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Severe exacerbations and BODE index: Two independent risk factors for death in male COPD patients

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Summary
Objectives: 1) To determine whether severe exacerbation of COPD is a BODE index independent risk factor for death; 2) whether the combined application of exacerbations and BODE (e-BODE index), offers greater predictive capacity than BODE alone or can simplify the model, by replacing the exercise capacity (BODEx index).
Methods: A prospective study was made of a cohort of COPD patients. In addition to calculation of the BODE index we register frequency of exacerbations. An analysis was made of all-cause mortality, evaluating the predictive capacity of the exacerbations after adjusting for the BODE. These variables were also used to construct two new indexes: e-BODE and BODEx.
Results: The study included 185 patients with a mean age of 71 ± 9 years, and FEV_1% 47 ± 17%. Severe exacerbation appeared as an independent adverse prognostic variable of BODE index. For each new exacerbation the adjusted mortality risk increased 1.14-fold (95% CI: 1.04–1.25). However, the e-BODE index (C statistic: 0.77, 95% CI: 0.67–0.86) didn't improve prognostic capacity of BODE index (C statistic: 0.75, 95% CI: 0.66–0.84) (p = NS). An interesting finding was that BODEx index (C statistic: 0.74, 95% CI: 0.65–0.83) had similar prognostic capacity than BODE index.

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Conclusions: Severe exacerbations of COPD imply an increased mortality risk that is independent of baseline severity of the disease as measured by the BODE index. The combined application of both parameters (e-BODE index) didn't improve the predictive capacity, but on replacing exacerbation with exercise capacity the multidimensional grading system is simplified without loss of predictive capacity.

At present, chronic obstructive lung disease (COPD) is the fourth most common cause of death in the world and the future perspectives are equally discouraging.[1,2] Therefore, we urgently need to adopt preventive and therapeutic strategies designed to revert this trend. A key element in this sense is the study of the causes of death and particularly the associated risk factors. Traditionally it has been accepted that the forced expiratory volume in one second (FEV_1) and its accelerated decrease over time is one of the best predictors of mortality.[3,4] For decades, this fact conditioned the therapeutic objective in patients with COPD. However, with the exception of smoking cessation, very few interventions have been able to slow the loss of lung function and improve the prognosis.[5,6] In contrast, we now know that COPD is a complex chronic inflammatory disease with multiple dimensions — some of which also have important prognostic implications. Celli et al.[7] developed a multidimensional index that integrates these principal prognostic determinants: the BODE [body mass index (BMI), airflow obstruction, dyspnea and exercise capacity] index. This score showed to be more effective than FEV_1 as a prognostic variable,[7] and unlike the latter, it contains a number of dimensions that can be modified — such as dyspnea, exercise tolerance and even BMI.[8]

Acute exacerbations (AECOPD) are among the prognostic factors that have generated most interest in recent months.[9] However, the BODE index does not include such events. In an observational study of 304 patients, our group found severe exacerbations to be an independent prognostic factor of the baseline severity of the disease. The frequency of exacerbations was adjusted for different confounding variables, including FEV_1, BMI, age, gas exchange or comorbidity. However, the 6-minute walking distance test (6MWD) was not used in this cohort, and no measurements were made of dyspnea; as a result, the model could not be adjusted for the BODE index, and this raised questions regarding interaction between the two prognostic factors.

The main objective of the present study was to determine whether severe AECOPD is a BODE index independent risk factor for death. In turn, the secondary objectives were: 1) to determine whether the combined application of both parameters, exacerbations and BODE (e-BODE index), offers greater predictive capacity than BODE alone; and 2) to explore whether exacerbations can simplify the model, by replacing the 6MWD with the registry of severe exacerbations (BODEx index).

Method

Patients

A prospective study was made of a cohort of 185 COPD outpatients. The subjects were included between January 1999 and June 30, 2004. The diagnosis and classification of COPD was carried out according to the latest Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, and was based on the current or past smoking history (>10 pack-year) and postbronchodilator FEV_1/forced vital capacity (FVC) ratio <70%.[1] Patients previously diagnosed with bronchial asthma, bronchiectasis, cystic fibrosis, upper airways obstruction or bronchiolitis related to systemic pathology were excluded. All included patients were required to be in a stable phase of the disease, i.e., without exacerbation in the month preceding the study. The study was approved by local ethic committee.

