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# Predictors of first-year survival in patients with advanced COPD treated using long-term oxygen therapy

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Received 1 July 2007; accepted 3 December 2007

Available online 10 January 2008

## KEYWORDS

Pulmonary disease;  
Chronic obstructive/  
mortality;  
Dyspnea;  
Oxygen inhalation  
therapy/utilization

## Summary

Little evidence-based guidance is available to aid clinicians in determining short-term prognoses in very severe COPD patients. Therefore, the present study was designed to provide a prospective assessment (1) of the mortality rates and (2) whether the baseline measurements may be determinants of 1-year mortality in hypoxemic COPD patients receiving long-term oxygen therapy (LTOT).

Seventy-eight clinically stable patients with advanced COPD treated using LTOT were enrolled in a prospective cohort study. Outcome variable: first-year mortality. Baseline measurements: categorical variables: age (<60 or ≥60 years); gender; body mass index (<20 or ≥20 kg/m<sup>2</sup>); fat-free mass (FFM) index (<16 [men] and <15 kg/m<sup>2</sup> [women]; baseline dyspnea index (BDI) (≤3 or >3); and corticosteroid use. Continuous variables: smoking history; lung function; FFM; fat mass; hemoglobin; hematocrit; arterial blood gases; forearm muscle strength; St. George's Respiratory Questionnaire (SGRQ); and comorbidity score. By the end of 1-year of follow-up, 12 patients (15.4%) had died. Kaplan–Meier curves showed that BDI≤3 was the only variable associated with higher mortality. Cox proportional hazards analysis revealed that lower PaO<sub>2</sub> and SpO<sub>2</sub>, higher PaCO<sub>2</sub> and SGRQ scores were associated with reduced survival. In the multivariate analysis,

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BDI remained predictive of mortality (hazard ratio [HR], 0.50; 95% confidence interval [CI], 0.31–0.81), as did  $PaO_2$  (HR, 0.49; 95% CI, 0.26–0.95).

These data suggest that readily available parameters as dyspnea intensity and hypoxemia severity may be useful in predicting first-year survival rates in advanced COPD patients receiving LTOT.

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## Introduction

COPD is currently the fourth leading cause of death in the world, and further increases in the prevalence and mortality of the disease have been predicted for the coming decades.<sup>1</sup> Studies indicate that approximately 10% of the adult population in Europe, 13.9% in the USA and 15.8% in Brazil has COPD and 0.2–1.4% can be defined as having severe disease.<sup>2–4</sup>

COPD is a progressive disease that often leads to respiratory failure. Long-term oxygen therapy (LTOT) is the single treatment that has proven effective in increasing survival in patients with chronic hypoxemia.<sup>5,6</sup> Nevertheless, the 1-year survival rate in severely hypoxemic COPD patients receiving LTOT is poor, ranging from 70% to 82.8%,<sup>7–10</sup> albeit decidedly better than the 5-year survival rate, which ranges from 19.1% to 41.5%.<sup>7,9,10</sup>

Mortality in patients with severe COPD has been associated with age,<sup>8,9,11</sup> gender,<sup>12</sup> airflow obstruction,<sup>8,13</sup> malnutrition,<sup>10,14,15</sup> concomitant malignancy,<sup>10,16</sup> smoking habits,<sup>16</sup> hypoxemia<sup>16</sup> and exercise tolerance.<sup>11</sup> However, there is little evidence-based guidance to aid clinicians in determining short-term prognoses for patients with advanced COPD.<sup>17</sup> We hypothesized that predictors of first-year survival in hypoxemic COPD patients might be different from those previously described for long-term survival. Therefore, the present study was designed to provide a prospective assessment (1) of the mortality rates and (2) the baseline measurements that may be determinants of mortality after 1-year of follow up in hypoxemic COPD patients admitted to a LTOT program.

