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Clinical Application of the COPD Assessment Test: Longitudinal Data from the CHAIN Cohort

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Abstract

Rationale: The Chronic Obstructive Pulmonary Disease (COPD) Assessment Test (CAT) was proposed for assessing health status in COPD, but little is known about its longitudinal changes.

Objective: To evaluate one-year CAT variability in stable COPD patients and relate its variations to changes in other disease markers.

Methods: We evaluated the following variables in smokers with and without COPD at baseline and after one year: CAT score, age, gender, smoking status, pack-years history, BMI, modified Medical Research Council (MMRC) scale, 6MWD, lung function, BODE index, hospital admissions, Hospital and Depression Questionnaire, and the Charlson comorbidity score. In COPD patients we explored the association of CAT scores and its one-year changes with the studied parameters.

Results: 824 smokers with COPD and 126 without were evaluated at baseline, and 441 smokers with COPD and 66 without one year later. At 1 year, CAT scores for COPD patients were similar (±4 points) in 56%, higher in 27%, and lower in 17%. Interestingly, MMRC scores were similar (± 1 point) in 46% of patients, worse in 36% and better in 18% at 1 year. One-year CAT changes were best predicted by changes in MMRC scores (β coefficient 0.47, $p<0.001$). A similar behavior was found for CAT and MMRC in smokers without COPD.

Conclusions: One-year longitudinal data shows variability in CAT scores among stable COPD patients, similar to what happened to MMRC that was the best predictor of one-year CAT changes. Further longitudinal studies should confirm the long-term CAT variability and it clinical applicability.

Keywords: COPD; Health Related Quality of life

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Introduction

Chronic obstructive pulmonary disease (COPD) remains a major public health problem and is expected to be the fifth burden of disease worldwide in 2020 (1). COPD is characterized by a persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and lung to noxious particles or gases, primarily cigarette smoke (2).

The recently updated Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy (2) recommends that the assessment of COPD severity include an evaluation of the severity of the airflow limitation, degree of dyspnea, impairment of the patient's health status, and the risk of future events (e.g., exacerbations, hospital admissions).

The GOLD strategy recommends the use of the COPD Assessment Test (CAT), a validated eight-item questionnaire designed to assess and quantify the impact of COPD symptoms on patients' health status (3). CAT scores correlate well with other specific heath-related quality of life indicators in COPD patients (4), capturing the effect of different treatments, such as those included in COPD exacerbation or pulmonary rehabilitation (5, 6). CAT scores have been associated with important representative parameters of the disease (5), such as lung function, dyspnea, exercise capacity, and exacerbation in the previous year, and behave well across different European countries (4). However, little is known about its longitudinal behavior.

Therefore, we explored the database of the COPD History Assessment In SpaiN (CHAIN) cohort, a large ongoing longitudinal Spanish study that aimed to determine the natural history of the disease through a multidimensional evaluation of COPD patients. The main objective of the present work was to evaluate one-year follow-up

CAT variability in stable COPD patients and relate its changes to changes in other well-recognized disease markers.

Methods

Participants

CHAIN is a Spanish multicenter study carried out at pulmonary clinics that includes active and former smokers with COPD and a control group of non-COPD patients. COPD was defined by a history of smoking at least 10 pack-years and FEV_1/FVC ratio less than 0.70 after 400 µg of inhaled albuterol. The main goal of this prospective observational study was to perform a multidimensional evaluation of the evolution of COPD patients to better define the natural history and phenotypes of the disease (ClinicalTrials.gov Identifier: NCT01122758). The control group included active or former smokers without COPD, defined by a history of smoking at least 10 pack-years and an FEV_1/FVC ratio ≥ 0.70 after 400 µg of inhaled albuterol. The recruitment period was January15, 2010 to March 31, 2012. The patients are currently in the follow-up period, but the data analyzed in the present study were from the baseline and one year appointment data available at the time of analysis (February 2013). We evaluated anthropometric data (i.e., age, gender, height, weight, and body mass index (BMI)), comorbidities, smoking status and pack-years history, respiratory symptoms (modified Medical Research Council (MMRC) scale), self-reported exacerbations during the previous year (hospital admissions), health-related quality of life using CAT, anxiety and depression, treatments, respiratory function (i.e., spirometry, lung volume, diffusion capacity), exercise capacity (6-minute walking distance (6MWD)), arterial blood gases, and the BODE index in COPD patients. The methodological aspects of the study were published previously (7). Patient data were anonymized in a database with hierarchical

access control in order to guarantee secure access to the information. To participate in the study, the participants provided informed consent as approved by each of the ethics committees of the participating centers ("Comité de Etica de la Investigación, Universidad de Navarra IRB nº: 043/2006").

Clinical and physiological measurements

In a personal interview, trained personnel obtained the following information at the time of recruitment and yearly appointments: age, gender, and BMI. A specific questionnaire was used to determine smoking status (current or former) and smoking history (age at initiation and discontinuation, as well as intensity). From this information, we calculated the total smoking exposure and expressed it as pack-years. The presence of comorbidities was evaluated by the Charlson comorbidity index (8). Pulmonary function tests were performed following ATS guidelines (9). The diffusion capacity for carbon monoxide (DLCO) was determined by the single breath technique following the ERS/ATS guidelines (9). Arterial blood gases were measured from an arterial radial puncture at rest (after 15 minutes), breathing room air at least 45 minutes in the sitting position. The 6MWD test measured the better of two walks separated by at least 30 minutes (10). Dyspnea was evaluated by the MMRC scale (11). The FEV_1 %, BMI, 6MWD, and MMRC values were integrated into the BODE index as previously described (12).

COPD Assessment Test (CAT)

To evaluate health-related quality of life, we used the CAT, a validated eight-item questionnaire designed to assess and quantify the impact of COPD symptoms on patient health status. The resulting score out of 40 indicates disease impact, with a higher score associated with a worse health-related quality of life. (3). We used the Spanish validated version of CAT (6), and it was self-administered by each patient.

Hospital Anxiety and Depression Questionnaire (HAD)

The HAD is a self-administered test with a 14-item scale that generates ordinal data (13). The score is designed to assess both anxiety and depression symptoms; seven of the items relate to anxiety and seven relate to depression. The scores are categorized as normal (0-7), mild (9-11), and moderate or severe (12-15).

Statistical analysis

Quantitative data with a normal distribution were described using mean and standard deviation (SD). Quantitative data with non-normal distribution were described by median and interquartile range (IQR). Categorical data were described using relative frequencies. Associations between baseline CAT scores and the studied parameters were estimated using a univariate linear regression model. Significant associations (p<0.05) were included in a multiple regression model to determine those that best predict CAT scores. We arbitrarily defined two cut-off values for changes in the CAT scores at one year: +4 and –4 points, a variation previously described to be associated with exacerbations (5, 6, 13, 14), and +2 and –2 points, a variation recently proposed by Jones (15) for mapping the 4 points associated with the minimum clinically important difference (MCID) in the Saint George's Respiratory Questionnaire (SGRQ). For changes in the CAT score, we explored its association with the other studied parameters using univariate and multivariate linear regression models as described for baseline CAT scores. Calculations were performed using statistical package SPSS version 20.0 Inc. (Chicago, IL, USA).

Results

A total of 824 smokers with COPD and 126 smokers without COPD were evaluated at baseline. Their clinical and physiological characteristics are provided in Table 1. This

mainly middle-aged male population of COPD patients had a median smoking history of 50 pack-years, one-third still smoke, and represented all degrees of airway obstruction with few comorbidities and hospital admissions. The COPD patients had mild symptomatic impairment with a median MMRC score of 1, median CAT score of 11, and median anxiety and depression scores of 12 and 8, respectively, implying that these patients had symptoms of anxiety and depression. Figure 1 and 2 in the Appendix section provide the frequencies of each CAT score for COPD patients and smokers. The COPD patients were older than the smokers without COPD, had a greater number of pack-years smoking, fewer were actively smoking, impaired lung function parameters, less exercise capacity, and higher CAT scores. However, the two groups had similar BMI, comorbidity index values, and HAD scores.

Table 2 shows the independent association between CAT scores and representative parameters of the disease. CAT scores were directly associated with female gender, pack-years, MMRC scale, BODE index, and HAD scores and indirectly associated with FEV_1%, PaO_2, and 6MWD. Table 3 shows the results of a multivariate linear regression model, indicating that MMRC, HAD anxiety, and HAD depression were the best independent predictors of baseline CAT scores.

At the time of this analysis, only 441 smokers (53.5%) with COPD and 66 smokers (52.3%) without COPD were able to complete the follow-up at one year. At one year, 96% (423/441) of COPD patients remained on the same treatment. The baseline characteristics of the COPD patients lacking one-year follow-up data are provided in the Appendix. No differences were found between the COPD patients with and without one-year follow-up data ($p>0.05$ for all comparisons).

The intra-class correlation coefficient between baseline and one year CAT scores was r= 0.58 ($p<0.001$) for COPD patients. CAT scores improved in 27% and worsened in

17% of COPD patients using ±4 points as the cut-off value (Fig. 1A), whereas CAT scores improved in 32% and worsened in 21% of COPD patients using ±2 points as the cut-off value (Fig. 1B). The intra-class correlation coefficient between baseline and one year CAT scores was r= 0.60 (p<0.001) in smokers without COPD. Figure 2 shows the changes in CAT score at one year in smokers without COPD. Using ±4 points as the cut-off value, the CAT scores improved in 21% and worsened in 14% of smokers without COPD (Fig. 2A), whereas CAT scores improved in 36% and worsened in 26% of smokers without COPD using ±2 points as the cut-off value (Fig. 2B). Interestingly, when we evaluated one-year changes in MMRC (at least ± 1 point), we found that the MMRC score improved (36%), worsened (18%), or remained the same (46%) in a similar percentage of COPD patients as when the 4-point cut-off was used for changes in the CAT score. The MMRC scores improved in 27%, worsened in 11%, and remained the same in 62% of smokers without COPD.

Figures 1 and 2 clearly show regression to the mean ;high scores tended to decrease when measured again in the following year. Therefore, this phenomenon was considered when the multivariate analysis was performed.

COPD patients that exhibited greater variability at one year had baseline scores between 10 and 25. As shown in Table 4, changes in the CAT scores at one year were independently associated with changes in MMRC, BODE, HAD anxiety, and HAD depression but not with changes in FEV_1% or hospital admissions during the previous year. Only 40 COPD patients (9%) suffered at least one hospital admission during the follow-up. Patients who were admitted to the hospital had higher baseline CAT scores (11; 11 to 19) than those who were not (11; 7 to17, p<0.05), but this admission did not cause changes in the CAT score during the following year (-1; -4 to 3 vs. 0; -4 to 3, p>0.05).

The multivariate linear regression analysis shown in Table 5 indicates that the best predictors of changes in the CAT scores of COPD patients were changes in MMRC dyspnea, with borderline prediction by HAD scores. Interestingly, patients with baseline HAD scores >7, indicating at least mild anxiety and depression symptoms, had greater variation in their median changes compared to normal baseline HAD scores (median; 25-75th percentiles: -1; -6 to 2 vs. 0; -3 to 3, p=0.02).

