

Original Research

# Exploring Clinical Control of COPD: Insights From a Portuguese Outpatient Population

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## Abstract

**Purpose:** Chronic obstructive pulmonary disease (COPD) remains a challenging condition to manage due to its variability in clinical presentation and progression. While disease control is a well-defined concept in asthma, its relevance in COPD is less clear. This study aimed to evaluate the clinical utility of a COPD control framework, developed in Spain, in Portuguese outpatients by analyzing exacerbation rates among controlled and uncontrolled patients.

**Methods:** This prospective, observational study enrolled 133 COPD outpatients, evaluated at baseline (V0), 6 months (V1), and one year (V2). Patients were classified as controlled or uncontrolled based on criteria assessing clinical stability and disease impact, incorporating dyspnea severity, rescue medication use, physical activity, sputum color, and recent exacerbation history. Patients classified as controlled and uncontrolled were compared regarding the occurrence of an exacerbation (hospitalization, emergency visit, or ambulatory exacerbation) during follow-up.

**Results:** At baseline, 33.1% of patients were classified as controlled. This proportion increased to 46.2% at V1 but decreased to 31.6% at V2. Notably, only 12% remained consistently controlled throughout follow-up. There was a consistent trend of higher exacerbation rates among those previously uncontrolled. Only the difference in emergency visits at 12 months reached statistical significance (27.1% versus 7.8% in controlled patients,  $p=0.023$ ).

**Conclusions:** This study provides a first independent validation of COPD control criteria in a Portuguese cohort. Although the control framework proved feasible for clinical application, its predictive value for exacerbations was low in this severe-disease cohort. Future research should expand on these findings in diverse populations to optimize COPD management strategies.

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## Abbreviations:

**BD**=bronchodilator; **CAT**=COPD Assessment Test; **COPD**=chronic obstructive pulmonary disease; **CTR**=current treatment regimen; **DLCO\_SB%**=diffusing capacity of the lung for carbon monoxide, single-breath; **FEV<sub>1</sub>**=forced expiratory volume in 1 second; **FVC**=forced vital capacity; **ICS**=inhaled corticosteroid; **LABA**=long-acting beta2-agonist; **LAMA**=long-acting muscarinic antagonist; **LTOT**=long-term oxygen therapy; **mMRC**=modified Medical Research Council dyspnea scale; **SD**=standard deviation; **VNI**=noninvasive ventilation

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## Introduction

Chronic obstructive pulmonary disease (COPD) is a persistent and heterogeneous lung disease characterized by symptoms such as cough, dyspnea, sputum production, and exacerbations.<sup>1</sup> The management of COPD poses significant challenges due to the fluctuating nature of its symptoms over time.<sup>2,3</sup>

Although disease control has been clearly defined in asthma, encompassing the absence of activity limitations, minimal or no symptoms (daytime or nocturnal), minimal or no use of rescue medication, absence of exacerbations, and normal pulmonary function,<sup>4,5</sup> this concept has proven more elusive in COPD.<sup>6</sup> Indeed, achieving control in COPD patients is often considered unattainable.<sup>7</sup>

In 2014, Soler-Cataluña et al introduced the concept of COPD control, linked to 2 critical therapeutic dimensions: stability and impact.<sup>7</sup> Stability is a longitudinal concept, referring to the absence of significant clinical changes or exacerbations over time. Impact, on the other hand, is a static cross-sectional concept that evaluates the immediate effects of COPD on the patient's daily life at a specific moment.<sup>3,7</sup> This framework was subsequently refined and culminated in 2021 with the proposal of comprehensive criteria for assessing COPD control levels, as outlined in Spanish guidelines.<sup>8</sup>

These updated criteria incorporate exacerbation history, core symptoms, and spirometry results as predictors of short-term exacerbation risk. Stability in this context is measured by the absence of exacerbations in the preceding 3 months and the patient's subjective perception of their condition. Impact is evaluated based on sputum color, frequency of rescue medication use, activity levels in the past week, dyspnea severity (using the modified Medical Research Council [mMRC] scale), and the degree of airway obstruction quantified by forced expiratory volume in 1 second (FEV<sub>1</sub>) (Figure 1).<sup>9</sup>

By combining these dimensions, clinicians can assess whether the disease remains stable and whether its impact is low or high; overall disease control is considered achieved when a patient meets the criteria for both stability and low impact.