## Methods

### Patients

We conducted a prospective cohort study of patients with COPD enrolled in the LTOT program of a tertiary-care university hospital (Botucatu Medical School, Botucatu, Brazil). Between October 2003 and December 2005, a total of 131 patients initiated LTOT. The initial selection consisted of patients who met the criteria set forth in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and by the Brazilian Thoracic Society (BTS) for COPD diagnosis (postbronchodilator forced expiratory volume ( $FEV_1$ )/forced vital capacity (FVC) ratio of less than 0.70) and for LTOT.<sup>1,18</sup> Additional inclusion criteria were as follows: (1) clinically stable condition (i.e., no changes in medication dosage or frequency and no exacerbations of disease or hospital admissions in the preceding 6 weeks); and (2) use of LTOT for at least 3 months (to avoid inclusion of patients with temporary oxygen supplementation).

A total of 53 patients were excluded from the follow-up. In 47 patients the primary diagnosis was not COPD: restrictive lung disorder ( $n = 14$ ), vascular pulmonary disease ( $n = 9$ ), bronchiectasis ( $n = 6$ ), respiratory sleep disorders ( $n = 5$ ) and miscellaneous diagnoses ( $n = 13$ ). Five patients did not perform spirometry and therefore did not comply with the previously described COPD diagnosis criteria. Only one patient with confirmed COPD diagnosis was unavailable for follow-up. Therefore, the final sample consisted of 78 COPD patients.

All patients were optimized in terms of standard medical therapy according to the GOLD and BTS guidelines.<sup>1,18</sup> Participants were aware of the proposed study procedures and freely gave written informed consent. All procedures were approved by the Research Ethics Committee of the Botucatu Medical School University Hospital.

### Design

Data related to the following were collected at baseline: gender; age; smoking history; body composition variables; dyspnea sensation; spirometry; arterial blood gases; chest X-ray; electrocardiogram; forearm muscle strength; health status; and comorbid conditions. All patients were evaluated every 3 months in order to assess LTOT compliance, determine the occurrence of exacerbations/hospitalizations and adjust the oxygen flow if necessary. They were followed for at least 1 year or until death. For patients who missed a follow-up appointment, data on patient survival were obtained by telephone interview with the family. Basic causes of death were reviewed on the death certificates when available.

### Methods

Smoking history was determined based on the number of pack-years. Lung function and reversibility tests were performed using the Med-Graph 1070 spirometer (Medical Graphics Corporation; St. Paul, MN, USA), according to the criteria set by the American Thoracic Society.<sup>19</sup> Values of  $FEV_1$  are expressed in liters, in percentages of FVC and as percentages of reference values.<sup>20</sup> For  $PaO_2$  and  $PaCO_2$  measurements (kPa), arterial blood was drawn from the radial artery under standard anaerobic conditions, while the patient was at rest and breathing room air (Stat Profile 5 Plus; Nova Biomedical; Waltham, MA, USA). Peripheral oxygen saturation ( $SpO_2$ ) was assessed using a portable Onyx oxymeter (Model 9500 Oximeter; Nonin Medical Inc.; Minneapolis, MN, USA).

Body weight and height were measured. Body mass index (BMI = weight in kg/height in  $m^2$ ) was calculated. Body

composition was evaluated using a bioelectrical impedance analyzer (BIA 101A; RJL systems; Detroit, MI, USA). Resistance was measured on the right side of the body with the patient in the supine position, in accordance with the ESPEN guidelines.<sup>21</sup> Fat-free mass (FFM) was estimated (in kg) using a group-specific regression equation developed by Schols et al.<sup>22</sup> and the FFM index (FFMI) was also calculated (expressed as FFM/height<sup>2</sup>). Fat mass (FM) was calculated as total body weight minus FFM. Forearm muscle strength was estimated based on handgrip strength (HGS) of the dominant hand, as measured using a dynamometer (TEC-60; Technical Products; Clifton, NJ, USA).

Comorbidity was quantified according to the index devised by Charlson et al.<sup>23</sup> and designated the Charlson comorbidity index (CCI). This index was designed to predict the impact that comorbidity has on prognosis in patients with chronic diseases. It assigns each disease a score of 1–6, which is proportional to the disease-related risk of death. Myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, COPD, connective tissue disease, peptic ulcer disease, mild liver disease and diabetes are assigned a score of 1. A score of 2 is assigned to diabetes with end-organ damage, hemiplegia, renal disease and malignancies, including leukemia and lymphoma. A score of 3 is assigned to moderate or severe liver disease, whereas AIDS and metastatic malignancies are assigned a score of 6.