Discussion

This one-year longitudinal observational study of a well-characterized cohort of stable COPD patients who were maintained on the same treatment demonstrated that changes in CAT scores are associated only with changes in the degree of dyspnea measured by the MMRC scale. The one-year longitudinal CAT scores of stable COPD patients exhibited variability similar to that of their MMRC scores or the CAT scores in smokers that lacked airway obstruction. The MMRC scale and CAT perform equally well in smokers with and without airway obstruction.

Current guidelines for COPD management recommend a multidimensional evaluation of the disease, including assessment of the patient's health status. The 2013 update to the GOLD strategy includes the use of the CAT to evaluate symptoms, defining a score ≥10 as health impairment and including them in GOLD grades B and D (2). CAT is an easy to use, validated, and reproducible tool that allows disease severity to be categorized (4) and is sensitive to health status changes during exacerbation and following pulmonary rehabilitation (PR) (5). The CAT behaves the same way across different European countries (4). The CAT is also associated with other descriptors of the disease, such as dyspnea evaluated by the MMRC score, degree of obstruction evaluated by FEV_1%, exercise capacity evaluated by the 6MWD, the presence of

comorbidities, and the number of exacerbations reported during the last 12 months (5). The association of CAT scores with other important prognostic parameters, such as the BODE index, PaO_2, and potential determinants of patient health status, including anxiety and depression, is unknown. Most importantly, nothing is known about the longitudinal behavior of CAT scores at one year in patients in stable condition.

Cross-sectional data

Jones et al. (3) first reported that the negative relationship between CAT scores and FEV_1% is weak (r=-0.23, $p<0.001$) when studying a large sample of European COPD patients (n= 1817). In a later, smaller study Jones et al. (5) investigated changes in CAT scores following exacerbation and PR, exploring the response to PR (n = 61-121). They found association of CAT scores at baseline with FEV_1% (-0.23, p=0.07), MMRC (0.42, p=0.007), and 6MWD (-0.24, p=0.009), and the number of exacerbations during the previous 12 months (-0.12, p=0.30). The present work confirmed these associations and the lack of association with the number of exacerbations during the previous year, which was unexpected. This finding was confirmed by the longitudinal data and indicates that the number of admissions during the one- year follow up inthe present study did not affect changes in the CAT score. Similarly, our data support the presence of comorbidities having little impact on CAT scores (4).

The novel information presented by this study indicates that an important physiological prognostic parameter, such as the degree of arterial oxygenation (PaO_2), is indirectly and significantly associated with CAT scores. This finding can be explained by the fact that patients with low PaO_2 levels have an important effect on some of the most important items evaluated by the CAT score: breathless going up hills/stairs, activity limitations at home, sleep, and energy.

Another finding is the direct association with the BODE index, a multidimensional evaluation of disease severity that predicts mortality in COPD patients (12). This finding could imply that the CAT is an easy to use tool that can capture the multidimensional aspects of the disease represented in the BODE index: nutritional status, airway obstruction, dyspnea, and exercise capacity.

Lastly, the present study also showed that CAT scores are directly associated with symptoms of anxiety and depression measured by the HAD questionnaire. This association has not been previously reported in COPD patients and highlights the importance of anxiety and depression symptoms and their impact on health status.

Longitudinal changes at one year

The present study presents the first longitudinal data on CAT scores in a large population of stable COPD patients. Previous longitudinal data on CAT scores came from two small studies investigating changes in CAT scores after exacerbation (14 days) or a PR program (42 days) (5) and another Spanish study in which CAT scores were measured at the time of exacerbation and 4 weeks later (6). Here, we presented a different type of longitudinal data not related to any intervention and with the aim of investigating the stability of the signal at one year. The data at one year indicated that the CAT has a strong and significant intra-class association ($r=0.58$, $p<0.001$) with baseline scores. Interestingly, the same association was also found in smokers without COPD ($r=0.60$, $p<0.001$). This information indicates the consistency of CAT measurements at one year. Based on the previous data published on CAT score variations during COPD exacerbation (5, 6, 14), we arbitrary designated ±4 points as a significant longitudinal variation in the CAT score. We acknowledge the potential limitations of this cut-off value, but due to the limited information available on longitudinal changes in CAT scores, we decided to use the available data to select a

score that is known to indicate changes beyond the natural variation and is associated with an exacerbation of the disease. With the onset of exacerbation, Mackay et al. showed an increase of 4.7 points (14) and Agustí et al. (6) a "much better" and "slightly better" health status associated with a decrease of 8.9 and 4.6 points, respectively. In the present study, more than 50% of the patients had the same CAT score (baseline score ±4 points), which was similar in smokers without COPD, probably indicating a similar variability in the signal at one year in this population with lower baseline CAT scores (median; 25-75th percentiles: 6; 2.5-11.5). If we decide to use the ±2 points proposed by Jones as the possible MCID for the CAT associated with significant changes after PR (5, 16), a lower percentage of COPD patients and smokers without COPD had similar scores at one year (47% and 38%, respectively). This finding suggests great variability in the CAT score at one year in stable COPD patients with the same maintenance therapy.

The patients with greater variability were those with baseline CAT scores between 10 and 25 (Figure 1 A). In this CAT score range, a greater proportion of smokers with COPD improved at one year, indicating the beneficial effect of being incorporated into a longitudinal follow-up study. This information should be considered in the longitudinal clinical follow-up of COPD patients because they have baseline scores compatible with an impaired health status that is susceptible to changes at one year and are potential targets of specific therapies.

In patients in whom the CAT scores changed, the changes were significantly associated with only MMRC dyspnea. These variations were not associated with exacerbations during the previous year or with physiological domains of the disease, but they were associated with the most important predictor of health status in COPD, the degree of dyspnea. This association is not surprising, considering that the CAT includes 2

questions that evaluate breathless and exercise limitation: “When I walk up hill or one flight of stairs I am very breathless” and “I am very limited doing activities at home”. This information implies that treatment options that target the degree of dyspnea may be associated with changes in health status captured by the CAT, as recommended by the GOLD strategy.

Interestingly, when we compared the longitudinal behavior of the CAT to another patient-centered outcome (PCO), the MMRC dyspnea score (17), both signals had a similar profile of change over one year. This finding supports the previous report from Oga et al. (18) indicating that dyspnea (MMRC) and health status (CAT) reflect the longitudinal variability of PCOs in a multidimensional disease like COPD.

In a cross sectional study of 1817 COPD patients, including a well representation of all grades of disease severity, Jones et al (19) showed a clear relationship between MMRC with health status scores measured by different tools (CAT, SGRQ, Short –Form Health Survey and the Functional Assessment of Chronic Illness Therapy Fatigue).

Interestingly, an MMRC score ≥1 and CAT score ≥10 were approximately equivalent in determining low-symptom patients, and some patients with MMRC grade 0 had modestly elevated health status scores (CAT 11.7±6.8).

As mentioned by its developers, the CAT is a health status tool for the assessent and quantification of COPD patients’ symptoms. The present study also suggests that CAT captures a symptomatic domain present in some smokers without COPD, wich changes over a one-year time period to a similar degree as in COPD patients. This symptomatic signal captured by the CAT is consistent in smokers with and without COPD and behaves the same as the signal captured by the MMRC scale. This a novel finding based on the inclusion of a control group of smokers without COPD.

Another interesting finding of the present work was that CAT scores need to be evaluated based on the baseline psychological status of the patient because patients with HAD values >7 (suggesting mild anxiety and depression symptoms) have greater changes in longitudinal CAT scores at one year. This important information should be considered in the longitudinal evaluation of COPD patients using the CAT.

The present study has limitations. First, this study is only a one-year follow up assessment that could include measurements noise, therefore serial measurements for a longer period of time would likely show a reliable trend of variability. Anyway this the first study showing one year longitudinal data in COPD patients. Second, the findings should be restricted to the type of patients studied. Third, the impact of maintenance therapy over health status was not studied, as it was not the aim of the study. Most (96%) of the patients received the same maintenance therapy, and the potential impact that the different treatments could have had on disease exacerbation did not seem to impact health status. Fourth, we selected an arbitrary cut-off value to determine a longitudinal change in the CAT score. This selection was based on the available evidence (5,6,14) and the proposed score suggested by mapping the MCID of the SGRQ (15). As previously mentioned, the MCID for the CAT is unknown and appropriately designed longitudinal studies will determine this threshold. This study also has several strengths; this is the first report of longitudinal data for the CAT in COPD patients that also includes a control population of smokers without COPD.

In conclusion, in this large well-characterized cohort, CAT scores exhibited variability at one year in a high percentage of stable COPD patients similar to the observations in MMRC dyspnea. This behavior was also found in smokers without COPD. In COPD patients, one-year variations in CAT scores were associated with changes in the degree of dyspnea evaluated by the MMRC score. The MMRC scale and CAT perform equally

well in smokers with and without airway obstruction. Our data suggest that either tool could allow a longitudinal evaluation of changes in COPD patients' symptoms. Further long-term longitudinal studies should confirm our findings and help elucidate the applicability of these tools in clinical practice, as suggested by the GOLD Guidelines.

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Table 1. Baseline characteristics of all participants.

Clinical and Physiological Characteristics	Smokers Without COPD n=126	All COPD patients n=824	*p*-value
Age in years (mean; SD)	57(10)	67 (9)	<0.001
Gender (%male/%female)	(66/33)	(81/19)	<0.001
BMI in kg/m^2 (mean; SD)	28 (5)	28 (5)	0.22
Pack-years (median; IQR)	40 (26-57)	50 (37-70)	<0.001
Current Smoking %	63	29	<0.001
MMRC points (median; IQR)	0 (0-1)	1 (1-2)	<0.001
FEV_1% (mean; SD)	93 (16)	59 (20)	<0.001
FVC% (mean; SD)	97 (15)	88 (64)	<0.001
FEV_1/FVC (mean; SD)	77	52 (11)	<0.001
GOLD obstruction levels I-II-III-IV %	NA	17; 48; 28; 7	NA
2011 GOLD clasification A-B-C-D %	NA	19-44-3.4-33.6	NA
PaO_2 (mean; SD)	77 (9)	67 (10)	<0.001
DLCO % (median; IQR)	84 (72-99)	74 (57-90)	<0.001
6MWD metes (median; IQR)	525 (441-579)	446 (374-510)	<0.001
BODE index (median; IQR)	NA	2 (0-3)	NA
Charlson score (median; IQR)CAT scores by GOLD grades (median; IQR)	1 (1-1) NA	1 (1-1)A: 7;4-10 B: 12; 8-17 C:6; 3-11 D: 13; 9-18	0.20
CAT score (IQR)	6 (2.5-11.5)	11 (7-17)	<0.001
Hospital admissions (median; IQR)	0 (0-0)	1 (1-2)	0.004
HAD anxiety score (median; IQR)	15 (7.5- 15)	12 (8-15)	0.55
HAD depression score (median; IQR)	9 (3-14)	8 (5-12)	0.29
Treatment **Inhaled anticholinergic***	NA	75%	

Inhaled β2-agonist*	NA	74%	
Inhaled corticosteroid*	NA	65%	

BMI: body mass index; MMRC: Modified Medical Research Council dyspnea scale; FEV1: forced respiratory volume in the 1st second; FVC: forced vital capacity; GOLD: Global Initiative for Obstructive Lung Diseases; PaO2: arterial oxygen pressure; DLCO: carbon monoxide diffusion capacity; 6MWD: six minute walking distance; BODE: body mass index+obstruction+dyspnea+exercise capacity; CAT: COPD Assessment Test; HAD: Hospital Anxiety and Depression scale.