This control tool has been validated in large COPD cohorts, providing valuable insights into disease management<sup>10-12</sup>; and it has also shown to be highly informative in tracking changes in the status of COPD patients, demonstrating greater sensitivity than the Global initiative for chronic Obstructive Lung Disease (GOLD)<sup>13</sup> A-D classification or clinical phenotypes in predicting changes in clinical stages.<sup>14</sup> Besides that, it has also been described that controlled patients have

lower symptom load and a better quality of life than uncontrolled patients,<sup>11</sup> which reinforces the importance of seeking this stability in COPD patients.

Despite these promising findings, the applicability of COPD control criteria to the Portuguese population remains largely unexamined. Therefore, this study aims to apply the control criteria in a cohort of Portuguese COPD outpatients and to compare exacerbation rates over time between patients classified as controlled versus uncontrolled. Such insights could help optimize COPD management strategies within Portuguese health care settings.

## Methods

### Study Design

This is a prospective, observational study with a 1-year follow-up in a cohort of patients diagnosed with COPD.

All the cases were assessed in the COPD outpatient clinic on the initial visit (V0), at 6 months (V1), and at 1 year of follow-up (V2). The study was executed in compliance with the Declaration of Helsinki and received approval from the Committee of Ethics and Clinical Investigation of the *Unidade Local de Saúde de Santo António*.

### Patients

The study included patients >40 years of age diagnosed with COPD, defined by the presence of FEV<sub>1</sub> to forced vital capacity after bronchodilatation <0.7, and persistent respiratory symptoms. The exclusion criteria were as follows: active neoplastic disease, inability to carry out follow-up, patients participating in clinical trials, and all patients presenting with an exacerbation within the previous 2 weeks. The recruitment was consecutive, and all patients attending the outpatient COPD clinic who fulfilled the inclusion criteria were considered for the study. The study was explained to them, and those who accepted to participate provided informed consent and were included.

### Exacerbations

The absence of exacerbations was established using patient-reported information combined with a review of medical records. This was characterized by the absence of hospitalizations, emergency visits, and ambulatory exacerbations. At V0, this assessment covered the previous 3 months, whereas at V1 and V2, assessment covered the preceding 6-month period.

### Clinical Control Status

Patients were classified as controlled or uncontrolled

**Figure 1. Questionnaire Proposed in the Spanish Guidelines<sup>a</sup> to Evaluate COPD Control**

Questionnaire on clinical control in COPD			
Stability	S <sub>1</sub>	How have you been since your last visit?	
	<input type="checkbox"/>	Better	<input type="checkbox"/> The same <input type="checkbox"/> Worse
	S <sub>2</sub>	Have you had any exacerbations in the last 3 months?	
	<input type="checkbox"/> No	<input type="checkbox"/> Yes	
Impact	<input type="checkbox"/>	Stable (Must meet all criteria)	<input type="checkbox"/> Unstable (If any of the criteria are met)
		What color has your sputum been in the last few days?	
	<input type="checkbox"/>	White / clear or no sputum	<input type="checkbox"/> Dark
		How many times have you used the rescue medication in the past week? (Number of occasions rescue medication is required, regardless of the number of inhalations used each time)	
	<input type="checkbox"/>	< 3 times / week	<input type="checkbox"/> ≥ 3 times / week
		How long (on average) have you walked per day in the last week?	
	<input type="checkbox"/>	≥ 30 minutes a day	<input type="checkbox"/> < 30 minutes a day
		What is the current grade of dyspnea (mMRC scale)?	
	<input type="checkbox"/>	FEV <sub>1</sub> ≥ 50% Dyspnea 0 - 1	<input type="checkbox"/> FEV <sub>1</sub> < 50% Dyspnea 0 - 2
	<input type="checkbox"/>	FEV <sub>1</sub> ≥ 50% Dyspnea ≥ 2	<input type="checkbox"/> FEV <sub>1</sub> < 50% Dyspnea ≥ 3
Control	<input type="checkbox"/>	Low impact (Must meet 3 of the 4 criteria)	<input type="checkbox"/> High impact (If at least 2 criteria are met)
	<input type="checkbox"/>	Grade 0: No dyspnea, except with strenuous exercise Grade 1: Dyspnea when hurrying on a level or when walking up a slight hill Grade 2: Dyspnea makes it impossible for them to keep up with other people of the same age on a level, or forces them to stop or rest when walking on level ground at their own pace Grade 3: Dyspnea when walking less than 100 meters on level ground Grade 4: Dyspnea prevents the patient from leaving home or appears with activities such as dressing or undressing	
Control	Stability <input type="checkbox"/> + <input type="checkbox"/> Low impact	Instability <input type="checkbox"/> or <input type="checkbox"/> High impact	
	<input type="checkbox"/> Control (Must meet all criteria)	<input type="checkbox"/> No control (If any of the criteria are met)	