A translated version of the St. George's Respiratory Questionnaire (SGRQ), validated for use in Brazil, was used to evaluate patient health-related quality of life (QoL).<sup>24</sup> A similarly Brazilian modified version of the baseline dyspnea index (BDI), developed by Mahler et al.,<sup>25,26</sup> was used to determine the degree of dyspnea. The BDI incorporates information related to the individual components of dyspnea (functional impairment, as well as the magnitude of the task and the amount of effort required to induce dyspnea). The total BDI score ranges from 0 to 12, higher values representing better function.

## Oxygen treatment

Oxygen therapy was prescribed for at least 18 h/day, using nasal prongs. The flow rate necessary to obtain an SpO<sub>2</sub> ≥ 90% was determined in the LTOT clinic. The oxygen was delivered from an oxygen concentrator in most patients and from cylinders in a few cases. The patients and their families were instructed in the use of the oxygen delivery system. The oxygen equipment was provided by the supplier, which also provided in-home technical service to patients. The LTOT compliance data were evaluated by self-reporting obtained from patients and their caregivers and characterized as appropriated by the investigator if the use reported was in compliance with the prescription.

## Statistical analysis

All data were analysed using the SAS statistical package (version 9.1.3; SAS Institute Inc., Cary, NC, USA). Means and standard deviations are reported for baseline characteristics. Assessment of baseline homogeneity between survivors and deceased patients was performed using the

unpaired *t*-test for continuous variables or the Mann–Whitney test for ordinal variables.

Patients were categorized by age (<60 or ≥60 years), gender (0 = male; 1 = female) and BDI (≤3 or >3). The cut-off for BDI was the lowest quartile (0 to 25th percentile). Corticosteroid use was defined as receiving oral corticosteroids for >3 months during the previous year (0 = no; 1 = yes). Patients were stratified into two categories according to the following variables: BMI (<20 or ≥20 kg/m<sup>2</sup>),<sup>10,14</sup> and FFMI (<16 kg/m<sup>2</sup> [for men] and <15 kg/m<sup>2</sup> [for women] or ≥16 kg/m<sup>2</sup> [for men] and ≥15 kg/m<sup>2</sup> [for women]).<sup>27</sup>

Kaplan–Meier survival curves were created to display differences in survival by selected risk factors: age, gender, oral corticosteroid use, BMI, FFMI and BDI. The differences between survival curves were assessed using the log rank test. The univariate analysis was based on the Cox proportional hazards models using each of the potential predictors of survival as independent variables and survival status as the dependent variable. For each continuous variable, the Cox proportional hazards models was adjusted for smoking history, FVC, FEV<sub>1</sub>, FEV<sub>1</sub>/FVC, hemoglobin, hematocrit, PaO<sub>2</sub>, PaCO<sub>2</sub>, SpO<sub>2</sub>, FFM, FM, HGS, CCI and SGRQ score (symptom, activity, impact and total score).

Independent variables associated with mortality (presenting a *p* < 0.20) in the univariate analysis were then incorporated into a forward stepwise multivariate analysis likewise based on the Cox proportional model. Prior to the multivariate analysis, confounding factors were evaluated, as were the interactive effects between variables, as well as their possible colinearity.

In all analyses, values of *p* < 0.05 were considered statistically significant.

## Results

### Clinical characteristics

From a total of 131 patients initiating LTOT during the study period, 78 (43 males and 35 females) were included in the study. The mean age was 66.0 ± 8.9 years. Baseline characteristics of the 78 COPD patients, together with 1-year survival data, are shown in Table 1. As expected, the majority of the patients included presented severe airflow obstruction, severe hypoxemia and mild hypercapnia. Pharmacological treatment included inhaled β<sub>2</sub>-agonists (in 56.4%), inhaled ipratropium (in 62.8%), inhaled corticosteroids (in 20.5%), diuretics (in 53.9%), xanthines (in 6.4%) and oral corticosteroids (in 9.0%). Comparison between survivors and non-survivors revealed that, among the patients who eventually died, PaO<sub>2</sub> values were lower, SpO<sub>2</sub> values were lower, dyspnea sensation was greater (Figure 1), and SGRQ impact scores were higher, as were SGRQ total scores.

