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COPD Clinical Control: predictors and long-term follow-up of the CHAIN cohort

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Abstract

Background: Control in COPD is a dynamic concept that can reflect changes in patients' clinical status that may have prognostic implications, but there is no information about changes in control status and its long-term consequences.

Methods: We classified 798 patients with COPD from the CHAIN cohort as controlled/uncontrolled at baseline and over 5 years. We describe the changes in control status in patients over long-term follow-up and analyze the factors that were associated with longitudinal control patterns and related survival using the Cox hazard analysis.

Results: 134 patients (16.8%) were considered persistently controlled, 248 (31.1%) persistently uncontrolled and 416 (52.1%) changed control status during follow-up. The variables significantly associated with persistent control were not requiring triple therapy at baseline and having a better quality of life. Annual changes in outcomes (health status, psychological status, airflow limitation) did not differ in patients, regardless of clinical control status. All-cause mortality was lower in persistently controlled patients (5.5% versus 19.1%, p = 0.001). The hazard ratio for all-cause mortality was 2.274 (95% CI 1.394–3.708; p = 0.001). Regarding pharmacological treatment, triple inhaled therapy was the most common option in persistently uncontrolled patients (72.2%). Patients with persistent disease control more frequently used bronchodilators for monotherapy (53%) at recruitment, although by the end of the follow-up period, 20% had scaled up their treatment, with triple therapy being the most frequent therapeutic pattern.

Conclusions: The evaluation of COPD control status provides relevant prognostic information on survival. There is important variability in clinical control status and only a small proportion of the patients had persistently good control. Changes in the treatment pattern may be relevant in the longitudinal pattern of COPD clinical control. Further studies in other populations should validate our results.

Trial registration: Clinical Trials.gov: identifier NCT01122758.

Keywords: Chronic obstructive pulmonary disease, Control, Management

Background

Over the last decade, we have seen new evidence that has led to a new vision of chronic obstructive pulmonary disease (COPD) with the recognition of the multidimensional component and the concept of phenotype, which has meant a step forward on the road to personalized medicine and individualization of treatment [1–3].

Clinical practice guidelines in COPD establish the reduction of symptoms and minimization of risk as the main therapeutic objectives [4, 5]. These objectives make it necessary to adapt actions to the changes experienced

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by patients throughout their evolution, considering therapeutic success to mean achieving disease control.

The concept of COPD control is a new dimension that is proposed as a tool to help make therapeutic decisions and to modulate treatment [6, 7]. According to this proposal, control is defined as a state of low clinical impact and an absence of exacerbations maintained over time. The prespecified criteria for clinical control were described by Soler Cataluña [6] and have subsequently been evaluated in several studies [8–10].

Control in COPD is a dynamic concept that can reflect changes in patients' clinical status that may have prognostic implications. Some studies have observed a potential predictive value for poor outcomes and previous studies have shown that improvement in control status in the short term was associated with better outcomes, improvement in health status, less frequent exacerbations [11] and a longer delay until hospitalization [8]. However, this new concept requires validation in terms of its ability to predict outcomes and to provide additional clinical management insight. Given the limited information about the changes in clinical control in patients with COPD and the relationship with outcomes in those patients, we assessed clinical control at baseline and longitudinally (annually over 5 years) in patients participating in the CHAIN (COPD History Assessment in Spain) cohort, aiming to use CHAIN data to explore the changes and consequences of clinical control in a large cohort of patients with COPD.

We hypothesized that worse persistent control would relate to worse clinical outcomes. We followed longitudinal changes in physiological outcomes and patient-reported outcomes for health status, dyspnea and psychological status over 5 years in patients with COPD. The objectives of the present study were as follows: (1) to evaluate the degree of control in patients with COPD; (2) to provide information on the longitudinal evolution of clinical control and to determine the factors associated with worse control; (3) to validate the concept of control as a predictor of the risk of poor outcomes.

Methods

The CHAIN methodology has been extensively reported previously [12]. Briefly, CHAIN is a Spanish multicenter study carried out at pulmonary clinics. The main goal of this prospective observational study was to multidimensionally evaluate the progression of patients with COPD to better define the natural history and phenotypes of the disease. The recruitment period began on January 15, 2010, and is ongoing (Clinical Trials.gov: identifier NCT01122758). All participants signed the informed consent approved by the ethics committees of the participating centers (Hospital Universitario la Candelaria, Tenerife; Spain; IRB No. 258/2009). COPD was defined as a smoking history of at least 10 pack-years and an FEV1/FVC ratio less than 0.70 after inhaling 400 mg of albuterol. Patients were stable for at least 6 weeks and received optimal medical therapy. Exclusion criteria were uncontrolled comorbidities such as malignancy or other confounding diseases that could interfere with the study. The follow-up of the subjects included annual office visits and a telephone call was scheduled every 6 months to compile data about the number of exacerbations, clinical impact (health-related quality of life, subjective perception) and to verify the subject's vital status. COPD treatment followed national [5] and international guidelines. Data analyzed in the present study was obtained from the recruitment date through September 2018. Data was anonymized with hierarchical access control in order to guarantee that information was secure.

Clinical and physiological measurements

Trained staff obtained information on age, sex, body mass index (BMI) and smoking status at baseline and subsequent visits. Comorbidities were scored using the Charlson index [13]. Pulmonary function tests were performed according to international criteria [14, 15]. Dyspnea was evaluated using the modified Medical Research Council (mMRC) scale [16]. To evaluate health-related quality of life, the Spanish validated version of the COPD Assessment Test was used, which was self-administered by each patient under the supervision of the interviewer [17]. Anxiety and depression were evaluated using the Hospital Anxiety and Depression Scale (HAD) questionnaire [18]. Exacerbations were defined as a worsening of respiratory symptoms (dyspnea, cough or sputum) that required the use of antibiotics, systemic corticosteroids, or both, or symptoms that necessitated an emergency room visit or hospital admission. All-cause mortality was recorded using information obtained from the family and then confirmed by reviewing the medical record.

Clinical control status assessment

Control status was evaluated based on low clinical impact and stability, according to clinical criteria. A patient was considered controlled when disease was clinically stable and had low clinical impact, adjusted for the level of disease severity. Stability was defined as the absence of exacerbations in the previous 6 months plus no change or improvement in subjective perception referred to by the patient. Clinical impact was classified as low according to the information collected on the dyspnea (mMRC) scale (0–1 if FEV1 $\geq$ 50% and 0–2 if FEV1 < 50%) and rescue medication usage (not needing to use rescue inhalers regularly). The level of control was evaluated longitudinally during visits every 6 months. All participants had

a minimum of 12 months of follow-up with clinical control measurements. Based on the clinical control status evaluated at each visit during follow-up, the cohort was divided into three subgroups: persistently controlled, intermittently controlled and persistently uncontrolled patients.

Statistical analysis

Data is summarized as frequencies for categorical variables, median (5th–95th percentile) for ordinal or non-normal scale variables and mean ± SD for normally distributed scale variables. Comparisons were made between groups using Pearson's chi-squared test, the Kruskal–Wallis H test or the Mann–Whitney U test and one-way ANOVA or the t-test as appropriate.

Logistic regression was used to investigate factors contributing to clinical control in patients with COPD. A multivariate analysis considered variables with a statistically significant association ($p < 0.05$). In the multivariate model, we considered the following independent variables: age, pack-years, chronic bronchitis, dark sputum, eosinophils, Charlson index, FEV1, KCO, triple therapy, CAT score and HDAS depression.

We chose the best predictive model, which only had the variables CAT score and triple therapy because the others weren't as relevant to provide a good model. To select the model, we used the Akaike and Bayesian information criteria. The final set of variables was selected using a backward stepwise selection algorithm ($p < 0.10$ to remain in the model). The discrimination capacity of the predictive model was analyzed by calculating the area under the Receiver Operating Characteristics (ROC) curve along with a confidence interval at 95%.

An unpaired t -test was used to compare baseline data and annual changes between persistently controlled and persistently uncontrolled status. P values less than 0.05 were considered to be statistically significant.

A Kaplan–Meier analysis for survival due to all causes was performed in persistently uncontrolled patients. Finally, to predict the risk of death, we performed Cox proportional hazard regression analyses with the persistently controlled and uncontrolled subgroups. Significance was established as two-tailed $p < 0.05$.

Results

Participant characteristics

The population of this study was 798 patients with COPD from the CHAIN study who underwent a minimum of 12 months of follow-up with clinical control measurements. Stability was defined as the absence of exacerbations in the last 12 months during the recruitment visit. A total of 264 (33%) patients met the criteria for controlled status at recruitment. A comparison of controlled versus uncontrolled patient characteristics is presented in Table 1. Uncontrolled patients were older and had a higher body mass index and greater degree of airflow limitation, with more chronic bronchitis and the presence of dark sputum, more comorbidities and a poor quality of life. Regarding pharmacological treatment, uncontrolled patients more frequently used inhaled triple therapy.