<sup>a</sup>de la guía española de EPOC (GesEPOC). Material and copyright belong to the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR), reprinted with permission.<sup>9</sup>COPD=chronic obstructive pulmonary disease; mMRC=modified Medical Research Council; FEV<sub>1</sub>=forced expiratory volume in 1 second

according to a clinical criterion developed by the Spanish Researcher Group.<sup>10,12,15</sup> This classification was performed at baseline, and subsequently at 6-month and 12-month follow-up visits.

A patient was considered controlled if the following 2 subcriteria were met: low clinical impact and clinical stability.

*Low clinical impact* was considered when patients met at least 3 of the following 4 parameters:

- Dyspnea:
  1. For patients with  $FEV_1 \geq 50\%$  (assessed at baseline), a dyspnea grade of  $\leq 1$  on the mMRC scale.
  2. For patients with  $FEV_1 < 50\%$ , a dyspnea grade of  $\leq 2$  on the mMRC scale.
- Use of rescue medication: No more than 3 instances of usage within the preceding week.
- Sputum color: White, clear, or no sputum.
- Physical activity: engagement in walking for more than 30 minutes per day during the preceding week.

*Clinical stability* was considered if both of the following 2 criteria were met:

- Subjective perception of improvement: patients reported their clinical status as "unchanged" or "improved" relative to the previous medical consultation.
- Exacerbations in the last 3 months at baseline or in the last 6 months for follow-up visits, at 6 or 12 months: None.

Patients were also classified according to changes in clinical control status from baseline to 12-month follow-up:

*Always controlled:* if classified as controlled at baseline and at the 6-month and 12-month follow-up visits;

*Always uncontrolled:* if classified as uncontrolled at baseline and at the 6-month and 12-month follow-up visits;

*Variably controlled:* if classified as controlled at least at 1 of the visits and as uncontrolled at least at 1 of the visits.

*Unknown:* if the patient didn't meet any of the above conditions.

## Statistical Analysis

As a first step, patients were categorized as controlled, uncontrolled, or unknown based on clinical criteria at baseline, as well as at the 6-month and 12-month follow-up visits. Next, the proportions of patients in each category were calculated for every visit. However, at the 6-month and 12-month follow-ups, these proportions were further

analyzed separately for each classification group from the previous visit. Lastly, the distribution of patients according to changes in clinical control status over the 12-month period—classified as always controlled, always uncontrolled, variably controlled, or unknown—was described as proportions.

Descriptive statistics were used to describe the demographic and clinical characteristics of those classified as controlled and those classified as uncontrolled based on clinical criteria. Categorical variables were described as proportions and compared using Pearson's Chi-squared test or Fisher's exact test, as appropriate. Quantitative variables were described as mean and standard deviation and compared using the independent samples *t*-test, after the necessary assumptions were checked graphically for all analyses.