Protocol

Age, sex, smoking history, comorbidity, BMI, 6MWD, forced spirometry and arterial blood gases data were collected in all patients. The BODE index was calculated in all patients using the score proposed by Celli et al.[7] BMI was calculated by dividing patient body weight (kg) by the square of height (m^2). Dyspnea was assessed using the modified Medical Research Council scale.[10] FEV_1 was determined by forced spirometry (Vmax Spectra, SensorMedics Corporation, USA), following the guidelines established by the Spanish Society of Pneumology and Chest Surgery (SEPAR).[11] The FEV_1 and FVC results are expressed as percentages of the adult reference values.[12] Postbronchodilator FEV_1 was used as airflow limitation index, because it is regarded as a better predictor of mortality than prebronchodilator FEV_1.[3] The 6MWD was performed according to ATS guidelines.[13] We used the best of two 6MWD separated by at least 30 min. Comorbidity was quantified according to the index of Charlson et al.[14]

Exacerbations

All exacerbation episodes requiring hospital management (emergency visits or admissions) (AECOPD) during the previous year to inclusion were collected. We have an informatic system where all hospital contacts are registered. A prospective collection was also made of all exacerbation episodes requiring hospital management during the first year of follow-up. The patients were divided into three groups according to the recorded frequency of severe AECOPD: Group A (patients with no severe AECOPD); Group B (patients with one or two severe AECOPD); Group C (patients with 3 or more severe AECOPD). Severe AECOPD was defined as any sustained increase in respiratory symptomatology vs the patient baseline situation, requiring modification of habitual medication and hospital care (emergency visit or admission).[15]

e-BODE index (BODE plus exacerbation)

To construct the e-BODE index we used the 10 categories previously described by Celli et al.[7] adding three further possibilities according to the frequency of severe exacerbations. The absence of severe AECOPD was scored as 0, the presence of 1–2 severe AECOPD episodes received 1 point, and cases with three or more severe AECOPD were scored as 2. Thus, the e-BODE presents a score range of between 0 and 12 points. This score was divided into quartiles as follows: quartile 1 = 0–2 points, quartile 2 = 3–4 points; quartile 3 = 5–6 points; and quartile 4 = 7–12 points.

BODEx index

The methodology for developing this simplified index involved replacing the four categories of the walking test (0–3 points) with the three categories generated by the exacerbations (0, 1 or 2 points). The score range for this index is therefore between 0 and 9 points. The following quartiles were considered: quartile 1 = 0–2 points; quartile 2 = 3–4 points; quartile 3 = 5–6 points; and quartile 4 = 7–9 points.

Statistical analysis

Descriptive statistics were used to describe the study population at baseline. The comparison of means among the three study groups was based on analysis of variance (ANOVA), with chi-square testing and Bonferroni correction for the comparison of proportions. All-cause mortality was evaluated. We first conducted univariate analyses based on the Cox proportional hazards model using each of the potential predictors of respiratory mortality as independent variables, and survival status as the dependent variable.[16] Survival curves for AECOPD groups were estimated by the Kaplan–Meier product limit method and compared with the log-rank test.[17] Multivariate analysis was also based on the Cox proportional model. An interaction term between the variables and time was introduced in the model to analyze risk proportionality. To compare the capacity of predicting all-cause mortality of the exacerbations, BODE index, e-BODE index and BODEx index, we obtained ROC Type II curves and estimated the C statistics for each one in those patients with a follow-up of over 5 years. The null value for the C statistic is 0.5, with a maximum of 1.0 (higher values being better).[18] A method developed by Halney and McNeil was used to compare ROC curves derived from the same cases.[19] All statistical analyses were carried out using a statistical software package (SPSS for Windows, version 11.5; SPSS Inc., Chicago, IL, USA). A p-value of < 0.05 was considered to be significant.

