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Potentially modifiable predictors of mortality in patients treated with long-term oxygen therapy☆

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Summary
Introduction: Anemia is considered a systemic manifestation of Chronic Obstructive Pulmonary Disease (COPD); however, few studies have described its influence on chronic respiratory failure (CRF) prognosis. We aimed to test the hypotheses that anemia negatively influences survival and also to identify the cut-off points of hematocrit (Htc) and hemoglobin (Hb) associated with higher mortality in CRF patients using long-term oxygen therapy (LTOT).
Methods: One-hundred forty two patients with CRF in use of LTOT were evaluated at baseline and followed for three years or until death. Baseline assessment included identification, diagnosis, body composition, dyspnea, health status (HS), spirometry, arterial blood gases, Hb and Htc. Univariate and Cox proportional hazard models were used to evaluate predictors of mortality. We performed ROC curve to identify the best cut-off point of the variables related to survival to construct the Kaplan–Meier curves.
Results: Eight-three patients (58%) died after three years. Baseline values of Hb and Htc were significantly lower in the non-survivors group and both, Htc (HR, 0.96; 95%CI 0.91–0.99; $p = 0.04$), Hb (HR, 0.86; 95%CI 0.76–0.98; $p = 0.02$) were selected as predictors of mortality after three years. The cut-off points determined were: the value of HB is < 11g/dl (sensitivity 95% specificity 85%), Htc $\leq 33\%$ (sensitivity 97% specificity 89%). Other prognostic factors were: male gender, low $PaCO_2$ and SpO_2, higher dyspnea perception and impairment of HS.

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Conclusions: Our study shows that anemia is a predictor of mortality in patients with CRF under LTOT treatment. Although anemia is potentially modifiable, the effects of raising hemoglobin on mortality remain undetermined.

Introduction

The advanced stage of lung, heart and systemic diseases may be associated with the development of chronic respiratory failure (CRF). The treatment of this complication includes the use of long-term oxygen therapy (LTOT); a single treatment that has proven to be effective in increasing survival in hypoxemic patients with chronic obstructive pulmonary disease (COPD).[1,2] LTOT has also been associated with significant improvement in health status (HS), reduction of exacerbations and hospitalization due to COPD.[3] Approximately 67.8—81.6% of patients under LTOT have COPD[4,5]; however, patients with chronic hypoxemia from any cause can be included in treatment.[6]

Age, gender and concomitant malignancy are non-modifiable predictors for mortality in patients with LTOT.[7—14] Some potentially modifiable predictors of mortality in these patients have also been identified such as active smoking, malnutrition, dyspnea, airflow obstruction, hypoxemia, hypercapnia and pulmonary hypertension.

Anemia is recognized as comorbidity in many chronic inflammatory diseases including COPD.[16] Hemoglobin is a major carrier of oxygen and two previous studies showed influence of anemia on survival in patients with severe airflow obstruction[15] and with chronic hypoxemia.[12] However, the values of hemoglobin (Hb) and hematocrit (Htc) associated with higher mortality have not been established. Anemia is a potentially modifiable prognostic factor and we will test the hypothesis that lower values of Hb and/or Htc negatively influence survival and intend to identify the cut-off points associated with higher mortality in patients using LTOT.

Methods

Individuals

We evaluated 168 consecutive patients referred to the LTOT program of a tertiary-care university hospital (Botucatu Medical School, Botucatu, Brazil). Eleven patients did not fulfill the criteria for LTOT according to the Brazilian guidelines for COPD patients[17]; therefore, 157 patients were enrolled in the study and monitored for three years or until death. However, data were incomplete in 15 patients, so this research will present the results for 142 patients (Fig. 1). In 95 patients (67%) the principal diagnosis was COPD. Other diagnoses in order of prevalence were: interstitial lung disease in 13 patients (9%), pulmonary vascular disease in 9 (6%); bronchiectasis in 6 (4%), obstructive sleep apnea in 4 (3%), cardiac diseases in 4 (3%) and 11 patients (8%) had miscellaneous diagnostics. Patients with CRF of any etiology that meet the criteria for LTOT recommended for patients with COPD and chronic hypoxemia[17] were included in the study. Additional inclusion criteria were as following: 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); 2) use of LTOT for at least 3 months (to avoid inclusion of patients with temporary oxygen supplementation). All patients were optimized in terms of standard medical therapy according to guidelines for the primary diagnosis. 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.

