



Early Desaturation During 6-Minute Walk Test is a Predictor of Mortality in COPD

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Abstract

Background Oxygen desaturation during exercise is mainly observed in severe cases of chronic obstructive pulmonary disease (COPD) and is associated with a worse prognosis, but little is known about the type of desaturation that causes the greatest risk of mortality.

Material and Methods We studied all of the 6-min walk tests performed periodically at a tertiary hospital over a period of 12 years in patients with moderate or severe COPD. We classified patients as non-desaturators if they did not suffer a drop in oxygen saturation (SpO₂ < 88%) during the test, early desaturators if the time until desaturation was < 1 min, and non-early desaturators if it was longer than 1 min. The average length of follow-up per patient was 5.6 years.

Results Of the 319 patients analyzed, 126 non-desaturators, 91 non-early desaturators and 102 early desaturators were identified. The mortality analysis showed that early desaturators had a mortality of 73%, while it was 38% for non-early desaturators and 28% for non-desaturators, with a survival of 5.9 years compared to 7.5 years and 9.6 years, respectively (hazard ratio of 3.50; 95% CI 2.3–5.3; $p < 0.0001$).

Conclusions The early desaturation seen in patients with chronic obstructive pulmonary disease is associated with greater mortality and is likely responsible for the poor prognosis shown globally in patients who desaturate. The survival of patients with early desaturation is almost 4 years less with respect to non-desaturators, and they, thus, require closer observation.

Keywords COPD · Exercise desaturation · Early desaturation · Mortality

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Abbreviations

COPD	Chronic obstructive pulmonary disease
SpO ₂	Peripheral oxygen saturation
6MWT	6-Minute walk test
ND	Non-desaturator patients
NED	Non-early desaturator patients.
ED	Early desaturator patients

Introduction

Chronic obstructive pulmonary disease (COPD) has a high prevalence in the general population and is expected to be the third leading cause of death in 2030. The most common symptoms are cough, expectoration, and dyspnea during exercise [1]. The latter is related to the degree of obstruction, dynamic hyperinflation, and exercise-induced desaturation (EID). Factors such as age, degree of airflow obstruction as determined by FEV₁ value (volume exhaled in one second in forced spirometry), baseline PaO₂ (partial oxygen pressure in arterial blood), DLCO (diffusion capacity for CO), pulmonary hypertension, and distance walked in the 6-min walk test (6MWT) [2] have been shown to have prognostic value. Recent publications point to oxygen desaturation during the 6MWT as a predictor of mortality in patients with COPD [3], although the possible importance of different types of desaturation in patient survival has not been studied. Our hypothesis is that patients who suffer early desaturation in the 6MWT have lower survival rates than subjects with no early desaturation.

The aim of this study is to analyze survival in patients with COPD and early and non-early desaturation during the 6MWT.

Methods

We designed a longitudinal observational study in a cohort of patients diagnosed with COPD in a tertiary hospital and selected patients who had completed the 6MWT as part of the routine study in clinical practice for patients with moderate or severe obstruction. After the hospital ethics committee approved the study, we retrospectively reviewed the records of patients diagnosed between February 2008 and December 2021 who had completed the 6MWT in the Respiratory Department of the University Hospital Nuestra Señora de Candelaria. The inclusion criteria were former smokers with a pack-year index over 10 who were diagnosed with COPD (FEV₁/FVC < 70 and FEV₁ < 80%) who had completed the 6MWT. Patients with an exacerbation in the past month, those with pulmonary hypertension or interstitial lung disease, those with musculoskeletal disease that prevented them

from walking, and those receiving long-term home oxygen therapy were excluded.

All patients studied had completed their walk test without supplementary oxygen and the meters walked, degree of dyspnea reached, and initial and minimum saturations obtained were recorded, according to ATS recommendations [4].

Based on the 6MWT results, patients were classified as “desaturators” if their minimum saturation fell by at least 4% and hit levels under 88%, or as “non-desaturators” (ND) if it did not. In the first group, those with a decrease in oxygen saturation (SpO₂) occurring within the first minute of starting the walk test were labeled “early desaturators” (ED), and those who desaturated after this time were considered “non-early desaturators” (NED). We consider these three saturation patterns, the main independent variable of our study.