All statistical tests were 2-tailed and a *P*-value lower than 0.05 was considered to be statistically significant. Statistical analyses of the data were performed with SPSS, version 28.0.

## Results

A total of 152 patients were initially recruited for the study. However, 19 patients were excluded as they did not meet the inclusion criteria, resulting in a final study sample of 133 patients. At baseline, the mean age of the study sample was 68.1 years old, 73.7% were male, the mean mMRC score was 2.15, the mean COPD Assessment Test (CAT) score was 13.1, and the mean  $FEV_1$  (%) was 46.7%. Patients were classified as either controlled (33.1%) or uncontrolled (66.9%) according to the clinical criteria. Of those classified as controlled at baseline, the majority remained controlled (72.7%), and 33.7% of those classified as uncontrolled at baseline were classified as controlled at the 6-month visit (Table 1).

Of the 133 patients, the number classified as controlled increased from 44 (33.1%) at baseline to 62 (46.2%) at the 6-month visit. Overall, the number of patients classified as controlled at the 12-month visit was 42 (31.6% of all 133 patients), but there was an increase in the number of patients who could not be classified. Of those classified as controlled at the 6-month visit, 24/62 (38.7%) remained controlled at the 12-month visit, and of those uncontrolled at the 6-month visit, 12/53 (22.6%) changed to the controlled classification at the 12-month visit. Table 2 summarizes the changes in patients' classification from baseline to the 12-month visit, showing that only 22.6% of patients were always uncontrolled. Although only 12% of the patients were always classified as controlled, a total of 67.7% were controlled at least at 1 of the visits (Table 2).

Table 3 shows a comparison of the characteristics of participants classified as controlled and uncontrolled at baseline and at the 6-month and 12-month follow-up



**Table 1. Clinical Control Status at the Baseline Visit and at the Follow-Up Visits<sup>a</sup>**

Total	Baseline n (%)	Visit 6 Months n (%)	Visit 12 Months n (%)
<b>N=133</b>	Controlled: 44 (33.1)	Controlled: 32 (72.7)	Controlled: 16 (50.0)
			Uncontrolled: 8 (25.0)
			Unknown: 8 (25.0)
		Uncontrolled: 9 (20.5)	Controlled: 1 (11.1)
			Uncontrolled: 6 (66.7)
			Unknown: 2 (22.2)
	Uncontrolled: 89 (66.9)	Unknown: 3 (6.8)	Uncontrolled: 1 (33.3)
			Unknown: 2 (66.7)
			Controlled: 8 (26.7)
		Controlled: 30 (33.7)	Uncontrolled: 17 (56.7)
			Unknown: 5 (16.7)
			Controlled: 11 (25.0)
	Uncontrolled: 44 (49.4)	Uncontrolled: 30 (68.2)	Uncontrolled: 30 (68.2)
			Unknown: 3 (6.8)
			Controlled: 5 (33.3)
	Unknown: 15 (16.9)	Uncontrolled: 5 (33.3)	Uncontrolled: 5 (33.3)
			Unknown: 5 (33.3)
			Unknown: 5 (33.3)

<sup>a</sup> 6 months and 12 months**Table 2. Summary of Changes in Clinical Control Status From Baseline to Follow-Up<sup>a</sup>**

Status	n	(%)
Always Controlled	16	(12.0)
Always Uncontrolled	30	(22.6)
Variably Controlled	64	(48.1)
Unknown	23	(17.3)
<b>Total</b>	<b>133</b>	<b>100.0</b>

<sup>a</sup> 6 months and 12 months

visits. At baseline, the 2 groups were similar in terms of age ( $68.1 \pm 10$ ), sex (73.7% male), and tobacco use. The clinically controlled group had significantly higher values for FEV<sub>1</sub>% and for single-breath diffusing capacity of the lung for carbon monoxide (DLCO\_SB%) and a significantly lower occurrence of exacerbations in the previous year and use of long-term oxygen therapy. At all visits, baseline, 6 months, and 12 months, patients classified as controlled had a significantly lower dyspnea grades and CAT scores, and a significantly higher proportion reported walking more than 30 minutes per day.