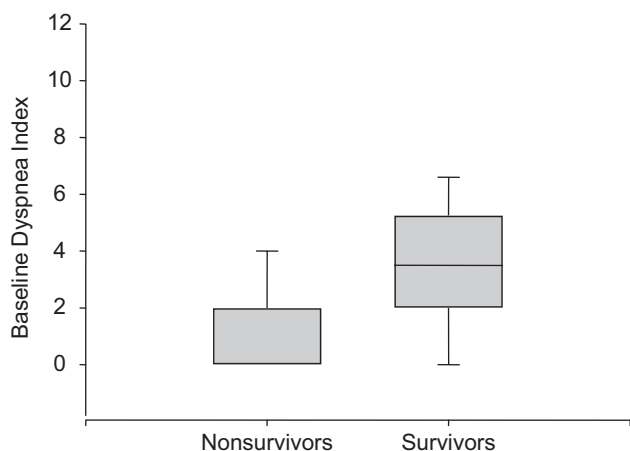
### Follow up and mortality

By the end of the 1-year follow-up period, 12 patients (15.4%) had died. The Kaplan–Meier analysis showed that BDI ≤ 3 was the only categorical variable associated with higher mortality (*p* = 0.03) (Figure 2).

**Table 1** Baseline characteristic of the 78 COPD patients on LTOT according to the survival after 1-year follow-up.

	Overall (n = 78)	Survivors (n = 66)	Non-survivors (n = 12)	p Value
Age (years)	66.0±8.9	65.6±9.1	68.2±7.9	0.37
Smoking (pack-years)	51.9±41.9	51.3±44.6	54.8±24.3	0.39
FVC (% pred)	68.8±17.5	70.4±17.8	60.4±12.7	0.07
FEV <sub>1</sub> (% pred)	40.7±16.1	41.7±16.8	35.4±10.9	0.22
FEV <sub>1</sub> /FVC (%)	47.0±11.2	47.1±11.1	46.6±12.3	0.89
PaO <sub>2</sub> (kPa)	7.0±1.5	7.1±1.4	6.1±1.5	0.03
PaCO <sub>2</sub> (kPa)	6.4±1.3	6.2±1.0	7.0±2.2	0.37
SpO <sub>2</sub> (%)	83.5±8.3	85.0±6.8	75.7±11.4	0.004
Hemoglobin (g/dL)	15.1±2.6	15.2±2.7	14.9±2.5	0.79
Hematocrit (%)	48.2±8.8	48.2±8.9	48.2±7.7	0.99
BMI (kg/m <sup>2</sup> )	24.9±6.7	25.1±6.9	23.7±5.2	0.51
FFMI (kg/m <sup>2</sup> )	15.9±3.1	16.1±3.2	15.1±2.4	0.35
FFM (%)	68.6±9.3	68.5±9.6	69.2±7.8	0.98
FM (%)	31.0±8.5	31.0±8.7	30.8±7.8	1.00
HGS (kgf)	26.8±10.1	27.5±10.2	23.0±9.3	0.24
CCI	4.0±1.8	3.9±1.6	4.5±2.5	0.62
BDI	3.4±2.6	3.8±2.5	1.1±1.6	<0.001
<b>SGRQ</b>				
Symptoms (%)	69.0±22.4	66.9±23.4	80.9±9.7	0.07
Activities (%)	74.7±15.4	73.5±15.8	81.2±11.6	0.11
Impact (%)	50.1±18.6	47.9±18.8	62.6±11.8	0.01
Total (%)	60.7±16.1	58.8±16.3	71.3±10.0	0.01

