

Relationship Between Clinical Control, Respiratory Symptoms and Quality of Life for Patients with COPD

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Background: The concept of clinical control has been proposed as an instrument for evaluating patients with COPD. However, the possible association between clinical control, reduced symptom severity and HRQoL has yet to be confirmed.

Methods: This multicentre, prospective and observational study was carried out in 15 pulmonology clinics in Spain. The patients were followed up for six months, with a baseline visit (V0), followed by visits at three months (V1) and six months (V2). Clinical control was determined at V1, with the application of both clinical criteria and the COPD assessment test (CAT). All patients reported their symptoms by a validated symptom diary (E-RS) using a portable device, and their HRQoL was assessed using the EQ5D questionnaire. The relationship between clinical control and E-RS and HRQoL during follow-up was assessed with *t*-test.

Results: A total of 126 patients were screened. After application of the inclusion/exclusion criteria, 93 were finally included (mean age 66 ± 8 years, 84.9% male), with a mean FEV₁ predicted of $49.8\% \pm 16.5\%$. Of these patients, 44 (47.3%) achieved clinical control at V1, according to CAT criteria, and 50 (53.8%), according to clinical criteria. The E-RS scores differed between controlled and uncontrolled patients at all time points, both according to CAT (mean differences of -4.6, -5.6 and -6.2 units at V0, V1 and V2, respectively, $p < 0.005$ for all comparisons) and to clinical criteria (mean differences of -3.3, -5.6 and -4.99 units, respectively, $p < 0.005$ for all comparisons). The controlled patients also presented a significantly better HRQoL, measured by the EQ5D questionnaire (mean difference 0.13 and 0.10 at V2 by CAT or clinical criteria, respectively, $p < 0.05$).

Conclusion: Clinical control in patients with COPD, whether measured by CAT or by clinical criteria, is associated with a lower symptom load and a better HRQoL.

Keywords: control, symptoms, quality of life, impact, COPD

Background

COPD (Chronic Obstructive Pulmonary Disease) is a chronic respiratory disease, with a prevalence above 10% in Spain,¹ that mainly affects older age groups, provoking long-term disability and placing a significant burden on health systems.² One of the major limitations associated with COPD is dyspnea, which significantly worsens patients' health-related quality of life (HRQoL), even among those who suffer a relatively mild limitation of airflow.^{3,4} Furthermore, dyspnea is a prognostic factor per se in COPD, and is associated with a greater mortality.⁵ In addition to this predominant symptom, others such as cough and expectoration are cited by patients as factors that limit their daily activities.^{6,7} These symptoms can be evaluated via clinical questions or using validated questionnaires or by means of

self-completed symptom diaries, such as the EXACT Respiratory Symptoms (E-RS[®]) questionnaire.⁸ The E-RS is a patient-reported outcome (PRO) which has been approved as a validated tool for assessing respiratory symptoms during clinical trials and observational studies in a daily basis.

The concept of clinical control in COPD has been proposed as a dynamic means of detecting changes in patients' clinical situation that may be related to prognostic implications.^{9,10} Clinical control is defined as the long-term persistence of a situation of low clinical impact; in other words, it is composed of a transversal dimension (the clinical impact) together with a longitudinal one (clinical stability), determined by exacerbations or worsening over time. Studies have shown that clinical control can be achieved by a high proportion of patients, even among those with greater airflow limitation,^{11–14} although control status may vary over time,¹⁵ and that patients whose condition is uncontrolled are at greater risk of unfavourable outcomes.¹⁶ However, in the absence of previous research in this area, it is unclear whether patients who are clinically controlled have less symptom burden and a better HRQoL than those who are not.

In view of these considerations, our study aim was to determine whether patients who present clinical control have fewer respiratory symptoms and better HRQoL (based on a validated symptom diary such as the E-RS) than those whose condition was uncontrolled.

