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Prediction of risk of COPD exacerbations by the BODE index

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Summary
Objectives: This study assesses the power of the BODE index, a multidimensional grading system that predicts mortality, to predict subsequent exacerbations in patients with COPD.
Design: Prospective cohort study.
Patients and interventions: A total of 275 COPD patients were followed every 6 months up to 8 years (median of 5.1 years). Baseline clinical variables were recorded and the BODE index was calculated. We investigated the prognostic value of BODE quartiles (scores 0–2, 3–4, 5–6 and 7–10) for both the number and severity of exacerbations requiring ambulatory treatment, emergency room visit, or hospitalization.
Results: The annual rate of COPD exacerbations was 1.95 (95% CI, 0.90–2.1). The mean time to a first exacerbation was inversely proportional to the worsening of the BODE quartiles (7.9 yrs, 5.7 yrs, 3.4 yrs and 1.3 yrs for BODE scores of 0–2, 3–4, 5–6 and 7–10, respectively). Similarly, the mean time to a first COPD emergency room visit was 6.7 yrs, 3.6 yrs, 2.0 yrs and 0.8 yrs for BODE quartiles (all $p < 0.05$). Using ROC curves, the BODE index was a better predictor of exacerbation than the FEV_1 alone ($p < 0.01$).
Conclusions: The BODE index is a better predictor of the number and severity of exacerbations in COPD than FEV_1 alone.

Introduction

Chronic obstructive pulmonary disease (COPD) will become the third most common cause of death and the fourth cause

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of disability in the world by the year 2020.[1] As COPD progresses, patients develop more frequent and severe exacerbations,[2,3] and have an increased rate of emergency room visits and hospitalizations.[2,4]

Hospitalizations for COPD exacerbations account for most of the economic burden of the disease.[5–9] Recurrent exacerbations are associated with worsening of lung function[4,10,11] and of health-related quality of life (HRQoL),[12] and with decreased survival.[13–15] The mechanisms underlying COPD exacerbations are poorly understood, and it is a high priority to identify factors that help predict their occurrence.[16] Few factors have been associated with the prediction of exacerbations. These include a history of prior hospitalizations for COPD, a lower FEV_1, and more severe respiratory symptoms.[9,17] These descriptors however were obtained from studies that defined exacerbations using only short-term changes in symptoms, did not describe the type of medical intervention needed,[9] or only included patients with severe disease that required admissions to the hospital.[13,17]

The BODE index is a multidimensional index of disease severity in COPD that incorporates four factors known to be independent predictors of survival in this disease: the body mass index (BMI), the degree of airflow obstruction assessed by the FEV_1, the functional dyspnea assessed by the modified Medical Research Council (mMRC) questionnaire, and the exercise capacity assessed by the 6 min walking distance (6MWD) test. The BODE index proved to be a good predictor of survival in a large cohort of patients with COPD.[18] It also predicts hospitalizations[19] and has been shown to comprehensively reflect the detrimental changes occurring during exacerbations.[20] Considering that exacerbations are related to poor clinical outcomes such as mortality and health status, we hypothesized that the BODE index could also be a good predictor of future exacerbations assessed with different definitions. Accordingly, we conducted this study to assess the value of the BODE index as a predictor of both the number and the severity of COPD exacerbations.

Methods

Patients

Subjects with a diagnosis of COPD were recruited between January 1997 and June 2002 at the outpatient pulmonary clinics of two tertiary teaching hospitals in Tenerife and Zaragoza, both in Spain. The study group was part of a larger study examining the value of the BODE index as predictor of survival in COPD.[18] Inclusion criteria were 1) a history of smoking >20 pack-year, 2) a maximal ratio of $FEV_1/FVC < 0.7$ measured 20 min after the administration of inhaled salbutamol and, 3) a stable clinical condition for at least 8 weeks prior to enrolment. Exclusion criteria were 1) uncontrolled co-morbidities likely to result in death, 2) a history of asthma or an increase in the FEV_1 greater than 15% or more than 200 ml from baseline after the administration of inhaled salbutamol and 3) the inability to perform the required tests. The study was approved by the human-research review board at each institution, and written informed consent was obtained from all patients.