Results

Subject characteristics

A total of 185 men were included in the study. The baseline characteristics of the patients are shown in Table 1. An increasing frequency of exacerbations was associated with older age, a higher dyspnea score, a lower predicted FEV_1%, shorter distance in the 6MWD and higher BODE score. Comorbidity and BMI were similar in all groups. The mean follow-up was 36 ± 24 months. In 110 cases (59.5%), follow-up lasted over 5 years.

Table 1 Baseline characteristics of the patients ($n = 185$).

	Global sample ($n = 185$)	Groups of AECOPD			
		A ($n = 102$, 55.1%)	B ($n = 48$, 25.9%)	C ($n = 35$, 18.9%)	p-value
Age (years)	71 ± 9	69 ± 9	72 ± 8	74 ± 8	0.027
BMI (kg/m^2)	28.1 ± 5.2	28.4 ± 5.6	27.8 ± 4.6	27.8 ± 4.8	0.738
Current smoking (%)	33 (17.8)	16 (15.7)	10 (20.8)	7 (20.0)	0.337
Pack-year	62 ± 36	58 ± 31	71 ± 41	60 ± 40	0.121
Charlson index	0.80 ± 0.96	0.67 ± 0.87	1.00 ± 1.23	0.91 ± 0.74	0.105
Dyspnea (MMRC)	2.12 ± 1.01	1.92 ± 0.93	2.10 ± 1.09	2.71 ± 0.92	<0.001
PaO_2	64 ± 12	66 ± 10	62 ± 15	61 ± 11	0.022
$PaCO_2$	44 ± 7	43 ± 6	44 ± 8	44 ± 6	0.322
FEV_1 (l)	1.17 ± 0.44	1.25 ± 0.52	1.15 ± 0.32	0.99 ± 0.26	0.072
FEV_1% (predicted)	47.9 ± 15.5	50.0 ± 18.2	45.8 ± 11.5	44.2 ± 9.6	0.003
GOLD classific, n (%)					0.002
Stage I	10 (5.4)	9 (8.8)	1 (2.1)	–	
Stage II	53 (28.6)	37 (36.3)	12 (25.0)	4 (11.4)	
Stage III	60 (32.4)	34 (33.3)	13 (27.1)	13 (37.1)	
Stage IV	62 (33.5)	22 (21.6)	22 (45.8)	18 (51.4)	
6MWD (m)	379 ± 111	398 ± 117	361 ± 106	348 ± 91	0.032
BODE index	3.5 ± 2.1	3.0 ± 2.0	3.7 ± 2.4	4.5 ± 1.6	<0.001
AECOPD (n)	1.43 ± 2.41	–	1.42 ± 0.50	5.63 ± 2.65	<0.001
Admissions (n)	0.56 ± 1.03	–	0.60 ± 0.64	2.05 ± 1.41	<0.001

AECOPD: acute exacerbations of COPD requiring hospital care. BMI: body mass index. MMRC scale: score on the modified Medical Research Council (MMRC) dyspnea scale; Stage I–IV: GOLD criteria stratification. 6MWD: 6-minute walking distance test. Values are expressed as the mean ± standard deviation.

Univariate survival analysis

The overall median survival was 63 months (95% CI: 48—77 months). A total of 71 (38.4%) deaths were recorded. The survival probability after 3, 5 and 7 years was 67%, 52% and 42%, respectively. Forty-three deaths (60.6%) were due to respiratory causes, 15 patients (21.1%) died of cardiovascular disease, 4 (5.6%) of malignant disease, and 7 (9.9%) of other diseases. In two cases (2.8%) the cause of death was not known. Nineteen patients were lost in the course of the 5-year follow-up period (follow-up rate: 89.7%).