Table 2. Univariate analysis with baseline CAT scores in COPD patients as the dependent variable.

Variable	Coefficient	CI	Standardized Coefficient	*p*-value
Age	-0.01	-0.07 to 0.04	-0.01	0.64
Gender (female vs male)	1.9	0.5 to 3.3	0.09	0.007
BMI	0.4	-0.13 to 0.05	-0.03	0.37
Pack-years	0.03	0.01 to 0.05	0.12	<0.001
MMRC	3.5	3.09 to 3.9	0.50	<0.001
FEV1%	-0.11	-0.14 to -0.09	-0.31	<0.001
PaO_2	-0.18	-0.26 to –0.10	-0.24	<0.001
6MWD	-0.01	-0.02 to –0.01	-0.21	<0.001
BODE	1.6	1.3 to 1.8	0.41	<0.001
Hospital admission	1.6	-0.5 to 3.7	0.10	0.12
HAD anxiety	0.4	0.3 to 0.5	0.29	<0.001
HAD depression	0.4	0.3 to 0.5	0.30	<0.001

BMI: body mass index; MMRC: Modified Medical Research Council dyspnea scale; FEV1: forced respiratory volume in the 1st second; PaO2: arterial oxygen pressure; DLCO: carbon monoxide diffusion capacity; 6MWD: six minute walking distance; BODE: body mass index+obstruction+dyspnea+exercise capacity; CAT: COPD Assessment Test; HAD: Hospital Anxiety and Depression scale.

Table 3. Multivariate analysis with baseline CAT scores in COPD patients as the dependent variable.

Variable	Coefficient	CI	Standardized Coefficient	*p*-value
MMRC	3.6	3.1 to 4.2	0.54	<0.001
HAD anxiety	0.4	0.2 to 0.5	0.21	<0.001
HAD depression	0.2	0.1 to 0.4	0.13	0.003

MMRC: Modified Medical Research Council dyspnea scale; HAD: Hospital Anxiety and Depression scale.
Variables included in the model: gender, pack-years, MMRC, FEV1%, PaO2, 6MWD, HAD anxiety, and HAD depression. r^2=0.86

Table 4. Univariate analysis with CAT changes in COPD patients at one year as the dependent variable

Variable	Coefficient	CI	Standardized Coefficient	*p*-value
Change in MMRC	1.1	0.5 to 1.7	0.16	0.01
Change in FEV1%	-0.05	-0.11 to 0.01	-0.07	0.11
Change in BODE	0.7	0.1 to 1.2	0.12	0.01
Change in Hospital admission	2.5	-3.7 to 8.7	0.03	0.42
Change in HAD anxiety	0.3	0.1 to 0.4	0.21	<0.001
Change in HAD depression	0.2	0.1 to 0.4	0.14	0.001

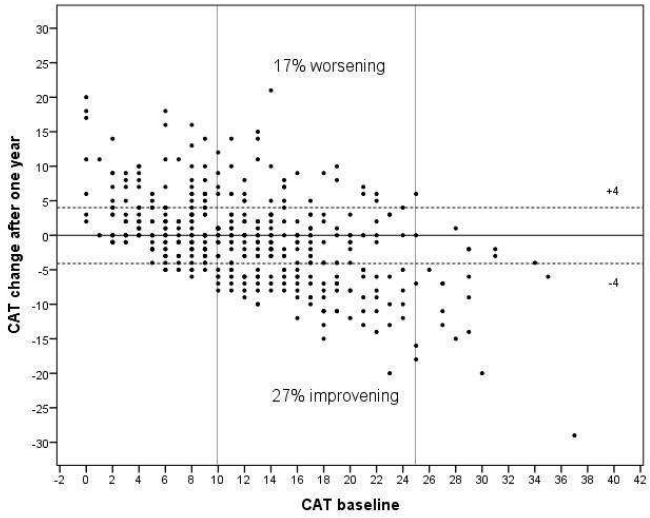
MMRC: Modified Medical Research Council dyspnea scale; FEV1: forced respiratory volume in the 1st second; BODE: body mass index+obstruction+dyspnea+exercise capacity; HAD: Hospital Anxiety and Depression scale.

Table 5. Multivariate analysis with CAT changes in COPD patients at one year as the dependent variable

Variable	Coefficient	CI	Standardized Coefficient	*p*-value
Change in MMRC	1.4	0.6 to 2.1	0.19	<0.001
Change in HAD anxiety	0.1	-0.1 to 0.3	0.12	0.06
Change in HAD depression	0.1	-0.1 to 0.3	0.12	0.06

MMRC: Modified Medical Research Council dyspnea scale; HAD: Hospital Anxiety and Depression scale.
Variables included in the model: MMRC, HAD anxiety, and HAD depression. r^2= 0.34 adjusted

Figure 1. Panel A



Panel B

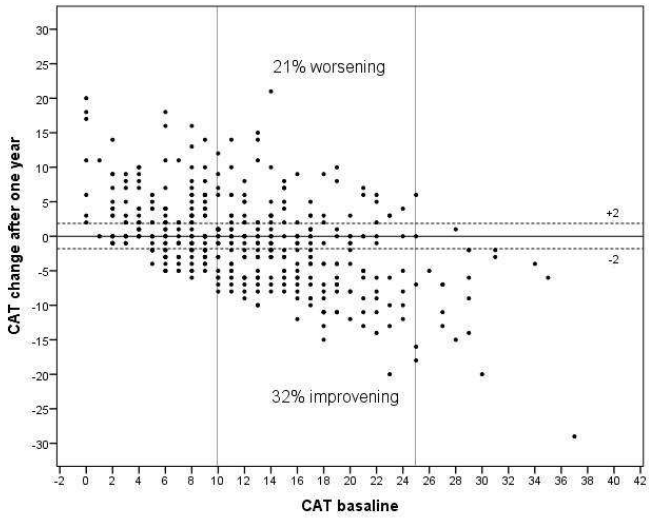
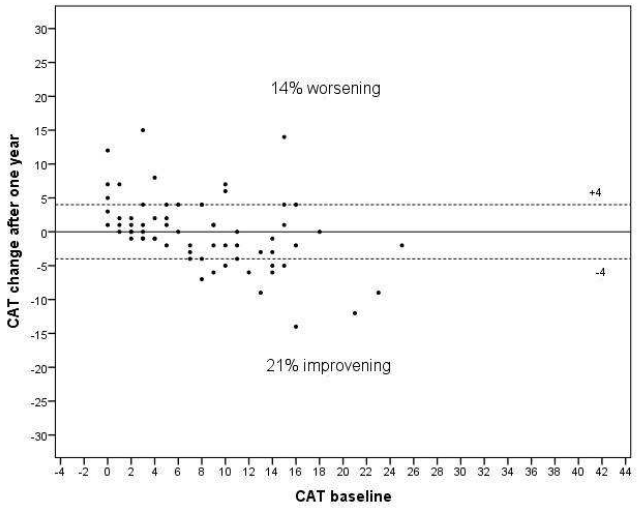
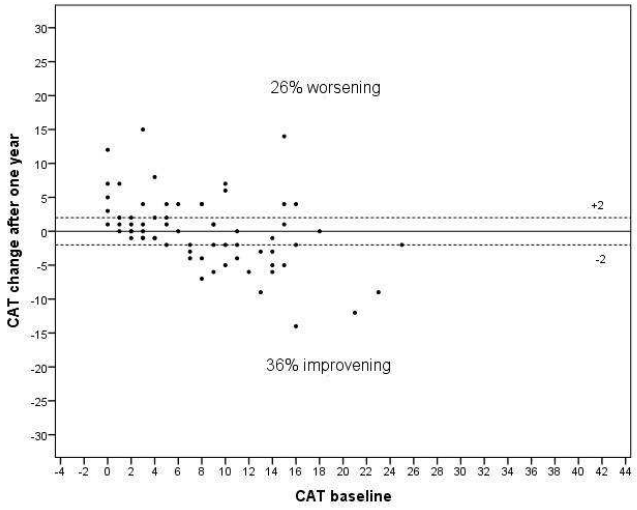


Figure 2. Panel A



Panel B



Appendix

Table 1. Clinical and physiological characteristics of the patients lacking one-year follow-up data

Clinical and Physiological Characteristics	All COPD patients n=383
Age in years (SD)	67 (10)
Gender (%male/%female)	(83/17)
BMI in kg/m^2 (SD)	28 (5)
Pack-years (IQR)	50 (32-70)
Current Smoking %	29
MMRC points (IQR)	1 (1-2)
FEV_1% (SD)	58 (20)
FVC% (SD)	84 (22)
FEV_1/FVC	51 (11)
GOLD obstruction levels I-II-III-IV %	17; 47; 25; 11
PaO_2 (SD)	64 (10)
DLCO % (IQR)	73 (56-90)
6MWD meters (IQR)	424 (360-490)
BODE index (IQR)	2 (1-4)
Charlson score (IQR)	1 (0-2)
CAT score (IQR)	12 (7-18)
Hospital admissions (IQR)	0 (0-0)
HAD anxiety score (IQR)	11 (6-15)
HAD depression score (IQR)	9 (4-12)

Figure 1. Appendix

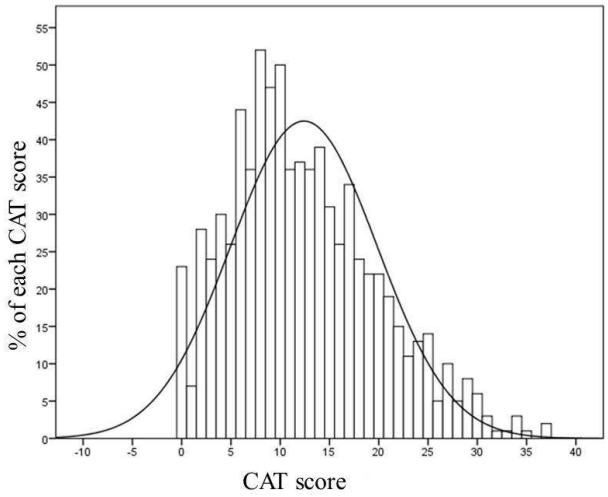


Figure 2. Appendix

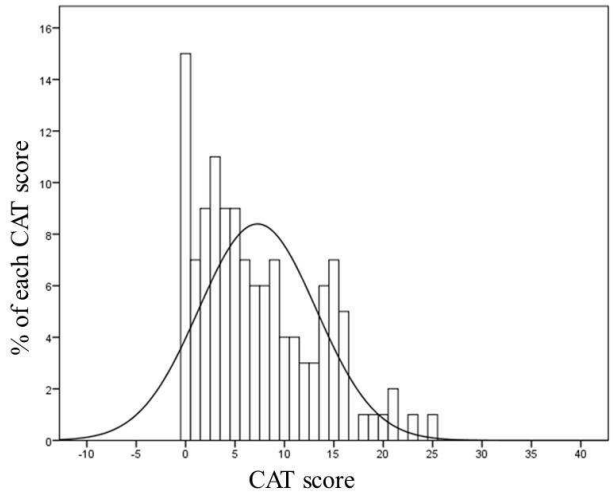


Figure legends

Manuscript Figures

Figure 1.

