

# Modified BODE Index to Predict Mortality in Individuals With COPD: The Role of 4-Min Step Test

Elaine B Vieira, Luiza H Degani-Costa, Beatriz C Amorim, Lígia B Oliveira, Talita Miranda-Silva, Priscila CA Sperandio, Wladimir M Medeiros, Flávio F Arbex, Roberta P Ramos, and Luiz E Nery

**BACKGROUND:** The BODE (body mass index, air-flow obstruction, dyspnea, exercise capacity) index is a composite prognostic marker that predicts mortality in COPD. It includes body mass index, air-flow obstruction, dyspnea score, and exercise capacity by using the 6-min walk distance. However, a 30-m-long corridor is necessary to perform the test and this limits its use in clinical practice. Step tests may elicit distinct physiologic responses compared with the 6-min walk test but are easy to perform in the office setting. We sought to investigate whether a 4-min step test would be a suitable surrogate of the 6-min walk test, in a modified BODE step index (simplified BODE index), to predict mortality in COPD. **METHODS:** Individuals with COPD performed a self-paced 4-min step test, and the simplified BODE index was calculated by replacing the 6-min walk distance by the number of steps climbed. Cutoff values were determined by receiver operating characteristic curve analysis as follows: score 0 for >60 steps; score 1 for 50–60 steps; score 2 for 40–49 steps; and score 3 for <40 steps. **RESULTS:** A total of 186 individuals with COPD were enrolled from 2011 to 2016 (60% males; mean  $\pm$  SD age, 65  $\pm$  9 y; mean  $\pm$  SD FEV<sub>1</sub>, 50  $\pm$  17 L). There were 36 deaths among the study cohort. The simplified BODE index was a prognostic marker, independent of cardiovascular comorbidities and oxygen desaturation (HR 1.12, confidence interval (CI) [1.03–1.22]). Individuals with simplified BODE index scores  $\geq 7$  were at higher risk of death from any cause ( $P < .001$ , log-rank test). **CONCLUSIONS:** This was the first study, to our knowledge, to show that the 4-min step test as a surrogate of exercise capacity in the BODE index (simplified BODE index) is an independent predictor of mortality in COPD and may help to spread its use among practicing physicians. *Key words:* COPD; step test; exercise capacity; BODE index; 6-min walking distance; 6-min walk test. [Respir Care 2020;65(7):977–983. © 2020 Daedalus Enterprises]

## Introduction

Limited exercise tolerance is a key feature of COPD that carries significant prognostic information.<sup>1–4</sup> Although FEV<sub>1</sub> has been largely used as a tool for stratifying disease

severity,<sup>5</sup> it is well known that spirometric values may not accurately predict exercise capacity.<sup>6–8</sup> Cardiopulmonary exercise testing is the accepted standard method for assessing aerobic capacity,<sup>9–11</sup> but it remains costly<sup>12</sup> and largely unavailable worldwide. In this context, field tests emerge as simpler and inexpensive alternatives for routine evaluation of patients with COPD.<sup>13</sup> The total distance walked on the 6-min walk test (6MWT), for example, has been shown to predict mortality in COPD<sup>3,14,15</sup> and was

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All authors are affiliated with Pulmonary Function and Exercise Physiology Unit, Division of Respiratory Diseases, Department of Medicine, Universidade Federal de São Paulo, São Paulo, Brazil.

Ms Vieira and Dr Degani-Costa contributed equally to this manuscript.

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Correspondence: Roberta P Ramos MD PhD, Pulmonary Function and Clinical Exercise Physiology Unit, Respiratory Division, Universidade

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Federal de São Paulo, Rua Francisco de Castro, 54, Vila Clementino, São Paulo, Brazil 04039-002. E-mail: robertapulcheri@gmail.com.