Table 2 reflects the prognostic influence of the variables included in the univariate analysis. All of the BODE components, with the exception of BMI, were associated to an increased mortality risk. For each unit increase in the BODE index, the mortality risk increased 33% (HR: 1.33, 95% CI: 1.20—1.48), and for each new severe AECOPD the risk increased 17% (HR: 1.17, 95% CI: 1.09—1.26). There was a moderate but significant correlation between AECOPD during the first year of follow-up and the previous year to inclusion into the study ($r = 0.37$, $p < 0.001$). The C statistic for the BODE index in quartiles was 0.75 (95% CI: 0.66—0.84) vs 0.70 (95% CI: 0.60—0.80) for the AECOPD during the first year of follow-up and 0.67 (95% CI: 0.57—0.78) for the severe exacerbations that were registered during the previous year.

Multivariate survival analysis

Table 3 shows the regression model for exacerbations adjusted for age, comorbidity, blood gases and BODE index. Severe AECOPD suffered during the previous year to inclusion appeared as an independent adverse prognostic variable — with an adjusted mortality risk 2.24-fold greater who presented one or two severe exacerbations and 2.80-fold greater for patients three or more severe AECOPD, than for patients without AECOPD.

The severe exacerbations during the first year of follow-up appeared as an independent adverse prognostic factor (HR: 1.04, 95% CI: 0.54—2.01 for group B and HR: 2.66, 95% CI: 1.37—5.16 for group C, $p = 0.007$) only if we excluded of the previous exacerbations of the model. For each new exacerbation the adjusted mortality risk increased 1.14-fold (95% CI: 1.04—1.25). No significant interaction was observed between the BODE index and the prognostic effect of AECOPD. The risk proportionality test proved nonsignificant. Hazard ratios were unchanged over time.

e-BODE index

Fig. 1 shows the survival curves according to e-BODE quartiles adjusted by the other variables. Forty-seven (25.3%) of the patients were allotted to quartile 1 (0—2 points), 63 (33.9%) to quartile 2 (3—4 points), 40 (21.5%) to quartile 3 (5—6 points), and 36 (19.3%) to quartile 4 (7—12 points). Table 4 shows the death hazard ratios for e-BODE, after adjusting the model for age, comorbidity and blood gases. For each unit increase in this combined index, the adjusted mortality risk increased 35% (HR: 1.35, 95% CI: 1.21—1.51, $p < 0.0001$). The C statistic for the e-BODE index was 0.77 (95% CI: 0.67—0.86).

BODEx index

The index combining BMI, FEV_1%, dyspnea and exacerbations also showed an independent predictive value for mortality, after adjusting the model for age, Charlson index and blood gases (Table 5, Fig. 2). For each point increase in the BODEx index, the adjusted mortality risk increased 44% (HR: 1.44, 95% CI: 1.25—1.66, $p < 0.001$). The C statistic for the BODEx index was 0.74 (95% CI: 0.65—0.83).

Table 2 Predictors of mortality: univariate analysis.

	Hazard ratio (crude)	95% CI	*p*-value
Age (years)	1.07	1.04—1.11	<0.001
Cumulative smoking (pack-year)	0.99	0.99—1.01	0.430
Comorbidity index	1.35	1.04—1.76	0.024
BMI (kg/m^2)			
≤21	1.24	0.54—2.88	0.606
Dyspnea (MMRC scale)			<0.001
0—1	—	—	
2	1.52	0.63—3.62	
3	3.33	1.47—7.57	
4	5.10	1.97—13.17	
FEV_1 (% predicted)			0.031
≥65	—	—	
50—64	1.47	0.58—3.74	
36—49	2.23	0.96—5.19	
≤35	2.99	1.30—6.87	
6MWD (m)			<0.001
≥350	—	—	
250—349	2.75	1.58—4.78	
150—249	2.44	1.26—4.72	
<149	8.18	3.13—21.38	
BODE quartiles			<0.001
Quartile 1	—	—	
Quartile 2	1.62	0.80—3.25	
Quartile 3	3.28	1.66—6.49	
Quartile 4	5.93	2.82—12.47	
AECOPD groups (previous year to inclusion)			<0.001
Group A	—	—	
Group B	1.96	1.05—3.63	
Group C	2.96	1.70—5.13	
AECOPD groups (first year of follow-up)			<0.001
Group A	—	—	
Group B	1.77	0.99—3.17	
Group C	3.76	2.14—6.50	

BMI: body mass index. 6MWD: 6-minute walking distance test. AECOPD: acute exacerbations of COPD requiring hospital care. Group A: No AECOPD; Group B: patients with one or two AECOPD (emergency visits or hospitalizations); Group C: patients with 3 or more AECOPD.

