Relationship Between Clinical Control, Respiratory Symptoms and Quality of Life for Patients With Copd

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Abstract

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.

Method: This multicentre, prospective and observational study was carried out in 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.

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% ± 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).

Conclusions: 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.

Background

COPD 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' 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 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 an acceptable 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. Patients were invited to participate during their Visit 0, with follow-up controls at three (visit 1, V1), and six months (visit 2, V2).

**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 the start of the study 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 E-RS at the end of the study (V2) between patients controlled or non-controlled at baseline (V1).
The secondary study objectives were to compare the EQ5D 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. 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 at V0 and V2 (21). The EQ5D is a generic HRQoL questionnaire consisting of five domains, 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 some patient-reported outcomes questionnaires, such as the COPD Assessment Test CAT (23). 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 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, the patients were classified as controlled or uncontrolled, according to CAT and clinical criteria (12), as defined in Table 1.
Table 1
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% |
| Low Impact (at least 3 of the 4) | Dyspnea | 0-1 | 0-2 |
|                               | Rescue med | ≤ 3 times/week |
|                              | Sputum | White |
|                              | Physica l Activity | ≥ 30 minutes/d |
| Stability (3 mo follow up)    | Exacerb ations | None |
|                              | Subjective perception | Same/ Better |
| Clinical Control              | Low impact + Stability | |

Statistical analysis

The study data are presented as mean (SD) for the continuous variables and as n (% of total) for the ordinal variables. Normal distribution of variables was tested using the Kolmogorov-Smirnov test. Normally distributed continuous variables were compared by Student's t-test of by ANOVA. For non-normal continuous variables, the Mann-Whitney U non-parametric test of 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 FEV$_1$ 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 2  
Baseline clinical characteristics of participants

| Total (n=93) | Clinical Criteria | CAT Criteria |
|--------------|-------------------|--------------|
|              | Controlled        | Not controlled | p-value | Controlled | Not controlled | p-value |
| 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 & 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 C≥ 2 | 49 (52.8%) | 19 (34%) | 30 (74.4%) | 0.001 | 17 (37.6%) | 30 (63.8%) | 0.037 |

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
| 6MW T | ± | 108.4 | ± | 94.2 | ± | 122.3 | ± | 105.8 | ± | 107.7 |
|-------|---|--------|---|------|---|--------|---|--------|---|--------|
| 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%) | | |

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 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 53.8% according to CAT and to 59.2%, 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% to 21% changed from uncontrolled to controlled, according to clinical criteria or CAT respectively. (Table 4).
Table 3
Impact, stability and control during study visits (V1 & V2) among study participants according to clinical or CAT criteria

| CAT Evaluation (CAT) | V1 | V2 | Clinical Evaluation | V1 | V2 |
|----------------------|----|----|---------------------|----|----|
| Impact (CAT)         |    |    | Impact (CAT)        |    |    |
| 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%) |

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%) |

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 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-RStotal 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.

**Table 5**
Mean weekly E-RS scores at V0, V1 and V2 among controlled and not controlled patients at V1 by CAT criteria

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

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

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

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.

**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 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 (8,24-26). 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. 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 pharmacoeconomic analysis 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 (better) than those reported in previous studies of patients with COPD in Spain (27).

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 the CAT score. 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, this changes in control status are associated with the risk of future exacerbations (16,28). 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 multicentre 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 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, 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.

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.

**List Of 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.

FEV$_1$: 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

Declarations

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.

Availability of data and materials

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

Competing interest

Dr. Alcázar-Navarrete reports grants and personal fees from GSK, grants, personal fees and non-financial support from Novartis AG, personal fees and non-financial support from Boehringer Ingelheim, personal fees and non-financial support from Chiesi, grants, personal fees and non-financial support from LaboratoriosMenarini, personal fees from Gebro, personal fees from Astra- Zeneca, personal fees from LaboratoriosRovi, personal fees from Laboratorios Ferrer, outside the submitted work.

Dra. Fuster has nothing to disclose.

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**Author contribution**

BAN is responsible for study design, data acquisition, data analysis and manuscript draft. AF, PGS, JLGR, BA, AP, EM, AV, AB, FJC, MP, JAR and RG are responsible for data acquisition. JJS and MM made substantial contributions to the study design and data interpretation as well as manuscript review.

All the authors have approved the submitted version (and any substantially modified version that involves the author's contribution to the study).

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E-RS® is a registered trademark of Evidera Inc. The authors used this questionnaire

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**Figures**
**Figure 1**

STROBE (STrengthening the Reporting of OBServational studies in Epidemiology) diagram of study participants.
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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
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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
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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
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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
Figure 4

Mean EQ5D values at V2 between controlled and not controlled patients at V1 according to CAT criteria (left) and clinical criteria (right). *p<0.05
Figure 4

Mean EQ5D values at V2 between controlled and not controlled patients at V1 according to CAT criteria (left) and clinical criteria (right). *p<0.05
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Mean EQ5D values at V2 between controlled and not controlled patients at V1 according to CAT criteria (left) and clinical criteria (right). *p<0.05