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incorporated into the BODE index, a composite prognostic marker, which also takes into account body mass index, air-flow obstruction ( $FEV_1$ ), and severity of dyspnea evaluated by using the modified Medical Research Council questionnaire.<sup>16</sup> However, 6MWT has 2 major drawbacks that limit its use in clinical practice: first, it requires a 30-m-long corridor to be performed; second, the 6MWT may be a submaximal test in fitter patients with mild disease, being poorly responsive to therapeutic interventions.<sup>17</sup>

Step tests elicit distinct physiologic responses compared with the 6MWT.<sup>18</sup> The work against gravity and the need to recruit muscle groups that are not often used in everyday life result in higher metabolic and ventilatory responses than those seen in the 6MWT.<sup>19</sup> Recently, a variety of step tests,<sup>20</sup> which used different lengths and step heights,<sup>21-23</sup> self-paced,<sup>24-26</sup> or outer-paced,<sup>27</sup> have been used to evaluate the severity of pulmonary diseases. Although lacking standardization, there is preliminary evidence that step tests could also be used to assess patient prognosis. In fact, oxygen desaturation on the 4-min step test proved to be a strong predictor of mortality in patients with idiopathic pulmonary fibrosis,<sup>28</sup> but no study has addressed the potential prognostic role of this test for patients with COPD. Therefore, the aim of this study was to investigate whether desaturation and exercise performance on the 4-min step test may predict mortality in individuals with COPD. In addition, we sought to determine if a modified BODE index, including the 4-min step test in place of the 6MWT would also be able to indicate prognosis.

## Methods

### Subjects and Study Design

After ethics approval, we conducted a single-center prospective cohort study in which individuals with COPD and Global Initiative for Chronic Obstructive Lung Disease (GOLD)<sup>29</sup> stages of 1–4 with COPD were enrolled between April 2011 and April 2016. The subjects were required to be clinically stable, without exacerbations or changes in therapy over the past 2 months. Exclusion criteria were the use of long-term oxygen therapy, untreated angina or known ischemic heart disease, or with any orthopedic or neurological disease that might limit exercise performance.

### Protocol

The subjects were initially evaluated by a pulmonologist [FFA] to ensure eligibility, determine baseline dyspnea intensity, and inquire after known comorbidities. Eligible individuals were then asked to perform the 4-min step test and spirometry. Each participant was followed up for a minimum of 1 year, with periodic visits or telephone calls made by the study investigators.

## QUICK LOOK

### Current knowledge

The BODE (body mass index, air-flow obstruction, dyspnea, exercise capacity) index is a composite prognostic marker that predicts mortality in patients with COPD, but the logistic complexity of assessing exercise capacity in real-life setting limits its use. The original BODE index includes the 6-min walk distance, which requires a 30-m-long corridor to perform the evaluation. A 4-min step test, however, is easy to perform in the office setting and has been shown to predict mortality in other patient populations.

### What this paper contributes to our knowledge

Oxygen desaturation < 90% and climbing < 65 steps with the 4-min step test were associated with higher mortality in the subjects with COPD. A modified BODE index that replaced the 6-min walk distance for the number of steps climbed during the 4-min step test was able to predict mortality independent of age, comorbidities, and oxygen desaturation. In our study sample, the subjects with simplified BODE index scores  $\geq 7$  showed a higher risk of death from any cause.

## Spirometry

Spirometry followed the quality and reproducibility criteria recommended by current guidelines<sup>30</sup> and was performed with a portable spirometer (EasyOne Model 2001 Spirometer, ndd Medical Technologies, Chelmsford, Massachusetts). Spirometric variables were expressed as the percent of predicted values,<sup>31</sup> and response to bronchodilators was assessed after administration of 400  $\mu$ g of inhaled salbutamol.

## 4-Min Step Test

The subjects were instructed to step up and down a single 20-cm-high step as fast as possible for 4 min, being allowed to pause and resume exercise as often as needed. Verbal stimulation was offered every minute according to the American Thoracic Society guideline for the 6MWT.<sup>32</sup> Arterial blood pressure was measured with a stethoscope and sphygmomanometer by the indirect auscultatory method at baseline and at peak exercise, whereas measurements of heart rate and oxyhemoglobin saturation were obtained by  $S_{pO_2}$  (Onyx 9500, Nonin Medical, Minnesota) at baseline, at the second minute, and immediately after the test was finished. Oxygen desaturation was defined as a decrease in  $S_{pO_2}$  of  $\geq 4\%$  and the lowest  $S_{pO_2}$  was recorded for analysis. The