Data are presented as mean±SD. The statistical tests used were the unpaired *t*-test or the Mann–Whitney test. FVC, forced vital capacity; % pred, % of predicted; FEV<sub>1</sub>, forced expiratory volume in 1 s; PaO<sub>2</sub>, arterial oxygen tension; PaCO<sub>2</sub>, arterial carbon dioxide tension; SpO<sub>2</sub>, peripheral oxygen saturation; BMI, body mass index; FFMI, fat-free mass index; FFM, fat-free mass; FM, fat mass; HGS, handgrip strength; kgf, kilogram-force CCI, Charlson comorbidity index; BDI, baseline dyspnea index; SGRQ, St. George's Respiratory Questionnaire.



**Figure 1** Distribution of baseline dyspnea index (BDI) at baseline according to the survival after 1-year follow-up. The boxes with bars give the percentiles 5%, 25%, 50% (median), 75% and 95% of BDI for patients in the study.

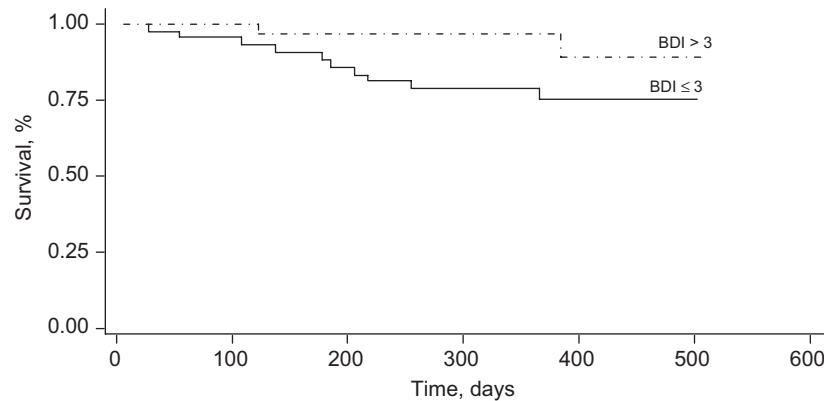
In the univariate Cox proportional hazards model, lower PaO<sub>2</sub>, lower SpO<sub>2</sub>, higher PaCO<sub>2</sub>, higher SGRQ impact score and higher SGRQ total score were associated with reduced survival (Table 2). Variables presenting a *p*<0.20 in the univariate analysis (FVC, PaO<sub>2</sub>, PaCO<sub>2</sub>, SpO<sub>2</sub>, HGS and SGRQ scores) were included in the multivariate Cox proportional

hazards models. In the multivariate analysis, BDI remained predictive of mortality after adjusting for all other variables included in the model (hazard ratio [HR], 0.50; 95% confidence interval [CI], 0.31–0.81; *p* = 0.005), as did PaO<sub>2</sub> (HR, 0.49; 95% CI, 0.26–0.95; *p* = 0.04) (Table 3).

## Discussion

In this study, we found that greater dyspnea and accentuated hypoxemia were predictive of first-year mortality in a cohort of patients with very severe COPD and receiving LTOT. To our knowledge, this is the first study in which dyspnea sensation was included in the analysis of predictive factors for short-term survival in severe COPD patients under LTOT. Our results suggest that dyspnea sensation, which is a highly significant symptom from the patient perspective, is a valid indicator of first-year survival.

The cut-off point for BDI was defined as ≤3, a value associated with severe functional impairment and dyspnea upon mild exertion.<sup>25</sup> In the present study, BDI values associated with higher mortality were presented by 92% of the non-survivors and by only 8% of the survivors. This cut-off point for BDI showed a sensibility of 92% and specificity of 55% to predict mortality. In addition, its negative predictive value was 97% and the positive predictive value was of 25%. To our knowledge, only one study identified the modified Medical Research Council dyspnea scale as a predictor



**Figure 2** Survival curves for patients with  $BDI \leq 3$  versus those with  $BDI > 3$ , ( $p = 0.03$ ). Kaplan–Meier survival curves for COPD patients under LTOT.