Control status according to degree of airflow limitation at recruitment

Of a total of 300 patients with severe/very severe airflow limitation, 228 patients (76%) were defined as having low-impact disease and 100 patients (33.3%) had stable disease; therefore, 26.7% were defined as controlled patients. In mild/moderate COPD, there was a greater proportion of patients with stable disease: 262 patients (52.6%). Of these, 36.9% patients were defined as controlled (Table 2).

Prevalence and longitudinal follow-up of clinical control

Over a period of 5 years, the proportion of persistently controlled patients with COPD was 16.8%, persistently uncontrolled patients accounted for 31.1% and intermittently controlled patients represented 52.1% (Fig. 1). There were significant differences in baseline clinical and physiological characteristics between the persistently controlled patients with COPD compared to those who were persistently uncontrolled or intermittently controlled (Table 3).

During this follow-up over 5 years, the median follow-up time in the persistently controlled patient group was 2.4 (1.7) years, 4.2 (1.2) years in the intermittently controlled group and 1.8 (1.3) years for persistently uncontrolled patients. The loss of patients during follow-up was 35.7%.

Factors accounting for persistently controlled patient status

A backward logistic multivariate model was developed with persistent control as the independent variable and the dependent variables were clinical and demographic variables, which were not related to the definition of control. The adjusted model showed that triple therapy (OR, 0.3026; 95% CI, 0.1776–0.51573; $p < 0.001$) and CAT (OR, 0.9399; 95% CI 0.9032–0.9781; $p < 0.001$) were independently and significantly associated with persistently controlled status. The AUC was 0.7029 (95% CI, 0.64209–0.76367).

Changes in treatment patterns for COPD in persistently controlled and uncontrolled patients

Regarding pharmacological treatment, persistently uncontrolled patients more frequently used inhaled corticosteroids, particularly as part of triple therapy (72.2%). Of these, 71.8% showed no changes in

Table 1 Characteristics of the study population according to control status at recruitment

	Total n = 798	Controlled n = 264 (33%)	Uncontrolled n = 534 (66.8%)	P-value
Age (years), m (SD)	65.7 (10.5)	62.8 (11.6)	67.2 (9.7)	< 0.001
Gender (male), n (%)	663 (82.9)	226 (85.6)	435 (81.5)	0.144
Active smoker, n (%)	229 (28.6)	92 (34.8)	136 (25.5)	0.006
Tobacco exposure, pack-years, m (SD)	56.3 (28.7)	52.6 (25.8)	58.2 (29.9)	0.018
BMI (kg/m^2), m (SD)	28.0 (5.1)	27.2 (4.7)	28.4 (5.2)	0.001
Post-bronchodilator FEV1 (%), m (SD)	60.2 (25.9)	68.0 (20.8)	56.4 (27.3)	< 0.001
Post-bronchodilator FEV1 (mL), m (SD)	1629.9 (690.4)	1944.0 (746.4)	1476.6 (602.7)	< 0.001
K_{CO}%, median (P25-P75)	73 (51–92.9)	76.05 (60–95)	70 (46–91)	0.002
Chronic bronchitis, n (%)	466 (58.2)	132 (50.0)	334 (62.5)	0.001
Dark sputum, n (%)	122 (15.2)	29 (11.0)	93 (17.4)	0.018
Bronchial asthma, n (%)	26 (3.3)	11 (4.2)	15 (2.8)	0.309
Eosinophils (%), median (P25-P75)	2.3 (1.5–3.6)	2.4 (1.6–3.6)	2.3 (1.5–3.6)	0.666
Charlson index, m (SD)	1.2 (1.5)	1.0 (1.5)	1.3 (1.5)	0.009
Treatment, n (%)				
Inhaled triple therapy	454 (56.8)	105 (39.8)	348 (65.2)	< 0.001
Theophylline	73 (9.1)	8 (3.0)	65 (12.2)	< 0.001
Influenza vaccine	430 (53.7)	102 (38.6)	328 (61.4)	< 0.001
LTOT	104 (13.0)	9 (3.4)	95 (17.8)	< 0.001
Home ventilation	41 (5.1)	9 (3.4)	32 (6.0)	0.120
CAT score, m (SD)	12.6 (7.2)	10.3 (6.5)	13.8 (7.3)	< 0.001
Anxiety, HDAS, m (SD)	11.1 (4.8)	11.06 (4.8)	11.19 (4.9)	0.576
Depression, HDAS, m (SD)	8.6 (4.7)	8.2 (4.5)	8.9 (4.7)	0.088

BMI body mass index, *FEV1* forced expiratory volume in 1 s, K_{CO} carbon monoxide transfer coefficient, Inhaled triple therapy: long-acting beta-2 agonist (LAMA) with corticosteroids (ICS) with long-acting antimuscarinic agent (LAMA), *LTOT* long-term oxygen therapy, *CAT* COPD Assessment Test, *HDAS* Hospital Anxiety and Depression Scale

Table 2 Factors accounting for the control status of patients with COPD by level of severity at recruitment

	Total (n = 798)	FEV1 ≥ 50% (n = 498)	FEV1 < 50% (n = 300)	P-value
Clinical impact				< 0.001
Low, n (%)	546 (68.4)	318 (63.9)	228 (76.0)	
High, n (%)	252 (31.6)	180 (36.1)	72 (24.0)	
Stability				
Stable, n (%)	362 (45.4)	262 (52.6)	100 (33.3)	
Not stable, n (%)	436 (54.6)	236 (47.4)	200 (66.7)	< 0.001
Control status				
Controlled, n (%)	264 (33.0)	184 (36.9)	80 (26.7)	
Uncontrolled, n (%)	534 (67.0)	314 (63.1)	220 (73.3)	0.003

FEV1 forced expiratory volume in 1 s

treatment during follow-up, 13.3% underwent de-escalation and 14.9% escalation in treatment. Patients who were persistently controlled more frequently used bronchodilators, particularly monotherapy (53%), followed by triple therapy (37%). Of these, 5.2% de-escalated treatment and 19.4% scaled up their treatment, with triple therapy being the most frequent therapeutic pattern (Fig. 2).

Outcomes in patients with COPD according to longitudinal control status pattern

Longitudinal changes in clinical outcomes (health status, psychological status and airflow limitation) according to a persistently uncontrolled or controlled longitudinal control status pattern are shown in Table 4.

Regarding the baseline data, persistently uncontrolled patients were significantly worse as rated by CAT and HDAS scores and FEV1 levels. However, there were no significant differences in annual changes in outcomes between persistently controlled and uncontrolled patients.

Regarding survival, there were 94 (24.6%) deaths in 382 patients with a persistently uncontrolled or controlled status pattern, of which 73 (19.1%) were persistently uncontrolled and 21 (5.5%) were persistently controlled (p = 0.001). The Kaplan–Meier analysis for all-cause mortality showed that persistently uncontrolled status was associated with a shorter survival time (3.58 years; 95% CI, 3.31–3.85) than persistently controlled status