Methods

Study Design

This observational, prospective, multicentre study was conducted in outpatient pulmonology consultations in Spain, with a six-month follow-up. Centers were selected based on geographical distribution and similar care across different healthcare systems. Patients were included consecutively. Three visits were scheduled (V0, V1 and V2). Study design and visits procedures are available on [table S1](#).

Study Population

The study population consisted of adult patients aged >40 years with a diagnosis of COPD, according to national and international recommendations.^{17,18} All were smokers or ex-smokers with an accumulated tobacco consumption of at least 10 pack-years and with a postbronchodilator forced expiratory volume in 1 second (FEV₁)/forced vital

capacity (FVC) <0.7.¹⁸ These patients had been followed for at least three months before V0 and were able to record their symptoms on a portable device for this purpose and to perform the study procedures required at each follow-up visit. The exclusion criteria were exacerbation during the four weeks prior to V0, the presence of concomitant respiratory disease (such as alpha-1 antitrypsin deficiency or diffuse bronchiectasis) or participation in any other research study or in a respiratory rehabilitation programme.

Study Objectives

The main objective of this study was to determine the differences in symptoms measured by the mean weekly E-RS scores at the end of the study (V2 ± 3 days) between patients controlled or non controlled at V1.

The secondary study objectives were to compare the European Quality of Life 5 dimension (EQ5D-5L) scores between the controlled and uncontrolled patients and to examine differences in the E-RS subscales (Breathlessness, Chest symptoms and Cough & Sputum) between the same groups of patients at V2.

Study Variables

Anthropometric data, details of comorbidities and COPD characteristics were obtained for each study participant as well as BODE, BODEx and COTE (COPD comorbidity) indexes. All participants had a spirometry at V0 with bronchodilator test, after inhaling 400 mcgr of salbutamol, in accordance with national and international guidelines.^{19,20}

The patient's HRQoL was assessed by EQ5D-5L at V0 and V2.²¹ This questionnaire was filled by the patients in a printed version. The EQ5D-5L is a generic HRQoL questionnaire consisting of five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) each with five possible responses, producing scores ranging from 0 to 1 (the higher the score, the better the quality of life). It has been extensively studied in cost-effectiveness studies in the field of COPD.²²

At each visit, the patient was instructed to complete PROs questionnaires, such as the COPD Assessment Test CAT.²³ CAT is a PRO that reports patient symptoms using 8 questions which can be answered in a Likert scale ranging from 0 (low symptom burden) to 40 (worse symptom burden). In addition, each patient recorded their respiratory symptoms every day, using a portable device and reporting the outcomes using the E-RS[®] questionnaire (EXACT© 2013, Evidera Inc., Bethesda, USA), which uses 11

Table I Criteria for Clinical Control Based on Clinical Criteria or CAT Criteria

Clinical Criteria for Control				CAT Criteria for Control			
Concept	Item	FEV1 ≥ 50%	FEV1 < 50%	Concept	Item	FEV1 ≥ 50%	FEV1 < 50%
Low Impact (at least 3 of the 4)	Dyspnea	0–1	0–2	Low impact	CAT	0–10	0–16
	Rescue med	≤ 3 times/week		Stability (3 mo follow up)	Changes in CAT	≤ 2 points	
	Sputum	White		Control		Low impact+ Stability	
	Physical Activity	≥ 30 minutes/d					
Stability (Both needed at 3 mo)	Exacerbations	None					
	Subjective perception	Same/Better					
Clinical Control		Low impact + Stability					

questions to establish a symptom score. The 11 items on the E-RS capture the severity of the cardinal respiratory symptoms of COPD, including breathlessness, cough, sputum, chest congestion, and chest tightness. The RS-Total score quantifies respiratory symptom severity. The 3 subscales embedded in the measure include RS-Breathlessness, RS-Cough & Sputum, and RS-Chest Symptoms. The E-RS

produces a total E-RS score (scores ranging from 0 to 40, with higher values indicating greater severity of respiratory symptoms). The E-RS subscales produce scores from 0 to 17 (RS-Breathlessness), 0 to 11 (RS-Cough & Sputum) and 0 to 12 (RS-Chest Symptoms).⁸