Measurements

Forced spirometry was performed according to the guidelines of the American Thoracic Society.[21] The best of two 6MWD tests was performed as described elsewhere.[22,23] Functional dyspnea was assessed using the mMRC dyspnea scale.[24] To quantify the degree of co-morbidity we used the Charlson index.[25] The BODE index was computed as previously reported.[18]

Follow-up

Patients included in the cohort attended the clinics every six months or until death, and a history of exacerbations of COPD was obtained at each clinic visit. Exacerbations were defined as events characterized by a sustained worsening of baseline respiratory symptoms that lasted for at least 3 days and that required treatment intervention with antibiotics, and/or systemic corticosteroids. The severity of the exacerbation was estimated according to the level of health-care resources utilized (sequentially a non-scheduled visit to their primary care physician, assessment at the emergency room, or hospitalization). These episodes were confirmed by reviewing the medical and the hospital records.

Statistical analysis

Data are expressed as means with 95% confidence intervals or medians for normally and non-normally distributed variables, respectively. Rates per year of the three different types of exacerbations were calculated as the number of hospitalizations, emergency room, and ambulatory exacerbations due to COPD divided by the time of follow-up. We used a Kaplan–Meier analysis to determine time to exacerbations. The correlation between the BODE index and exacerbation rates was explored using the Rho Spearman coefficient. The change of variables with time was measured with a Cox proportional hazard regression.[26] The area under the receiver–operator curve (ROC) and an odds ratio were used as measures for the diagnostic validity of the BODE index to predict exacerbations.[27] The Youden index, defined as sensitivity + specificity − 1, is also reported. Their respective confidence intervals are computed with asymptotic or bootstrap distributions. Individual slopes of decline of FEV_1 and FVC were pooled according to BODE index and compared by means of the *U* of Mann–Whitney test. A p value of less than 0.05 was considered for statistical significance.

Results

A total of 275 COPD patients were followed up to 8 years (median of 5.1 years). Mean age was 65 years. Characteristics of the patients at entry by study centre are shown in Table 1. Patients from the Tenerife site had less pack-years of smoking, a lower dyspnea score, greater exercise capacity, more use of inhaled corticosteroids and long-acting bronchodilators, and more COPD exacerbations in the previous year than patients from the Zaragoza site. All

Table 1 Baseline demographic and clinical characteristics, by centre site.

	Zaragoza ($n = 136$)	Tenerife ($n = 139$)	p Value
Age, yr	65.85 ± 7.36	64.31 ± 9.02	0.121
BMI, kg/m^2	27.64 ± 27.33	27.03 ± 4.55	0.276
Pack-years	56.23 ± 25.37	48.51 ± 21.76	0.007
FEV_1, liters	1.38 ± 0.56	1.24 ± 0.48	0.037
FEV_1, %	49.57 ± 17.60	48.47 ± 19.16	0.621
FEV_1/FVC, %	45.92 ± 12.16	46.40 ± 12.32	0.748
GOLD 1 (%)	6 (4.4%)	8 (5.8%)	
GOLD 2 (%)	57 (41.9%)	50 (36%)	
GOLD 3 (%)	42 (30.9%)	42 (30.2%)	
GOLD 4 (%)	31 (22.8%)	39 (28.1%)	
MMRC dyspnea scale	1.73 ± 1.09	1.29 ± 1.25	0.002
6MWT, meters	449 ± 92	478 ± 87	0.009
BODE index score	2.59 ± 2.08	2.42 ± 1.99	0.488
CHARLSON index	2.74 ± 1.39	2.53 ± 1.32	0.200
Chronic hyper-secretion, %	19.9	15.2	0.315
Previous ICS use, %	55.9	71.7	0.008
Previous LABA use, %	57.4	86.3	0.000
Previous home oxygen, %	9.6	13.8	0.348
Exacerbations of COPD in the previous year	1.11 ± 1.45	2.21 ± 2.75	0.000

other variables were equally distributed in both centres, with a similar BODE and co-morbidity indices at baseline, and all were treated according to the same treatment and management protocols.

Two hundred and forty of the 275 patients included in the cohort (87.3%) experienced at least one exacerbation over the study period. The mean annual rate of exacerbations was 1.95 per year. No individuals with BODE 0 required hospitalization because of an exacerbation of COPD, whereas all individuals with BODE 8 and above experienced COPD exacerbations that required hospitalization.