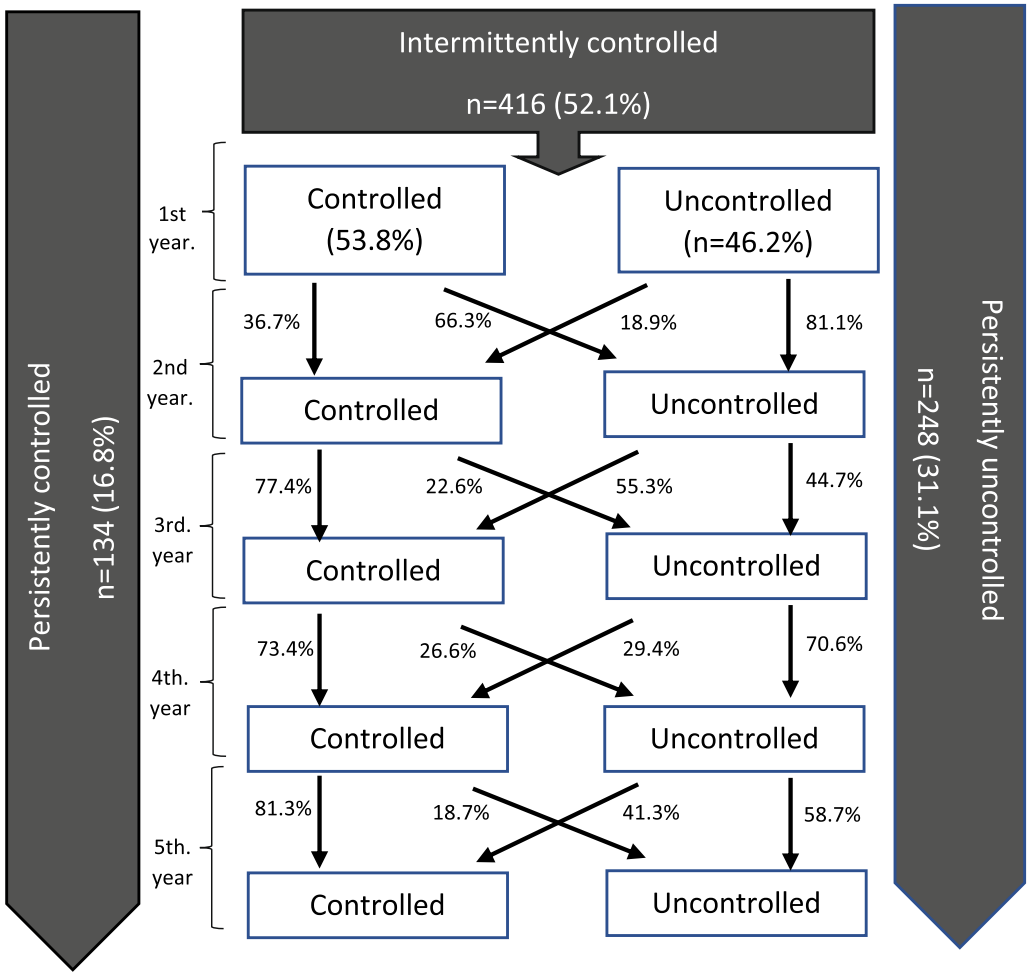

Fig. 1 The evolution of the clinical control pattern every year

(4.43 years; 95% CI, 4.19–4.67) (Fig. 3). The hazard ratio for all-cause mortality was 2.274 (95% CI, 1.394–3.708; p = 0.001).

Discussion

This study provides novel information on the longitudinal evolution of clinical control in a large cohort of patients with COPD as well as factors associated with persistent clinical control and their clinical consequences.

The main results of our study indicate three things. First, in the population with COPD, there were frequent changes in clinical control status. Only a small percentage of patients could be classified as persistently controlled over the following 5 years. Secondly, the main variables associated with persistent clinical control are a better quality of life as evaluated by the CAT and not requiring inhaled triple therapy. Finally, the clinical consequences of persistent clinical control are observed in the risk of death.

The current analysis describes the progression of clinical control in a well-characterized COPD cohort over a period of 5 years as monitored at pulmonary clinics. In our study, only 33% of patients with different degrees of COPD severity met the criteria required to be considered controlled at recruitment. In the mild or moderate subgroup of patients, 36.9% were defined as controlled whereas only 26.7% of severe patients were defined as controlled. These results are similar to those obtained in an international multicenter study, obtaining an overall control value of 32% using the clinical evaluation of control criteria [10]. Another prospective study showed similar results, with only 27.5% [8] of patients being considered controlled. However, it should be mentioned that unlike these studies, almost 40% of the sample analyzed in our study had severe airflow obstruction. In addition, the level of physical activity referred to by the patient and the presence of sputum purulence were not included in the clinical impact assessment. In our study population,

Table 3 Baseline characteristics of longitudinal clinical control patterns

	Persistently controlled (n = 134)	Intermittently controlled (n = 416)	Persistently uncontrolled (n = 248)	P-value
Demographics and clinical data				
Male, n (%)	117 (87.3)	336 (80.6)	209 (84.3)	0.153
Age (years), m (SD)	63.2 (9.7)[a,b]	64.9 (10.9)	68.5 (9.9)	< 0.001
Pack-years, m (SD)	53.5 (26.1)	54.6 (28.4)	60.8 (30.2)[c]	0.013
Active smoker, n (%)	48 (35.8)	115 (27.6)	66 (26.6)	0.128
BMI (kg/m^2), m (SD)	27.1 (4.6)	28.0 (4.8)	28.5 (5.6)	0.060
Chronic bronchitis, n (%)	71 (53.0)[d]	233 (55.9)	162 (65.3)	0.022
Dark sputum, n (%)	15 (11.2)[d]	54 (12.9)	53 (21.4)[c]	0.005
Bronquial asthma, n (%)	5 (3.7)	9 (2.2)	12 (4.8)	0.164
Eosinophils (%), median (P25-P75)	2.6 (1.6–3.9)[d]	2.4 (1.6–3.6)	2.1 (1.3–3.3)[c]	0.002
Charlson index, m (SD)	1.2 (1.6)	1.0 (1.4)	1.5 (1.6)[e]	0.002
Physiology				
FEV1 (L), median (P25-P75)	2050 (1467–2505)[b]	1600 (1190–2050)[a]	1360 (940–1730)£	< 0.001
FEV1%pred, median (P25-P75)	72 (55–88)[b]	60 (46–74)[a]	51 (39–63)£	< 0.001
FVC (L), median (P25-P75)	3585 (2847–4380)[b]	3100 (2450- 3710)[a]	2745 (2197–3227)[e]	< 0.001
FVC %pred, median (P25-P75)	94 (80–110)[b]	84 (71–101)[a]	75 (63–90)[e]	< 0.001
FEV1/FVC, median (P25-P75)	58 (49–65)[b]	54 (44–63)[f]	51 (41–60)[c]	< 0.001
K_{CO}%, median (P25-P75)	79.5 (62.5–99.7)[b]	72.6 (52.2–92.8)[f]	66 (41–85.2)[c]	< 0.001
Treatment				
Triple therapy, n (%)	50 (37.3)[b]	226 (54.2)[f]	178 (71.8)[e]	< 0.001
Influenza vaccine, n (%)	50 (37.3)[b]	213 (51.1)[f]	167 (67.3)[c]	< 0.001
LTOT, n (%)	3 (2.2)[b]	37 (8.9)	64 (25.8)[e]	< 0.001
VMNI, n (%)	5 (3.7)[b]	12 (2.9)	24 (9.7)[c]	< 0.001
CAT score, median (P25-P75)	8 (5–14.2)[b,f]	11 (7–16)	14 (9–21)[e]	< 0.001
HDAS anxiety score, median (P25-P75)	11 (6–15)	12 (8–15)	12 (8–15)	0.576
HDAS depression score, median (P25-P75)	8.0 (4.6)	8.5 (4.5)	9.3 (4.9)	0.048
Follow-up time (years), m (SD)	2.4 (1.7) [d]	4.2 (1.2)[a]	1.8 (1.3)[e]	< 0.001

BMI body mass index, *FEV1* forced expiratory volume in 1 s, *FVC* forced vital capacity, K_{CO} carbon monoxide transfer coefficient, *Triple therapy* long-acting beta-2 agonist (LAMA) with corticosteroids (ICS) with long-acting antimuscarinic agent (LAMA), *LTOT* long-term oxygen therapy, *CAT* COPD Assessment Test, *HDAS* Hospital Anxiety and Depression Scale

[a] $p < 0.001$ persistently controlled compared with intermittently controlled

[b] $p < 0.001$ persistently controlled compared with persistently uncontrolled

[c] $P \leq 0.05$ persistently uncontrolled compared with intermittently controlled

[d] $P < 0.05$ persistently controlled compared with persistently uncontrolled

[e] $P \leq 0.001$ persistently uncontrolled compared with intermittently controlled

[f] $p \leq 0.05$ persistently controlled compared with intermittently controlled

the use of rescue medication as a high impact criterion was present in 70% of patients classified as having a high clinical impact. This is a widely justified criterion if we fear that the increased use of rescue medication has been associated with an increased risk of future exacerbations [19]. However, sputum color has shown the lowest discriminative property for the level of impact [10]. In our study, dark sputum was present in 11.2% of persistently controlled patients compared to 21.4% of persistently uncontrolled patients ($p = 0.015$).

