predicts mortality (16, 17), hospitalizations (18) and reflects disease modification after LVRS (19), non surgical volume reduction (20), and pulmonary rehabilitation (21). It also reflects the deleterious effects of exacerbations and hospitalizations (22).

Cardoso and colleagues recently developed a modified BODE index (mBODE) by replacing the 6MWD with peak VO₂ (23). The authors reported an excellent correlation between the value expressed as a percent of predicted (mBODE%) and BODE, which was better than with mBODE expressed in ml/Kg/min.

The purpose of this study was to test the hypothesis that the modified index using VO₂ max expressed as a percent of predicted had a similar predictive power for mortality than the original BODE index that includes the 6 MWD in a cohort of patients with COPD.

METHODS

Patients

The cohort consisted of 444 patients with COPD, recruited at the Bay Pines Veterans administration Health Care System (n=292), St. Elizabeth's Medical Center (119) and the Miguel Servet Hospital in Spain (33) between 1996 and 2006 and followed until June of 2008. The human research committees at each institution approved the study and all patients gave informed consent. Enrollment criteria have been previously published (16). The patients were clinically stable for 6 weeks and had to be able to perform both tests.

Measurements

The spirometry and the 6MWD were completed following the ATS recommendations (24, 6). Co-morbidity was determined with the Charlson score (25). For exercise ergometry the patients started with a 2-min period of unloaded pedaling at 60 cycles per minute, followed by a 10-15 watt/min increment (26) and were

encouraged to cycle until exhaustion. Heart rate and blood pressure were monitored continuously. Minute ventilation and its components were measured using a pneumotachograph. The concentrations of expired oxygen and carbon dioxide were analyzed breath by breath. We used 30-s averages of minute ventilation (VE), tidal volume (VT), respiratory rate (RR), oxygen uptake (VO_2), carbon dioxide output (VCO_2), and gas exchange ratio (R). Predicted maximal oxygen consumption (VO_2 max) was calculated using standard equations (26). The heart rate reserve (HRR) was calculated as $\text{HR max} = 220 - \text{age}$ minus the observed peak HR. The CPET and the 6MWD were performed on separate days, at least one day apart and within one month of enrollment into the study. To avoid bias, the two tests were performed in random order.

The BODE Indexes.

The BODE index was calculated as previously reported (16). The modified BODE index was calculated by replacing the 6MWD by the peak VO_2 expressed as a percent of predicted as follows: score 0= >70%; score 1= 60-69%; score 2= 40-59%; and score 3= <40% (27). In the study of Cardoso (23) as well as in calculations conducted in our cohort (data not presented), the VO_2 expressed as percent predicted offered similar if not better discriminating power than the absolute value.

Statistical Analysis

The data are presented as mean \pm SD and range. The differences in physical characteristics, pulmonary function test, and exercise parameters in patients stratified by BODE quartiles, were evaluated using ANOVA. Pearson's correlation test was used to assess the relationship between the indexes and mortality. Mortality was evaluated over time using Kaplan Meier analysis. Logistic regression analysis was used to

investigate the relationship between the indexes and mortality. Receiver Operating Curves were used to assess the diagnostic power of both indexes with mortality as an outcome. A probability value of less than 0.05 was considered significant. Statistical analysis was completed with a commercial package (GBStat, St. Louis, USA).

RESULTS

The characteristics of the 444 patients are shown in Table 1. The cohort was predominantly male (87%), Caucasian (99%) and 23% of the patients were oxygen dependent. Using ATS/ERS/GOLD criteria 2% were on stage I, 27% in stage II, 47% in stage III, and 24 % in stage IV. When the patients were stratified by the conventional BODE index, 23% were in quartile 1, 35% in quartile 2, 29% in quartile 3, and 13% in quartile 4. Conversely, when stratified by mBODE% 10% were in Q1, 22% were in Q2, 32% were in Q3 and in Q4 36%. The mean BODE index for the cohort was 4.11 ± 2 and the mBODE% index was 5.5 ± 2.1 , $p < 0.001$ with a difference of 1.4 points.