The 6MWT consisted of walking as fast as possible down a 30-m walkway, without carrying portable oxygen, stopping to rest as needed and then resuming walking. After finishing the test, the patients with no desaturation and those with desaturation before or after the first minute of starting the walk test were recorded.

The retrospective collection of data from the clinical history of each patient covered the period from when the 6MWT was conducted (“time 0” for each patient) until their death or the end of the study in December 2021; the follow-up per patient was calculated for the posterior analysis. Consequently, our main dependent variable was living/deceased status.

We observed that patients usually maintained the same desaturation pattern over time. If not, we selected the test with the worst desaturation pattern and the patients were then included in the corresponding desaturation groups.

In addition to the 6MWT variables, covariates including age, BMI (body mass index), Charlson comorbidity index, FEV₁, PaO₂, and DLCO were recorded.

Statistical Analysis

Quantitative variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR), depending on whether or not the distribution was normal. Normality of the quantitative variables was assessed using the Kolmogorov–Smirnov test. Categorical variables were expressed as frequency (percentage).

Mortality comparisons between the different groups of patients according to their desaturation pattern (“ND,” “ED,” and “NED”) were explored using parametric or nonparametric tests as appropriate: we carried out chi-square bivariate tests or the Mann–Whitney U test between mortality and the different desaturator types, as well as by the previously outlined variables of interest. A Kaplan–Meier model and a

log-rank test were used to compare survival in the 3 groups. Variables showing significant difference between statuses (deceased/living) in bivariate contrasts were subjected to multivariate analyses based on the Cox proportional hazard model to estimate the adjusted hazard ratio of the ED pattern on mortality. The significance level was established as $p < 0.05$. No a priori sample size calculation was performed. All patients who met the aforementioned inclusion criteria were included. Likewise, posteriori analysis of the statistical power was carried out. All analyses were performed using the IBM SPSS statistical program (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).

Results

A total of 319 patients were included in the present study. Based on the 6MWT results, they were classified into three groups: 126 (39.5%) as “non-desaturators” (ND) and 193 (60.5%) as “desaturators” (D), of which 102 (32%) were “early desaturators” (ED) and 91 (28.5%) “non-early desaturators” (NED). The characteristics of all the patients are shown in Table 1 according to desaturator type. Demographic characteristics (age and sex) were similar among the three groups ($p > 0.05$), with participants being predominantly male (76.8%) with an average age of 65.3 years (± 8.8). Comorbidity (measured by age-adjusted comorbidity according to the Charlson index) and BMI were similar between the three groups

($p > 0.05$). The respiratory parameters showed significant differences without clinical relevance, with patients in the early desaturation group having the most severe values. We observed initial saturations of 92.9%, 94%, and 95% for the ED, NED, and ND groups, respectively, and minimal saturation was 81%, 84%, 93% for each group. Major desaturation can be seen in the ED group. PO₂ was 64 mmHg, 70 mmHg, and 72 mmHg, respectively, and a lower value for the ED group with respect to the NED and ND groups was observed. However, we observed less difference in the FEV₁% and DLCO values between the ED, NED, and ND groups: 43%, 43%, and 54%, and 46%, 48%, and 64%, respectively.

The median follow-up for the entire study population was 6 years (P₂₅ 3 years and P₇₅ 8 years), although distribution was different according to desaturator type, observing a median of 7 years, 6 years, and 4 years if the patient belonged to the ND, NED, or ED groups, respectively ($p = 0.001$).

Overall mortality reached 45% ($n = 144$), showing growing differences according to whether the patient was ND (27.8%), NED (38.5%), or ED (72.6%), Fig. 1 ($p < 0.001$). Taking the ND group as a reference, the estimate of the crude hazard ratio (HRc) for the NED group was 1.5 (95% CI 0.97–2.5) and 3.5 (95% CI 2.3–5.3) for ED (Table 2).