A: Changes in the CAT scores of COPD patients at one year compared to baseline (cut-off values ±4 points).

B: Changes in the CAT scores of COPD patients at one year compared to baseline (cut-off values ±2 points).

Figure 2.

A: Changes in the CAT scores of smokers without COPD at one year compared to baseline (cut-off values ±4 points).

B: Changes in the CAT scores of smokers without COPD at one year compared to baseline (cut-off values ±2 points).

Appendix Figures

Figure 1.

Distribution of different CAT scores in COPD patients.

Figure 2.

Distribution of different CAT scores in smokers.

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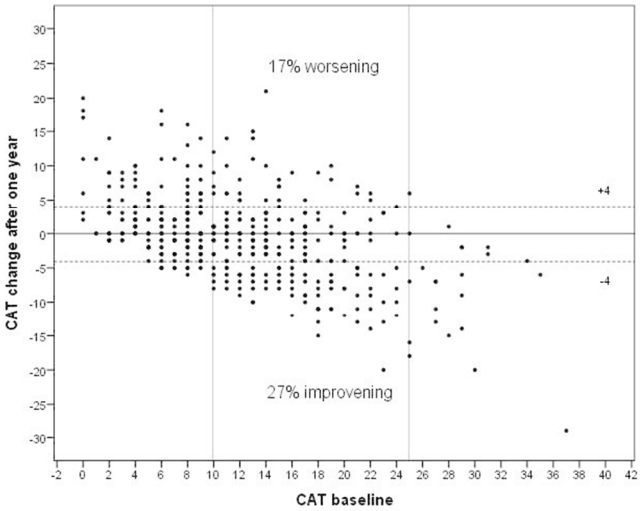

Changes in the CAT scores of COPD patients at one year compared to baseline (cut-off values ±4 points).
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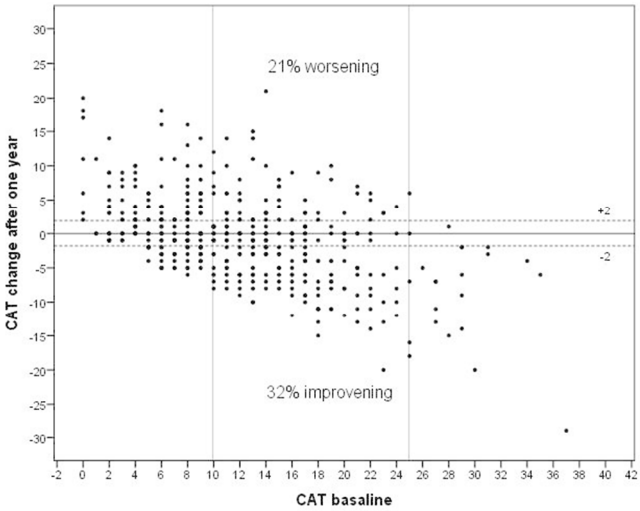

Changes in the CAT scores of COPD patients at one year compared to baseline (cut-off values ±2 points).
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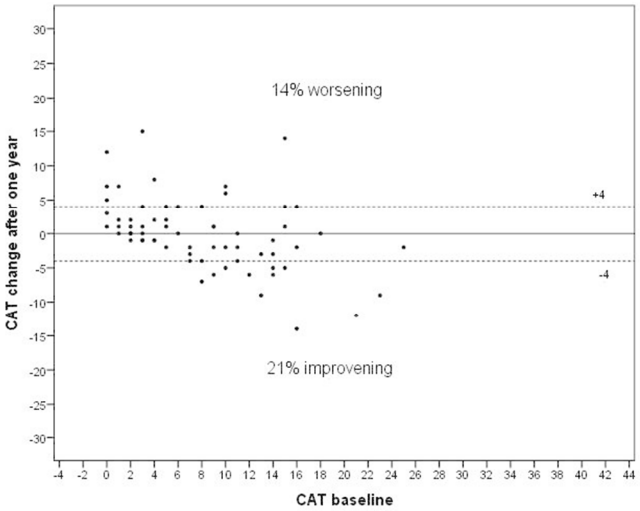

Changes in the CAT scores of smokers without COPD at one year compared to baseline (cut-off values ±4 points).
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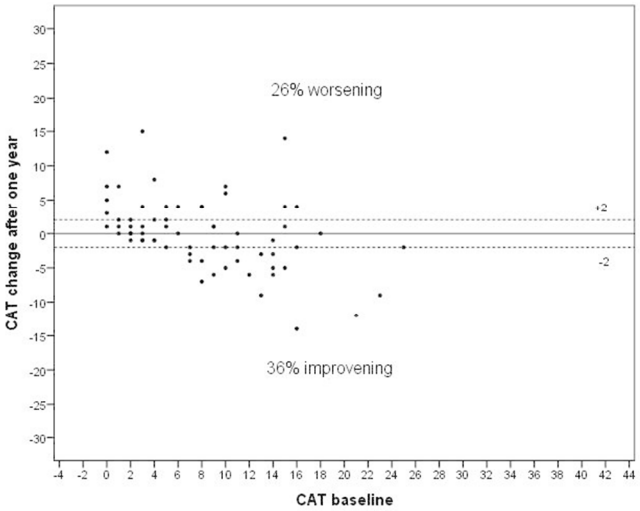

Changes in the CAT scores of smokers without COPD at one year compared to baseline (cut-off values ±2 points).
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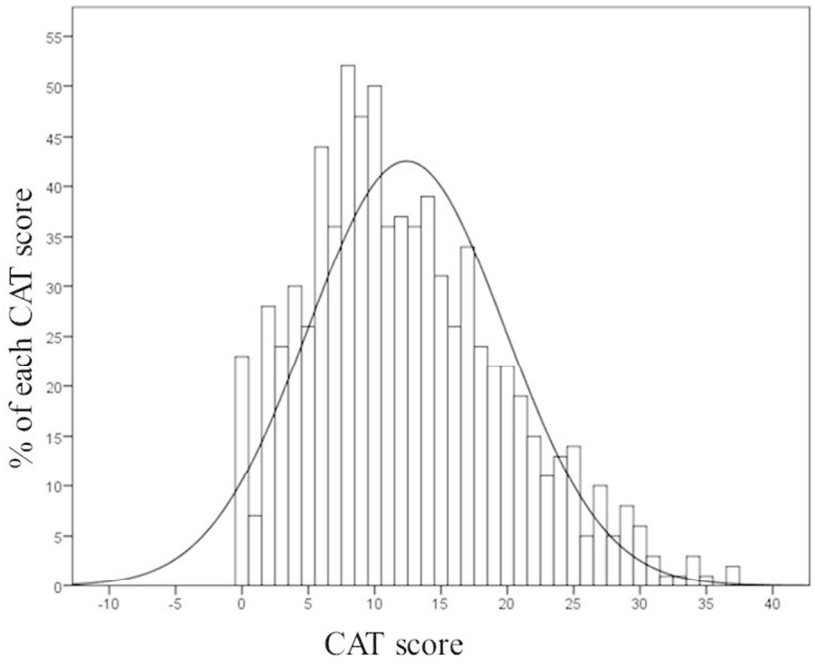

Distribution of different CAT scores in COPD patients.
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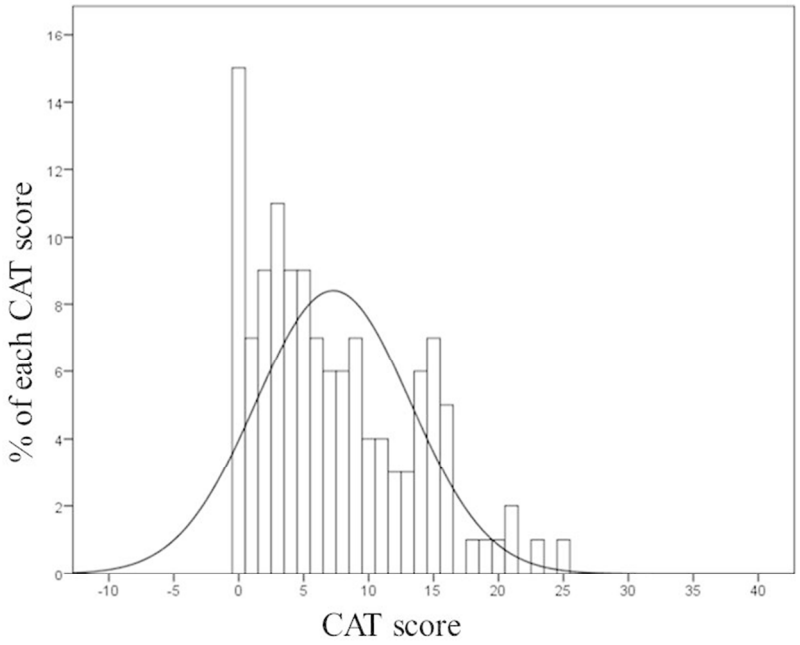

Distribution of different CAT scores in smokers.
254x190mm (96 x 96 DPI)

Clinical Application of the COPD Assessment Test: Longitudinal Data from the CHAIN Cohort

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Running Head: Clinical application of the COPD Assessment Test

Word count: 3617 **Methods Word count**: 759

None of the authors have declared a conflict of interest with the data presented.

Abstract

Rationale: The Chronic Obstructive Pulmonary Disease (COPD) Assessment Test (CAT) was proposed for assessing health status in COPD, but little is known about its longitudinal changes.

Objective: To evaluate one-year CAT variability in stable COPD patients and relate its variations to changes in other disease markers.

Methods: We evaluated the following variables in smokers with and without COPD at baseline and after one year: CAT score, age, gender, smoking status, pack-years history, BMI, modified Medical Research Council (MMRC) scale, 6MWD, lung function, BODE index, hospital admissions, Hospital and Depression Questionnaire ~~scores~~, and the Charlson comorbidity score. In COPD patients we explored the association of CAT scores and its one-year changes with the studied parameters.