Table 1. Baseline Characteristics of the Subjects With COPD

Characteristic	Results
Demographic/anthropometric	
Age, mean $\pm$ SD y	65 $\pm$ 9
Males, <i>n</i> (%)	113 (60)
BMI, mean $\pm$ SD kg/m <sup>2</sup>	25 $\pm$ 5
Smoking history	
Current smokers, <i>n</i> (%)	37 (20)
Pack-years, mean $\pm$ SD	56 $\pm$ 38
Comorbidities: Charlson index, <i>n</i> (%)	
1	85 (45)
2	32 (17)
$\geq 3$	69 (37)
Symptoms: mMRC scale score, <i>n</i> (%)	
0–1	40 (21)
2–3	112 (60)
4	34 (18)
Spirometry, mean $\pm$ SD	
FEV <sub>1</sub> /FVC	0.4 $\pm$ 0.2
FEV <sub>1</sub> % predicted	42 $\pm$ 13
FVC% predicted	48 $\pm$ 25
GOLD stage	
1–2	77 (41)
3–4	109 (58)

*N* = 186.

BMI = body mass index

mMRC = modified Medical Research Council

GOLD = Global Initiative for Chronic Obstructive Lung Disease

predicted peak heart rate (beats/min) was calculated as 220 beats/min minus the subject's age in years.

## Statistical Analysis

The sample size calculation for survival was based on an overall expected mortality rate of 20% over 5 years. We used an equation based on a study by Peduzzi et al,<sup>33</sup> which states that  $N = 10k/p$  (where  $N$  is the minimum number of cases needed,  $k$  is the number of risk factors, and  $p$  is the proportion of events). Therefore, when considering age and the 2 variables listed in the hypothesis, the minimum sample size required was 150 individuals. Numeric data are presented as mean  $\pm$  SD or median (25–75% quartiles), whereas categorical data are expressed as values or frequency. All-cause mortality was defined as the primary end point, with the remaining cases designated as censored. Receiver operating characteristic curves were constructed for the lowest  $S_{pO_2}$  and the number of steps climbed and cutoff values were obtained according to the maximum Youden index.

The simplified BODE index was calculated similarly to the original BODE index,<sup>16</sup> but the 6-min walk distance was replaced by the number of steps climbed, as follows: score 0 for  $>65$  steps; score 1 for 50–64 steps, score 2 for 36–49 steps, and score 3 for  $<35$  steps. The extreme values

Table 2. Variables Obtained During the 4-Min Step Test in the Subjects With COPD

Variable	Result
No. climbed steps, mean $\pm$ SD	61 $\pm$ 21
Rest $S_{pO_2}$ , mean $\pm$ SD %	94 $\pm$ 2
Nadir $S_{pO_2}$ , mean $\pm$ SD %	88 $\pm$ 5
Heart rate, mean $\pm$ SD beats/min	110 $\pm$ 18
Heart rate, mean $\pm$ SD % predicted	71 $\pm$ 12
SBP, mean $\pm$ SD mm Hg	147 $\pm$ 19
Dyspnea, Borg scale score, mean $\pm$ SD	4 $\pm$ 2
Lower limbs fatigue, Borg scale score, mean $\pm$ SD	4 $\pm$ 3
Pauses, no.	
1–2	96 (51)
3–4	10 (5)
Pause time, median (25–75% quartiles) s	50 (30–73)

*N* = 186.

SBP = systolic blood pressure

that indicated scores 0 and 3 were obtained by receiver operating characteristic curve analysis as follows: 65 steps corresponded to the maximum Youden index, whereas 35 steps was the most specific value to indicate mortality. Intermediate values were randomly selected to have the same number of steps in each strata. A Kaplan-Meier survival analysis was carried out, and the curves were compared by the log-rank test. A Cox proportional hazards model was constructed to assess survival from the first assessment to the time of death or censoring. Univariate analyses of potential confounders were conducted, and a multivariate model was constructed by performing stepwise forward regression. Statistical software SPSS 19.0 (SPSS, Chicago, Illinois) was used for data analysis.

## Results

### Subject Characteristics

After exclusion of 12 individuals who did not manage to complete the 4-min step test, 186 subjects with COPD were enrolled from April 2011 to February 2016. They were predominantly men with mild dyspnea on exertion (Table 1) and 37% of them had  $\geq 3$  comorbidities. At the time of inclusion, 41.3% were classified as being at accepted stage 1 and 2, and 58.6% at accepted stage 3 and 4. The variables obtained during the 4-min step test are shown in Table 2. There were no adverse events during testing. Of note, 57% of the subjects needed to pause at least once, and exercise was resumed after a median resting period of median (25–75% quartiles). The subjects who needed to pause presented similar mean  $\pm$  SD FEV<sub>1</sub>% predicted values (51  $\pm$  18% vs 49  $\pm$  15%;  $P = .43$ ) but were older (mean  $\pm$  SD 68  $\pm$  11 y vs 64  $\pm$  9 y,  $P = .03$ ) than those