Table 3 Predictors of mortality: multivariate analysis for exacerbation frequency. Adjusted model for age, comorbidity, blood gases and BODE index.

	Hazard ratio (adjusted)	95% CI	*p*-value
Age (years)	1.07	1.03—1.12	<0.001
Charlson index	1.04	0.77—1.41	NS
PaO_2 (mmHg)	1.02	0.99—1.04	NS
$PaCO_2$ (mmHg)	1.07	1.02—1.11	0.003
BODE quartiles			0.001
Quartile 1	—	—	
Quartile 2	1.15	0.48—2.76	
Quartile 3	2.32	0.98—5.50	
Quartile 4	4.30	1.72—10.75	
AECOPD groups (previous year to inclusion)			0.010
Group A	—	—	
Group B	2.24	1.05—4.79	
Group C	2.80	1.43—5.48	
AECOPD groups (first year of follow-up)			NS
Group A	—	—	
Group B	0.86	0.44—1.70	
Group C	1.78	0.87—3.65	

CI: confidence interval. *p*-value: level of significance. AECOPD: acute exacerbations of COPD requiring hospital care. Group A: No AECOPD; Group B: patients with one or two AECOPD (emergency visits or hospitalizations); Group C: patients with 3 or more AECOPD.

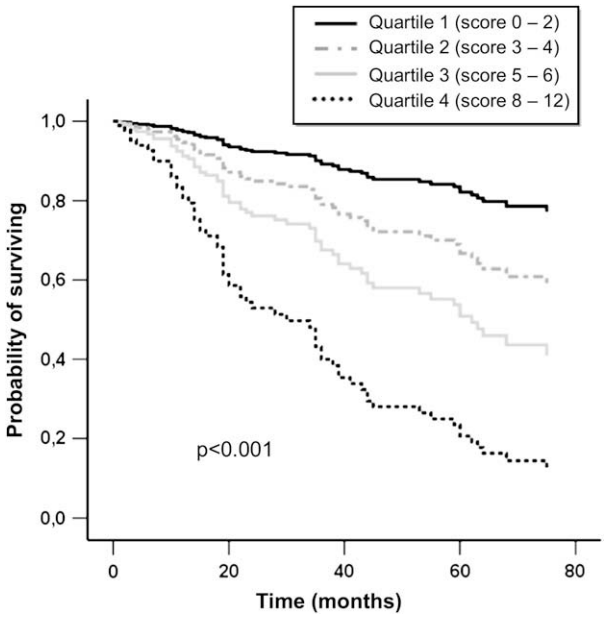


Figure 1 Survival curves by e-BODE index (BODE index plus exacerbation frequency) in patients with COPD, adjusted by confounding variables. The scores range from 0 to 12 points, the highest quartile the highest mortality.

Table 4 Predictors of mortality: multivariate analysis for e-BODE index. Adjusted model for age, comorbidity and blood gases.

	Hazard ratio (adjusted)	95% CI	*p*-value
Age (years)	1.07	1.03—1.11	<0.001
Charlson index	1.10	0.83—1.44	NS
PaO_2 (mmHg)	1.00	0.98—1.02	NS
$PaCO_2$ (mmHg)	1.05	1.01—1.09	0.016
e-BODE quartiles			<0.001
Quartile 1	—	—	
Quartile 2	1.59	0.56—4.50	
Quartile 3	3.22	1.22—8.48	
Quartile 4	9.71	3.36—28.10	

CI: confidence interval. *p*-value: level of significance.