Results: 824 smokers with COPD and 126 without were evaluated at baseline, and 441 smokers with COPD and 66 without one year later. At one year, CAT scores for COPD patients were similar (±4 points) in 56%, higher in 27%, and lower in 17%. Interestingly, MMRC scores were similar (± 1 point) in 46% of patients, worse in 36%, and better in 18% at 1 year. One-year CAT changes were best predicted by changes in MMRC scores (β coefficient 0.47, p<0.001). A similar behavior was found for CAT and MMRC in smokers without COPD.

Conclusions: One-year longitudinal data shows high variability in CAT scores among stable COPD patients, ~~similar to smokers without COPD.what happened to~~and MMRC ~~that~~ was the best predictor of one-year CAT changes. Further longitudinal studies should confirm the long-term CAT variability and its clinical applicability.

Keywords: COPD; Health Related Quality of life

Word count: 248

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Introduction

Chronic obstructive pulmonary disease (COPD) remains a major public health problem and is expected to be the fifth burden of disease worldwide in 2020 (1). COPD is characterized by a persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and lung to noxious particles or gases, primarily cigarette smoke (2).

The recently updated Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy (2) recommends that the assessment of COPD severity include an evaluation of the severity of the airflow limitation, degree of dyspnea, impairment of the patient's health status, and the risk of future events (e.g., exacerbations, hospital admissions).

The GOLD strategy recommends the use of the COPD Assessment Test (CAT), a validated eight-item questionnaire designed to assess and quantify the impact of COPD symptoms on patients' health status (3). CAT scores correlate well with other specific heath-related quality of life indicators in COPD patients (4), capturing the effect of different treatments, such as those included in COPD exacerbation or pulmonary rehabilitation (5, 6). CAT scores have been associated with important representative parameters of the disease (5), such as lung function, dyspnea, exercise capacity, and exacerbation in the previous year, and behave well across different European countries (4). However, little is known about its longitudinal behavior.

Therefore, we explored the database of the COPD History Assessment In SpaiN (CHAIN) cohort, a large ongoing longitudinal Spanish study that aimed to determine the natural history of the disease through a multidimensional evaluation of COPD patients. The main objective of the present work was to evaluate one-year follow-up

CAT variability in stable COPD patients and relate its changes to changes in other well-recognized disease markers.

Methods

Participants

CHAIN is a Spanish multicenter study carried out at pulmonary clinics that includes active and former smokers with COPD and a control group of non-COPD patients. COPD was defined by a history of smoking at least 10 pack-years and FEV_1/FVC ratio less than 0.70 after 400 µg of inhaled albuterol. The main goal of this prospective observational study was to perform a multidimensional evaluation of the evolution of COPD patients to better define the natural history and phenotypes of the disease (ClinicalTrials.gov Identifier: NCT01122758). The control group included active or former smokers without COPD, defined by a history of smoking at least 10 pack-years and an FEV_1/FVC ratio ≥ 0.70 after 400 µg of inhaled albuterol. The recruitment period was January15, 2010 to March 31, 2012. The patients are currently in the follow-up period, but the data analyzed in the present study were from the baseline and one year appointment data available at the time of analysis (February 2013). We evaluated anthropometric data (i.e., age, gender, height, weight, and body mass index (BMI)), comorbidities, smoking status and pack-years history, respiratory symptoms (modified Medical Research Council (MMRC) scale), self-reported exacerbations during the previous year (hospital admissions), health-related quality of life using CAT, anxiety and depression, treatments, respiratory function (i.e., spirometry, lung volume, diffusion capacity), exercise capacity (6-minute walking distance (6MWD)), arterial blood gases, and the BODE index in COPD patients. The methodological aspects of the study were published previously (7). Patient data were anonymized in a database with hierarchical

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access control in order to guarantee secure access to the information. To participate in the study, the participants provided informed consent as approved by each of the ethics committees of the participating centers ("Comité de Etica de la Investigación, Universidad de Navarra IRB nº: 043/2006").

Clinical and physiological measurements

In a personal interview, trained personnel obtained the following information at the time of recruitment and yearly appointments: age, gender, and BMI. A specific questionnaire was used to determine smoking status (current or former) and smoking history (age at initiation and discontinuation, as well as intensity). From this information, we calculated the total smoking exposure and expressed it as pack-years. The presence of comorbidities was evaluated by the Charlson comorbidity index (8). Pulmonary function tests were performed following ATS guidelines (9). The diffusion capacity for carbon monoxide (DLCO) was determined by the single breath technique following the ERS/ATS guidelines (9). Arterial blood gases were measured from an arterial radial puncture at rest (after 15 minutes), breathing room air at least 45 minutes in the sitting position. The 6MWD test measured the better of two walks separated by at least 30 minutes (10). Dyspnea was evaluated by the MMRC scale (11). The FEV_1 %, BMI, 6MWD, and MMRC values were integrated into the BODE index as previously described (12).

COPD Assessment Test (CAT)

To evaluate health-related quality of life, we used the CAT, a validated eight-item questionnaire designed to assess and quantify the impact of COPD symptoms on patient health status. The resulting score out of 40 indicates disease impact, with a higher score associated with a worse health-related quality of life. (3). We used the Spanish validated version of CAT (6), and it was self-administered by each patient.

Hospital Anxiety and Depression Questionnaire (HAD)

The HAD is a self-administered test with a 14-item scale that generates ordinal data (13). The score is designed to assess both anxiety and depression symptoms; seven of the items relate to anxiety and seven relate to depression. The scores are categorized as normal (0-7), mild (9-11), and moderate or severe (12-15).

Statistical analysis

Quantitative data with a normal distribution were described using mean and standard deviation (SD). Quantitative data with non-normal distribution were described by median and interquartile range (IQR). Categorical data were described using relative frequencies. Associations between baseline CAT scores and the studied parameters were estimated using a univariate linear regression model. Significance associations ($p<0.05$) were included in a multiple regression model to determine those that best predict CAT scores. We arbitrarily defined two cut-off values for changes in the CAT scores at one year: +4 and –4 points, a variation previously described to be associated with exacerbations (5, 6, 13, 14), and +2 and –2 points, a variation recently proposed by Jones (15) for mapping the 4 points associated with the minimum clinically important difference (MCID) in the Saint George's Respiratory Questionnaire (SGRQ). For changes in the CAT score, we explored its association with the other studied parameters using univariate and multivariate linear regression models as described for baseline CAT scores. Calculations were performed using statistical package SPSS version 20.0 Inc. (Chicago, IL, USA).

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Results

A total of 824 smokers with COPD and 126 smokers without COPD were evaluated at baseline. Their clinical and physiological characteristics are provided in Table 1. This

mainly middle-aged male population of COPD patients had a median smoking history of 50 pack-years, one-third still smoke, and represented all degrees of airway obstruction with few comorbidities and hospital admissions. The COPD patients had mild symptomatic impairment with a median MMRC score of 1, median CAT score of 11, and median anxiety and depression scores of 12 and 8, respectively, implying that these patients had symptoms of anxiety and depression. Figures 1 and 2 in the Appendix provide the frequencies of each CAT score for COPD patients and smokers. The COPD patients were older than the smokers without COPD, had a greater number of pack-years smoking, fewer were actively smoking, impaired lung function parameters, less exercise capacity, and higher CAT scores. However, the two groups had similar BMI, comorbidity index values, and HAD scores.

Table 2 shows the independent association between CAT scores and representative parameters of the disease. CAT scores were directly associated with female gender, pack-years, MMRC scale, BODE index, and HAD scores and indirectly associated with FEV_1%, PaO_2, and 6MWD. Table 3 shows the results of a multivariate linear regression model, indicating that MMRC, HAD anxiety, and HAD depression were the best independent predictors of baseline CAT scores.

At the time of this analysis, only 441 smokers (53.5%) with COPD and 66 smokers (52.3%) without COPD were able to complete the follow-up at one year. At one year, 96% (423/441) of COPD patients remained on the same treatment. The baseline characteristics of the COPD patients lacking one-year follow-up data are provided in the Appendix. No differences were found between the COPD patients with and without one-year follow-up data (p>0.05 for all comparisons).

The intra-class correlation coefficient between baseline and one year CAT scores was r= 0.58 (p<0.001) for COPD patients. CAT scores improved in 27% and worsened in

17% of COPD patients using ±4 points as the cut-off value (Fig. 1A), whereas CAT scores improved in 32% and worsened in 21% of COPD patients using ±2 points as the cut-off value (Fig. 1B). The intra-class correlation coefficient between baseline and one year CAT scores was r= 0.60 (p<0.001) in smokers without COPD. Figure 2 shows the changes in CAT score at one year in smokers without COPD. Using ±4 points as the cut-off value, the CAT scores improved in 21% and worsened in 14% of smokers without COPD (Fig. 2A), whereas CAT scores improved in 36% and worsened in 26% of smokers without COPD using ±2 points as the cut-off value (Fig. 2B). Interestingly, when we evaluated one-year changes in MMRC (at least ± 1 point), we found that the MMRC score improved (36%), worsened (18%), or remained the same (46%) in a similar percentage of COPD patients as when the 4-point cut-off was used for changes in the CAT score. The MMRC scores improved in 27%, worsened in 11%, and remained the same in 62% of smokers without COPD.

Figures 1 and 2 clearly show regression to the mean; high scores tended to decrease when measured again the following year. Therefore, this phenomenon was considered when the multivariate analysis was performed.

COPD patients that exhibited greater variability at one year had baseline scores between 10 and 25. As shown in Table 4, changes in the CAT scores at one year were independently associated with changes in MMRC, BODE, HAD anxiety, and HAD depression but not with changes in FEV_1% or hospital admissions during the previous year. Only 40 COPD patients (9%) suffered at least one hospital admission during the follow--up ~~time~~. ~~Those that had~~Patients who were admitted to the ~~a~~ hospital ~~admission have~~had ~~a~~ higher baseline CAT scores (15; 11 to 19) ~~compared with~~than those ~~that do~~who were not admitted (~~15; 11 to 19 vs.~~ 11; 7 to17, p<0.05), ~~although~~but this

Comment [AP4]: As requested, we only edited the red text. We made grammatical and verbal changes in an attempt to increase readability and/or correctness. These changes will not be called out with a comment balloon unless likely to affect content. Please review the text carefully to ensure the meaning has not been inadvertently altered at any point. Thank you.

admission did not cause changes in the~~ir~~ CAT score during the following year (-1; -4 to 3 vs. 0; -4 to 3, $p>0.05$).

The multivariate linear regression analysis shown in Table 5 indicates that the best predictors of changes in the CAT scores of COPD patients were changes in MMRC dyspnea, with borderline prediction by HAD scores. Interestingly, patients with baseline HAD scores >7, indicating at least mild anxiety and depression symptoms, had greater variation in their median changes compared to normal baseline HAD scores (median; 25-75th percentiles: -1; -6 to 2 vs. 0; -3 to 3, p=0.02).

Discussion

This one-year longitudinal observational study of a well-characterized cohort of stable COPD patients who were maintained on the same treatment demonstrated that changes in CAT scores are associated only with changes in the degree of dyspnea measured by the MMRC scale. The one-year longitudinal CAT scores of stable COPD patients exhibited variability similar to that of their MMRC scores or the CAT scores in smokers that lacked airway obstruction. The MMRC scale and ~~the~~ CAT perform equally well in smokers with and without airway obstruction.