At V1 and V2, the patients were classified as controlled or uncontrolled, according to CAT and clinical criteria,¹²

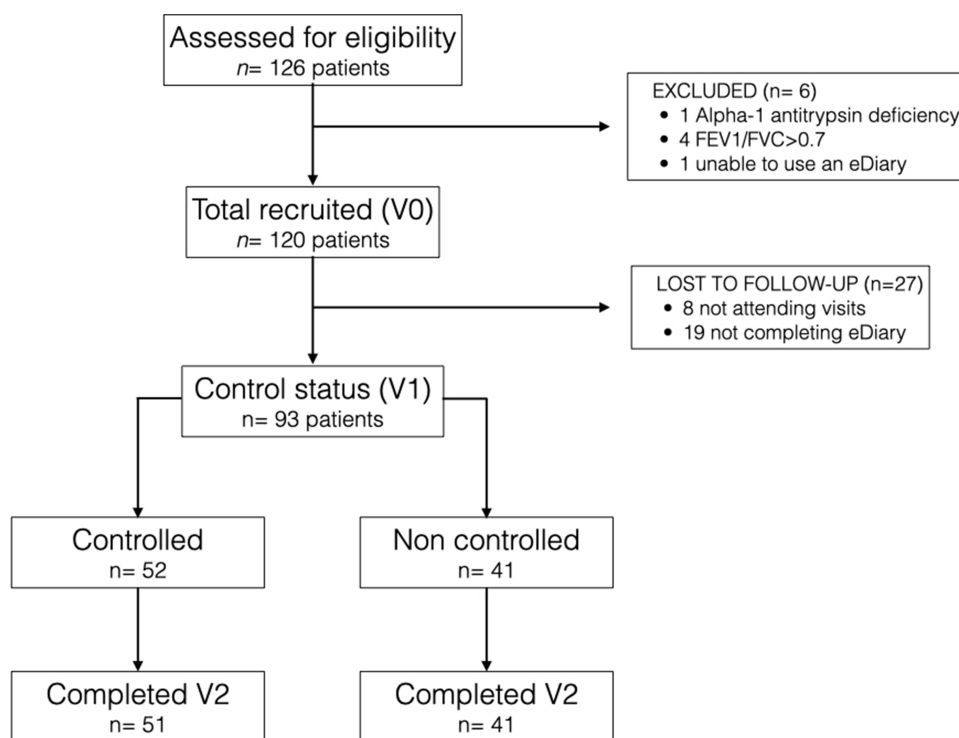
**Figure 1** STROBE (STrengthening the Reporting of OBServational studies in Epidemiology) diagram of study participants.²⁴