As quantified by different estimators of validity (Table 2), the BODE index was able to predict well all three types of COPD exacerbations explored in this study. The correlation between the rate of exacerbation with the BODE index was the best for total COPD exacerbations (Rho of Spearman = 0.720) and for those requiring primary care only, with all likelihood due to their wider range of values than for more severe COPD exacerbations. For all other estimators, COPD exacerbations requiring hospitalization had the best area under the ROC, odds ratio, highest threshold of BODE, and best Youden index (Table 2). The area under the ROC of the BODE index to predict COPD hospitalizations was 0.88 (Fig. 1, panel A) and emergency room visits (Fig. 1, panel B) was 0.78 and both were significantly better than FEV_1 alone ($p < 0.005$). The risk of having a COPD exacerbation increased with BODE, with the larger relative risk being seen with COPD hospitalizations (RR = 2.51). Similarly, for a given COPD individual, the BODE threshold to observe a COPD exacerbation requiring ambulatory care was 1.9, while the BODE threshold for observing a COPD exacerbation requiring emergency care or hospitalization was 2.9.

Fig. 2 presents the time to an exacerbation requiring hospitalization (panel A) or an emergency room visit (panel B) according to BODE quartiles. Most patients with the lowest BODE quartile (0, 1 or 2) experienced no hospitalizations. Increasing BODE quartiles were associated with the occurrence of exacerbations requiring hospitalization (p value <0.01 for all comparisons). Of interest, all COPD

Table 2 Association of exacerbation definitions with the BODE index.

Coefficient	Total	Primary care	ER	Hospitalizations
Rho of Spearman	0.720	0.661	0.585	0.608
AUC[a]	0.81 (0.75—0.87)	0.78 (0.71—0.85)	0.78 (0.73—0.84)	0.88 (0.83—0.92)
Odds ratio[a]	2.56 (1.77—3.70)	2.09 (1.57—2.79)	2.09 (1.68—2.60)	2.51 (1.99—3.17)
Threshold of BODE[b]	1.9 (0.9—2.1)	1.9 (0.9—2.1)	2.9 (1.9—3.1)	2.9 (2.9—4.1)
Sensitivity[a]	0.71 (0.68—0.73)	0.71 (0.68—0.73)	0.58 (0.55—0.61)	0.86 (0.84—0.87)
Specificity[a]	0.77 (0.75—0.79)	0.71 (0.68—0.73)	0.87 (0.86—0.88)	0.73 (0.71—0.75)
Youden index[b]	0.48 (0.40—0.64)	0.43 (0.33—0.55)	0.45 (0.36—0.54)	0.59 (0.49—0.68)

ER: emergency room.
[a] 95% Asymptotic confidence interval.
[b] 95% Bootstrap confidence interval.

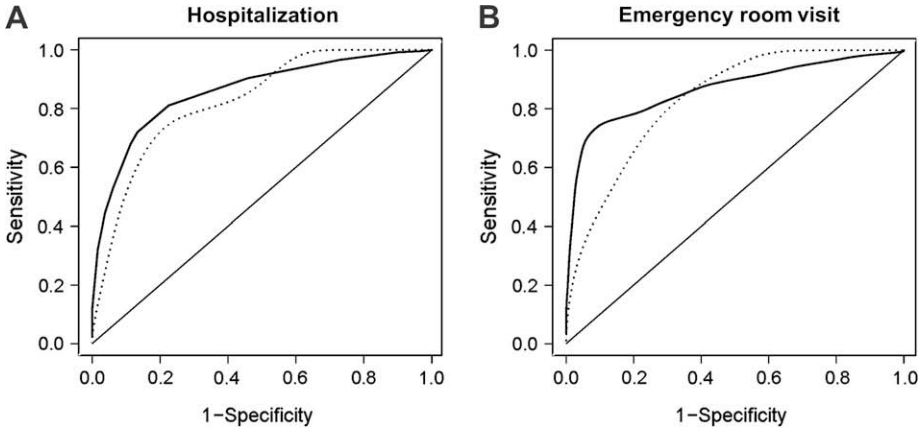

Figure 1 Receiver—operator curves for increasing BODE index (continuous line) and decreasing FEV_1 (dotted line) as predictors of an exacerbation before one year: (A) hospitalization and (B) emergency room visit.