The Kaplan–Meier analysis shows the survival difference in the three groups, where the lowest survival was seen in the ED group compared to the NED and ND groups (log-rank test $p < 0.001$; Fig. 2). A survival time of almost

Table 1 Demographic and clinical features of COPD patients (Baseline and at 6MWT)

N	All	ED	NED	ND	<i>p</i> -value
Variables, units	319	102 (32%)	91 (28.5%)	126 (39.5%)	
Gender Male (%)	76.8	74.5	74.7	80.2	0.517
Age years, mean \pm SD	65.3 \pm 8.8	65.2 \pm 8.6	66.9 \pm 9.1	64.2 \pm 8.6	0.068
Age, Range (%)					0.067
< 60	26.0	22.5	20.9	32.5	
60–69	42.0	46.1	37.4	41.8	
70+	32.0	31.4	41.8	25.4	
Charlson Index, mean \pm SD	4.2 \pm 1.8	4.0 \pm 1.6	4.4 \pm 1.9	4.2 \pm 1.9	0.321
BMI, mean \pm SD	26.8 \pm 5.1	26.7 \pm 5.1	26.3 \pm 4.9	27.2 \pm 5.3	0.395
Respiratory parameters Time “0”	94.6 \pm 1.9	92.9 \pm 1.7	94.7 \pm 1.4	95.9 \pm 1.4	0.001
Initial S (%), mean \pm SD					
Min S (%), mean \pm SD	87.1 \pm 6.4	81.6 \pm 5.0	84.7 \pm 4.5	93.4 \pm 2.0	0.001
FEV ₁ (%) mean \pm SD	47.9 \pm 15.3	43.6 \pm 14.7	43.7 \pm 13.9	54.4 \pm 14.6	0.001
DLCO (%), mean \pm SD	54.1 \pm 17.9	46.5 \pm 15.4	48.2 \pm 15.0	64.6 \pm 16.8	0.001
PO ₂ (mmHg), mean \pm SD	69.4 \pm 6.7	64.9 \pm 5.1	70.1 \pm 6.4	72.6 \pm 6.4	0.001
RV (%), mean \pm SD	166.0 \pm 47.2	177.5 \pm 46.4	166.9 \pm 50.6	156.2 \pm 43.5	0.003
Meters (m) mean \pm SD	444.8 \pm 108.4	403 \pm 109.8	451.1 \pm 112.6	474.9 \pm 93.5	0.001
Follow-up, years, median [P25 -P75]	6 [3–8]	4 [2–7]	6 [3–8]	7 [5–8]	0.001

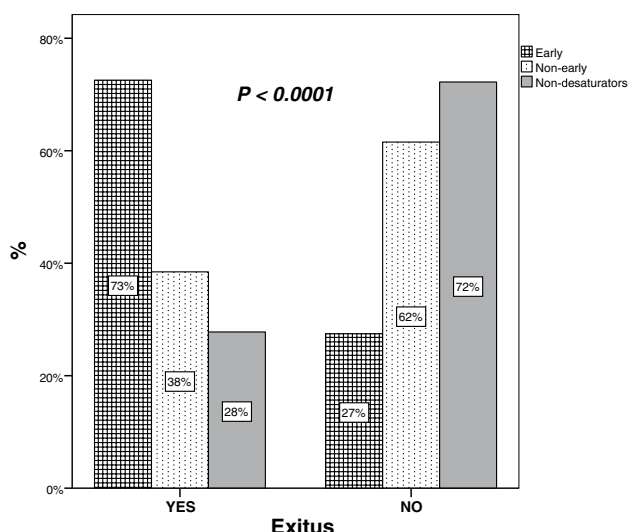


Fig. 1 Mortality rate by desaturator type at average follow-up of 5.6 yr

Table 2 Mortality Rates and Crude Hazard Ratio by Desaturator Type

	ND	NED	ED	<i>p</i> -value
Deaths, n, (%)	35 (28%)	35 (38.5%)	74 (72.6%)	
Mean Survival (years)	9.6	7.5	5.9	
95% CI	8.9–10.3	6.7–8.1	4.9–6.9	
Crude Hazard Ratio	1	1.556	3.502	
95% CI		0.97–2.5	2.3- 5.3	
Log Rank (Mantel-Cox)				0.0001

ND Non-Desaturators. NED Non-Early Desaturators. ED Early Desaturators

6 years (95% CI 4.9–6.9) was seen in this group, compared to 7.5 years in NED (95% CI 6.7–8.1) and 9.6 years (95% CI 8.9–10.3) in ND patients (Table 2).

Prior to the multivariate adjustment of the association analysis between the aforementioned desaturation types and survival, we proceeded to assess the demographic and clinical features according to the main dependent variable, that is, living or deceased status, as mentioned in the methods section.