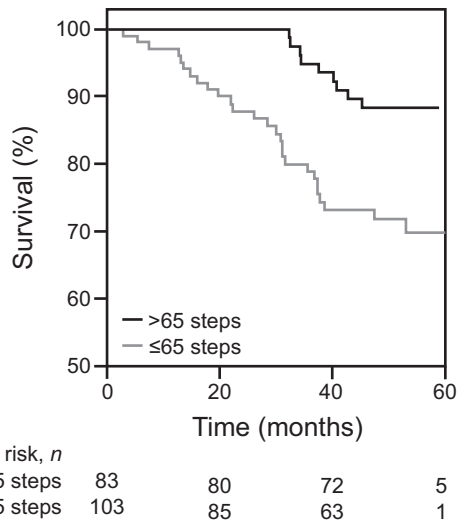


Fig. 1. Kaplan-Meier survival curves of subjects with COPD according to the number of steps climbed during the 4-min step test.  $P = .002$ , log-rank test;  $P = .001$ , Breslow test.

who completed the 4-min step test without interruption. Overall, oxygen desaturation was observed in 81% of the subjects and 58% presented the lowest  $S_{pO_2}$ , of <90%.

### Performance and Desaturation on 4-Min Step Test and Mortality

By the end of a mean follow-up period of 49 (95% CI 48–51) months, 36 individuals had died. The number of steps climbed was significantly associated with survival ( $P = .02$ ). Indeed, the Kaplan-Meier estimate of 5-year survival rate for subjects who managed to climb >65 steps was 88.7% (95% CI 81.1–96.3%), as opposed to 70.6% (95% CI 61–80.2%) for those who climbed ≤65 steps (log-rank test, chi-square 8.5,  $P = .003$ ) (Fig. 1). Similarly, the median survival time was significantly lower in individuals who desaturated during the 4-min step test (Fig. 2). Further investigation with the Cox proportional hazard regression analysis indicated that those with the lowest  $S_{pO_2} \leq 90\%$  were 2.8 times more likely to die within the observation period than those without desaturation.

### The Modified Simplified BODE Index and Its Ability to Predict Survival

The new simplified BODE index was calculated for each individual, as described in Table 3. The simplified BODE index score quartiles were then defined by using the same cutoffs of the original BODE index: quartile 1, a score of 0–2; quartile 2, a score of 3–4; quartile 3, a score of 5–6; and quartile 4, a score of 7–10. A Kaplan-Meier survival curve analysis according to quartiles is presented in Figure 3 and shows that the top 2 quartiles had a significantly

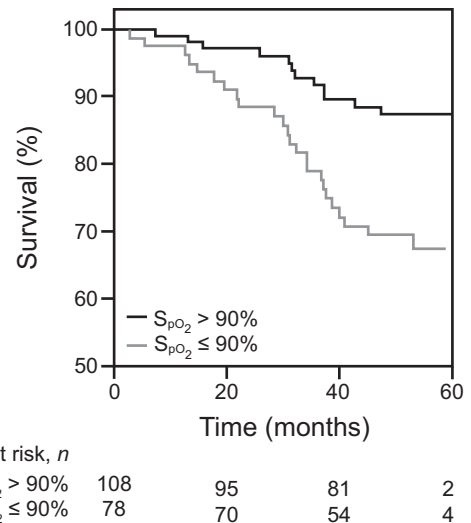


Fig. 2. Kaplan-Meier survival curves of subjects with COPD according to desaturation during the 4-min step test.  $P = .002$ , log-rank test;  $P = .002$ , Breslow test.