Assessment procedures

The initial assessment included the following data: personal identification (age, gender, primary diagnosis, comorbidity conditions and smoking history), maintenance medications, body composition measurements, handgrip strength, spirometry, arterial blood gases and blood counts (Hb and Htc). We also evaluated dyspnea sensation and health status. The patients were followed with regular appointments in the LTOT clinic every three months during the first year and thereafter every six months. In those appointments the adherence to treatment (flow and number of hours of oxygen prescribed) and the number of exacerbations and hospitalizations in the

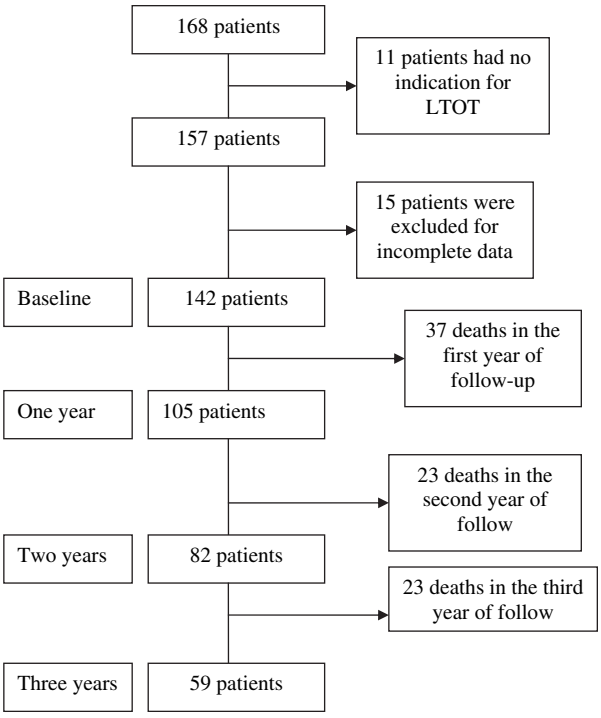

Figure 1 Diagram showing the flow of participants of the study.

period were investigated. Family or patients that missed an appointment were contacted and in case of death, the cause was investigated.

Smoking history was determined based on the number of pack-years.[18] We determined values of the forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) based on the flow–volume curve obtained using a spirometer (Medical Graphics Corporation; St. Paul; MN, USA), before and 20 min after inhalation of a beta 2-agonist (fenoterol 400 μg) according to the criteria set by the American Thoracic Society.[19] Values of FEV_1 are expressed in liters, in percentages of FVC and as percentages of reference values.[20] For partial pressure of oxygen (PaO_2) and partial pressure of carbon dioxide ($PaCO_2$) measurements, 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). Pulse oximetry (SpO_2) was assessed using a portable Onyx oximeter (Model 9500 Oximeter; Nonin Medical Inc.; Minneapolis, MN, USA). Hematological tests were performed according to the criteria and using the methods for conducting the routine examination of the Technical Section of Laboratory and Clinical Analysis of Botucatu Medical School. The values considered as references for anemia were: for women (Hb $<$ 12 g/dl or Htc $<$ 35%) and men (Hb $<$ 13 g/dl or Htc $<$ 40%).[21] 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 in the supine position, in accordance with the ESPEN guidelines.[22] Fat-free mass (FFM) was estimated (in kg) using a group-specific regression equation developed by Schols et al. and the FFM index (FFMI) was also calculated (expressed as FFM/height^2).[23] The arm muscle strength was estimated based on handgrip strength of the dominant hand (HGS dh) and non-dominant hand (HGS ndh), as measured using a dynamometer (TEC-60; Technical Products; Clifton, NJ, USA).[24] Comorbidity was quantified according to the Charlson comorbidity index (CCI).[25] A translated version of the St. George's Respiratory Questionnaire (SGRQ), validated for use in Brazil, was used to evaluate health status (HS).[26] A similarly Brazilian modified version of the baseline dyspnea index (BDI), developed by Mahler,[27] was used to determine the degree of dyspnea. The total BDI score ranges from 0 to 12, lower values of BDI representing worst dyspnea.