The baseline variables that showed significant differences between deceased and living patients in our study (age, BMI, FEV1, DLCO, and PaO2) were considered covariates to adjust the mortality risk function according to type of desaturator as possible modifiers of the hazard ratio of 3.5 found in the ED group. The final model with covariates that remained significant after adjustment is described in Table 3. In this way, considering the age, BMI, and DLCO of patients in our Cox model, the mortality risk of the “early” type was

2.5 times greater than that of ND patients ($p=0.001$), and we did not find differences in risk between NED and ND ($p=0.920$).

These results are graphically reflected in Fig. 3, which details the cumulative adjusted hazard risk on the y-axis (dynamic measurement of prospective studies) and the follow-up in years on the x-axis.

As mentioned in the methods section, posteriori analysis of the statistical power was carried out. The statistical power showed that it was greater than 85% in the estimates derived from our results.

Discussion

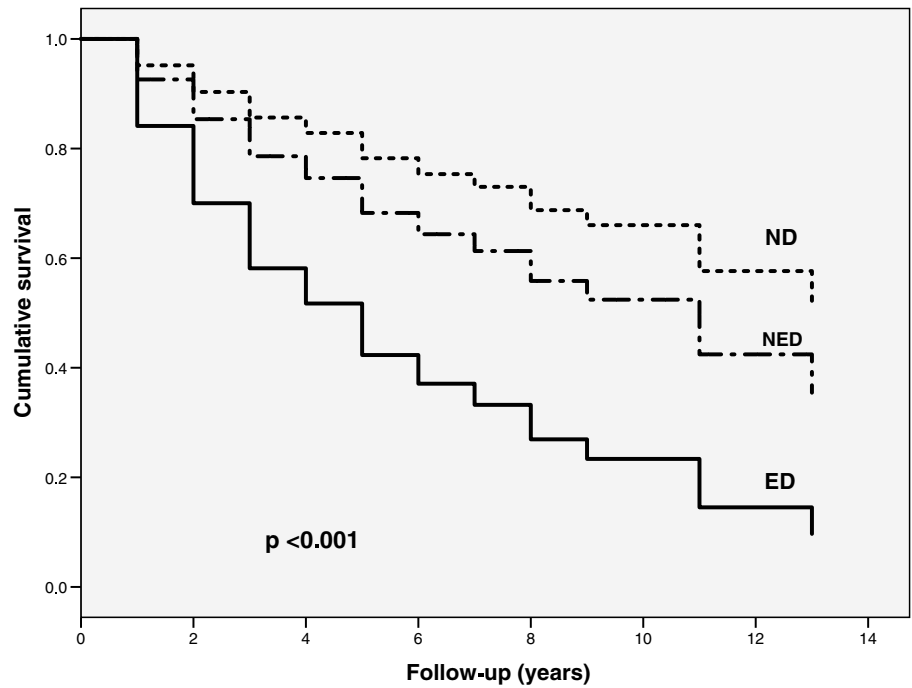
The data obtained indicate that normoxic patients with COPD who desaturate within the first minute of starting the 6MWT have a greater risk of mortality compared to NED or ND patients. Survival in the latter two groups tends to overlap.

This conclusion coincides, in part, with the results of previous studies [3, 5, 6] which found that EID was a mortality risk factor in patients with COPD. However, we have added another mortality risk factor, early desaturation, which has an evidently worse prognosis.

We initially carried out a comparative analysis between desaturators and non-desaturators as well and also found a significant difference, with greater mortality in desaturators. Our objective, however, was to analyze survival in ED patients and, upon analyzing the survival curves, we found accumulated survival in years and observed the ED group had reduced survival (Fig. 2), with the estimated survival time being significantly lower in this group of patients with respect to the NED and ND groups (5.9, 7.5, and 9.6 years, respectively). The mortality risk for the ED group was comparatively 3.5 times higher than the ND group (Table 2). We found a marked difference in mortality in the group of patients with early desaturation, 73% compared to 38% in the non-early desaturators group. This percentage is nearly double and translates to an almost 4-year shorter survival among ED patients. In light of these results, the greatest mortality among desaturators seems to be in the early desaturators group, a finding that has not been evaluated in previous studies.

When we included factors modifying mortality risk (age, BMI, and DLCO) (Table 3) in the multivariate analysis, early desaturation continued to show higher risk compared to the ND group (HR 2.5; 95% CI 1.6–3.8). No difference in risk was found in patients classified as NED compared to the ND patients that we used as a reference group (HR 1.03; 95% CI 0.62–1.69). The multivariate analysis maintains observed significance for early desaturators.