Table 2 Baseline Clinical Characteristics of Participants at V1

	Total (n=93)	Clinical Criteria		p-value	CAT Criteria		p-value
		Controlled	Not controlled		Controlled	Not controlled	
Age	65.9± 8.4	64.9±8.1	66.3±8.5	0.410	64.2±6.7	67.0±9.5	0.111
Sex (M), n (%)	79 (84.9%)	46 (88.0%)	33 (75.9%)	0.274	38 (86.4%)	39 (83.0%)	0.655
Smoking history							
Current smokers, n (%)	22 (23.7%)	14 (28.0%)	8 (20.5%)	0.417	13 (25.9%)	9 (19.1%)	0.247
Tobacco consumption, pack-years	52.8±31.2	45.9±21.3	59.9±41.1	0.054	55.4±34.7	50.4± 28.4	0.451
FEV1, % predicted	49.8±16.5	51.6±16.5	48.8±16.5	0.426	49.5±16.7	50.5± 16.7	0.774
Mod and Severe exacerbations, prev year	0.9± 1.1	0.6± 1.1	1.0±0.9	0.120	0.5± 0.8	1.1± 1.2	0.005
Dyspnea, mMRC≥ 2	49 (52.8%)	19 (34%)	30 (74.4%)	0.001	17 (37.6%)	30 (63.8%)	0.037
6MWT	427.6±108.4	444.5±94.2	415.8±122.3	0.233	453.0±105.8	405.2± 107.7	0.043
GOLD grade, n (%)							
GOLD A	37(39.8%)	28 (58%)	9 (22%)	0.008	29 (65%)	8 (17%)	<0.001
GOLD B	24 (25.8%)	12 (24%)	12 (30%)		6 (13%)	18 (38%)	
GOLD C	11 (11.8%)	4 (6%)	7 (17%)		8 (18%)	3 (6%)	
GOLD D	21 (22.6%)	8 (12%)	13 (32%)		2 (4%)	19 (39%)	
COPD phenotype, n (%)							
Non exacerbator	49 (52.7%)	32 (64%)	17 (43%)	0.047	29 (66%)	20 (42%)	0.025
ACO	13 (14.0%)	8 (16%)	5 (11%)		7 (16%)	6 (14%)	
Frequent exacerbator with CB	20 (21.5%)	2 (4%)	7 (18%)		1 (2%)	9 (19%)	
Frequent exacerbator with emphysema	11 (11.8%)	8 (16%)	11 (28%)		7 (16%)	12 (25%)	
COTE index	0.9±1.6	0.8±1.6	1.1±1.7	0.374	0.7±1.1	1.1±1.9	0.256
COTE index >4 points, n (%)	7 (7.6%)	3 (6.0%)	4(10.3%)	0.223	3 (6.8%)	4 (8.5%)	0.306
Symptom burden							
CAT score	11.0±6.7	9.1±6.7	13.0±6.7	0.007	6.7±3.4	14.8±6.4	<0.001

Abbreviations: FEV1, forced expiratory volume at 1st second; mMRC, modified Medical Research Council; 6MWT, 6 minutes walking test; ACO, asthma; COPD, overlap; COTE, comorbidities index; CAT, COPD assessment test; CCQ, Clinical COPD questionnaire.

Table 3 Impact, Stability and Control During Study Visits (V1 and V2) Among Study Participants According to Clinical or CAT Criteria

CAT Evaluation	V1	V2	Clinical Evaluation	V1	V2
Impact (CAT)			Clinical Impact		
Low	60 (64.4%)	57 (61.3%)	Low	62 (66.7%)	68 (73.1%)
High	33 (35.5%)	36 (38.8%)	High	31 (33.4%)	25 (26.9%)
Stability (CAT)			Stability (Exacerbations)		
Stable	73 (78.5%)	68 (73.1%)	Stable	68 (73.1%)	66(70.9%)
No	20 (21.6%)	25 (26.9%)	No	25 (26.9%)	27 (29.1%)
Control (CAT)			Control		
Controlled	45 (48.4%)	50 (53.8%)	Controlled	52 (55.1%)	55 (59.2%)
Not controlled	48 (51.6%)	43 (46.2%)	Not controlled	41 (44.1%)	38 (40.8%)

as defined in Table 1. Investigators were not aware about the control status, and clinical decisions were made as usual care.

Statistical Analysis

The study data are presented as mean (SD) for the continuous variables and as n (% of total) for the ordinal

Table 4 Changes in Control Status Among Study Participants Between V1 and V2, Either by CAT Criteria or Clinical Criteria

	CAT Criteria	Clinical Criteria
Persistent controlled	34 (38.6%)	41 (44.8%)
Persistent non- controlled	29 (31.3%)	29 (31.3%)
Achieving control from V1 to V2	21 (21.7%)	14 (15.4%)
Losing control from V1 to V2	9 (8.4%)	9 (8.5%)

variables. Normal distribution of variables was tested using the Kolmogorov–Smirnov test. Normally distributed continuous variables were compared by Student's *t*-test or by ANOVA. For non-normal continuous variables, the Mann–Whitney U non-parametric test or the Kruskal–Wallis non-parametric test were used. Ordinal variables were compared by the chi-square test. E-RS measures were compared between controlled and uncontrolled patients using a general linear model for repeated measures, and the estimated marginal means were calculated. All statistical analyses were performed using the SPSS statistical package version 24.0.0.0 (IBM, Armonk, NY, USA). A value of $p < 0.05$ was considered significant.