Regarding the longitudinal clinical control patterns, we found that there were frequent changes in clinical control status, with 42.1% of patients changing control status during the observation period. Few studies have shown data on the progression of clinical control in COPD. A recent international study showed that 53.7% of patients

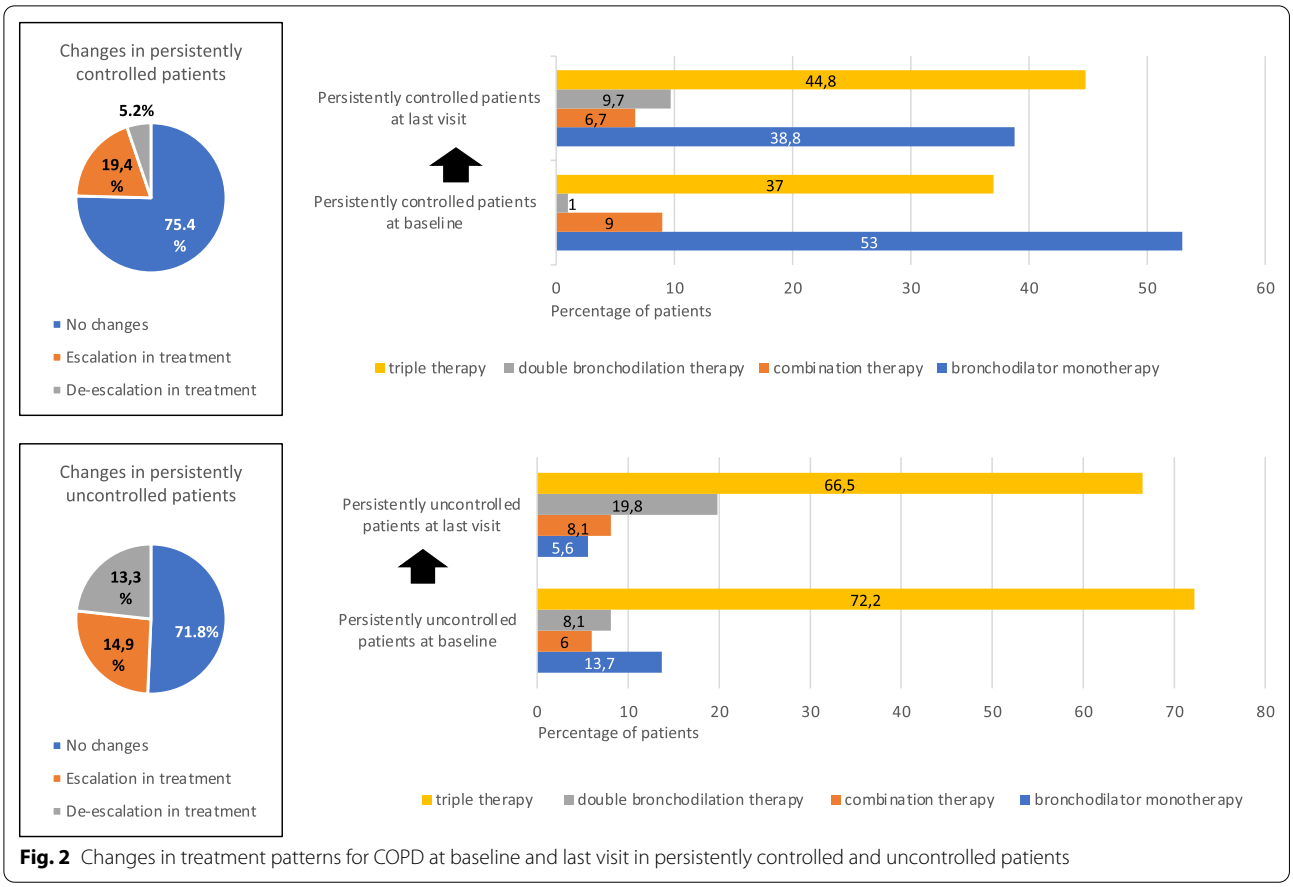

Fig. 2 Changes in treatment patterns for COPD at baseline and last visit in persistently controlled and uncontrolled patients

Table 4 Comparisons of baseline data and annual changes between persistently controlled patients and persistently uncontrolled patients during 5 years of follow-up

Characteristics	Baseline data		Annual changes (/year)	
	Persistently controlled	Persistently uncontrolled	Persistently controlled	Persistently uncontrolled
CAT score	9.6 (5.9)	15.5 (7.8)*	0.0 (− 1.0–1.7)	0.2 (− 2.5–3.0)
HDAS anxiety	10.7 (4.8)	11.1 (4.8)	0.0 (− 1.0–2.0)	0.3 (− 1.0–3.0)
HDAS depression	8.0 (4.6)	9.3 (4.9)*	0.5 (− 0.3–2.3)	0.0 (− 1.6–3.0)
FEV1, %pred	71.2 (20.8)	52.3 (19.9)*	0.3 (− 2.8–3.0)	− 0.2 (− 3.4–1.5)

CAT COPD Assessment Test; *HDAS* Hospital Anxiety and Depression Scale; *FEV1* forced expiratory volume in 1 s

Data is presented as mean (SD) or median (5th–95th percentile)

*Statistically significant differences between persistently uncontrolled and persistently controlled patients ($p < 0.05$)

changed control status, 29.8% of patients remained controlled and 16% persistently uncontrolled during an 18-month follow-up [20]. These results are not comparable to our analysis, where follow-up is greater. Another observational study analyzed changes in control over a 3-month period and showed that 29.2% changed their control status [11]. In this study, these changes were significantly more frequent than changes in GOLD stage, risk level or in phenotype, which further suggests that control status could be used as a supplementary assessment tool for decision-making at each medical visit, similar to the evaluation of asthma control. Table 5 summarizes studies that examined the proportion of controlled patients and changes in clinical control.

In our study, 31.1% of patients had persistently poor disease control during follow-up and only a small proportion (16.8%) of patients had persistently good control. We found that persistently controlled patients were

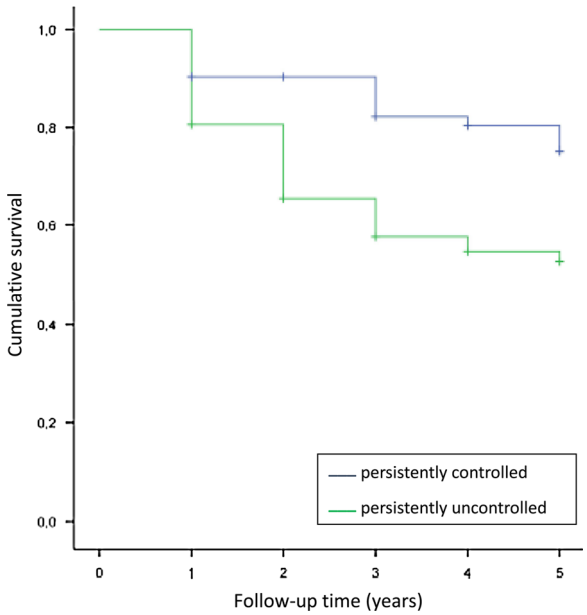

Fig. 3 Kaplan–Meier analysis for all-cause mortality. Persistently controlled patients were associated with a longer survival time than persistently uncontrolled patients

younger, had less frequent chronic bronchitis, a lower degree of airflow obstruction, lower involvement in the diffusion test, a better quality of life as evaluated by the CAT and a higher level of peripheral eosinophilia. In previous studies [9, 10, 20, 21], the presence of chronic bronchitis, female sex, lower BMI and a history of prior exacerbations were identified as variables that were significantly associated with poor control. In addition, poor lung function and worse health status were demonstrated to be the best predictors of the risk of future exacerbations and were associated with a significant increase in the risk of mortality [22]. However, our study found that sex, tobacco history, BMI and comorbidities such as bronchial asthma or anxiety and depression were similar in patients, irrespective of longitudinal clinical control status. These results are similar to those reported by Calverley et al. [23], who showed that tobacco history and BMI were similar in individuals with frequent exacerbations and those who never experienced an exacerbation over the 2 years of follow-up. However, continued smoking in patients with COPD has been associated with higher disease impact and increased exacerbations [24]. In addition, former smokers had a significantly reduced risk of death and hospitalization compared to active smokers [25]. In our study, the majority of the patients maintained their tobacco use status. There were no differences in longitudinal clinical control patterns regarding smoking cessation during follow-up.

The use of maintenance respiratory therapy is usually thought to reduce risk. However, data reported in the ECLIPSE [26] and SPIROMICS [27] cohorts reported that patients did shift from high-risk to low-risk groups over time, though the reasons for doing so were unclear. In any case, adequate therapy seems to improve the ratio of infrequent to frequent exacerbators over time [28–30]. In our study, triple therapy at baseline was less frequent in persistently controlled patients (37%) versus persistently uncontrolled patients (72.2%). At the end of the follow-up period, 20% of persistently controlled patients had scaled up their treatment, with triple therapy being the most frequent therapeutic pattern. On the contrary, in persistently uncontrolled patients, 13.3% had increased their pharmacological treatment while 15% had decreased it, observing a decrease in triple therapy and an increase in double bronchodilator therapy. These results for the changes in treatment pattern according to longitudinal control status provide interesting information, showing an increase in triple therapy in persistently controlled patients. In our study, not requiring triple therapy at baseline and having a better quality of life were identified as variables that were significantly associated with persistent disease control. A likely explanation why patients are given triple therapy to prevent exacerbations is because they are believed to be progressing more poorly and are thus more likely to relapse in the future, irrespective of any positive effect of their therapy.