Comparison among all indexes

Fig. 3 shows the ROC Type II curves corresponding to exacerbations and the BODE, e-BODE and BODEx indexes. The best result corresponded to the combined e-BODE index, followed by the original BODE index, BODEx index and finally the frequency of exacerbations. However, we didn't observe statistical differences in C statistic when comparing BODE index vs exacerbation alone during the previous year or first year of follow-up, e-BODE index or BODEx index.

Discussion

The present study confirms the idea that severe exacerbations of COPD (emergency visits or admission) are an important and independent indicator of poor patient prognosis. Indeed, even after adjusting for a multidimensional severity scale such as the BODE index, the mortality risk is maintained if the patient suffers severe exacerbations. In the case of patients with a recent history of frequent exacerbations the mortality risk were near triple (HR: 2.80, 95% CI: 1.43—5.48), after adjusting the model for

Table 5 Predictors of mortality: multivariate analysis for BODEx index. Adjusted model for age, comorbidity and blood gases.

	Hazard ratio (adjusted)	95% CI	*p*-value
Age (years)	1.09	1.05—1.13	<0.001
Charlson index	1.12	0.83—1.51	NS
PaO_2 (mmHg)	1.00	0.98—1.03	NS
$PaCO_2$ (mmHg)	1.05	1.01—1.10	0.016
BODEx quartiles			<0.001
Quartile 1	—	—	
Quartile 2	1.52	0.66—3.53	
Quartile 3	3.16	1.37—7.30	
Quartile 4	5.86	2.42—14.17	

CI: confidence interval. *p*-value: level of significance.

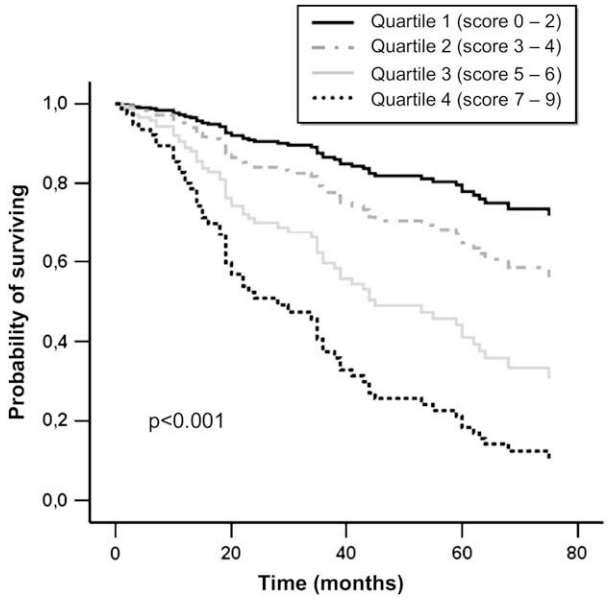
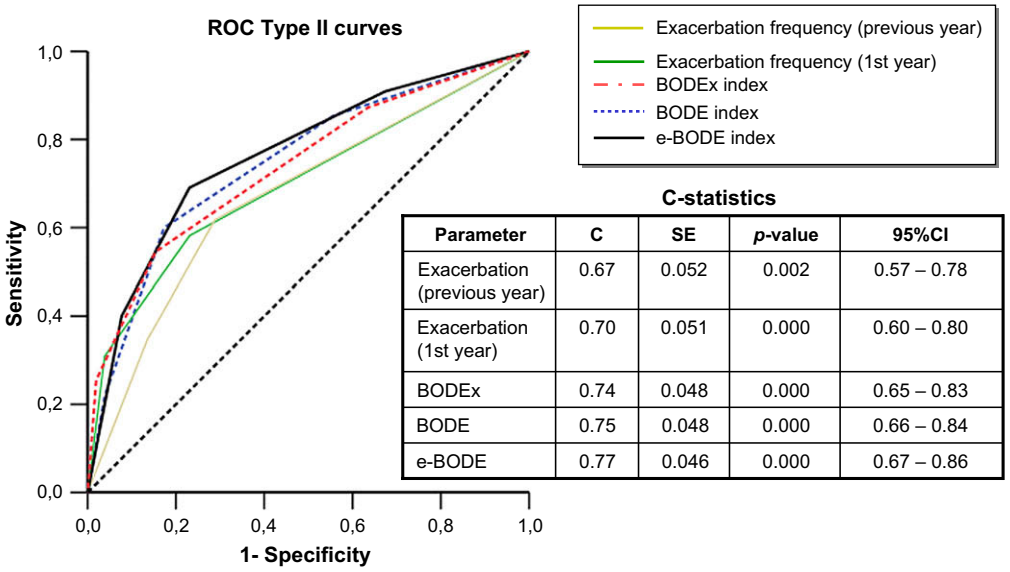