The following outcomes were considered during follow-up: the occurrence of a hospital admission, an emergency visit, an ambulatory exacerbation in the previous 6 months, or having had at least 1 previous exacerbation (Table 4). Overall, only 15% and 30.8% of patients reported having at least 1 exacerbation in the previous 6 months at the 6-month and 12-month visits, respectively. The proportion of exacerbations recorded at the 6-month and 12-month visits was compared between patients classified as controlled and uncontrolled at baseline and at the 6-month visit. With only one exception, there was a trend towards an increased proportion of exacerbations in the group of patients classified

as uncontrolled at the previous visit, but this increase was only statistically significant for the report of emergency visits at the 12-month follow-up visit (27.1% versus 7.8% in the controlled group,  $P=0.023$ ). The occurrence of exacerbations during the entire 12-month follow-up period was also compared between patients classified as controlled/uncontrolled at baseline, and although the same trends were observed, none were statistically significant.

## Discussion

This study represents the first known validation of COPD control criteria by a research team independent of the original developers and in a Portuguese population. External validation of previously published data is essential for confirming the robustness of any clinical tool, across diverse health care environments and patient populations.

Our findings indicate that only one-third of the patients were classified as controlled at baseline, and merely 12% remained controlled throughout the 12-month follow-up. Notably, half of the patients experienced at least one change in their control status over this period, suggesting that longitudinal fluctuations in disease control are common in this cohort.

**Table 3. Demographic and Clinical Characteristics, and Comparison Between Controlled and Uncontrolled Patients Using Clinical Criteria, at Baseline and at the 6-Month and 12-Month Follow-Up Visits**