patients with BODE higher than 7 had an exacerbation that required hospitalization before 4 years. The mean time to a first COPD hospitalization was 7.9 yrs, 5.7 yrs, 3.4 yrs and 1.3 yrs for BODE quartiles of 0—2, 3—4, 5—6 and 7—10, respectively. A similar trend was observed for exacerbations requiring an emergency room visit (Fig. 2, panel B). The mean time to a first COPD emergency room visit was 6.7 yrs, 3.6 yrs, 2.0 yrs and 0.8 yrs for the same BODE thresholds. For comparison, in Fig. 3 the same Kaplan—Meier curves are presented by thresholds of FEV_1. It can be shown that curves spread out more for BODE than for FEV_1, especially within the milder COPD subgroups, and differentiate time to a COPD exacerbation earlier with BODE than with FEV_1 alone ($p < 0.05$).

Discussion

This study shows that the BODE index is a good predictor of both the number and severity of exacerbations in patients with COPD. In addition, it predicts COPD hospitalizations better than less severe COPD exacerbations, namely those that required primary care or emergency room visit only.

Exacerbations of COPD contribute to accelerated lung function decline,[4,10,11] decreased HRQoL,[12] mortality,[13,14] and the high socio-economic burden of the disease.[5—9] Preventing exacerbations of COPD, and in particular hospitalizations, is therefore a major goal in the management of patients with this condition. A better understanding of the predictors of exacerbations and of hospitalizations becomes essential for effective implementation of preventive interventions.[16] Our results show that the BODE index may help achieve this goal. To date only a few studies have attempted to tease out the factors that may help predict exacerbations. In the East London Cohort study, patients who experienced a high frequency of exacerbations in one year were likely to have more episodes during the following year.[12] This observation has been confirmed in clinical trials, which also demonstrated that ''frequent exacerbators'' exhibited the worse baseline FEV_1.[4] However, the predictive value of FEV_1 was mostly observed at values lower than 50%.[28,29] In these studies, patients with lower scores in HRQoL questionnaires were also noted to have more frequent exacerbations.[12] Regrettably, several important clinical variables such as exercise capacity, functional dyspnea or nutritional status were not evaluated in those studies. In addition, the observations were made in patients with relatively mild exacerbations attending outpatient clinics, and the definition used relied only in the change of symptoms as registered in daily cards in the East London Cohort reports, and

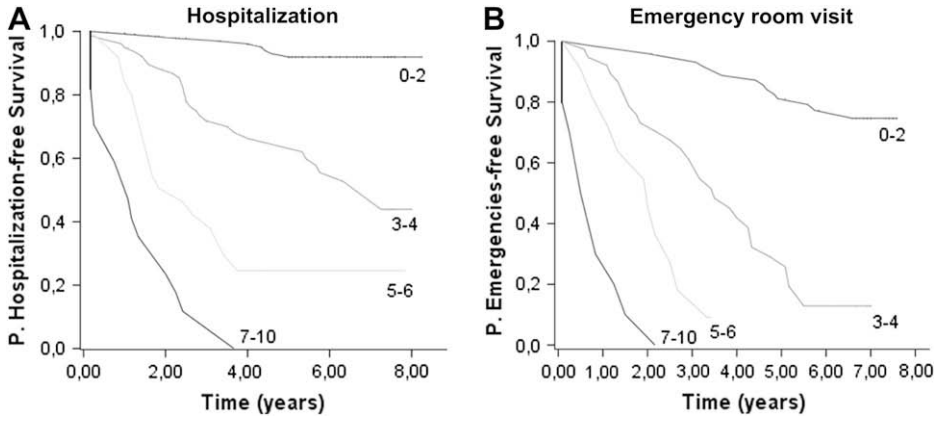

Figure 2 Time to exacerbation by BODE quartile: (A) hospitalization and (B) emergency room visit.