Figure 2 Survival curves by BODEx index (BODE index with exercise capacity replaced by exacerbation frequency) in patients with COPD, adjusted by confounding variables. The scores range from 0 to 9 points, the highest quartile the highest mortality.

age, comorbidity, blood gases, exacerbations during the first year of follow-up and BODE index (Table 3). On combining both prognostic factors (frequency of exacerbations and BODE index) in the form of the e-BODE index, the mortality risk predictive capacity didn't show a significant improvement (C statistic for BODE index 0.75 vs 0.77 for e-BODE index, p = NS). The most remarkable finding was that registry of the severe exacerbations allows simplification of the BODE index, since on replacing the 6MWD with the frequency of exacerbations (thus forming the BODEx index), the predictive capacity was similar to BODE index (C statistic of the BODEx index: 0.74 vs 0.75 for the BODE index, p = NS) (Fig. 3).

Severe exacerbations, i.e., those requiring hospital care (visits to the emergency service or admissions to hospital) are an independent mortality risk factor. In a recent study involving 304 male patients with a mean predicted FEV_1% of 46 ± 17%, our group found that as the frequency and severity of exacerbations increases, mortality risk also increases — this effect moreover being independent of other classical prognostic factors such as patient age, FEV_1, BMI, PaO_2, $PaCO_2$ or comorbidity.[9] The consequences of this observation are relevant, since the prevention of severe exacerbations could have beneficial effects the survival of these patients. However, before accepting these results, it is necessary to contrast the prognostic importance of COPD exacerbations with new studies involving adjustment of the predictive model for new and potent prognostic dimensions such as the BODE index.[7] Different studies have revealed a somewhat bidirectional relationship between this index and exacerbations.[20–22] In effect, as the severity of the disease increases, and the BODE index therefore rises, so does the frequency of exacerbations. Ong et al.,[20] in a study of 127 COPD patients with a mean FEV_1 of 43.7%, found the BODE index to be useful for predicting hospital admission risk — its predictive capacity being even greater than that of the COPD staging system as defined by the GOLD. Similar results have been obtained recently by a Spanish group.[21] In the opposite sense, it has been reported that with the appearance of new exacerbations, the BODE index undergoes longitudinal deterioration. Cote et al.,[22] in a study of 205 consecutive patients prospectively followed-up during two years, showed that moderate exacerbations induce longitudinal deterioration of the BODE index — the latter worsening an average of 1.38 points during exacerbation, and remaining altered an



C-statistics

Parameter	C	SE	*p*-value	95%CI
Exacerbation (previous year)	0.67	0.052	0.002	0.57 – 0.78
Exacerbation (1st year)	0.70	0.051	0.000	0.60 – 0.80
BODEx	0.74	0.048	0.000	0.65 – 0.83
BODE	0.75	0.048	0.000	0.66 – 0.84
e-BODE	0.77	0.046	0.000	0.67 – 0.86

Figure 3 Comparative ROC Type II curves and C statistics value for exacerbation frequency (during the previous year to inclusion and during the first year of follow-up), BODE index, BODEx index and e-BODE index as predictors of mortality in patients with COPD. The sensitivity and specificity of e-BODE was the highest, but there were not statistical differences between ROC curves.

average of 0.8 and 1.1 points above the baseline score after one and two years, respectively. These changes are not seen in patients without exacerbations. These results point to an important association between the BODE index and COPD exacerbations; consequently, any prognosis predictive model should include both variables. This was done in the present study, adjusting the predictive capacity of exacerbations to the BODE index. Here again, the frequency of severe exacerbations was seen to constitute an independent adverse prognostic factor, even with respect to the above multidimensional severity index (Table 3). These results confirm the prognostic importance of COPD exacerbations, and thus stress the need for preventive measures. Only male patients were included in our study and therefore we cannot advance the same results for a female COPD populations.