Results

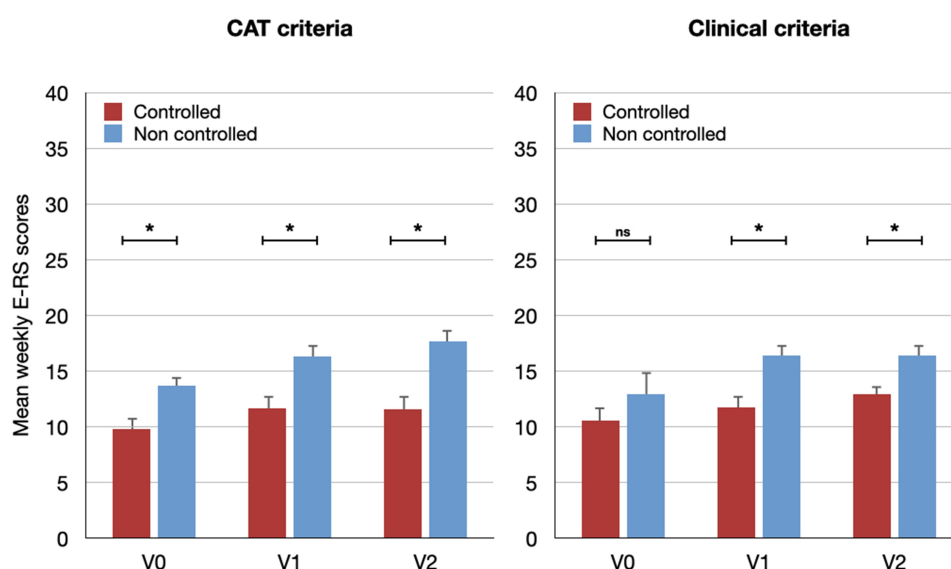
From June 2017 to October 2018, 126 patients at 15 hospitals throughout Spain were invited to participate in this study. Of these, 120 completed V0 and were recruited. However, 27 participants were lost to follow up, leaving

a final study population of 93 patients. Figure 1 shows the STROBE diagram for the selection of participants.

Table 2 shows the characteristics of the study population, comparing controlled vs uncontrolled patients at V1, by clinical criteria and by CAT. The majority of the study participants (84.9%) were male, with a mean age of 65.9 years (SD 8.4) and 23.7% were active smokers. The mean FEV₁ was 49.8% (SD 16.5%) predicted. The most frequent GOLD group was A and the comorbidity load was low according to the COTE index. In general, differences were observed between controlled and uncontrolled patients in clinical phenotype, GOLD classification and dyspnea, and in their CAT scores.

Table 3 shows the impact, stability and control achieved at V1 and V2, according to clinical criteria and CAT. At V1, 48% and 55% of patients were controlled, according to CAT and clinical criteria, respectively. During the study, the proportion of patients who achieved clinical control increased to 53% according to CAT and to 59%, according to clinical criteria. During follow-up, more than a third of the patients remained controlled, a third remained uncontrolled, and 8% changed from controlled to uncontrolled and between 15% and 21% changed from uncontrolled to controlled, according to clinical criteria or CAT, respectively. (Table 4).

Figure 2 shows the E-RS scores at V2 between controlled and non-controlled patients, either by CAT or clinical criteria. Controlled patients had statistically significant lower E-RS scores at V2 than non-controlled patients regardless criteria

**Figure 2** Mean (SE) values of E-RS scores among patients controlled and not controlled (by CAT criteria-left- or by clinical criteria-right) at study visits. * $p < 0.05$.