Baseline	Clinical Criteria (n=133)			
	All (n=133)	Controlled (n=44)	Uncontrolled (n=89)	P-value
Age (years), mean (SD)	68.1 (10.0)	66.8 (9.7)	68.7 (10.2)	0.300
Sex, men, n (%)	98 (73.7)	34 (77.3)	64 (71.9)	0.652
Active Smokers, n (%)	38 (28.6)	11 (25.0)	27 (30.3)	0.662
Pack Years, mean (SD)	62.4 (37.9)	55.6 (29.8)	65.7 (41.0)	0.133
FVC (ml), mean (SD)	249.4 (89.4)	263.3 (106.6)	242.5 (79.4)	0.267
FVC (%), mean (SD)	68.6 (17.4)	71.8 (20.2)	67.1 (15.8)	0.186
FEV <sub>1</sub> (mL) After BD, mean (SD)	137.2 (78.4)	159.6 (96.5)	126.2 (65.6)	0.048
FEV <sub>1</sub> (%) After BD, mean (SD)	46.7 (21.6)	54.0 (27.2)	43.0 (17.1)	0.017
FEV <sub>1</sub> /FVC, mean (SD)	53.5 (14.8)	57.0 (15.1)	51.8 (14.4)	0.059
DLCO <sub>SB</sub> %, mean (SD)	53.4 (22.3)	62.0 (20.1)	49.1 (22.2)	0.002
VNI, n (%)	28 (21.1)	8 (18.2)	20 (22.5)	0.730
Exacerbations in the Previous Year, n (%)	53 (39.8)	8 (18.2)	45 (50.6)	<0.001
LTOT, n (%)	29 (29.3)	7 (15.9)	32 (36.0)	0.029
mMRC, mean (SD)	2.15 (1.12)	1.32 (0.91)	2.56 (0.98)	<0.001
CAT Score, mean (SD)	13.1 (7.6)	7.4 (5.5)	15.9 (6.9)	<0.001
>30 Minutes Walked/Day, n (%)	47 (35.3)	29 (65.9)	18 (20.2%)	<0.001
CTR, n (%)	N/A			
None	2 (1.5)	2 (4.5)	0 (0.0)	
LABA+LAMA	34 (25.6)	17 (38.6)	17 (19.1)	
ICS+LABA	6 (4.5)	5 (11.4)	1 (1.1)	
ICS+LABA+LAMA	85 (63.9)	20 (45.5)	65 (73.0)	
Intensificada BD	6 (4.5)	0 (0.0)	6 (6.7)	
Visit 6 months	(n=132)	(n=62)	(n=53)	
mMRC, mean (SD)	1.84 (1.13)	1.16 (0.85)	2.62 (0.93)	<0.001
Exacerbations in the Previous 6 Months <sup>a</sup> , n (%)	19 (15.0)	0 (0.0)	19 (35.8)	<0.001
CAT Score, mean (SD)	13.0 (7.3)	9.9 (6.7)	17.1 (6.3)	<0.001
>30 Minutes Walked/Day, n (%)	28 (24.8)	23 (37.1)	5 (9.8)	0.002
CTR, n (%)	N/A			
None	2 (1.6)	2 (3.2)	0 (0.0)	
LAMA	3 (2.4)	3 (4.8)	0 (0.0)	
LABA+LAMA	22 (17.3)	12 (19.4)	5 (9.4)	
ICS+LABA	2 (1.6)	1 (1.6)	1 (1.9)	
ICS+LAMA	1 (0.8)	1 (1.6)	0 (0.0)	
ICS+LABA+LAMA	90 (76.4)	43 (69.4)	47 (88.7)	
Visit 12 months	(n=117)	(n=41)	(n=67)	
mMRC, mean (SD)	1.92 (1.15)	1.54 (0.93)	2.20 (1.19)	0.002
Exacerbations in the Previous 6 Months <sup>a</sup> , n (%)	33 (30.8)	0 (0.0)	33 (50.0)	<0.001
CAT Score, mean (SD)	13.56 (7.72)	10.28 (6.65)	15.69 (7.71)	<0.001
>30 Minutes Walked/Day, n (%)	22 (20.0)	15 (36.6)	6 (9.0)	0.001
CTR, n (%)	N/A			
None	2 (1.8)	2 (4.9)	0 (0.0)	
LAMA	1 (0.9)	1 (2.4)	0 (0.0)	
LABA+LAMA	15 (13.6)	9 (22.2)	6 (9.0)	
ICS+LABA	3 (2.7)	1 (2.4)	2 (3.0)	
ICS+LABA+LAMA	89 (80.9)	28 (68.3)	59 (88.1)	

<sup>a</sup>Exacerbations: hospitalization or emergency visit or ambulatory exacerbationSD=standard deviation; FVC=forced vital capacity; FEV<sub>1</sub>=forced expiratory volume in 1 second; BD=bronchodilator; DLCO<sub>SB</sub>=diffusing capacity of the lung for carbon monoxide, single-breath; VNI=noninvasive ventilation; LTOT=long-term oxygen therapy; mMRC=modified Medical Research Council; CAT=COPD Assessment Test; CTR=current treatment regimen; LABA=long-acting beta2-agonist; LAMA=long-acting muscarinic antagonist; ICS=inhaled corticosteroid

**Table 4. Exacerbations<sup>a</sup> in the Previous 6 Months Recorded at the 6-Month and 12-Month Follow-Up Visits, and Their Comparison Between Patients Classified as Controlled and Uncontrolled at the Previous Follow-Up Visit According to Clinical Criteria**