**Table 2** Results of the univariate mortality model analysis in 78 patients with very severe COPD.

Variable	Hazard ratio (95% CI)	<i>p</i> Value
Smoking (pack-years)	1.00 (0.99–1.01)	0.85
FVC (% pred)	0.97 (0.93–1.00)	0.07
FEV <sub>1</sub> (% pred)	0.97 (0.93–1.02)	0.21
FEV <sub>1</sub> /FVC (%)	1.00 (0.95–1.05)	0.84
PaO <sub>2</sub> (kPa)	0.56 (0.35–0.91)	0.02
PaCO <sub>2</sub> (kPa)	1.57 (1.10–2.23)	0.01
SpO <sub>2</sub> (%)	0.91 (0.86–0.96)	0.0004
Hemoglobin (g/dL)	0.98 (0.78–1.22)	0.82
Hematocrit (%)	1.00 (0.94–1.07)	0.95
FFM (%)	1.01 (0.94–1.08)	0.85
FM (%)	1.00 (0.93–1.07)	0.94
HGS (kgf)	0.95 (0.90–1.01)	0.13
CCI	1.19 (0.89–1.61)	0.25
<b>SGRQ</b>		
Symptoms (%)	1.03 (1.00–1.07)	0.06
Activities (%)	1.04 (0.99–1.08)	0.12
Impact (%)	1.04 (1.01–1.08)	0.02
Total (%)	1.06 (1.01–1.11)	0.02

CI, confidence interval; FVC, forced vital capacity; % pred, % of predicted; FEV<sub>1</sub>, forced expiratory volume in 1 s; PaO<sub>2</sub>, arterial oxygen tension; PaCO<sub>2</sub>, arterial carbon dioxide tension; SpO<sub>2</sub>, peripheral oxygen saturation; FFM, fat-free mass; FM, fat mass; HGS, handgrip strength; kgf, kilogram-force CCI, Charlson comorbidity index; SGRQ, St. George's Respiratory Questionnaire.

variable for 1-year survival; however, in this study were included COPD patients with a wide range of disease severity.<sup>28</sup> Relationship between dyspnea perception and 5-year survival was evaluated in other studies.<sup>29,30</sup> Nishimura et al.<sup>29</sup> compared the effects that dyspnea sensation and COPD stage, as evaluated by FEV<sub>1</sub>, had on the 5-year survival rate of 227 COPD patients with a wide range of airway obstruction without hypoxemia. The Cox proportional hazards model revealed that the categorization of patients according to the level of dyspnea was more

**Table 3** Prognostic factors according to the multivariate mortality model.

Predictors	Hazard ratio (95% CI)	<i>p</i> Value
FVC (% pred)	1.01 (0.97–1.05)	0.53
PaO <sub>2</sub> (kPa)	0.49 (0.26–0.95)	0.04
PaCO <sub>2</sub> (kPa)	1.26 (0.77–2.05)	0.37
HGS (kgf)	0.93 (0.86–1.01)	0.08
BDI	0.50 (0.31–0.81)	0.005
SGRQ total score (%)	0.99 (0.94–1.05)	0.82

CI, confidence interval; FVC, forced vital capacity; PaO<sub>2</sub>, arterial oxygen tension; PaCO<sub>2</sub>, arterial carbon dioxide tension; HGS, handgrip strength; kgf, kilogram-force; BDI, baseline dyspnea index; SGRQ, St. George's Respiratory Questionnaire; % pred, % of predicted.

discriminative than disease stage to predict 5-year survival. In addition, a recent study by Oga et al.<sup>30</sup> showed that BDI score was significantly correlated with 5-year survival in patients with moderate to very severe COPD. However, 1-year survival and the presence of chronic hypoxemia were not stated in the manuscript.<sup>30</sup>

Studies have documented the prognostic value of hypoxemia in predicting survival in COPD patients with and without LTOT.<sup>8,16,31</sup> In a group of 487 patients with COPD, the prognosis was significantly affected by the degree of hypoxemia after exercise.<sup>31</sup> In addition, a PaO<sub>2</sub> < 8.7 kPa (65 mmHg) under oxygen administration was independently associated with reduced survival in a study evaluating 270 severely hypoxemic COPD patients under LTOT.<sup>8</sup> However, a higher PaO<sub>2</sub> positively affected the survival rate in a cohort of 47 chronic hypercapnic COPD patients.<sup>16</sup> The results of our multivariate analysis support these findings, suggesting that hypoxemia remains an important predictive factor for mortality in advanced COPD, even among patients receiving LTOT.