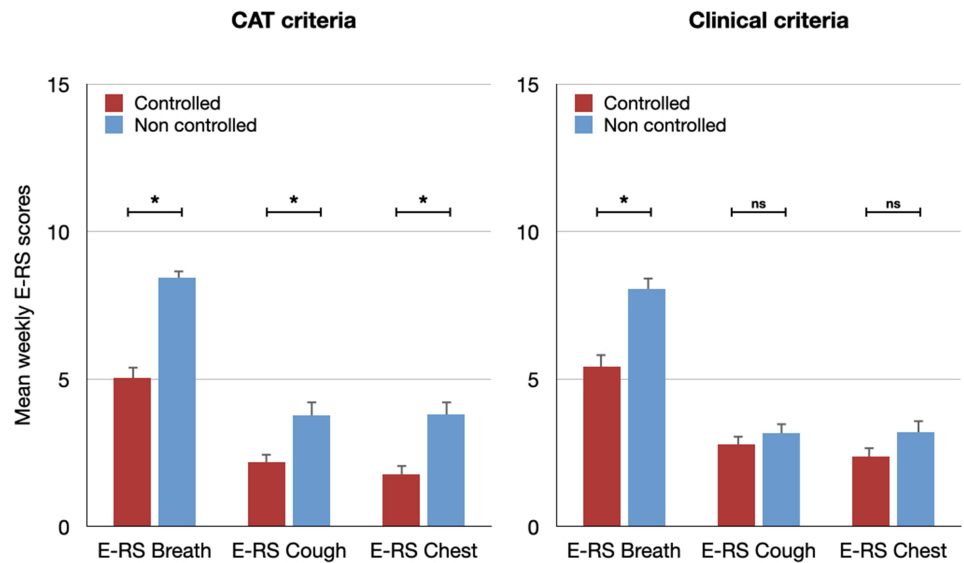


Figure 3 Mean (SE) weekly values of E-RS sub-scales scores (E-RS breath, E-RS cough and E-RS chest) at Visit 2 among controlled and not controlled patients (either by CAT criteria- left- or by clinical criteria-right). * $p<0.05$.

for control. E-RS scores showed also significant differences between controlled and non-controlled patients at V1.

The results obtained for the E-RS subscales at V2 are shown in [Figure 3](#). In this respect, there were statistically significant differences between controlled and uncontrolled patients in the three subscales, according to CAT. In terms of clinical criteria, statistically significant differences were only observed for the E-RS Breath subscale but not for Cough and Chest symptoms domains.

[Tables 5](#) and [6](#) reflect the outcomes achieved with respect to E-RS scores and subscales among the study visits either by clinical or CAT criteria. In summary, the E-RS total scores at V1 and V2 for the controlled patients were significantly better from those achieved by the uncontrolled patients, both by clinical criteria and by CAT.

[Figure 4](#) shows the HRQoL results obtained by EQ5D, both by CAT and by clinical criteria. In both cases, there were statistically significant differences between controlled and uncontrolled patients at V2. Full EQ5D results for controlled and non-controlled patients in males and females can be found at [tables S2](#) and [S3](#).

Discussion

The study results show that the controlled patients, either by CAT or by clinical criteria, recorded a lower symptom load on the E-RS symptom diary than uncontrolled patients, over a six-month follow-up. Furthermore, the controlled patients had a better HRQoL throughout this period. These results corroborate previous studies that have highlighted the value of the clinical control concept

Table 5 Mean Weekly E-RS Scores at V0, V1 and V2 Among Controlled and Not Controlled Patients at V1 by CAT Criteria