A previous publication described control status as a marker of increased risk of poor outcomes in the short term. According to data reported in the studies by Soler-Cataluña et al. [8] and Barrecheguren et al. [31], controlled patients showed a lower risk of complications, with a longer delay until the first combined event, the first exacerbation and hospitalization, as well as better health status at 1 year of follow-up. However, they did not report any significant difference in survival between controlled and uncontrolled patients. In the Miravitlles et al. [20] study, uncontrolled patient visits resulted in a highly significant increased risk of poor outcomes over the next 6 months, with an OR of 4.25 for hospitalization due to exacerbation compared to controlled patient visits. In addition, it has been reported that control status determined by clinical criteria was a better predictor of exacerbations compared to CAT criteria (AUC: 0.67 vs 0.57) [32]. Our analysis showed that although a further worsening in CAT and HDAS scores and FEV1 levels was observed in persistently uncontrolled patients, there were no significant differences in annual changes between persistently controlled and uncontrolled subjects. However, we found that persistently controlled patients had a significantly lower risk of death than those who were persistently uncontrolled. In our study, there were 94 (24.6%)

Table 5 Summary of studies that examined the distribution of control status, changes in clinical control and evaluated the predictive value of control

	Number of patients Study design	Investigation objective	Study findings
Baloira A et al. [9] (2016)	481 patients Spanish cross-sectional multicenter study (primary care vs respiratory care)	Distribution of control status	36.8% of patients were controlled
Nibber A [9] et al. (2017)	2788 patients Retrospective observational cohort study	To validate the concept of control Distribution of control status	4.5% of patients were controlled Time to first exacerbation was longer for controlled patients ($p < 0.001$)
Miravitlles M [10] et al. (2018)	314 patients Multicenter prospective observational study	To validate concept of control Distribution of control status	32% of patients were controlled
Soler-Cataluña JJ [8] et al. (2018)	265 patients Spanish multicenter prospective observational study	To validate "modified" control criteria To evaluate predictive value of control	61.5% of patients were controlled The time to the first combined event (emergency room visit, hospitalization, or death) was significantly greater in controlled patients ($p < 0.001$)
Barrecheguren [31] et al. (2020)	2044 patients Multicenter double-blind SPARK study	To validate the prospective value of control	20% of patients were controlled The rate of exacerbations was lower in controlled patients (OR 0.56, $p < 0.0001$) and time to first exacerbation was significantly delayed
Miravitlles [32] et al. (2020)	307 patients International, multicenter study	To validate the concept of control in COPD	65% of patients were controlled Time to first exacerbation was significantly delayed for controlled patients
Soler-Cataluña JJ [11] et al. (2020)	354 patients Prospective multicenter observational study	To compare changes in control over a 3-month period with changes in risk level and GOLD stage	50.3% of patients were controlled Changes in control over a 3-month period was 29.3%
Miravitlles M [20] et al. (2020)	267 patients International multicenter study Follow-up for 18 months	To describe the changes in control status during follow-up (18 months) and the predictive value of control (6 months)	During 18 months of follow-up, 29.8% of patients remained controlled, 16% persistently uncontrolled and the remaining 53.7% changed control status during follow-up

deaths in 5 years of follow-up, a mortality rate similar to that of the Spanish PAC-EPOC cohort (3.6 fatal events/year/100 patients) [33]. Specifically, there were 73 deaths in persistently uncontrolled patients and 21 in controlled patients. Our analysis further confirmed that subjects who died were older, had a greater degree of airway obstruction, and had worse health status than those who survived. These results are similar to those reported by Oga et al [34]. Changes in mortality occur after the first year and tend to increase in the second year, which could explain why this was not observed in previous studies [8].

Our study extends our understanding of the concept of control in COPD and its possible application in clinical practice. Previous studies have found that improvement in control status in the short term was associated with better outcomes, with a reduced frequency of exacerbations and improved health status. Our results show that patient control status frequently changes in subsequent clinical visits and we observed that there are long-term consequences: persistently uncontrolled patients have higher mortality. This is the first study to show the impact of control status on long-term mortality. This increased risk justifies the use of control evaluation as a warning sign to foster more careful evaluation of the patients and the adoption of therapeutic measures.

This study has several strengths. It included a large number of well-characterized patients being treated for COPD in "real life" with a long follow-up time, providing invaluable information on outcomes which is not usually available in most pharmacological trials. However, it is necessary to keep in mind some characteristics of the cohort in order to correctly interpret our results. The CHAIN cohort was obtained from an observational study of patients visiting pulmonary clinics and not from general medical practice. In fact, patients with COPD treated in a specialized clinic have been found to have better clinical control [35]. In the Baloira et al. [36] study, patients at the primary care level were more poorly controlled. However, our cohort included a large population of patients with different degrees of severity (16.4% mild, 46% moderate, 26.8% severe and 10.8% very severe). Another consideration is that few women were included in the cohort and the findings reported in relation to this must be interpreted with caution. There was also a loss of patients during follow-up that could result in measurement bias. Regarding the limitations of the present study, it is important to consider that the probability of change in clinical control status will be greater for a longer follow-up period. In our analysis, a minimum of 1 year of follow-up was established as a criterion to define the longitudinal pattern since our objective was to explore the differences between persistently controlled and uncontrolled classifications and to analyze their prognostic implications such as mortality. In this sense, it is worth mentioning that in our analysis, there was a higher number of exitus in the first year of follow-up: 48 patients defined as persistently uncontrolled and 13 as persistently controlled. In addition, if we establish a minimum of 3 years of follow-up as a criterion, the majority of patients (76.8%) would be classified as intermittently controlled. Therefore, we defined the longitudinal pattern with a minimum of 1 year of follow-up, also keeping in mind that this criterion perhaps most closely resembles ordinary clinical practice. Another limitation is that this was not an interventional study, we could not investigate whether a change in treatment could modify control status and influence the outcomes. This has to be demonstrated in future interventional studies.

Conclusions

This is the first study to show the impact of control status on long-term mortality. There is important variability in clinical control status and only a small proportion of patients had persistently good control. The study highlights the significantly increased risk of death in uncontrolled patients. Consequently, control criteria should be incorporated into clinical practice as a simple tool to help reassess patients with COPD at each follow-up visit. Further studies in other populations should validate our results.

Abbreviations

AECOPD: Acute exacerbations of COPD; BMI: Body mass index; CATTM: COPD assessment test; COPD: Chronic obstructive pulmonary disease; ICS: Inhaled corticosteroids; IQR: Interquartile range; LABA: Long-acting beta-2 agonists; LAMA: Long-acting antimuscarinic agents; mHealth apps: Health-related mobile applications; mMRC: Modified Medical Research Council.

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Authors' contributions

MCR, JLRH: conception and design, recruitment of patients, analysis and interpretation and drafting the manuscript for important intellectual content. JPT, JMM, CMG, AF, BC, GPB, IS, NFC, CC: conception and design, recruitment of patients, analysis and interpretation. JLL-C: conception and design, analysis and interpretation and drafting the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Availability of data and materials

Data can be shared upon request by writing to mcallerubio@gmail.com.

Ethics approval and consent for participation

All participants signed the informed consent approved by the ethics committees of the participating centers (Hospital Universitario la Candelaria, Tenerife;

Spain; IRB No. 258/2009). This manuscript does not contain any individual person's data.

Consent for publication
Not applicable.

Competing interests
MCR has received speaking fees from Boehringer Ingelheim, AstraZeneca, GlaxoSmithKline, Menarini and Novartis, and consulting fees from GlaxoSmith¬Kline, Gebro Pharma and Novartis. There is no real or perceived conflict of interest between these sources and the present paper. JLRH has received speaking fees from Boehringer Ingelheim and Gebro Pharma. There is no real or perceived conflict of interest between these sources and the present paper. JPT does not have a real or perceived conflict of interest. JMM does not have a real or perceived conflict of interest. CMG does not have a real or perceived conflict of interest. AF does not have a real or perceived conflict of interest. BC reports grants, personal fees and non-financial support from GSK; grants, personal fees and non-financial support from Chiesi; grants, personal fees and non-financial support from Astrazeneca; grants from Menarini and Boehringer-Ingheilm; non-financial support from Novartis; personal fees and non-financial support from Sanofi, outside the submitted work. GPB reports grants, personal fees and non-financial support from GSK, Boehringer Ingelheim, Chiesi and Orion Pharma. There is no real or perceived conflict of interest between these sources and the present paper. IS does not have a real or perceived conflict of interest. NFC does not have a real or perceived conflict of interest. JLLC reports personal fees and non-financial support from AstraZeneca; grants, personal fees and non-financial support from Boehringer Ingelheim; grants, personal fees and non-financial support from Chiesi; personal fees and non-financial support from CSL Behring; grants, personal fees and non-financial support from Esteve; personal fees and non-financial support from Ferrer; grants, personal fees and non-financial support from GebroPharma; grants, personal fees and non-financial support from GlaxoSmithKline; grants, personal fees and non-financial support from Grifols; grants, personal fees and non-financial support from Menarini; grants, personal fees and non-financial support from Novartis; grants, personal fees and non-financial support from Rovi; and grants, personal fees and non-financial support from Teva, outside the submitted work. CC has received speaker fees from Novartis, Menarini, Boehringer Ingelheim, AstraZeneca, GlaxoSmithKline and Teva, and consulting fees from AstraZeneca, Esteve, GlaxoSmithKline and Novartis.