Exercise parameters:

Table 2 shows that the exercise capacity was severely reduced at all stages except for quartile 1, whether patients were stratified by the traditional BODE index or the modified BODE index. We observed that only 39 patients (8.7%) in the cohort had normal exercise capacity ($>70\%$ predicted peak VO_2). With exemption of cardiac parameters which showed no differences, BODE reflected exercise impairment better than the mBODE.

Mortality:

There were 206 deaths during the study with a mean time from enrollment to death was 22 ± 29 months. 107 (51.4%) were due to COPD and 40 (19.4%) to lung cancer. The remaining deaths were due to cardiovascular disease, cancers other than lung and other medical reasons. Mortality was very high (61%) for patients who had a peak $VO_2\%$ of less than 40% predicted or a walking distance of less than 350 meters (63%). Conversely, COPD mortality among patients exceeding these values was low (18 and 15% respectively).

Logistic regression analysis identified the conventional BODE index, Charlson's co-morbidity, and watts as variables associated with COPD mortality. The model explained 17.16 % of the deviance, Odds ratio are shown in Table 3. Kaplan Meier survival analysis, (figure 1) also identified a better stratification between BODE quartiles than mBODE% quartiles. The Chi-Square for BODE was 58 vs. 40 for mBODE%, $p = < 0.00001$. Mortality was higher in all of the conventional BODE quartiles in particular in quartile 4 compared to the correspondent mBODE% index quartile. An ROC analysis showed discriminative values of 0.73 for BODE and 0.72 for mBODE, (Figure 2).

Correlations:

We performed Pearson's correlations between the indexes and found them to correlate very well, Figure 3. The correlation between the 6MWD and the peak VO_2 was modest but highly statistically significant, as it has been demonstrated before.

DISCUSSION

This study shows that in patients with a wide range of COPD severity, the conventional BODE index predicts mortality as well as the modified BODE index which replaces the 6MWD with the peak VO_2 as percent predicted obtained during a cardiopulmonary exercise test.

We have previously shown that the BODE index is a better predictor of mortality than the FEV_1 (16). The BODE index also predicts hospitalizations (18) and outcome following LVRS and pulmonary rehabilitation (17, 19-21). The BODE index incorporates the 6MWD as a measure of exercise capacity. Different modifications of the conventional BODE index have been proposed among them one that incorporates peak VO_2 and not the 6MWD. In one study (23), the modified BODE was reported to have an excellent correlation with the conventional BODE ($r = 0.97$) however its predictive value for mortality was not evaluated. In this study, we confirmed the findings of Cardoso et al, and further corroborate the modest but significant correlation between the 6MWD and peak $VO_2\%$.

Indeed, it seems logical that the peak VO_2 which represents the integral function of the cardiopulmonary system should be superior at predicting outcome in COPD and to reflect better the multi-systemic compromise of these patients than the 6MWD. It is also reasonable to expect that the 6MWD, which is considered a sub-maximal test, to have less of an overall predictive capacity, because it has been thought of as being less objective and accurate than the peak VO_2 . To our surprise, as shown in figures 1 and 2, the conventional BODE index which uses 6MWD, performed equally if not better than

the modified BODE index using peak VO_2 in predicting mortality in this cohort of patients.

It is possible that the different methodology during the CPET influences the information obtained with this test. An incremental load protocol during exercise testing may not be sustainable for sicker patients with COPD. Indeed in our cohort of 444 patients (27% stage I and II by ATS/ERS/GOLD) only 39 patients (8.7%) exceeded 70% of their predicted peak VO_2 . This impairment in exercise capacity even at lower stages of disease severity by ATS/ERS/GOLD has been reported before and its etiology is not clear. Unsuspected pulmonary hypertension, right ventricular after load, and impaired oxygen utilization have been proposed as possible mechanisms (27).