Oxygen treatment

During the initial assessment the titration was performed and the prescription of oxygen made. Oxygen therapy was prescribed for at least 18 h/day, using nasal prongs. The flow rate necessary to obtain an $SpO_2 \geq 90\%$ was determined in the LTOT clinic. Guidance was given to patients and their families on the proper use and handling of the oxygen concentrator. The oxygen equipment was provided by the supplier, which also provided in-home technical service to patients. Patients who were active smokers were strongly advised to stop smoking and conducted for treatment. The LTOT compliance data were evaluated by self-reporting obtained from patients and their caregivers and characterized as appropriate by investigator if the use reported was in compliance with the prescription. Portable oxygen was not provided.

Statistical analysis

We used the statistical package Sigma Stat 3.2 (Inc., Chicago, IL, USA) and SAS for Windows 9.1.3 (SAS Institute Inc., Cary, NC, USA). The descriptive analysis of quantitative variables was made using t-Student for variables with normal distribution and the Mann–Whitney (non parametric test) test for variables with non-normal distribution. The study of association between the qualitative variables and the death was performed using Chi-square or Fischer's exact test. The colinearity was avoided by exclusion of one of the variables for what the correlation between them was known. For analysis of each variable with the response (time of life) the Kaplan–Meier estimator (categorized variables) or Cox model (continuous variables) were applied. Independent variables associated with mortality (presenting a $p < 0.20$) in the univariate analysis were then incorporated into a forward stepwise multiple analysis likewise based on the Cox proportional model. We performed ROC curve to identify the points for the variables representing the best sensibility and sensitivity in separating between survivors and non-survivors during the follow-up period. These cut-off points were applied to construct the Kaplan–Meier curves to show the difference in survival by selected risk factors: BDI, SpO_2, Hb and Htc. Differences between survival curves were assessed using log-rank test. All findings in this study were discussed at the level of 5% significance.

Results

One hundred forty two patients (74 males and 68 females) were followed for three years of study or until death (Fig. 1). The measurements included in the statistical analysis were those obtained in initial assessment. At baseline, the mean age was 64.6 ± 12.9 years; 67% of patients presented COPD and 9% had interstitial lung disease (ILD); 83 (58%) died in the period of three years: 37 (26%) during the first year of follow-up, 23 (16%) in the second year and 23 (16%) in the third year. The main causes of deaths were respiratory (53%) and cardiovascular diseases (13%).

The baseline characteristics of all patients and comparison between the groups of survivors and non-survivors are presented in Table 1. The Hb and Htc were significantly lower in the non-survivors group. The sensation of dyspnea and the impairment of health status were more intense in patients who died during follow-up. There were not additional significant differences between survivors and non-survivors, however non-survivors were more likely to be males, older, and to have lower mean values of $PaCO_2$. Six non-survivors and 10 survivors were active smokers ($p = 0.21$).

The prevalence of different causes of chronic hypoxemia was similar between survivors and non-survivors ($p = 0.53$). However, patients with ILD showed higher risk of death when compared with COPD patients (HR = 1.54, 95% CI = 1.16–2.08, $p = 0.04$). Patients were using more than one class of drugs in the management of their diseases with no difference between survivors and non-survivors group.

Table 1 Baseline characteristics of the patients on LTOT according to the survival after 3-years of follow-up.