Table 3. Cutoff of Variables Used for the Computation of the Simplified BODE Index

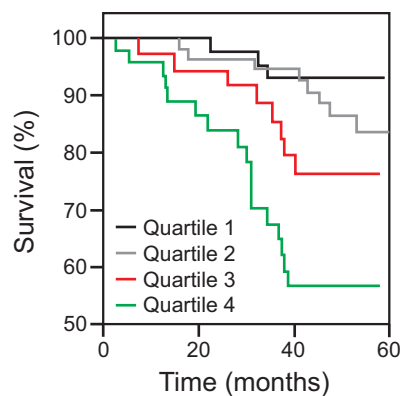
Variable	Simplified BODE Index Score			
	0	1	2	3
FEV <sub>1</sub> % predicted	≥65	50–64	36–49	≤35
mMRC dyspnea scale score	0–1	2	3	4
Body mass index	>21	≤21		
4-Min step test, no. steps	>65	55–65	45–54	<45

BODE = body mass index, air-flow obstruction, dyspnea, exercise capacity  
mMRC = modified Medical Research Council

higher overall survival compared with the bottom quartile (chi-square 15.2 and 11.02, log rank;  $P < .05$ ). The mean survival times for quartiles 2 and 3 were 57.3 (95% CI 54.6–60.0) months and 51.1 (95% CI 46.6–55.5) months, respectively ( $P = .25$ ). In the multivariate analysis (Table 4), an simplified BODE index score  $\geq 7$  was the strongest predictor of death, even when adjusted for age and comorbidities (Hazard ratio (HR) 4.10, confidence interval (CI) 2.02–8.30;  $P < .001$ ).

### Discussion

In this single-center study, we demonstrated that performance on the 4-min step test predicted all-cause mortality in mild to very severe COPD. Importantly, we were able to stratify the total number of steps climbed into 4 different categories and created a modified step BODE index (simplified BODE index), which can be used in routine clinical practice to assess patient prognosis. Although



Subjects at risk, <i>n</i>				
Quartile 1	46	44	39	4
Quartile 2	58	54	48	2
Quartile 3	36	34	26	0
Quartile 4	46	33	22	0

Fig. 3. Kaplan-Meier survival curves for modified BODE index. Quartile 1 is a score of 0–2, quartile 2 is a score of 3–4, quartile 3 is a score of 5–6, and quartile 4 is a score of 7–10.  $P < .001$ , log-rank test;  $P < .001$ , Breslow test. BODE = body mass index, air-flow obstruction, dyspnea, exercise capacity.

Table 4. Uni- and Multivariate Cox Proportional Hazard Analysis for Mortality in the Subjects With COPD

Analysis	Hazard Ratio	95% CI	<i>P</i>
<b>Univariate</b>			
Age $\geq 70$ y	2.63	1.36–5.07	.004
BMI $\leq 20$ kg/m <sup>2</sup>	2.58	1.29–5.16	.007
Charlson index	1.03	0.90–1.17	.63
mMRC score 3–4	2.54	1.31–4.91	.005
GOLD stage 3–4	3.19	1.40–7.30	.006
Nadir $S_{pO_2} \leq 90\%$	2.88	1.44–5.76	.003
Climbed steps $\leq 65$	3.05	1.39–6.69	.005
sBODE index score $\geq 7$	4.24	2.18–8.25	<.001
<b>Multivariate</b>			
Age $\geq 70$ y	2.17	1.12–2.17	.02
Charlson index	1.09	0.96–1.25	.16
Nadir $S_{pO_2} \leq 90\%$	2.51	1.23–5.10	.01
sBODE index score $\geq 7$	4.10	2.02–8.30	<.001

*N* = 186.

BMI = body mass index

mMRC = modified Medical Research Council

GOLD = Global Initiative for Chronic Obstructive Lung Disease

sBODE = simplified BODE (body mass index, air flow obstruction, dyspnea score and exercise capacity)

air-flow limitation is often regarded as the main cause of exercise intolerance in COPD, there are other pathophysiologic mechanisms, such as dynamic hyperinflation,<sup>34</sup> gas exchange abnormalities,<sup>35</sup> and central cardiovascular<sup>36–38</sup> and peripheral muscular alterations,<sup>39–41</sup> that can play important roles in the development of exercise limitation by patients with COPD. Thus, even though the spirometric GOLD classification remains an important tool to stratify

disease severity and establish prognosis,<sup>5</sup> it does not seem to be adequate to discriminate functional capacity, especially in the intermediate groups of severity.