When patients in stages of ATS/ERS/GOLD 0 to 2, (120 patients or 27% of the cohort) were analyzed separately, their peak $VO_2\%$ was only $57 \pm 16\%$ which suggests that this methodology of testing with incremental load might not be sustainable even for patients with mild disease. It is likely that the patients in our cohort developed symptoms of shortness of breath and/or leg fatigue which made them stop the exercise before they reached a “true” maximal VO_2 . As seen in Table 2, all patients had a reduced breathing reserve at all stages of disease by BODE and mBODE indexes. On the other hand, when patients are physically unable to walk more than a very short distance during the 6MWD in spite of being allowed to pace them selves and to pause as needed, this inability to walk may represent a greater vital compromise than that provided by a reduced peak VO_2 .

Our study has some limitations. First, the patients included here were mostly males attending specialized centers and therefore, our findings may not be extended to

female patients or to COPD patients attending other settings. However, the wide range of airflow obstruction in our cohort, represent most patients with COPD seen by clinicians. Second, we only included patients capable of performing both tests. Thus, the results may not apply to patients with conditions that limit the ability to walk.

In summary, this study shows that in patients with a wide range of COPD severity, the BODE index using the 6MWD is as good a predictor of mortality than the modified BODE index using peak VO_2 obtained in a cardiopulmonary exercise test but is much simpler to obtain. These results support the incorporation of simple practical tests to evaluate the multidimensional compromise of patients with COPD.

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TABLE 1. Baseline characteristics in a cohort of 444 patients with Chronic Obstructive Pulmonary Disease.

VARIABLE	ALL (n= 444)	RANGE
Age (Years)	66 ± 8	37 to 83
Smoking history (pack-year)	80 ± 44	10 to 250
PaO ₂ (mm Hg)	72 ± 11	52 to 96
BMI (Kg/m ²)	26.9 ± 5.4	14 to 50
FEV ₁ (%)	41 ± 15	15 to 90
FVC (%)	73 ± 17	32 to 120
FEV ₁ /FVC (%)	44 ± 12	16 to 70
MMRC (Points)	2.3 ± 0.8	0 to 4
6MWD (meters)	367 ± 114	54 to 712
BODE Index (points)	4.11 ± 2	0 to 10
mBODE % Index (points)	5.5 ± 2	0 to 10

O₂, oxygen; PaO₂, Partial arterial pressure of oxygen; BMI, body mass index; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; MMRC, Modified Medical Research Council Dyspnea Scale; 6MWD, six-minute walking distance; mBODE%, modified BODE index using peak oxygen uptake as percent of predicted.

Table 2. Exercise parameters of patients with Chronic Obstructive Pulmonary Disease stratified by BODE and mBODE quartiles.

VARIABLE	Quartile 1		Quartile 2		Quartile 3		Quartile 4	
	BODE	mBODE	BODE	mBODE	BODE	mBODE	BODE	mBODE
WATTS	97 ± 32	104 * ± 36	71 ± 24	82 * ± 26	53 ± 19	64 * ± 22	34 ± 16	45 * ± 18
VO2 (ml/kg/min)	1.25 ± 0.48	1.47 * ± 0.52	0.95 ± 0.33	1.15 * ± 0.25	0.79 ± 0.18	0.91 * ± 0.19	0.63 ± 0.26	0.68 ± 0.28
VO2 (% Predicted)	60.4	74 *	49	57 *	41	46 *	32	34
Resting HR (beats/min)	91 ± 16	88 ± 15	93 ± 15	94 ± 15	98 ± 13	95 ± 15	99 ± 10	97 ± 13
Peak HR (beats/min)	127 ± 16	130 ± 15	121 ± 18	130 ± 15	119 ± 15	120 ± 16	114 ± 18	117 ± 17
HR Reserve (%)	26	22	32	28	33	32	39	36
MVV (L)	68 ± 21	61 ± 20	49 ± 19	58 * ± 19	40 ± 13	49 * ± 19	31 ± 10	35 * ± 10
MV (L/min)	54 ± 18	72 * ± 21	41 ± 12	49 * ± 13	36 ± 10	40 * ± 21	30 ± 9	32 ± 9
BR (%)	14.00	9.00	8.00	9.00	4.00	9.00	1.00	3.00

- P= < 0.05

VO2= Oxygen consumption, HR= heart rate, MVV= maximal minute ventilation, MV= minute ventilation, BR= breathing reserve

Table 3. Logistic regression analysis and Odds ratios for COPD survival among patients with COPD.