The BODE index includes four classical prognostic factors of the disease, i.e., BMI, FEV_1, dyspnea and the 6MWD test. This multidimensional approach has been shown to offer a greater predictive capacity than the classical criterion still in use for classifying patients, i.e., FEV_1.[7] Given the BODE index independent adverse prognostic capacity of COPD exacerbations, our second objective was to determine whether the combined application of both parameters could improve the predictive capacity. We failed to show it perhaps due to the limited sample of our study. The e-BODE index, which incorporates all the BODE index components together with the frequency of recent severe exacerbations, yielded a C statistic of 0.77 (95% CI: 0.67—0.86), which is slightly superior to that of the BODE index alone (C statistic of 0.75, 95% CI: 0.66—0.84) and the frequency of past exacerbations considered isolatedly (C statistic of 0.67, 95% CI: 0.57—0.78). However, we didn't find statistical differences when comparing ROC curves using Hanley method.[19] BODE index proposed by Celli et al.[7] showed a similar C statistic of 0.74, which was superior to FEV_1. Casanova et al., by contrast, showed a C statistic of 0.795 for BODE which also was superior to FEV_1 and inspiratory-to-total lung capacity ratio.[23] In both studies authors didn't use statistical method to compare ROC curves and they accepted absolute values of C statistic as a superiority model for predictive capacity.

To assess severe exacerbations frequency we considered three threshold values (0: none; 1: one or two severe exacerbations; and 2: three or more severe exacerbations). We feel that this decision is arbitrary but are based on a previous study where patients were divided into the same 3 categories.[9] Other possible approach could be weighted on the hazard ratio for predicting death as previously reported[9] (0: none exacerbations; 2: one or two severe exacerbations; and 4: three or more severe exacerbations). However, with these scores we obtained similar results. Finally, we decided to employ the present threshold values for severe exacerbations because of similar approach to threshold values proposed by Celli et al.[7] To construct e-BODE index we used previous year exacerbations due to two reasons. First, we considered more easy for clinical practice to collect information about severe AECOPD appeared during last year, and to calculate e-BODE index. If we should use new exacerbations appeared during the first year of follow-up it would only calculate the score after this follow-up. And second, when both variables were included into the model, only previous year exacerbations were considered significant. The e-BODE index with new exacerbations was slightly superior (C statistic of 0.80, 95% CI; 0.72—0.88) but not applicable to clinical practice.

Although the BODE index has been shown to be superior to FEV_1, its implantation is proving to be slow and gradual. One of the possible factors limiting its implantation is the need to perform a 6MWD test. Although the test is simple and inexpensive, it requires personnel and time. For this reason we have tried to develop a simplified index (the BODEx index) in which the 6MWD has been replaced by the frequency of exacerbations. The C statistic of this test is similar to BODE index (0.75 vs 0.74) — a fact that opens the possibility of applying this simplified index. We feel that further studies are needed to prospectively validate the predictive capacity of this new index.

In conclusion, the frequency of severe exacerbations (AECOPD) is a first-order prognostic factor that has been shown to be independent even of the BODE index. As the frequency of severe exacerbations increases, the patient prognosis worsens. The adoption of preventive measures to reduce the impact of AECOPD is therefore a priority concern. The combined index of BODE plus exacerbations (the e-BODE index) didn't show to improve the capacity to predict mortality risk in COPD patients, but probably our sample was unpowered to find statistical differences. Finally, we like to remark that a simplified multidimensional version in which the 6-minute walking distance test is replaced by the frequency of exacerbations (i.e., the BODEx index), offers a good predictive capacity. This simplification could improve the implementation of a multidimensional score.

Conflict of interest statement

The authors have no conflicts to disclosure.

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