When considering the systemic manifestations of COPD, Celli et al<sup>16</sup> validated a multidimensional grading system, the BODE index, which integrates the body mass index, severity of air-flow obstruction, dyspnea burden (modified Medical Research Council questionnaire), and exercise capacity (6-min walk distance) in a cohort of 625 subjects with COPD. A few years later, a modified BODE index that replaced the 6-min walk distance for peak oxygen consumption on cardiopulmonary exercise testing (CPET) was also validated.<sup>42</sup> Both versions of the BODE index proved to be better than FEV<sub>1</sub> alone at predicting death in the subjects with COPD, which led to the incorporation of the BODE index score into the decision-making algorithm for assessing patients for pulmonary transplantation.<sup>43</sup>

Despite its clinical utility, the BODE index remains largely underused in clinical practice and, still today, is considered an optional assessment for the majority of patients with COPD.<sup>5</sup> The main reason for this lack of recognition by the clinical and scientific communities lies mostly on the tests chosen to evaluate exercise capacity, which are often not feasible as routine workup. Step tests, however, can be easily performed inside a medical office because they require no step >20-cm high, a pulse oximeter, and one health-care professional (respiratory therapist, nurse, or physician). Therefore, it made sense to investigate whether step tests could be useful as a surrogate of the 6MWT or CPET in a new BODE index (simplified BODE index).

Indeed, our study demonstrated that the number of steps climbed by the end of 4 min provided important prognostic information, with mortality being significantly lower among the subjects who were able to climb  $\geq 65$  steps. After creating 4 distinct block categories of steps climbed and integrating this information with dyspnea burden, body mass index, and postbronchodilator FEV<sub>1</sub>, the newly developed simplified BODE index proved to be a good predictor of 5-year survival, with a simplified BODE index score of  $\geq 7$  being associated with a 4-fold increase in mortality.

In addition to providing an index of exercise performance (number of climbed steps), step tests may also be useful to detect gas exchange abnormalities when pulse oximetry is added to the test. Desaturation during CPET also carries important prognostic value, but field tests such as the 6MWT and step tests seem to be more sensitive than cycling for detecting desaturation. Indeed, Dal Corso et al<sup>19</sup> performed an incremental step test in the subjects with COPD and concluded that the test was not only capable of eliciting maximum cardiovascular and metabolic responses but also generated greater hypoxemia than cycle ergometer exercise testing. A potential explanation for this finding was that the work against gravity may lead to higher



muscle oxygen extraction and lower mixed venous oxygen saturation.

In our study, oxygen desaturation was extremely frequent (81%) and the lowest  $S_{pO_2} \leq 90\%$  was associated with a poor outcome, independent of spirometric severity. This was in line with previous studies published by Takigawa et al<sup>44</sup> and Casanova et al,<sup>15</sup> which found that desaturation on the 6MWT was a predictor of mortality. In addition, recent research revealed that patients who desaturated during the 6MWT had a ~2-fold increased risk of death and a 50% increased risk for COPD exacerbations.<sup>45</sup> Similarly, Kramer et al<sup>21</sup> evaluated desaturation during the 15-step test and found a good correlation between a decrease in  $S_{pO_2}$  and spirometric severity of COPD.

### Study Limitations

Currently, step tests to assess exercise capacity in COPD are not standardized and, therefore, we could not extrapolate our results or cutoff values to different test protocols. Our choice to perform a 4-min self-paced step test was largely based on the fact that its prognostic value had already been demonstrated for subjects with idiopathic pulmonary fibrosis.<sup>28</sup> There also was a theoretical assumption that selecting longer test durations or fixing a minimum pace could potentially prevent patients with more severe conditions from completing the test. Indeed, even though we selected a short and self-paced protocol, some patients required several pauses to complete the test.

Another important limitation of our study was that the subjects did not routinely perform 6MWT or incremental CPET, so we could not calculate their BODE scores with these exercise protocols. As a result, we could not tell whether simplified BODE index scores matched the BODE scores when using 6MWT or incremental CPET in each individual subject. It is also important to highlight that our study protocol included only one 4-min step test, so we did not have data on reproducibility or possible learning effects, which are fairly common in field tests. However, previous studies have already demonstrated good reproducibility of step tests,<sup>19,26</sup> which makes it unlikely that a second test would significantly change our results.

### Conclusions

Oxygen desaturation < 90% and climbing < 65 steps with the 4-min step test were associated with higher mortality in the subjects with COPD. The modified BODE index, the simplified BODE index, when using the 4-min step test proved to be a prognostic marker independent of the age, comorbidities, and oxygen desaturation because the subjects with simplified BODE index scores  $\geq 7$  showed a higher risk of death from any cause. Because the 4-min step test is a simple and inexpensive test, the simplified BODE

index could easily be incorporated into the routine assessment of patients with COPD.

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