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References

1. Agusti A, MacNee W. The COPD control panel: towards personalised medicine in COPD. Thorax. 2013;68(1):687–90.
2. Miravitlles M, Soler-Cataluña JJ, Calle M, Soriano JB. Treatment of COPD by clinical phenotypes: putting old evidence into clinical practice. Eur Respir J. 2013;41(6):1252–6.
3. McDonald V, Higgins I, Wood LG, Gibson PG. Multidimensional assessment and tailored interventions for COPD: respiratory utopia or common sense? Thorax. 2013;68(7):691–4.
4. Vogelmeier CF, Criner GJ, Martínez FJ, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report: GOLD executive summary. Arch Bronconeumol. 2017;53(3):128–49.
5. Miravitlles M, Soler-Cataluña JJ, Calle M, et al. Spanish COPD guidelines (GesEPOC). 2017. Pharmacological treatment of stable chronic obstructive pulmonary disease. Arch Bronconeumol. 2017;53(6):324–335.
6. Soler-Cataluña JJ, Alcázar B, Miravitlles M. The concept of control of COPD in clinical practice. Int J Chron Obstruct Pulmon Dis. 2014;9:1397–405.
7. Soler-Cataluña JJ, Alcazar-Navarrete B, Miravitlles M. The concept of control in COPD: a new proposal for optimising therapy. Eur Respir J. 2014;44(4):1072–5.
8. Soler-Cataluña JJ, Marzo M, Catalán P, Miralles C, Alcazar B, Miravitlles M. Validation of clinical control in COPD as a new tool for optimizing treatment. Int J Chron Obstruct Pulmon Dis. 2018;13:3719–31.
9. Nibber A, Chisholm A, Soler-Cataluña JJ, Alcazar B, Price D, Miravitlles M. Validating the concept of COPD control: a real-world cohort study from the United Kingdom. COPD. 2017;14(5):504–12.
10. Miravitlles M, Sliwinski P, Rhee CK, et al. Evaluation criteria for clinical control in a prospective, international, multicenter study of patients with COPD. Respir Med. 2018;136:8–14.
11. Soler-Cataluña JJ, Alcázar B, Marzo M, Pérez J, Miravitlles M. Evaluation of changes in control status in COPD: an opportunity for early intervention. Chest. 2020;157:1138–46.
12. Lopez-Campos JL, Peces-Barba G, Soler-Cataluna JJ, et al. Chronic obstructive pulmonary disease history assessment in Spain: a multidimensional chronic obstructive pulmonary disease evaluation: study methods and organization. Arch Bronconeumol. 2012;48(12):453–9.
13. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373–83.
14. American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. Am Rev Respir Dis. 1991;144:1202–18.
15. Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J. 2005;26:720–35.
16. Mahler DA, Weels CK. Evaluation of clinical methods for rating dyspnea. Chest. 1988;93:580–6.
17. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline LN. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009;34(3):648–54.
18. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67:361–70.
19. Jenkins CR, Postma DS, Anzueto AR, et al. Reliever salbutamol use as a measure of exacerbation risk in chronic obstructive pulmonary disease. BMC PulmMed. 2015;15:97.
20 Miravitlles M, Sliwinski P, Rhee CK, et al. Changes in control status of COPD over time and their consequences: a prospective international, study. Arch Bronconeumol. 2020a. https://doi.org/10.1016/j.arbres.2020.06.003.
21. Busch R, Han MK, Bowler RP, et al. Risk factors for COPD exacerbations in inhaled medication users: the COPDGene study biannual longitudinal follow-up prospective cohort. BMC Pulm Med. 2016;16:28.
22. Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med. 2010;363(12):1128–38.
23. Calverley PM, Tetzlaff K, Dusser D, et al. Determinants of exacerbation risk in patients with COPD in the TIOSPIR study. Int J Chron Obstruct Pulmon Dis. 2017;12:3391–405.
24. Riesco JA, Alcazar B, Trigueros JA, Campuzano A, Perez J, Lorenzo JL. Active smoking and COPD phenotype: distribution and impact on prognostic factors. Int J Chron Obstruct Pulmon Dis. 2017;12:1989–99.
25. Josephs L, Culliford D, Johnson M, Thomas M. Improved outcomes in exsmokers with COPD: a UK primary care observational cohort study. Eur Respir J. 2017;49(5):1602114.

26. Donaldson GC, Müllerova H, Locantore N, et al. Factors associated with change in exacerbation frequency in COPD. Respir Res. 2013;14:79.
27. Han MK, Quibrera PM, Carretta EE, et al. Frequency of exacerbations in patients with chronic obstructive pulmonary disease: an analysis of the SPIROMICS cohort. Lancet Respir Med. 2017;5(8):619–26.
28. Vestbo J, Fabbri L, Papi A, et al. Inhaled corticosteroid containing combinations and mortality in COPD. Eur Respir J. 2018;52(6):1801230.
29. Singh D, Papi A, Corradi M, et al. Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β_2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. Lancet. 2016;388:963–73.
30. Lipson DA, Barnhart F, Brealey N, et al; IMPACT Investigators. Once-daily single-inhaler triple versus dual therapy in patients with COPD. N Engl J Med. 2018;378:1671–80.
31. Barrecheguren M, Kostikas K, Mezzi K, et al. COPD clinical control as a predictor of future exacerbations: concept validation in the SPARK study population. Thorax. 2020;75:351–3.
32. Miravitlles M, Sliwinski P, Rhee CK, et al. Predictive value of control of COPD for risk of exacerbations: an international, prospective study. Respirology. 2020b;25(11):1136–43.
33. Garcia-Aymerich J, Gómez FP, Antó JM, en nombre del Grupo Investigador del Estudio PAC-COPD. Caracterización fenotípica y evolución de la EPOC en el estudio PAC-COPD: diseño y metodología [Phenotypic characterization and course of chronic obstructive pulmonary disease in the PAC-COPD Study: design and methods]. Arch Bronconeumol. 2009;45:4–11.
34. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T. Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. Am J Respir Crit Care Med. 2003;167:544–9.
35. Calle Rubio M, Soler-Cataluña JJ, López-Campos JL, et al. Assessing the clinical practice in specialized outpatient clinics for chronic obstructive pulmonary disease: analysis of the EPOCONSUL clinical audit. PLoS ONE. 2019;14:e0211732.
36. Baloira A, Gonzalez-Moro JMR, Sanjuán E, Trigueros JA, Casamor R. Degree of control of patients with chronic obstructive pulmonary disease in Spain: SINCON study. BMC Pulm Med. 2018;18:183.

Publisher's Note

CHEST

Changes and Clinical Consequences of Smoking Cessation in Patients With COPD

A Prospective Analysis From the CHAIN Cohort

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BACKGROUND: Despite the existing evidence-based smoking cessation interventions, chances of achieving that goal in real life are still low among patients with COPD. We sought to evaluate the clinical consequences of changes in smoking habits in a large cohort of patients with COPD.

METHODS: CHAIN (COPD History Assessment in Spain) is a Spanish multicenter study carried out at pulmonary clinics including active and former smokers with COPD. Smoking status was certified by clinical history and co-oximetry. Clinical presentation and disease impact were recorded via validated questionnaires, including the London Chest Activity of Daily Living (LCADL) and the Hospital Anxiety and Depression Scale (HADS). No specific smoking cessation intervention was carried out. Factors associated with and clinical consequences of smoking cessation were analyzed by multivariate regression and decision tree analyses.

RESULTS: One thousand and eighty-one patients with COPD were included (male, 80.8%; age, 65.2 [SD 8.9] years; FEV_1, 60.2 [20.5]%). During the 2-year follow-up time (visit 2, 906 patients; visit 3, 791 patients), the majority of patients maintained the same smoking habit. Decision tree analysis detected chronic expectoration as the most relevant variable to identify persistent quitters in the future, followed by an LCADL questionnaire (cutoff 9 points). Total anxiety HADS score was the most relevant clinical impact associated with giving up tobacco, followed by the LCADL questionnaire with a cutoff value of 10 points.

CONCLUSIONS: In this real-life prospective COPD cohort with no specific antismoking intervention, the majority of patients did not change their smoking status. Our study also identifies baseline expectoration, anxiety, and dyspnea with daily activities as the major determinants of smoking status in COPD.

TRIAL REGISTRY: ClinicalTrials.gov; No. NCT01122758; URL: www.clinicaltrials.gov.