Current guidelines for COPD management recommend a multidimensional evaluation of the disease, including assessment of the patient's health status. The 2013 update to the GOLD strategy includes the use of the CAT to evaluate symptoms, defining a score ≥10 as health impairment and including them in GOLD grades B and D (2). CAT is an easy to use, validated, and reproducible tool that allows disease severity to be categorized (4) and is sensitive to health status changes during exacerbation and following pulmonary rehabilitation (PR) (5). The CAT behaves the same way across

different European countries (4). The CAT is also associated with other descriptors of the disease, such as dyspnea evaluated by the MMRC score, degree of obstruction evaluated by FEV_1%, exercise capacity evaluated by the 6MWD, the presence of comorbidities, and the number of exacerbations reported during the last 12 months (5). The association of CAT scores with other important prognostic parameters, such as the BODE index, PaO_2, and potential determinants of patient health status, including anxiety and depression, is unknown. Most importantly, nothing is known about the longitudinal behavior of CAT scores at one year in patients in stable condition.

Cross-sectional data

Jones et al. (3) first reported that the negative relationship between CAT scores and FEV_1% is weak (r=-0.23, $p<0.001$) when studying a large sample of European COPD patients (n= 1817). In a later, smaller study Jones et al. (5) investigated changes in CAT scores following exacerbation and PR, exploring the response to PR (n = 61-121), the association of CAT scores at baseline with FEV_1% (-0.23, p=0.07), MMRC (0.42, p=0.007), and 6MWD (-0.24, p=0.009), and the number of exacerbations during the previous 12 months (-0.12, p=0.30). The present work confirmed these associations and the lack of association with the number of exacerbations during the previous year, which. ~~This is an interesting~~ was unexpected. This finding was confirmed by the longitudinal data and indicates that the number of admissions during the one-year follow-up in the present study did not affect changes in the CAT score. Similarly, our data support the presence of comorbidities having little impact on CAT scores (4).

The novel information presented by this study indicates that an important physiological prognostic parameter, such as the degree of arterial oxygenation (PaO_2), is indirectly and significantly associated with CAT scores. This finding can be explained by the fact that patients with low PaO_2 levels have an important effect on some of the most

Comment [AP5]: The notation used for statistics is not consistent.

important items evaluated by the CAT score: breathless going up hills/stairs, activity limitations at home, sleep, and energy.

Another finding is the direct association with the BODE index, a multidimensional evaluation of disease severity that predicts mortality in COPD patients (12). This finding could imply that the CAT is an easy to use tool that can capture the multidimensional aspects of the disease represented in the BODE index: nutritional status, airway obstruction, dyspnea, and exercise capacity.

Lastly, the present study also showed that CAT scores are directly associated with symptoms of anxiety and depression measured by the HAD questionnaire. This association has not been previously reported in COPD patients and highlights the importance of anxiety and depression symptoms and their impact on health status.

Longitudinal changes at one year

The present study presents the first longitudinal data on CAT scores in a large population of stable COPD patients. Previous longitudinal data on CAT scores came from two small studies investigating changes in CAT scores after exacerbation (14 days) or a PR program (42 days) (5) and another Spanish study in which CAT scores were measured at the time of exacerbation and 4 weeks later (6). Here, we presented a different type of longitudinal data not related to any intervention and with the aim of investigating the stability of the signal at one year. The data at one year indicated that the CAT has a strong and significant intra-class association (r=0.58, $p<0.001$) with baseline scores. Interestingly, the same association was also found in smokers without COPD (r=0.60, $p<0.001$). This information indicates the consistency of CAT measurements at one year. Based on the previous data published on CAT score variations during COPD exacerbation (5, 6, 14), we arbitrary designated ±4 points as a significant longitudinal variation in the CAT score. We acknowledge the potential

limitations of this cut-off value, but due to the limited information available on longitudinal changes in CAT scores, we decided to use the available data to select a score that is known to indicate changes beyond the natural variation and is associated with an exacerbation of the disease. With the onset of exacerbation, Mackay et al. showed an increase of 4.7 points (14) and Agustí et al. (6) a "much better" and "slightly better" health status associated with a decrease of 8.9 and 4.6 points, respectively. In the present study, more than 50% of the patients had the same CAT score (baseline score ±4 points), which was similar in smokers without COPD, probably indicating a similar variability in the signal at one year in this population with lower baseline CAT scores (median; 25-75th percentiles: 6; 2.5-11.5). If we decide to use the ±2 points proposed by Jones as the possible MCID for the CAT associated with significant changes after PR (5, 16), a lower percentage of COPD patients and smokers without COPD had similar scores at one year (47% and 38%, respectively). This finding suggests great variability in the CAT score at one year in stable COPD patients with the same maintenance therapy.

The patients with greater variability were those with baseline CAT scores between 10 and 25 (Figure 1A). In this CAT score range, a greater proportion of smokers with COPD improved at one year, indicating the beneficial effect of being incorporated into a longitudinal follow-up study. This information should be considered in the longitudinal clinical follow-up of COPD patients because they have baseline scores compatible with an impaired health status that is susceptible to changes at one year and are potential targets of specific therapies.

In patients in whom the CAT scores changed, the changes were significantly associated with only MMRC dyspnea. These variations were not associated with exacerbations during the previous year or with physiological domains of the disease, but they were

associated with the most important predictor of health status in COPD, the degree of dyspnea. This association is not surprising considering that the CAT includes two questions that evaluate breathless and exercise limitation: “When I walk uphill or one flight of stairs I am very breathless” and “I am very limited doing activities at home”. This information implies that treatment options that target the degree of dyspnea may be associated with changes in health status captured by the CAT, as recommended by the GOLD strategy.

Interestingly, when we compared the longitudinal behavior of the CAT to another patient-centered outcome (PCO), the MMRC dyspnea score (17), both signals had a similar profile of change over one year. This finding supports the previous report from Oga et al. (18) indicating that dyspnea (MMRC) and health status (CAT) reflect the longitudinal variability of PCOs in a multidimensional disease like COPD.

~~As recently shown by Jones et al (19) i~~In a cross sectional study of 1817 COPD patients ~~, including a well~~ representing~~ation of~~ all grades of disease severity, Jones et al. (19) ~~the MMRC~~ showed a clear relationship ~~with~~between MMRC and ~~-~~health status scores measured by different tools (CAT, SGRQ, Short –Form Health Survey, and the Functional Assessment of Chronic Illness Therapy Fatigue). Interestingly, ~~it also showed that~~ an MMRC score≥1 and CAT score≥10 were approximately equivalent in determining low-symptom patients, and ~~that~~ some patients with MMRC grade 0 ~~could have~~had modestly elevated health status scores (CAT 11.7±6.8).

As mentioned by its developers, the CAT is a health status tool for the~~to~~ assessment and quantification of~~y~~ COPD patients’ symptoms. The present ~~work data~~study also suggests that CAT ~~it~~ captures a symptomatic domain ~~that is also~~ present in some smokers without COPD, which ~~and that~~ changes over a one--year time period to~~in~~ a similar degree ~~that happens~~as in COPD patients. This symptomatic signal captured by the CAT

is consistent in smokers with and without COPD and behaves the same as the ~~one~~ signal captured by the MMRC scale. This a novel finding ~~from the present work for~~based on the inclusion~~ding~~ of a control group of smokers without COPD.

Another interesting finding of the present work was that CAT scores need to be evaluated based on the baseline psychological status of the patient because patients with HAD values >7 (suggesting mild anxiety and depression symptoms) have greater changes in longitudinal CAT scores at one year. This important information should be considered in the longitudinal evaluation of COPD patients using the CAT.

The present study has limitations. First, this study is only a one-year follow-up assessment that could include measurement noise; therefore, serial measurements for a longer period of time would likely show a reliable trend of variability. However, this study is the first to report~~study showing~~ one-year longitudinal data in COPD patients. Second, the findings should be restricted to the type of patients studied. Third, the impact of maintenance therapy over health status was not studied, as it was not the aim of the study. Most (96%) of the patients received the same maintenance therapy, and the potential impact that the different treatments could have had on disease exacerbation did not seem to impact health status. Fourth, we selected an arbitrary cut-off value to determine a longitudinal change in the CAT score. This selection was based on the available evidence (5,6,14) and the proposed score suggested by mapping the MCID of the SGRQ (15). As previously mentioned, the MCID for the CAT is unknown and appropriately designed longitudinal studies will determine this threshold. This study also has several strengths; this is the first report of longitudinal data for the CAT in COPD patients that also includes a control population of smokers without COPD.

In conclusion, in this large well-characterized cohort, CAT scores exhibited variability at one year in a high percentage of stable COPD patients, similar to the

Comment [AP6]: "one" needed to refer to something.

observations~~what happened with~~ in MMRC dyspnea. This behavior was also found in smokers without COPD. In COPD patients, one-year variations in CAT scores were associated with changes in the degree of dyspnea evaluated by the MMRC score. The MMRC scale and ~~the~~ CAT perform~~s~~ equally well in smokers with and without airway obstruction. Our data suggest that either tool could allow a longitudinal evaluation of changes in COPD patients' symptoms. Further long-term longitudinal studies should confirm our findings and help elucidate the applicability of these tools in clinical practice, as suggested by the GOLD Guidelines.

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Conception and design: JPdT, CC, JMM, PdL, GPB, JJSC, JLLP, JS

Analysis and interpretation: JPdT, CC, JMM, CMG, PdL, IMV, BC, GPB, MCR, ISG, RAB, AdDD, NFC, IAM, RI, EB, ALC, JBGI, MMR, JJS, JLLC, JS.

Drafting the manuscript for important intellectual content: JPdT, CC, JMM, PdL, GPB, JJSC, JLLP, JS

JPdT is the guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article.

The PII DE EPOC of SEPAR endorsed this study.

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The funders~~founders~~ had no role in study design, data collection and analysis, decision to publish, or manuscript preparation.

Comment [AP7]: This appeared to be a typo.

Table 1. Baseline characteristics of all participants.