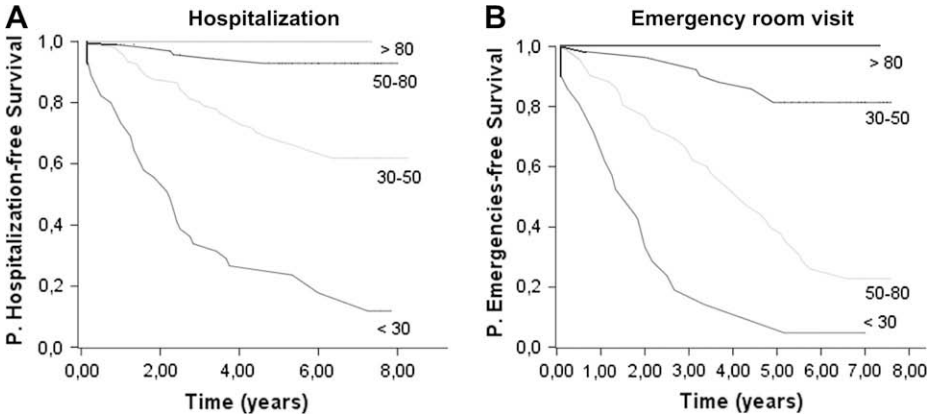

Figure 3 Time to exacerbation by FEV_1 (% predicted) as per the ATS-ERS severity staging: (A) hospitalization and (B) emergency room visit.

in other operational definitions used in the interventional trials. To date, only one study has evaluated the factors associated with admissions for COPD.[17] In this study, a history of prior hospitalizations, a lower FEV_1, and under prescription of oxygen therapy were associated with a higher risk for admission to the hospital as the result of a COPD exacerbation. Again, no data on variables such as functional dyspnea or exercise capacity were collected.

Consistent with our results, however, Ong et al. recently reported in 127 COPD patients followed up for a mean of 16 months that the BODE index helped to better predict hospitalizations for COPD than FEV_1 alone.[19] However, in that study no attempt was made to categorize the value of BODE as predictor of the severity of COPD exacerbation. In our cohort, a lower FEV_1 was associated with both the exacerbation rate and the risk for hospitalization (albeit with a lower statistical power compared to the BODE index). This is at variance with previous studies, where no relationship between baseline FEV_1 and exacerbation frequency was observed.[4,12] Further, in the East London Cohort study, daily cough and sputum were predictive factors of exacerbations, whereas in our series and in those of large clinical trials,[28,30] hyper-secretion did not correlate with an increased risk for exacerbations. These differences are likely related to the different definitions of COPD exacerbation used. In the East London Cohort study for example, a respiratory symptom-based definition was used, different to the health-care utilization-based definition used by our group and others. Such interventions include either a treatment with oral steroids or antibiotics, emergency room visit and/or hospitalization.

We observed that the integration of relatively simple clinical variables into the BODE index offered the best predictive value in the univariate and multivariate analysis. This suggests that a relatively simple integration of variables obtainable in any medical setting can help select patients likely to develop more frequent exacerbations. Given that COPD causes more deaths each year than both lung cancer and sepsis,[1] and that exacerbations are the single most important event driving both mortality and the cost of care for COPD patients, the use of BODE appears to be justified.

There are several limitations in our study. First, since few women were included, we cannot generalize the results to both genders. Second, our patients were recruited from those attending specialty clinics and therefore may not represent the COPD population at large, especially those with less severe disease. However, the patients included in our cohort likely represent the ones that are more likely to experience exacerbations. Third, and finally, the operational definition of exacerbation was purely health-care utilization-based, that is, it required a specific medical intervention. This definition has the advantage of being based in objective criteria so it is easily recognized, can be registered accurately, and is well suited as an outcome in clinical trials[31–35]; the drawback is that it may vary between countries or it may depend on local availability of health-care services. However, consistent with the observations by Ong et al.[19] and Cote et al.[20] our findings appear reasonably generalizable. It is unlikely that our results are subject to recall bias, as number and severity of COPD exacerbations were recorded and scored both from the hospital and primary care medical records of each patient.

In summary, we have shown that apart from being a predictor of mortality, the BODE index is also a good predictor of the number and severity of exacerbations in patients with COPD. The power to predict exacerbations is superior to that of FEV_1 alone, probably reflecting that BODE can assess more accurately the pulmonary and the systemic consequences of COPD.

Conflict of interest

We declare no significant conflicts of interest or any financial and personal relationships with other people or organisations that could inappropriately influence this work.

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