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KEY WORDS: cohort studies; COPD; smoking cessation; tobacco

ABBREVIATIONS: BODE = body mass index, airflow obstruction, dyspnea, and exercise capacity; CHAIN = COPD History Assessment in Spain; HADS = Hospital Anxiety and Depression Scale; LCADL = London Chest Activity of Daily Living; OR = odds ratio

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Cigarette smoking is the most important risk factor in economically advanced countries for developing COPD.[1] In addition, continuation of smoking in patients with COPD has been associated with symptom persistence, a higher impact of the disease, increased exacerbations, and worse lung function[2,3] Accordingly, current guidelines recommend a thorough strategy to help patients stop smoking[4,5] but, despite having different evidence-based smoking cessation interventions, the chances that patients with COPD will definitively give it up in real life are still low.[6]

Knowing which patient characteristics are associated with successful cessation might facilitate the design of more effective stop-smoking interventions in these patients. Previous studies have highlighted some clinical and functional features associated with smoking cessation.[7,8] More recently, a randomized controlled trial in a small COPD sample found that patients with COPD with a high level of education and a more favorable healthy living perception, and those living without a partner, appeared to be more likely to successfully stop smoking in the long term.[9] Interestingly, the progression of smoking habits in a large cohort and the factors that motivate patients to stop smoking have not been evaluated, and a larger sample is needed.

The potential impact of smoking cessation on clinical outcomes is another interesting subject of study. Although previous studies have shown that patients with COPD who continue to smoke have a higher prevalence of respiratory symptoms, an accelerated decline in lung function, and a higher mortality rate than nonsmokers,[2,3,10] the evaluation of smoking cessation by exploring different aspects is still lacking in a large population.

The COPD History Assessment in Spain (CHAIN) cohort is part of a multicenter prospective observational study carried out at pulmonary clinics; the cohort includes active and former smokers with COPD, and the study is intended to perform a multidimensional evaluation of the progression of COPD in patients to better define the natural history and phenotypes of the disease.[11-14] Herewith, we aimed to use CHAIN data to explore the behavior of patients with COPD in relation to the smoking of tobacco. In particular, we aimed to study the progression of smoking habits in a large cohort of patients with COPD, to determine the factors that motivate patients to stop smoking, and to describe the impact that smoking cessation has on functional and clinical characteristics of the disease.

Methods

The methodology of CHAIN has been extensively reported previously.[15] Briefly, CHAIN is a Spanish multicenter study carried out at pulmonary clinics that includes active and former smokers with COPD. COPD was defined by a history of smoking of at least 10 pack-years and an FEV_1/FVC ratio less than 0.70 after inhaling 400 μg of albuterol. The main goal of this prospective observational study was to perform a multidimensional evaluation of the progression of patients with COPD to better define the natural history and phenotypes of the disease (ClinicalTrials.gov; No. NCT01122758).

The BODE (body mass index, airflow obstruction, dyspnea, and exercise capacity) index[16] was established as the main variable of the study and basis for calculating the sample size. Assuming an α error

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of 5% and a power of 80%, for the comparison of the progression on the BODE index between two samples of COPD participants (severe vs very severe COPD, or mild vs moderate COPD), since in the reference group the BODE is 0 by definition, and considering a mean BODE of 3 and SD of 2, at least 300 participants are required per group in order to detect an increase of 0.6 units or higher in the BODE index between groups. Because of the number of participating centers, the reference was determined to be 50 case subjects and 10 control subjects per center.[15]

The recruitment period started on January 15, 2010 and is still ongoing. The follow-up of the subjects includes annual office visits and every 6 months a telephone call was programmed to compile data about the number of exacerbations and to verify the vital status of the subject. Finally, the patients were instructed that they could come for a consultation any time if they were having an exacerbation or had any clinical demand. These patients are currently being monitored, but data analyzed in the present study were taken from the baseline and the 2-year appointment available at the time of analysis (February 2016). COPD treatment followed national[5] and international guidelines.[4]

Before their inclusion in the study, the participants provided informed consent, which was approved by each of the ethics committees of the participating centers (Hospital Universitario Nuestra Señora de Candelaria, Tenerife, Spain; IRB No. 258/2009). Additional approvals were obtained from the various regions in the country if locally required according to their own legislation. Patient data were kept anonymous in a database with hierarchical access control in order to guarantee secure access to the information.

Clinical and Physiologic Measurements

In a personal interview, trained personnel obtained the following information at the time of recruitment and yearly appointments. We evaluated anthropometric data (ie, age, sex, height, weight, and body mass index). A detailed questionnaire assessing the presence of comorbidities was also administered to all patients. Pulmonary function tests were performed in accordance with current guidelines.[17] The 6-Minute Walk Test measured the best of two walks separated by at least 30 min.[18] Dyspnea was evaluated by the modified Medical Research Council scale.[19] To evaluate health-related quality of life, we used the Spanish validated version of the COPD Assessment Test, which was self-administered by each patient.[20] Daily activities were measured by the London Chest Activity of Daily Living (LCADL) scale. The LCADL scale is a tool aimed at assessing the level of dyspnea during activities of daily living.[21] It consists of 15 questions divided into four domains: self-care, household activities, physical activity, and leisure activities. Each question in each domain is scored by patients on a 0-to-5 scale, with 5 representing the greatest dyspnea-related impairment in activities of daily living. The total score may range from 0 to 75 points, with higher values translating to greater limitation in activities of daily living. The minimal clinically important difference has been set to 3.88 points in the global score.[22]

Smoking Status Assessment

Smoking status was evaluated from the clinical history and it was confirmed by co-oximetry (piCO Smokerlyzer; Bedfont Scientific) during each visit. A specific questionnaire was used to determine smoking status (current or former), and the total smoking exposure was expressed as pack-years. During follow-up, no other specific tobacco intervention was carried out to quit tobacco except for yearly minimal smoking cessation counseling. Whenever patients asked for help to stop smoking they were entered into a smoking cessation program providing one was available in the center.

Statistical Analysis

Statistical analysis was performed with SPSS Statistics 24 software (IBM Corporation). For the descriptive analysis, the absolute frequency (n), relative frequency (%), mean values, and SD were used. The progression of smoking habits during the first three yearly visits was described with a tree graph showing changes over the years. Concordance between carbon monoxide (CO) testing and self-reported smoking status was assessed by the kappa coefficient.

To study the determinants that motivate patients to stop smoking in the relevant population and its consequences, we first studied tobacco status changes during the second visit. Then, we compared those who stopped smoking during the second visit and persisted without smoking until the third visit vs those smoking during all three yearly visits. The variables from the second visit that predicted tobacco status during the third visit were evaluated. In this analysis, we selected to explore those variables that were not significantly different between smokers and ex-smokers during the first visit and became significantly different by the time of the second visit.

The bivariate inferential studies between groups of smokers and ex-smokers were performed with the Student t test for independent data, previous verification of the equality of variances with the Levene test, or by χ^2 test for the categorical variables. In case of not having a normal distribution, the Mann-Whitney U test was used. In this analysis, the following variables were specifically explored: age, sex, marital status, social situation, working situation, comorbidities (Charlson Comorbidity Index, neoplasms, history of anxiety or depression, insomnia), tobacco history (expressed as pack-years), presence of respiratory symptoms (cough, phlegm production, and dyspnea and previous exacerbations), previous treatments (long-acting bronchodilators, inhaled corticosteroids, cardiovascular medication, psychiatric medication), complementary tests (FEV_1, 6-Minute Walk Test), and questionnaires including the COPD Assessment Test and the LCADL scale. Those variables found to be significant were then entered in a binomial multivariate logistic regression analysis with "stop smoking" being the dependent variable, using a step-wise approach and expressing the results as odds ratios (ORs) with 95% confidence intervals.

Finally, in order to identify groups of patients significantly associated with quitting smoking or variables significantly changed after stopping the use of tobacco, an analysis based on decision trees was applied, which allows the identification of homogeneous groups, according to the dependent variable (smoker), and facilitates the construction of rules to make predictions about individual cases. In these trees, the significance of the different nodes was assessed by Snedecor F test or χ^2 test depending on the nature of the variable. Significance was established with a P value $< .05$ for all tests.

Results

One thousand and eighty-one case subjects were included in the analysis. Patients' characteristics as well as their smoking status at baseline are summarized in Table 1.

This was a typical COPD cohort with patients predominantly male in their seventh decade of age, with moderate to severe lung function impairment. The evolution of their smoking status is shown in Figure 1.