Clinical and Physiological Characteristics	Smokers Without COPD n=126	All COPD patients n=824	*p*-value
Age in years (mean; SD)	57(10)	67 (9)	<0.001
Gender (%male/%female)	(66/33)	(81/19)	<0.001
BMI in kg/m^2 (mean; SD)	28 (5)	28 (5)	0.22
Pack-years (median; IQR)	40 (26-57)	50 (37-70)	<0.001
Current Smoking %	63	29	<0.001
MMRC points (median; IQR)	0 (0-1)	1 (1-2)	<0.001
FEV_1% (mean; SD)	93 (16)	59 (20)	<0.001
FVC% (mean; SD)	97 (15)	88 (64)	<0.001
FEV_1/FVC (mean; SD)	77	52 (11)	<0.001
GOLD obstruction levels I-II-III-IV %	NA	17; 48; 28; 7	NA
2011 GOLD classification A-B-C-D %	NA	19-44-3.4-33.6	NA
PaO_2 (mean; SD) ~~DLCO % (IQR)~~	77 (9) ~~84 (72-99)~~	67 (10) ~~74 (57-90)~~	<0.001 ~~<0.001~~
DLCO % (median; IQR) ~~6MWD metes (IQR)~~	84 (72-99) ~~525 (441-579)~~	74 (57-90) ~~446 (374-510)~~	<0.001 ~~<0.001~~
6MWD metes (median; IQR) ~~BODE index (IQR)~~	525 (441-579) ~~NA~~	446 (374-510) ~~2 (0-3)~~	<0.001 ~~NA~~
BODE index (median; IQR) ~~Charlson score (IQR)~~	NA ~~1 (1-1)~~	2 (0-3) ~~1 (1-1)~~	NA ~~0.20~~
Charlson score (median; IQR) ~~CAT score (IQR)~~ CAT scores by GOLD grades (median; IQR)	1 (1-1) ~~6 (2.5-11.5)~~ NA	1 (1-1) ~~11 (7-17)~~ A: 7;4-10 B: 12; 8-17 C:6; 3-11 D: 13; 9-18	0.20 ~~<0.001~~
CAT score (IQR) ~~Hospital admissions (IQR)~~	6 (2.5-11.5) ~~0 (0-0)~~	11 (7-17) ~~1 (1-2)~~	<0.001 ~~0.004~~
Hospital admissions (median; IQR) ~~HAD anxiety score (IQR)~~	0 (0-0) ~~15 (7.5-15)~~	1 (1-2) ~~12 (8-15)~~	0.004 ~~0.55~~

HAD anxiety score (median; IQR) ~~HAD depression score (IQR)~~	15 (7.5- 15) ~~9 (3-14)~~	12 (8-15) ~~8 (5-12)~~	0.55 ~~0.29~~
HAD depression score (median; IQR)	9 (3-14)	8 (5-12)	0.29
Treatment Inhaled anticholinergic* Inhaled β2-agonist* Inhaled corticosteroid*	 NA NA NA	 75% 74% 65%	

BMI: body mass index; MMRC: Modified Medical R~~r~~esearch Council dyspnea scale; FEV1: forced respiratory volume~~n~~ in the 1st second; FVC: forced vital capacity; GOLD: Global Initiative for Obstructive Lung Diseases; PaO2: arterial oxygen pressure; DLCO: carbon monoxide diffusion capacity; 6MWD: six minute walking distance; BODE: body mass index+obstruction+dyspnea+exercise capacity; CAT: COPD Assessment Test; HAD: Hospital Anxiety and Depression scale.

Table 2. Univariate analysis with baseline CAT scores in COPD patients as the dependent variable.

Variable	Coefficient	CI	Standardized Coefficient	~~P~~ *p*-value
Age	-0.01	-0.07 to 0.04	-0.01	0.64
Gender (female vs. male)	1.9	0.5 to 3.3	0.09	0.007
BMI	0.4	-0.13 to 0.05	-0.03	0.37
Pack-years	0.03	0.01 to 0.05	0.12	<0.001
MMRC	3.5	3.09 to 3.9	0.50	<0.001
FEV1%	-0.11	-0.14 to -0.09	-0.31	<0.001
PaO_2	-0.18	-0.26 to –0.10	-0.24	<0.001
6MWD	-0.01	-0.02 to –0.01	-0.21	<0.001
BODE	1.6	1.3 to 1.8	0.41	<0.001
Hospital admission	1.6	-0.5 to 3.7	0.10	0.12

HAD anxiety	0.4	0.3 to 0.5	0.29	<0.001
HAD depression	0.4	0.3 to 0.5	0.30	<0.001

BMI: body mass index; MMRC: Modified Medical Rresearch Council dyspnea scale; FEV1: forced respiratory volume~~s~~ in the 1st second; PaO2: arterial oxygen pressure; DLCO: carbon monoxide diffusion capacity; 6MWD: six minute walking distance; BODE: body mass index+obstruction+dyspnea+exercise capacity; CAT: COPD Assessment Test; HAD: Hospital Anxiety and Depression scale.

Table 3. Multivariate analysis with baseline CAT scores in COPD patients as the dependent variable.

Variable	Coefficient	CI	Standardized Coefficient	*p*-value
MMRC	3.6	3.1 to 4.2	0.54	<0.001
HAD anxiety	0.4	0.2 to 0.5	0.21	<0.001
HAD depression	0.2	0.1 to 0.4	0.13	0.003

~~Variables included in the model: gender, pack-years, MMRC, FEV1%, PaO2, 6MWD, HAD anxiety, and HAD depression. r^2=0.86~~

MMRC: Modified Medical Research Council dyspnea scale; HAD: Hospital Anxiety and Depression scale.

Variables included in the model: gender, pack-years, MMRC, FEV1%, PaO2, 6MWD, HAD anxiety, and HAD depression. r^2=0.86

Table 4. Univariate analysis with CAT changes in COPD patients at one year as the dependent variable

Variable	Coefficient	CI	Standardized Coefficient	*p*-value
Change in MMRC	1.1	0.5 to 1.7	0.16	0.01
Change in FEV1%	-0.05	-0.11 to 0.01	-0.07	0.11
Change in BODE	0.7	0.1 to 1.2	0.12	0.01
Change in Hospital admission	2.5	-3.7 to 8.7	0.03	0.42
Change in HAD anxiety	0.3	0.1 to 0.4	0.21	<0.001
Change in HAD depression	0.2	0.1 to 0.4	0.14	0.001

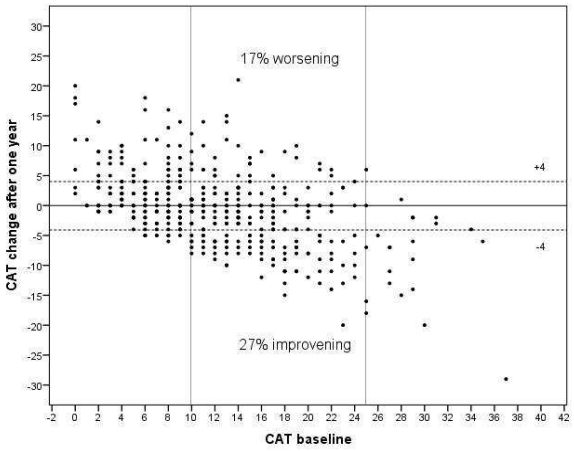
MMRC: Modified Medical Reresearch Council dyspnea scale; FEV1: forced respiratory volumen in the 1st second; BODE: body mass index+obstruction+dyspnea+exercise capacity; HAD: Hospital Anxiety and Depression scale.

Table 5. Multivariate analysis with CAT changes in COPD patients at one year as the dependent variable

Variable	Coefficient	CI	Standardized Coefficient	*p*-value
Change in MMRC	1.4	0.6 to 2.1	0.19	<0.001
Change in HAD anxiety	0.1	-0.1 to 0.3	0.12	0.06
Change in HAD depression	0.1	-0.1 to 0.3	0.12	0.06

MMRC: Modified Medical Research Council dyspnea scale; HAD: Hospital Anxiety and Depression scale.
Variables included in the model: MMRC, HAD anxiety, and HAD depression. r^2= 0.34 adjusted

Figure 1. Panel A



Panel B

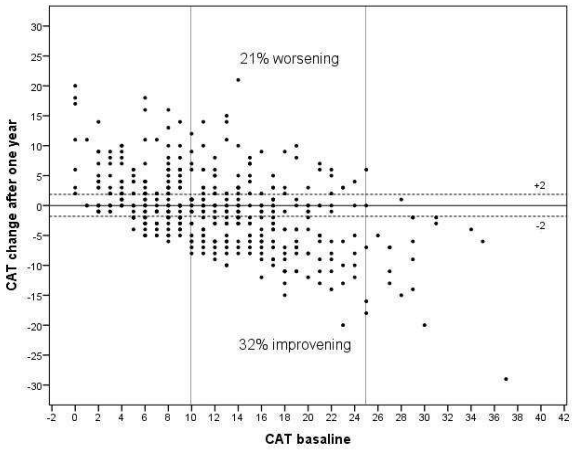
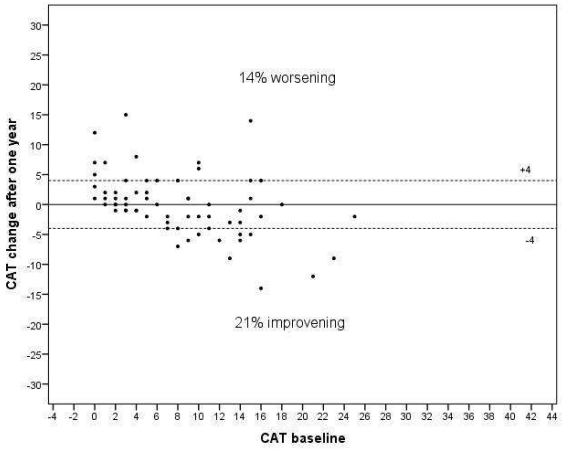
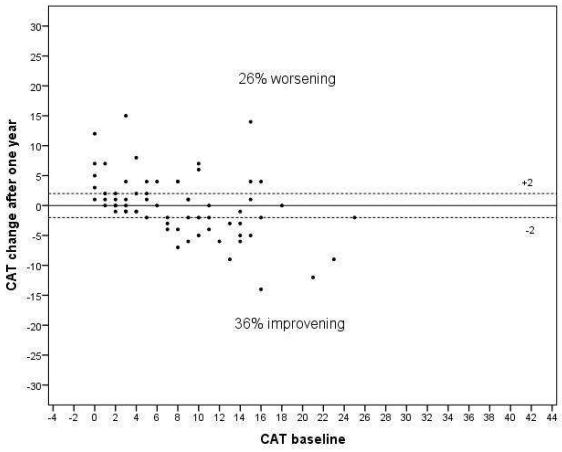


Figure 2. Panel A



Panel B

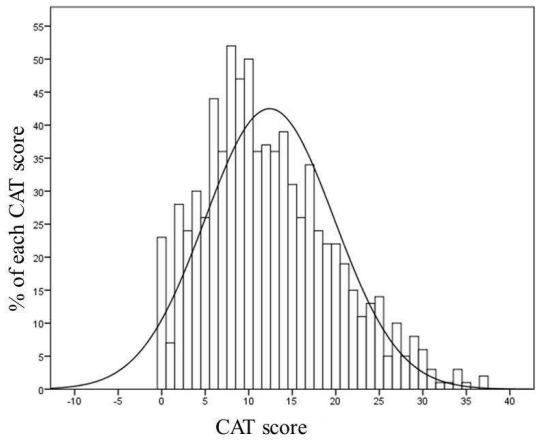


Appendix

Table 1. Clinical and physiological characteristics of the patients lacking one-year follow-up data