95.0% confidence intervals for odds ratios			
Parameter	Estimate	Lower Limit	Upper Limit
BODE	0.738009	0.72834	0.747806
Charlson	0.90021	0.888416	0.91216
Watts	1.02158	1.0082	1.03514
Likelihood Ratio Tests			
Factor	Chi-Square	Df	P-Value
BODE	14.7321	1	0.0001
Charlson	3.88384	1	0.0487
Watts	11.1606	1	0.0008

FIGURE 1:

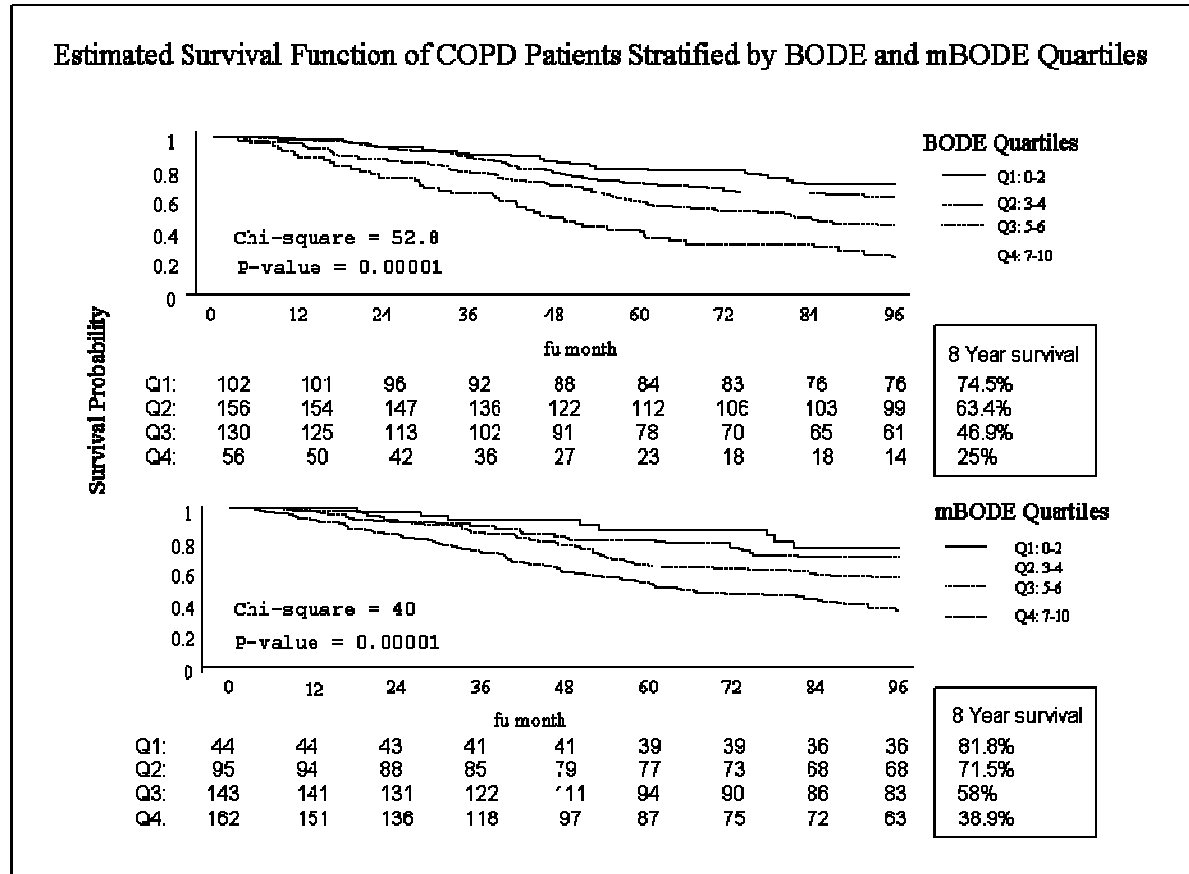


FIGURE 2: Receiver Operating Curves for both indexes in relation to survival.