		V0	P value	V1	P value	V2	P value
E-RS total score	Controlled Not controlled	9.5±4.3 14.1±4.6	<0.001	11.2±6.2 16.8±5.2	<0.001	11.6±6.2 17.8±6.2	<0.001
E-RS Breath	Controlled Not controlled	3.0±3.3 5.8±3.2	<0.001	4.4±3.5 8.2±3.7	<0.001	4.7±2.9 8.6±4.5	<0.001
E-RS Cough	Controlled Not controlled	2.0±2.0 3.8±2.2	<0.001	2.0±1.8 3.6±2.3	0.001	2.1±1.5 3.7±2.1	<0.001
E-RS Chest	Controlled Not controlled	0.9±1.5 2.2±2.1	0.001	1.7±2.1 3.3±2.3	0.001	1.7±2.0 3.9±2.5	<0.001

Notes: P values are referred to T test between controlled and not controlled patients at each visit.

Table 6 Mean Weekly E-RS Scores at V0, V1 and V2 Among Controlled and Not Controlled Patients at V1 by Clinical Criteria

		V0	P value	V1	P value	V2	P value
E-RS total score	Controlled Not controlled	10.2±4.5 13.6±4.8	0.001	11.3±5.5 16.9±5.2	<0.001	12.5±5.5 17.5±7.0	<0.001
E-RS Breath	Controlled Not controlled	3.6±3.1 5.4±3.8	0.015	4.8±3.7 8.4±3.6	<0.001	5.3±3.1 8.7±4.8	<0.001
E-RS Cough	Controlled Not controlled	2.4±2.1 3.4±2.4	0.041	2.1±1.8 3.6±2.2	0.001	2.6±1.5 3.4±2.4	0.069
E-RS Chest	Controlled Not controlled	1.2±1.7 1.7±2.1	0.205	2.0±2.3 3.1±2.2	0.024	2.3±2.3 3.7±2.8	0.16

Notes: P values are referred to T test between controlled and not controlled patients at each visit.

as a means of evaluating and monitoring patients with COPD.^{11–16}

The E-RS questionnaire is a validated clinical instrument that has been used as an outcomes measure in intervention studies (pharmacological or otherwise), detailing the respiratory symptoms of patients with COPD and their evolution over time.^{8,25–27} Since it is based on a symptom's diary reported by the patient (reflecting daily variations), the data interpretation is more robust than that of visit questionnaires such as CAT or CCQ (but lacks widespread use because it is designed for research purposes). The clinically important minimum difference is defined as two units on the E-RS scale,⁸ a difference that was exceeded between controlled and uncontrolled patients throughout the study. Furthermore, there were differences between controlled and uncontrolled patients for each of

the subscales, especially those of Breathlessness. These differences were of a similar magnitude when patients were classified as controlled or uncontrolled according to either CAT or clinical criteria.

The EQ5D is a generic HRQoL questionnaire that has been validated for the analysis of general quality of life in patients with COPD. Our results showed that controlled patients had a better HRQoL than those whose condition was uncontrolled. Moreover, the HRQoL values obtained were higher than those reported in previous studies of patients with COPD in Spain,²⁸ revealing better HRQoL in our population (probably due to a less severe disease).

Our findings regarding the proportion of controlled and uncontrolled patients are similar to those obtained in previous studies,^{12,15} with around 50% of patients achieving clinical control, whether assessed by clinical criteria or by