Fig. 2 Cumulative survival rate by desaturator type



ND: Non desaturators. NED: Non early desaturators. ED: Early desaturators

Table 3 Mortality Hazard Ratio by Desaturator type

	HAZARD RATIO	95% CI HR		P-value
		Low	Upper	
Desaturators Types				
	ND	1		
	NED	1.03	0.62 1.69	0.92
	ED	2.5	1.61 3.8	0
AGE range (years)				
	< 60	1		
	60–70	2.33	1.39 3.93	0.001
	> 70	3.97	2.34 6.712	0.001
BMI (units)	0.96	0.92	0.96	0.025
DLCO (units)	0.97	0.96	0.98	0.001

Cox Regression Adjustment

ND Non-Desaturators. NED Non-Early Desaturators. ED Early Desaturators. BMI Body Mass Index. DLCO Lung diffusion for carbon monoxide

It is important to remember that hypoxemia observed in patients with COPD is caused by alterations in the ventilation/perfusion relationship as a result of airflow obstruction and the presence of emphysema, and it can be exacerbated during sleep and exercise. Chronic hypoxemia can result in the development of pulmonary hypertension and polycythemia, can increase underlying systemic inflammation, and can also favor musculoskeletal dysfunction, which will impact quality of life and exercise tolerance,

as well as increase the risk of cardiovascular events and death [7].

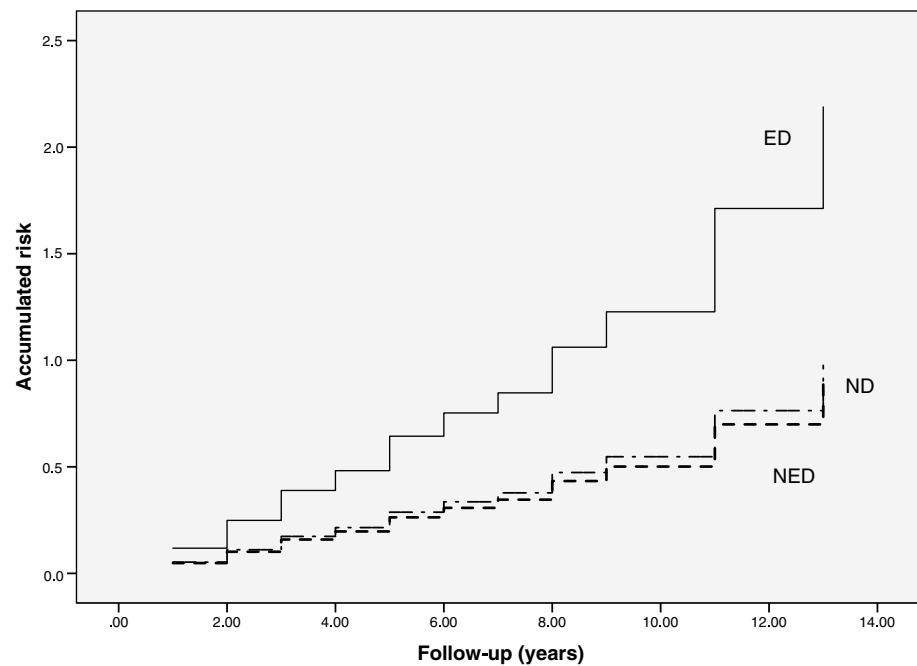
We also know that the 6MWT is a submaximal effort test, which evaluates functional exercise capacity and which is routinely used in managing patients with COPD. Unlike other lung function tests, it provides a global view of the patient’s exercise tolerance and does not require costly apparatuses like cardiopulmonary exercise testing [8]. At the same time, it is the most sensitive test to detect oxygen desaturation in patients with COPD [9].

We used the 6MWT in our study in order to show that the hypoxemia that appears with exercise can have different consequences depending on how long it takes to appear. Although desaturators are believed to have greater alterations in gas exchange in the ventilation/perfusion relationship and in diffusion, other physiopathological phenomena can occur in early desaturators that would explain this greater repercussion.

After discovering the EID phenomenon in patients with COPD, some authors described predictive factors such as decreased DLCO and SpO2 [10–13], a low FEV1 or PaO2 [14, 15] with different cut-off points [16], and associations with different physiopathological phenomena such as yearly FEV1 decline, dynamic hyperinflation, desaturation during sleep, and scores like the BODE index [17–21].