Variables	Overall $n = 142$	Non-survivors $n = 83$	Survivors $n = 59$	p value
Gender (M/F)	74/68	49/34	25/34	0.07
Age (years)	64.6 ± 12.9	66.2 ± 13.8	62.4 ± 11.8	0.08
Smoking (pack-years)	51.9 ± 39.4	53.8 ± 41.2	49.5 ± 37.2	0.56
Hemoglobin (g/dl)	14.9 ± 2.6	14.4 ± 2.6	15.5 ± 2.5	0.01
Hematocrit (%)	47.2 ± 8.4	45.8 ± 8.6	49.1 ± 7.9	0.02
FVC (%)	71.8 ± 22.7	70.2 ± 23.2	73.9 ± 22.1	0.27
FEV_1 (%)	50.1 ± 25.4	50.6 ± 27.1	49.4 ± 23.5	0.91
FEV_1/FVC (%)	55.1 ± 17.3	56.2 ± 18.4	53.7 ± 15.8	0.51
PaO_2 (mmHg)	53.1 ± 11.8	53.1 ± 13.4	53.3 ± 8.9	0.90
$PaCO_2$ (mmHg)	44.1 ± 9.6	42.9 ± 10.3	45.8 ± 8.2	0.09
SpO_2 (%)	84.4 ± 8.6	83.0 ± 10.1	86.3 ± 5.7	0.11
CCI	4.0 (3.0–5.0)	4.0 (3.0–5.0)	4.0 (3.0–5.0)	0.15
BMI (kg/m^2)	24.7 ± 6.5	24.1 ± 6.7	25.6 ± 6.3	0.18
FFMI (kg/m^2)	16.2 ± 3.0	15.9 ± 2.6	16.7 ± 3.4	0.20
HGS dh (kgf)	25.3 ± 11.1	24.5 ± 11.2	26.6 ± 10.9	0.30
HGS ndh (kgf)	23.4 ± 11.4	22.7 ± 11.7	24.3 ± 10.9	0.39
Exacerbation (no/years)	0.5 (0.0–1.3)	0.3 (0.0–1.7)	0.7 (0.3–1.2)	0.76
BDI	3.5 ± 2.9	2.8 ± 2.6	4.5 ± 3.1	< 0.001
SGRQ				
Symptoms (%)	64.6 ± 23.7	66.5 ± 22.6	62.0 ± 25.1	0.27
Activities (%)	72.1 ± 19.0	75.2 ± 17.3	67.7 ± 20.5	0.03
Impact (%)	48.2 ± 19.5	52.0 ± 19.2	43.0 ± 18.9	0.007
Total (%)	58.2 ± 17.5	61.5 ± 16.9	53.7 ± 17.6	0.01

Test *t*-student or Mann–Whitney was used. The data are presented as mean ± SD or median (quartile 1-quartile 3). M/F, male/female; FVC, forced vital capacity; FEV_1, Forced expiratory volume in 1 s; PaO_2, partial pressure of oxygen in arterial blood; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; SpO_2, pulse oximetry; CCI, Charlson comorbidity index; BMI, body mass index; FFMI, fat-free mass index; HGS dh, handgrip strength of the dominant hand; HGS ndh, handgrip strength of the non-dominant hand; BDI, baseline dyspnea index; $n = 57$ survivor group; $n = 77$ non-survivor; SGRQ, St. George's Respiratory Questionnaire; $n = 57$ survivor group, $n = 79$ non-survivor group.

Follow-up and mortality

By the end of the 3 year follow-up period, 83 patients (58%) had died. In average the survival since baseline in our study was 767 ± 406 days." The variables associated with reduced survival in the univariate analysis (Table 2) with $p < 0.20$ were included in the multiple Cox proportional hazard models (Table 3). To avoid colinearity we created two models, one included the variable Hb and other included Htc. Results showed that in both models the variables Htc (HR, 0.96; 95%CI 0.91–0.99; $p = 0.04$) and Hb (HR, 0.86; 95%CI 0.76–0.98; $p = 0.02$) were selected as predictors of mortality after three years. Other significant predictors of mortality were male gender, low $PaCO_2$ and SpO_2, higher dyspnea perception (BDI) and impairment of HS.

The cut-off points to identify the best survival values were as follows: BDI ≤ 1 (sensitivity 90% specificity 70%), SpO_2 ≤ 73% (sensitivity 97% specificity 87%), Hb ≤ 11 g/dl (sensitivity 95% specificity 85%), Htc ≤ 33% (sensitivity 97% specificity 89%). Kaplan–Meier survival curves for the above variables are presented in Fig. 2.

Discussion

In this study, we evaluated the predictors of mortality in patients with CRF receiving LTOT. Multiple regression analysis showed that the main risk factors for mortality after three years of follow-up were male gender, lower values of hemoglobin, hematocrit and $PaCO_2$, more intense hypoxemia and dyspnea sensation.