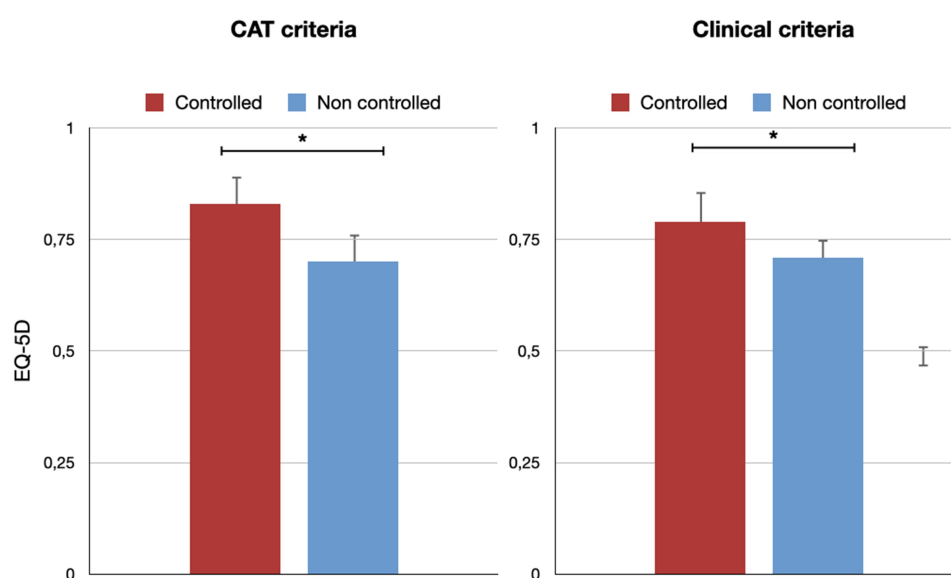


Figure 4 Mean EQ5D values at V2 between controlled and not controlled patients at V2 according to CAT criteria (left) and clinical criteria (right). *p<0.05.

the CAT score, with clinical criteria being more accurate than CAT to identify controlled patients (which could be explained by a more precise capture of COPD symptoms by clinical criteria). As previously demonstrated, this indicator is sensitive to changes in the patient's condition, with over 20% of patients presenting changes in control status during a 3-months follow-up period.¹⁵ Previous studies have shown that these changes in control status are more sensitive to changes in the clinical status of COPD than changes in phenotype, level of risk of GOLD groups A-D,¹⁵ and, furthermore, these changes in control status are associated with the risk of future exacerbations.^{16,29} Our results extend these observations by demonstrating that the control status is associated with the symptom burden and the HRQoL of patients with COPD. Taken together, these evidences suggest that the control status could be a valid tool for assessing effectiveness of treatment in routine clinical practice and guide changes in treatment during follow-up.

This study presents various strengths, including its multi-centre design, the use of a validated tool for recording respiratory symptoms in patients with COPD and the consistency between the results obtained and those previously reported from other studies analysing different aspects of the concept of control. On the other hand, there are also certain limitations, such as the low proportion of females (which is in line with other studies performed in Spain),^{7,15} the inclusion of patients attending to routine visits, the risk of selecting patients more prone to the use of technology and the loss of patients during the follow-up period (although this was to be expected in a study of this nature), the selection exclusively of patients seen at pulmonology consultations (which could have decreased the proportion of controlled patients), and the lack of data on the baseline medical treatment, due to limitations in this respect imposed by the administrative authorities during registration of the study. Another limitation is intrinsic to the COPD control concept, which is the inclusion of variables such as dyspnea that could impact CAT or EQ5D questionnaires.

In conclusion, clinical control, whether determined by clinical criteria or by CAT, is associated with a lower symptom load and a better HRQoL. These results, together with those obtained in previous studies about different aspects of the control tool, support the use of the control in clinical practice at any healthcare level.

Abbreviations

CAT, COPD Assessment Test; CCQ, clinical COPD questionnaire; COPD, chronic obstructive pulmonary

disease; E-RS, EXACT Respiratory Symptoms; EQ5D, European Quality of Life 5 Dimensions questionnaire; FEV₁, forced expiratory volume in the first second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HRQoL, health-related quality of life; PRO, patient reported outcomes.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical Approval and Consent to Participate

This study was designed in accordance with the principles of the Declaration of Helsinki and carried out in accordance with the protocol and with the norms of good clinical practice. It was submitted to the appropriate Clinical Research Ethics Committee (CEI Granada, Code 0458-N-16) for evaluation, and the Spanish Agency for Medicines and Health Products (AEMPS) was notified. All participants gave their written informed consent to take part in the study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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Dra. Fuster has nothing to disclose.

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