The objective of this study was not to analyze predictive factors for desaturation nor clinical situations associated with desaturation in the ED and NED groups. However, given the mortality observed in the ED group, there is a

Fig. 3 Accumulated risk of mortality by desaturator type



ND: Non desaturators. NED: Non early desaturators. ED: Early desaturators

possibility of finding another predictive factor, as well as other associated clinical situations.

In a previous study conducted by our group in 67 patients with COPD concerning the association between EID and desaturation that occurs during daily activities using 24-h pulse oximetry, we found that patients who desaturated 3.30 min or more after starting the walk test had a 100% probability of not desaturating during daily activities, while those who desaturated within the first minute also desaturated during their daily activities. We referred to the latter group as early desaturators [22].

However, the first studies that analyzed the 6MWT in patients with COPD placed more value on the distance walked than on oxygen desaturation during the test [23, 24], although some later studies revealed that both oxygen desaturation and distance walked were prognostic factors [25]. This led some authors to combine both factors in their analyses [26–28].

We also observed that ED patients had a greater need for long-term home oxygen than the group of NED patients at 5 years of follow-up [29]. This reveals the importance of the ED patient group, which was associated with desaturation during daily activities and was also predictive of chronic respiratory distress or a need for long-term home oxygen therapy.

On the other hand, recent studies have found that EID was a risk factor for mortality and exacerbation [3], was associated with a greater degree of emphysema in CT (computerized tomography) [30], and these patients had a 2.4–2.7 times greater risk of death [5, 6, 31] and a

higher prevalence of atrial fibrillation [32] compared to non-desaturators.

In our study, we did not record exacerbations but did register comorbidity using the Charlson index, without finding significant differences between the groups analyzed. However, we did find that obesity was associated with early desaturation in another recent study [33]. We did not expect to find such a large increase in mortality in the ED group and such a discreet increase in the NED group. The fact that early but not late desaturation is associated with desaturation during daily activities could likely explain this striking increase in mortality. The presence of intermittent hypoxia sustained over time, which potentially induces the physiopathological effects of chronic hypoxemia, as well as the more sedentary lifestyle of these patients and the associated nighttime hypoxemia [21] can potentially explain this increase found in mortality. This, along with the fact that survival curves overlapped for the NED and ND groups in the analysis, leads us to conclude that early desaturators have the greatest mortality among desaturators, with a hazard ratio of 2.5 in the multivariate analysis compared to non-desaturators (Figs. 2 and 3).

We can note that in the walk test, it is important not only to record the meters walked but also the time it takes to desaturate, in order to determine whether or not patients desaturate early, since late desaturation has a lower mortality that is similar to that observed in non-desaturators.

Furthermore, these observations suggest that many studies in patients with COPD that have analyzed EID without taking the time until desaturation into account could have

led to misguided conclusions with respect to mortality or the response to different treatments. Therefore, in survival studies following oxygen therapy in patients with COPD and exercise-induced desaturation, it should be determined whether or not they are early desaturators, since the response to some treatments or oxygen therapy could also be different and improve survival.

Our study has some limitations: it is an observational study with a retrospective analysis, the total number of patients is not very high (319), the percentage of women is not relevant, and it has focused on analyzing mortality and not other factors that can also be important (such as a decline in respiratory function or risk of exacerbations). However, it does emphasize early desaturation as a phenomenon to keep in mind as a prognostic factor. Future multicenter studies with a large sample size are needed to confirm these findings and also analyze the possible response to oxygen therapy in these patients.

Conclusions

Our results indicate that early desaturation, that is, desaturation observed within the first minute of starting the 6MWT, is an independent factor for mortality in patients with COPD, thus, the desaturation pattern analysis should be incorporated in the interpretation of the 6MWT and subjects in which this phenomenon is detected should receive more detailed follow-up. Non-early desaturators tend to behave like non-desaturators. It seems that what is relevant is early desaturation.

Author Contributions IGT: study design, data collection JM Figueira-Gonçalves: study design, data collection. RG: data interpretation CE: data interpretation CA: data interpretation. AU: literature search LPM: data analysis ACM: manuscript review and editing. All authors contributed equally.

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Declarations

Competing Interests The authors have no conflicts of interest

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