Although the univariate analysis data suggest that higher PaCO<sub>2</sub> was associated with mortality, this variable was not identified as a predictive factor in the multivariate analysis. Our data are in contrast with those of previous studies that identified hypercapnia as a predictive factor for mortality in

COPD patients under LTOT.<sup>9,32</sup> However, those were long-term survival studies and did not include dyspnea sensation as a possible predictive factor in their multivariate analyses. Similarly, we found health status measurements (SGRQ scores) to be predictive only in the univariate analysis, as observed in a previous study involving a cohort of patients with severe emphysema.<sup>11</sup>

Many investigators have suggested that FEV<sub>1</sub> is inversely associated with mortality in COPD patients.<sup>13–15</sup> However, FEV<sub>1</sub> was not found to be a predictive factor in our cohort. This discrepancy might be attributable to the fact that the previous studies did not include dyspnea sensation in their multivariate analyses. In fact, Nishimura et al.<sup>29</sup> found a weak correlation between FEV<sub>1</sub> and survival, suggesting that the degree of dyspnea had a more significant effect on survival than did disease severity, as determined based on FEV<sub>1</sub>. The authors suggested that the strong correlation between dyspnea and survival weakened the correlation between airway obstruction and dyspnea.

Long-term studies ( $\geq 3$  years in duration) have shown that nutritional depletion, reflected by low values of BMI or FFMI, is an independent risk factor for mortality in COPD patients, regardless of pulmonary function status.<sup>10,14,15,27,33</sup> In our sample, the prevalence of patients with BMI  $< 20$  kg/m<sup>2</sup> (21.8%) was similar to the values reported by Chailleux et al.<sup>14</sup> and higher than those observed in a recent study in which mortality was found to be higher among patients with advanced COPD receiving LTOT and presenting a BMI  $< 25$  kg/m<sup>2</sup>.<sup>10</sup> However, our analysis based on the Cox proportional hazards model did not identify BMI or FFMI as predictors of short-term mortality. Again, a possible explanation is that those studies did not evaluate dyspnea. In addition, the factors that are predictive of first-year survival might be different than those that are predictive of long-term survival.

Some potential limitations of the present study should be considered when interpreting our findings. First, our study had a limited number of participants who died during the follow-up period although the mortality rate, 15.4% in 1 year, is similar to other studies in comparable patients, ranging from 17.2% to 30%.<sup>7–10</sup> Therefore, we acknowledge the small size of our cohort and that our study may be underpowered to detect all the significant differences between survivors and non-survivors and also to detect relationships between the risk factors and mortality. Secondly, the adherence to LTOT was obtained by self-reporting and although smokers were ineligible for LTOT, smoking history was not biochemically confirmed. It is therefore possible that confounding due to these factors may have contributed to our results and suggests that larger studies are needed to obtain additional information on the risk factors for first-year survival in very severe COPD.

## Conclusion

Even though the small series of patients in this study should prevent us from drawing definitive conclusions, our results suggest that the intensity of dyspnea at baseline is a predictor factor for first-year survival in patients with very severe COPD treated with LTOT. Similarly, the severity of hypoxemia at baseline proved to be a predictive factor for

mortality, regardless of airways obstruction severity. However, larger trials are needed to evaluate whether therapeutic interventions to reduce dyspnea and measures to improve compliance with LTOT can influence survival in patients with advanced COPD.

## Conflict of interest statement

None of the authors of this study has any potential conflict of interest.

## Financial support

Karina Dela Coleta was partially supported of a Scholarship Grant from CAPES (Coordenadoria de Aperfeiçoamento do Pessoal de Nível Superior, Brazil).

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