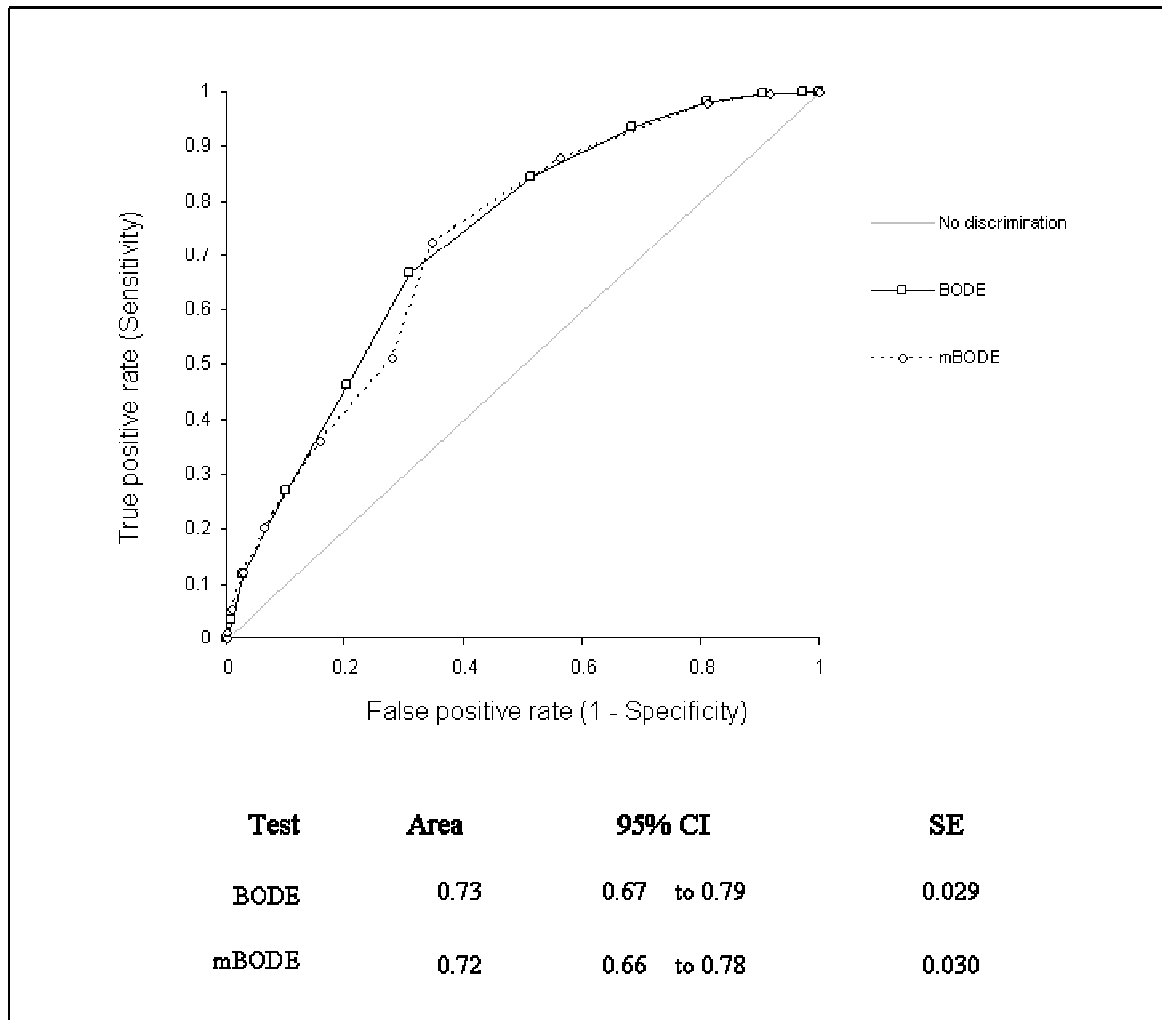


Figure 3.