Hematocrit and hemoglobin were significantly lower in the non-survivors group and both were predictors of mortality in the third year of follow-up. The cut-off point associated with higher mortality in our study was Hb ≤ 11 g/dl (sensitivity 95% specificity 85%) or Htc ≤ 33% (sensitivity 97% specificity 89%). These data are consistent with the results of a study that evaluated 2524 patients with COPD receiving LTOT[13] and showed that the survival rate at three years was 24% in patients with Htc < 35% and 70% in patients with Htc > 55%. Martinez et al.[16] also showed that the decrease in Hb was independently associated with higher mortality (OR = 1.38, 95%CI = 1.00–1.89, $p = 0.05$). However, in both studies the cut-off point of Hb/Htc associated with higher mortality was not determined.

The levels of Hb in patients with CRF related to chronic diseases reflect the balance between the stimulation of erythropoiesis by hypoxia and suppression by inflammation. In our study, 67% of patients presented COPD and 9% had ILD, both are well known chronic inflammatory diseases associated with various systemic manifestations.[28] In contrast with previous teaching, recent studies in COPD have shown a high prevalence of anemia (15–30%), particularly in patients with severe diseases, whereas

Table 2 Results of the univariate analysis for mortality after 3-years of follow-up in patients under LTOT.

All patients	
Variable	*p*
Gender (M/F)	0.09
Age (years)	0.09
Smoking (pack-years)	0.90
Hb (g/dl)	0.008
Htc (%)	0.009
Anemia (yes/no)	0.07
FEV_1 (% pred)	0.87
PaO_2 (mmHg)	0.71
$PaCO_2$ (mmHg)	0.04
SpO_2 (%)	0.0008
FFM (kg)	0.29
FFMI (kg/m^2)	0.02
HGS dh (kgf)	0.07
SGRQt	0.001
BDI	<0.0001

M/F, male/female; Hb, hemoglobin; Htc, hematocrit; FEV_1, forced expiratory volume; % pred., % of predicted; PaO_2, arterial oxygen tension; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; SpO_2, pulse oximeter; FFM, fat-free mass; FFMI, fat-free mass index; HGS dh, handgrip strength of the dominant hand; SGRQt, St. George's Respiratory Questionnaire (score total); BDI, baseline dyspnea index.

polycythemia is relatively rare (6%). The prevalence of anemia in the present study, according to values described in the literature (WHO),[21] was 17%. The anemia is usually of the normochromic normocytic type and has detrimental effects on clinical and economic outcomes.[29,30] Although inadequate levels of Hb could worsen tissue hypoxia and justify its negative effect on prognosis, it remains to be determined if the treatment of the anemia will result in better outcomes in patients with CRF under LTOT.

The severity of hypoxemia as measured by the SpO_2 was associated with mortality both in univariate analysis and multiple analysis of Cox and the cut-off point identified for $SpO_2 \leq 73\%$ presented with good sensitivity and specificity (sensitivity 97% specificity 87%). This is in agreement with previous findings of several authors showing that the degree of hypoxemia is an important prognostic factor in patients with COPD in use or not of LTOT.[7,31] Although hypoxemia may be adjusted with oxygen supplementation, utilization for at least 15 h a day of LTOT is necessary to achieve clinical outcomes[32]; however, adherence with LTOT is commonly less than ideal.[3] In general, adherence for LTOT varies between 45 and 65%.[3,33] In our study, adherence to treatment among patients who survived was 61% and 42% among the non-survivors. However, adherence data are subjective because they were obtained through the patient's report.

Table 3 Prognostic factors for mortality after 3-years of follow-up in patients under LTOT according to the multiple mortality model.