Baseline	All (N=133) n <sup>b</sup> (%)	Clinical Controlled (N=44) n(%)	Clinical Not Controlled (N=89) n(%)	P-value
<b>Classification at Visit 0 / Exacerbations at Visit 6 Months</b>				
Hospitalization	8 (6.3)	0 (0.0)	8 (9.4)	0.052 <sup>c</sup>
Emergency Visit	10 (7.9)	2 (4.8)	8 (9.4)	0.495 <sup>c</sup>
Ambulatory Exacerbations	5 (3.9)	1 (2.4)	4 (4.7)	1.000 <sup>c</sup>
At Least One Exacerbation <sup>b</sup>	19 (15.0)	3 (7.1)	16 (18.8)	0.141
<b>Classification at Visit 6 Months / Exacerbations at Visit 12 Months</b>				
Hospitalization	10 (9.3)	3 (6.3)	6 (12.5)	0.486 <sup>c</sup>
Emergency Visit	19 (17.3)	4 (7.8)	13 (27.1)	0.023
Ambulatory Exacerbations	12 (11.0)	8 (15.7)	4 (8.5)	0.439
At Least One Exacerbation <sup>b</sup>	33 (30.8)	14 (29.2)	17 (35.4)	0.662
<b>Classification at Visit 0 / Exacerbations During Follow-Up</b>				
At Least One Hospitalization	15 (14.0)	3 (9.7)	12 (15.8)	0.546 <sup>c</sup>
At Least One Emergency Visit	24 (21.8)	6 (17.6)	18 (23.7)	0.646
At Least One Ambulatory Exacerbation	16 (14.7)	3 (8.8)	13 (17.3)	0.382 <sup>c</sup>
At Least One Exacerbation <sup>b</sup>	43 (40.2)	10 (32.3)	33 (43.4)	0.395

<sup>a</sup>Hospitalization or emergency visit or ambulatory exacerbation<sup>b</sup>The sum of controlled and not controlled may not add up to the total due to missing values<sup>c</sup>Fisher exact test

We observed a general trend wherein uncontrolled COPD patients experienced more frequent exacerbations than those who were controlled. However, the correlation between exacerbation prediction and clinical control status was weaker than that reported in other studies.<sup>10,12,15,16</sup> A possible explanation for this discrepancy lies in our study population, which included patients treated in a dedicated COPD clinic – likely representing individuals with more severe disease. Consequently, these patients typically exhibit poorer lung function, increased symptom burden, and more frequent exacerbations than those managed elsewhere in our center.

This overrepresentation of severe cases may be influenced by several contextual factors. First, our center functions as a regional referral unit for chronic respiratory diseases, receiving a substantial proportion of patients whose conditions could not be adequately managed in primary or general secondary care. This referral pattern introduces a natural bias toward more advanced disease. Second, socio-economic disparities in our catchment area may contribute to diagnostic delays and reduced access to early treatment interventions, such as smoking cessation programs, inhaled therapies, or pulmonary rehabilitation. Finally, issues related to treatment adherence, either due to limited health literacy or fragmented follow-up in earlier stages, might have contributed to more frequent exacerbations and faster decline. These contextual elements are essential to consider when interpreting the apparent limited predictive value of control criteria in this particular population.

Our results align with a previous study,<sup>17</sup> which found that clinical control did not significantly differentiate

exacerbation rates among patients with severe COPD (defined as a Body mass index-airflow Obstruction-Dyspnea-Exercise capacity plus exacerbations score >4). Nonetheless, among patients with mild-to-moderate COPD, that study demonstrated lower exacerbation rates and a longer time to first exacerbation in those who were controlled compared to their uncontrolled counterparts.<sup>17</sup> In our study, the mean postbronchodilator FEV<sub>1</sub>% was 46.7%, which is lower than the values reported in earlier studies.<sup>10,15,17</sup> In addition, 29% of the patients in our cohort were under long-term oxygen therapy, compared with only 6.5% and 6.7% in other studies.<sup>15,18</sup> These findings underscore the likelihood that our cohort had more severe disease overall; thus, incorporating less severe cases might have enhanced the predictive ability of the criteria.

Another distinguishing feature of our protocol was the use of a single postbronchodilator (FEV<sub>1</sub>%) measurement (from V0) for both the 6-month (V1) and 12-month (V2) assessments, diverging from the methodology of prior studies.<sup>10,15,17</sup> In our clinical setting, repeating spirometry at every visit is not always feasible. Nevertheless, using baseline values might mirror real-world practice conditions and thus, provide additional insights into the applicability and robustness of these criteria.