Correlations BODE and mBODE indexes and 6MWD and Peak VO₂%

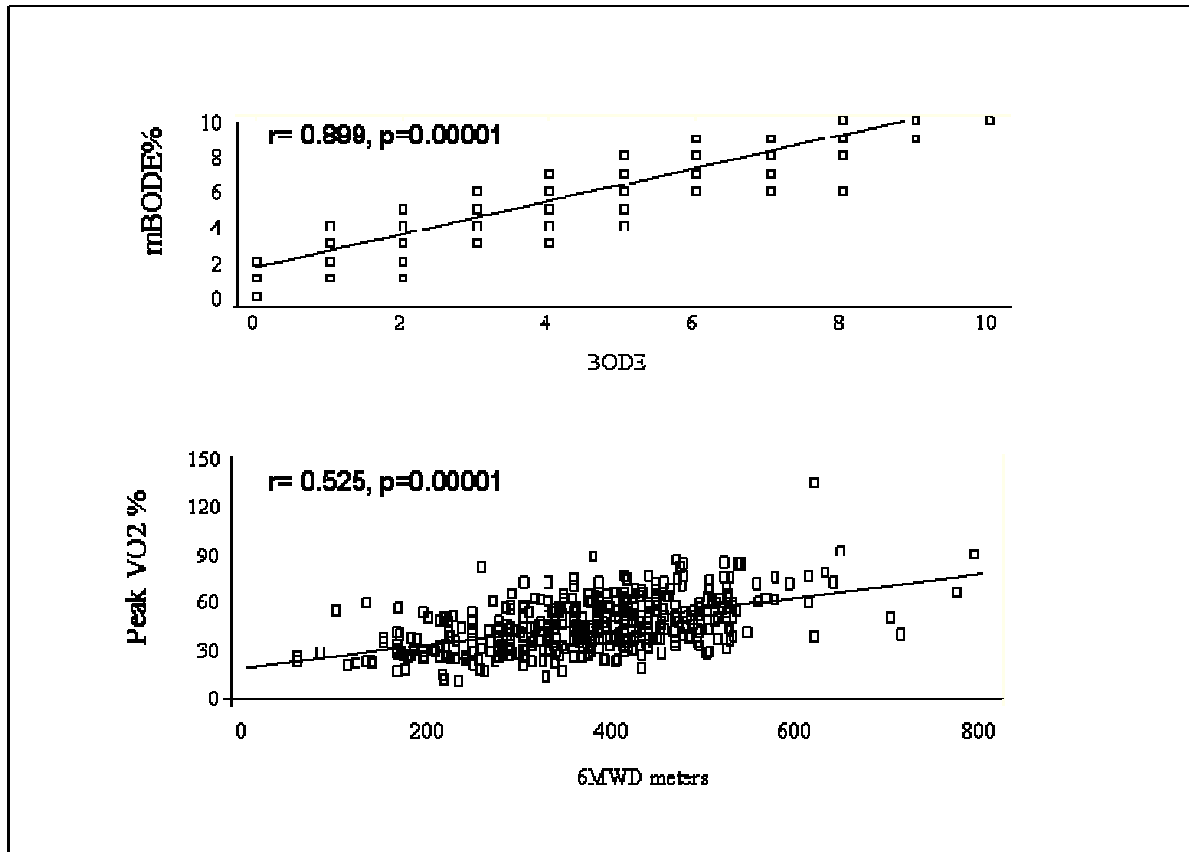


Figure legends:

Figure 1: Kaplan Meier survival curves for the modified BODE index that uses the peak VO_2 and the original BODE index that uses the 6 minute walk distance. Both are divided in quartiles. The original index better differentiated similar to the modified BODE.

Figure 2: Receiver Operating Curves for the conventional BODE index using the 6MWD test in meters and the modified BODE index using peak VO_2 as percent of predicted. No differences were observed between tests in their capacity to predict survival in COPD.

Figure 3: Pearson's correlations between the traditional BODE index and the modified BODE index. Although the correlation between the two indexes is excellent, a more modest but significant correlation is seen between 6MWD and peak $VO_2\%$.