Clinical and Physiological Characteristics	All COPD patients n=383
Age in years (SD)	67 (10)
Gender (%male/%female)	(83/17)
BMI in kg/m^2 (SD)	28 (5)
Pack-years (IQR)	50 (32-70)
Current Smoking %	29
MMRC points (IQR)	1 (1-2)
FEV_1% (SD)	58 (20)
FVC% (SD)	84 (22)
FEV_1/FVC	51 (11)
GOLD obstruction levels I-II-III-IV %	17; 47; 25; 11
PaO_2 (SD)	64 (10)
DLCO % (IQR)	73 (56-90)
6MWD meters (IQR)	424 (360-490)
BODE index (IQR)	2 (1-4)
Charlson score (IQR)	1 (0-2)
CAT score (IQR)	12 (7-18)
Hospital admissions (IQR)	0 (0-0)
HAD anxiety score (IQR)	11 (6-15)
HAD depression score (IQR)	9 (4-12)

Figure 1. Appendix



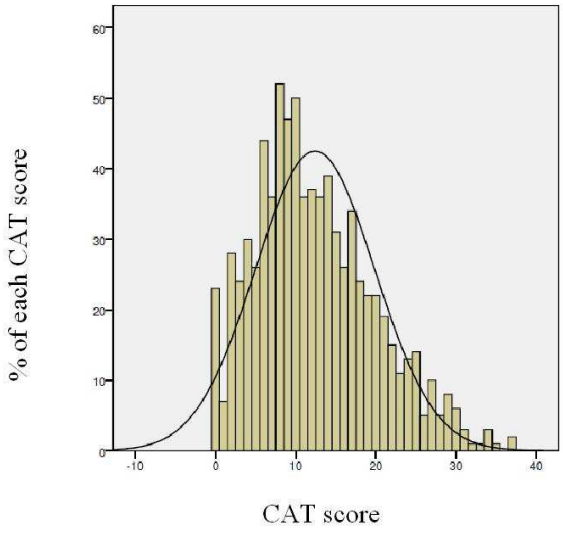
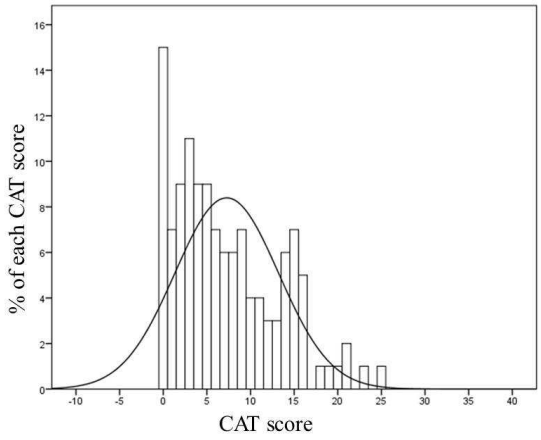


Figure 2. Appendix



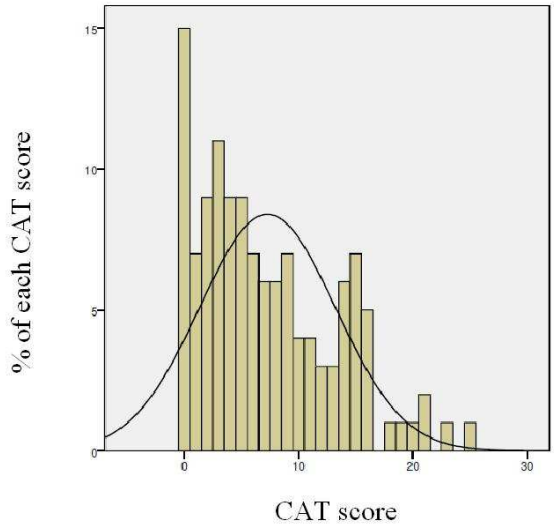


Figure legends

Manuscript Figures

Figure 1.

A: Changes in the CAT scores of COPD patients at one year compared to baseline (cut-off values ±4 points).

B: Changes in the CAT scores of COPD patients at one year compared to baseline (cut-off values ±2 points).

Figure 2.

A: Changes in the CAT scores of smokers without COPD at one year compared to baseline (cut-off values ±4 points).

B: Changes in the CAT scores of smokers without COPD at one year compared to baseline (cut-off values ±2 points).

Appendix Figures

Figure 1.

Distribution of different CAT scores in COPD patients.

Figure 2.

Distribution of different CAT scores in smokers.

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Comment [AP8]: It is not our policy to verify the relevance, accuracy, or format of the references. Once the text is finalized, please review the references to ensure they are properly presented.

Field Code Changed

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Dear Richard S. Irwin, MD, Master FCCP
Editor in Chief, CHEST

We really appreciate your comments as well as the reviewers' recommendations.
We believe they will substantially improve our manuscript. Following you will find a point by point answer to each one of the reviewers' comments:

Reviewer nº1

General comments
Interesting study that is the first to follow the "evolution" of CAT in a cohort of patients with COPD and very importantly in smokers controls without COPD. It is hard to get a central message, although it would seem to the reviewer that the most important message is that the MMRC performs equally well or at least similar to CAT. I feel the work could provide extra important information regarding the controls and the true meaning of the CAT.

Thank for thinking that our work is interesting. We do agree with this reviewer that the central message of our work is that the MMRC performs equally well or at least similar to CAT in stable COPD patients and smokers without airway obstruction. Although CAT probably provide additional symptomatic information of COPD patients most of this signal is already captured by the MMRC dyspnea scale. We now included this message in the discussion section of the manuscript (1st paragraph and in the conclusion section).

Specific Comments:
1. *One of the problems with "suggestive" tools to measure a disease progression (or improvement) is to try to anchor it to some outcome and to this reviewer it is interesting that there was no relationship to exacerbations. Was there some "outcome" to which we can relate the worsening of one year in the CAT to? Or for that matter those that got better? In other words what does an improvement of 4 units (or 2) means?*

We also found the lack of association between exacerbations (hospital admissions) and CAT changes at one year, an unexpected finding. Unfortunately the only important outcome available to anchor disease progression was hospital admissions.
It is important to note that in the present study only 40 COPD patients (9%) suffered at least one hospital admission during the follow up time. Those that had a hospital admission have a higher baseline CAT score compared with those that do not (15; 11 to 19 vs. 11; 7 to17, $p<0.05$), although this admission did not cause changes in their CAT score during the following year (-1; -4 to 3 vs 0; -4 to 3, $p>0.05$). This important information is now included in the results section of the manuscript. Unfortunately for the previously mentioned results we could not infer what does an improvement of 4 or 2 points in the CAT means and we just want to remind this reviewer that this was not the main goal of the present work. As we stated in the conclusions of the manuscript "further long term studies should confirm our findings and help elucidate the applicability of these tools in clinical practice".

2. *An important issue is the overlap in CAT between smokers with airflow obstruction and those without. I counted 23 of 66 subjects (1/3) whose CAT was higher than 10 points!!!.....if they do not have COPD (FEV1 and FEV1/FVC is normal) how can we say that the CAT is a "disease specific" QoL tool? Perhaps this comparison deserves a portion of the discussion. Further, a significant proportion of them got worse (14 or 26% depending on the cut) why? Perhaps the most important information in this work is the interpretation of the non-COPD smokers.*

The inclusion of a control group of smokers without COPD in our work is important.
Although we agree that probably CAT is not as "disease specific" as is claimed and that information regarding CAT scores in smokers without COPD is scarce, these were not the main goals of the present work. As mentioned by its developers, CAT is a health status tool to assess and quantify COPD patients' symptoms. A recent paper by Jones et al (*ERJ 2013; 42: 647-54)* showed that COPD patients with MMRC grade 0 could have modestly elevated health status scores (CAT 11.7±6.8). The present work data suggests that CAT capture a symptomatic domain that is also present in smokers without COPD and that changes over one year time period in a similar degree that happens in COPD patients. The symptomatic signal captured by CAT is consistent in smoker with and without COPD and behaves the

same as the one captured by the MMRC scale. Following your suggestion we now included a comment in the Discussion section of the manuscript.

Minor Comments

1. *Page 5 last section and page 6 first section, repeat the tests under description of the CHAIN and actual Methods. This could be condensed to avoid repetition.*

We are sorry, we did not understand this comment.

2. *Appendix Figures 1 and 2. The horizontal axis for both figures should read the same so that the values can be compared. It seems that the CAT in non-COPD smokers is not Gausian.*

Thank you for your suggestion, we now use the same values in the horizontal axis of both figures.
You are right, the non-COPD smokers have a non Gausian distribution.

Reviewer nº2

General comments

Moreover, this is an excellent study led by a panel of elite middle-aged, talented, Spanish chest physicians who have already contributed with relevant contributions in the past.

Thank you for appreciating our work and for your comment.

MAJOR CRITICISM

1) *In spite of the fact that the AA are very well aware of the 2011 GOLD Revision, they DO NOT present their data on COPD using the new assessment system. If they only counted hospitalizations and not exacerbations this could still be a surrogate for the new combined GOLD assessment of disease. The lack of the new GOLD assessment groups for this population is a shame and encourage them to consider this in order to extend and reinforce their main message.*

Following your suggestion we included the new GOLD classification distribution of our COPD population with their CAT scores. This information is now included in Table 1.

OTHER CRITICISMS/COMMENTS

2) *It has been recently shown (Jones P et al. ERJ 2013; 42: 647-54) that the MRC showed a clear relationship with health status scores. Although it might well be that their submission overlapped with this very recent publication, it should be very appropriate to include a comment and put their findings within the conclusions of this very recent paper.*

Thank you for your suggestion. We now included this reference and a comment in the discussion section.

3) *The study recorded hospitalizations (equal to 2 exacerbations according to the GOLD 2013 Update) and this is good news. What about exacerbations? Any news re: them?. If the data are available they should be also incorporated (see comment #2).*

Unfortunately the registration of self reported ambulatory exacerbations was not consistent along all participating centers. We do ask every investigator to register each patient hospitalization that was properly registered across all participating centers. We believe that this hard outcome allow us to classify our patients according to the new GOLD classification.

4) *Likewise, a summary of the anti-COPD therapeutic background should be added even though it is briefly mentioned in the paragraph devoted to the strengths and shortcomings of the study (2n part of pg 14).*

Thank you for your suggestion. We now included this important information in Table 1.

5) *The English writing needs a radical revision and be seriously updated as it is bit awkward in many places and detract from the quality of the scientific data. A major effort should be developed by the AA.*

As recommended professional editors performed a radical revision of the English writing (Paul Kretchmer, PhD Managing Director. San Francisco Edit).

6) *Tables and figures need to specify abbreviations and means or medians (with IQR), etc…, should be specified.*

Thank you. We now included in each table the appropriate abbreviations and mean or median with IQR as suggested.

7) *Last but not least, there is no disclosure at all of CoIs and this is not right and bad. This is an elite group of investigators that is very active in the Spanish chest academic community. As such, they lecture on many occasions and attend numerous and boards. This missing is unforgivable and should be completed at once.*

We asked each of the investigators to submit their COI forms disclosing all their conflicts of interest as requested.