Assessing disease progression in COPD presents a challenge due to its inherent pathophysiology. Typically, the diagnosis is made at an advanced stage of life when symptoms are already established, and there is no biomarker available to evaluate the disease's level of activity. Pulmonary function is considered a good method for assessing disease progression, but it also naturally declines over time, making

it difficult to distinguish between the effects of COPD and those of aging. Therefore, the concept of remission seems unrealistic in COPD, while the concept of stability, based on clinical and functional criteria, appears to be more appropriate.<sup>6</sup>

Despite the weaker association with exacerbations in our population, the proposed criteria remain clinically useful. Previous work has shown that patients classified as “controlled” experience fewer symptoms and report a better quality of life.<sup>11</sup> Furthermore, it is well established that daily physical activity can reduce the number of exacerbations<sup>19,20</sup> and hospitalizations<sup>21,22</sup> contributing to the overall control of COPD. Our findings align with this evidence, showing that patients who maintain regular physical activity of at least 30 minutes per day are at lower risk of exacerbation, reinforcing the benefits of regular physical activity. In addition, we observed that uncontrolled patients had a higher number of emergency visits at 6 months compared to controlled patients (Table 4,  $p=0.023$ ), further supporting the clinical value of the control classification in identifying patients at higher risk for acute care utilization. It is important to note that only COPD-related emergency visits were considered in this analysis. Over the 12-month follow-up period, a total of 29 emergency department visits were recorded: 6 due to disease progression and 23 related to infectious exacerbations. Among the latter, 9 were attributed to bacterial infections (with pathogen identification), 6 to viral infections, and 8 to clinical presentations consistent with respiratory infection—such as increased bronchial secretions and elevated inflammatory markers—but without microbiological confirmation. These data provide further insight into the clinical context of acute events and reflect the burden of both infectious triggers and disease instability in this more severe COPD cohort.

Our data support the ease of application of these criteria in a real-world setting; however, it also highlights the need for further investigations in broader COPD populations to more definitively determine the predictive power and clinical utility of this approach.

Recognizing the concept of disease control in COPD is crucial not only for physicians<sup>6</sup> but also for patients,<sup>23</sup> as it offers a goal-oriented perspective for disease management. While other studies have validated these criteria in different COPD populations, our findings suggest that additional research focusing on the Portuguese context is warranted, ideally encompassing a wider range of disease severities

and multiple clinical settings. Such efforts could more comprehensively illuminate the relationship between “controlled” status and critical outcomes, including exacerbation rates, quality of life, and symptom burden.

A key limitation of our study is the inclusion of a single-center, specialized COPD clinic cohort, which may limit the generalizability of the results to milder cases. Additionally, the lack of repeated postbronchodilator spirometry at each follow-up visit might have influenced the precision of our control assessments. Another important limitation was the small sample size, which restricts the robustness of the findings. Future multicenter studies, with larger sample sizes and, preferably, repeated measurements of lung function, are needed to confirm these results and to explore whether the concept of control can inform personalized management strategies that improve long-term patient outcomes. Larger samples would also allow for multivariable analyses of the association between exacerbations and control status, adjusting for potential confounders.

In conclusion, our study provides an independent evaluation of the COPD control criteria in a Portuguese setting, highlighting both their utility and limitations in a more severe disease cohort. Ongoing research in larger, more heterogeneous populations will be necessary to refine the role of these criteria in routine clinical practice and to fully realize their potential in guiding COPD management.

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**Author contributions:** BDF and MS worked on the idea and designed the project. BDF, CR, JG, FSC, and CL collected the data. BDF wrote the introduction and discussion. MFC worked on the data analysis and wrote the methods and results and prepared the tables. MS worked in the selection of suitable patients. All the authors reviewed and approved the manuscript.

## Declarations of Interest

MS reports consulting fees and honoraria for lectures from Bial, GSK, CSL Behring, and Grifols; support for attending events from Gasoxmed, CSL Behring, Grifols, VitalAire, Bial, and Menarini; and participation on a data safety monitoring board for Sanofi, GSK, and Bial.

BDF, MFC, CR, FC, CL, and JG have no conflicts of interest to declare.



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