Predictors	Hazard ratio (95% IC)	*p* value
Gender (M/F)	2.67 (1.15—6.18)	0.02
Age (years)	1.01 (0.98—1.04)	0.57
Hb (g/dl)	0.86 (0.76—0.98)	0.02
$PaCO_2$ (mmHg)	0.96 (0.92—0.99)	0.02
SpO_2 (%)	0.93 (0.89—0.97)	0.001
FFMI (kg/m^2)	1.14 (0.60—2.17)	0.70
HGS dh (kgf)	0.97 (0.92—1.02)	0.19
BDI	0.87 (0.76—0.99)	0.04
SGRQt (%)	1.02 (1.00—1.04)	0.04

Multiple analysis by Cox model; CI, confidence interval; M/F, male/female; Hb, hemoglobin; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; SpO_2, pulse oximeter; FFMI, fat-free mass index; HGS dh, handgrip strength of the dominant hand; BDI, baseline dyspnea index; SGRQt, Saint George Respiratory Questionnaire (total score).

The perception of dyspnea, assessed by the BDI was more intense in patients who died during follow-up and the BDI was associated with mortality in both univariate analysis and in multiple analysis of Cox. Furthermore, the domain of the SGRQ impact score, which includes several questions about the influence of dyspnea on functional capacity of the patient,[34] was higher in patients who died. The cut-off point for BDI was <1 (sensitivity 90% specificity 70%). This is in agreement with previous finding showing that BDI $\leq$ 3 was a main predictor of one-year mortality in COPD patients.[5] Oga et al.[33] also showed that the BDI was significantly correlated with survival in patients with moderate to severe COPD, over five years. Therefore, baseline dyspnea seems to be a strong predictor of mortality and an instrument to evaluate this symptom should be included in the management of these patients.

The literature shows controversial results on $PaCO_2$ and survival of patients using LTOT. In our study, the increase in $PaCO_2$ was associated with decreased mortality after three years of follow-up. According to our results, Dubois et al.[7] evaluated 270 patients with COPD receiving LTOT and the risk of mortality was lower in hypercapnic patients (HR = 0.86). Another study assessed patients receiving LTOT and showed that chronic hypercapnia was an independent factor for favorable prognosis in patients with tuberculosis and was not a factor for either favorable or poor prognosis in patients with COPD once they started receiving LTOT.[8] In contrast, Foucher et al.[9] analyzed the survival in 252 patients with COPD using LTOT and identified the hypercapnia as negative prognostic factor.

The risk of death in men was two times higher compared to women in our study, according to Miyamoto et al.[35] who evaluated 9759 patients with CRF and found higher survival in women regardless of pathology. Franklin et al.[36] studied 5689 patients with COPD in the use of LTOT and survival was also greater in women than in men (77% versus 69%). In contrast to our result, Machado et al.[14] studied the gender differences in COPD patients in use of LTOT and, in multivariate analysis, found that women had a significantly higher risk of death compared to men (HR = 1.54, 95%CI = 1.15—2.07, $p = 0.004$).

The present study is limited by a relative small number of patients. For future investigations, larger study populations are needed. This would allow investigating whether anemia is related to the primary disease process *per se* or to secondary systemic manifestations such as weight loss, loss of lean tissue mass, hypoxia, or systemic inflammation. In addition, no intervention to correct anemia was undertaken in the present study.

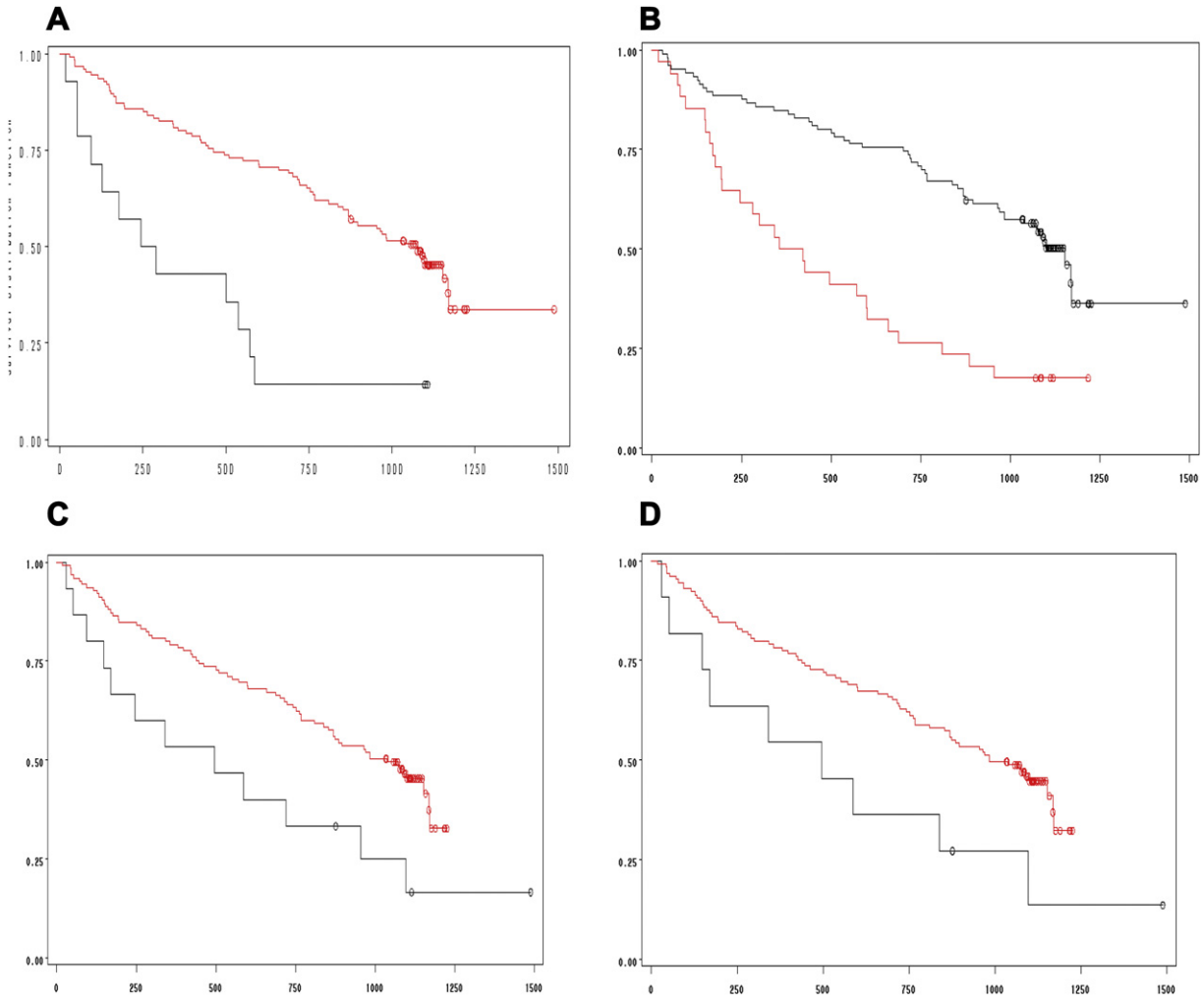

Figure 2 Kaplan–Meier survival curves of the study population. A – Survival curves for patients with $SpO_2 \leq 73\%$ versus those with $SpO_2 > 73\%$ ($p < 0.0001$). B – Survival curves for patients with BDI ≤ 1 versus those with BDI > 1 ($p < 0.0001$). C – Survival curves for patients with Hb ≤ 11 g/dl versus those with Hb > 11 g/dl ($p = 0.02$). D – Survival curves for patients with Htc $\leq 33\%$ versus those with Htc $> 33\%$ ($p = 0.03$).

In conclusion, our study shows that anemia is a potentially modifiable predictor of mortality in patients with chronic respiratory failure under LTOT treatment. However, the effects of raising hemoglobin on mortality remains undetermined, which justifies further studies to prospectively evaluate the effect of anemia correction on the prognosis of such patients.

Authorship

The authors' responsibilities were as follow Daniela F. Lima: worked directly to recruit patients, collect, analyze and interpret the data, and draft the final manuscript; Karina Dela Coleta: recruited patients and collected data; Suzana E. Tanni: performed selection and the medical assessment of the individuals; Liciana V.A. Silveira: participated of the study design and performed the statistical analysis of the data; Ilda Godoy: recruited patients and collected data; Irma Godoy: had overall responsibility for the study, designed the research, analyzed and interpreted the data, and wrote the final manuscript. All the authors contributed to the revision of the manuscript.

Conflicts of interest

None declared.

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