TABLE 1] Characteristics of Patients According to Smoking Status at Visit 1

Characteristic	Total	Ex-Smoker (n = 753)	Current Smoker (n = 328)	*P* Value
Sex, male	873 (80.8)	643 (85.4)	230 (70.1)	< .001
Age, y	65.2 (8.9)	66.6 (8.5)	61.8 (8.7)	< .001
Comorbidities, Charlson	1.4 (1.5)	1.5 (1.5)	1.2 (1.3)	.009
Tobacco exposure, pack-years	55.3 (28.2)	55.6 (29.3)	54.9 (25.7)	.549
Co-oximetry, ppm	7.2 (7.3)	4.2 (3.5)	13.9 (8.8)	< .001
BMI, kg/m^2	27.9 (5.1)	28.4 (4.9)	26.8 (5.2)	< .001
FVC, %	92.4 (120.1)	87.6 (60.9)	103.0 (196.2)	.058
FEV_1, %	60.2 (20.5)	58.6 (20.4)	63.6 (20.6)	< .001
Previous exacerbations, No.	0.59 (1.5)	0.61 (1.1)	0.55 (2.1)	.528
Dyspnea, mMRC	1.7 (0.8)	1.8 (0.8)	1.7 (0.8)	.332

mMRC = modified Medical Research Council.

Case subjects at visits 2 and 3 numbered 906 and 791, respectively. From the whole cohort, 638 patients (59.0%) continued with the same smoking habit during follow-up: they included 503 ex-smokers (46.5%) and 135 active smokers (12.4%). The kappa coefficient between self-reported tobacco status and CO testing was 0.618 for visit 1, 0.640 for visit 2, and 0.612 for visit 3 (all $P < .001$).

Factors Associated With Changes in Smoking Habit During Follow-Up

Among active smokers (n = 328), after 1 year of follow-up (at the time of the second visit), 80 patients stopped vs 198 who continued smoking (Fig 1). The only difference between quitters and active smokers was in FEV_1 during the first visit, which was significantly higher in those who continued smoking up to the second visit (1.7 [0.7] vs 1.8 [0.6] L; $P = .032$). Therefore, no multivariate model was constructed and no decision tree was built.

If we compare those who stopped smoking at the time of the second visit and persisted without smoking until the third visit (n = 53) vs those smoking during all three visits (n = 135), the variables found to be different

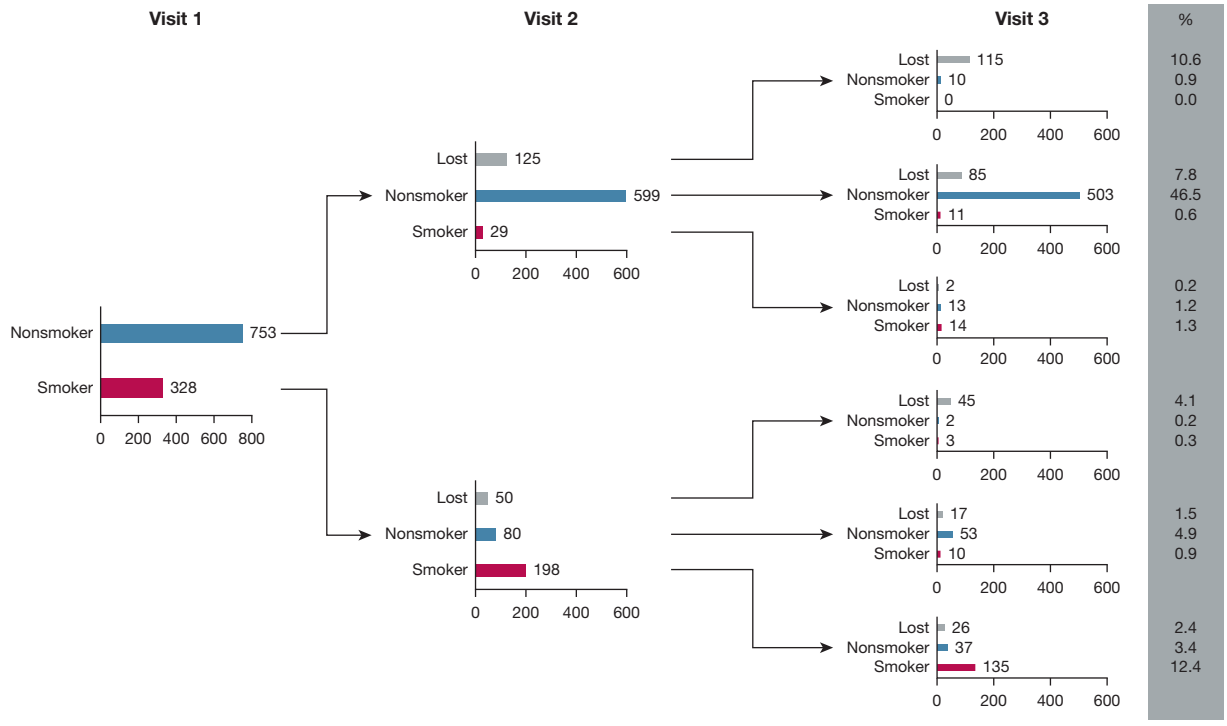

Figure 1 – *Distribution of smoking status over the visits.*

during the second visit that predicted tobacco status at the time of the third visit are displayed in Table 2. In the multivariate model, only post-bronchodilator FEV_1 (%) was found to be significant (OR, 1.036; 95% CI, 1.009-1.063; $P = .008$). The classification tree for patients according to these variables is presented in Figure 2, with a percentage of correct allocation of 84.0%. According to this scheme, expectoration is the most relevant variable to identify persistent quitters, followed by the punctuation in the LCADL questionnaire with a cutoff value of 9 points.

Clinical Consequences of Changing the Smoking Habit During Follow-Up

The bivariate associations of the clinical consequences of stopping the use of tobacco at the time of the second visit are summarized in Table 3. After the multivariate analysis, only phlegm production (OR, 2.443; 95% CI, 1.165-5.124; $P = .018$) and post-bronchodilation FEV_1 during the second visit (OR, 1.022; 95% CI, 1.003-1.042; $P = .023$) were significantly impacted by stopping smoking. The classification tree for patients according to these variables is presented in Figure 3, with a percentage of correct allocation of 85.3%. According to this analysis, variables associated with smoking cessation are as follows: expectoration, anxiety with a threshold value in the anxiety scale of the HADS of 7 points, an LCADL questionnaire with a cutoff value of 8 points, and the previous use of bronchodilator therapy.

The bivariate associations of the comparison between those patients who stopped smoking at the time of the second visit and continued without smoking until the third visit (n = 53), vs those who continued smoking at all three visits (n = 135), are summarized in Table 4. After the multivariate analysis, only phlegm production at the time of the second visit (OR, 5.11; 95% CI, 2.297-10.933; $P < .001$), previous bronchodilator therapy during the third visit (OR, 2.207; 95% CI, 1.005-4.846; $P = .049$), and total anxiety HADS score at the time of the third visit (OR, 1.125; 95% CI, 1.075-1.197; $P < .001$) were significantly affected by smoking cessation. The classification tree for patients, taking into account these variables, is presented in Figure 4, with a percentage of correct allocation of 83.5%. According to this analysis, total anxiety HADS score is the most relevant variable associated with smoking cessation, followed by LCADL questionnaire with a cutoff value of 10 points.

TABLE 2] Variables Associated With Those Who Stopped Smoking at Visit 2 and Persisted Without Smoking Until Visit 3 vs Those Smoking at All Three Visits

Variable	Visit	Stopped Smoking (n = 53)	Continued Smoking (n = 135)	*P* Value
Previous history: anxiety	1	8 (15.1%)	24 (17.8%)	.419
	2	0 (0.0%)	23 (17.0%)	< .001
Previous history: depression	1	8 (15.1%)	29 (21.5%)	.218
	2	0 (0.0%)	26 (19.3%)	< .001
Cough	1	31 (58.5%)	78 (57.8%)	.531
	2	9 (17.0%)	69 (51.1%)	< .001
Expectoration	1	38 (71.7%)	96 (71.1%)	.544
	2	14 (26.4%)	98 (72.6%)	< .001
Treatment with bronchodilators	1	30 (56.6%)	85 (63.0%)	.261
	2	18 (34.0%)	85 (63.0%)	< .001
Charlson Comorbidity Index	1	0.9 (1.1)	1.3 (1.5)	.076
	2	0.5 (1.6)	1.2 (1.5)	< .001
Post-bronchodilator FEV_1, L	1	1.6 (0.7)	1.8 (0.6)	.006
	2	1.5 (0.6)	1.8 (0.6)	.046
Post-bronchodilator FEV_1, %	1	59.8 (19.5)	65.9 (19.6)	.065
	2	55.8 (19.1)	65.9 (19.1)	.018
COPD Assessment Test	1	12.3 (7.9)	13.0 (8.3)	.838
	2	6.1 (8.1)	10.6 (7.6)	< .001
London Chest Activity of Daily Living scale	1	13.3 (11.3)	12.0 (13.4)	.608
	2	7.9 (13.2)	14.7 (10.3)	< .001

Data expressed as mean (SD) or absolute (relative) frequency as appropriate.

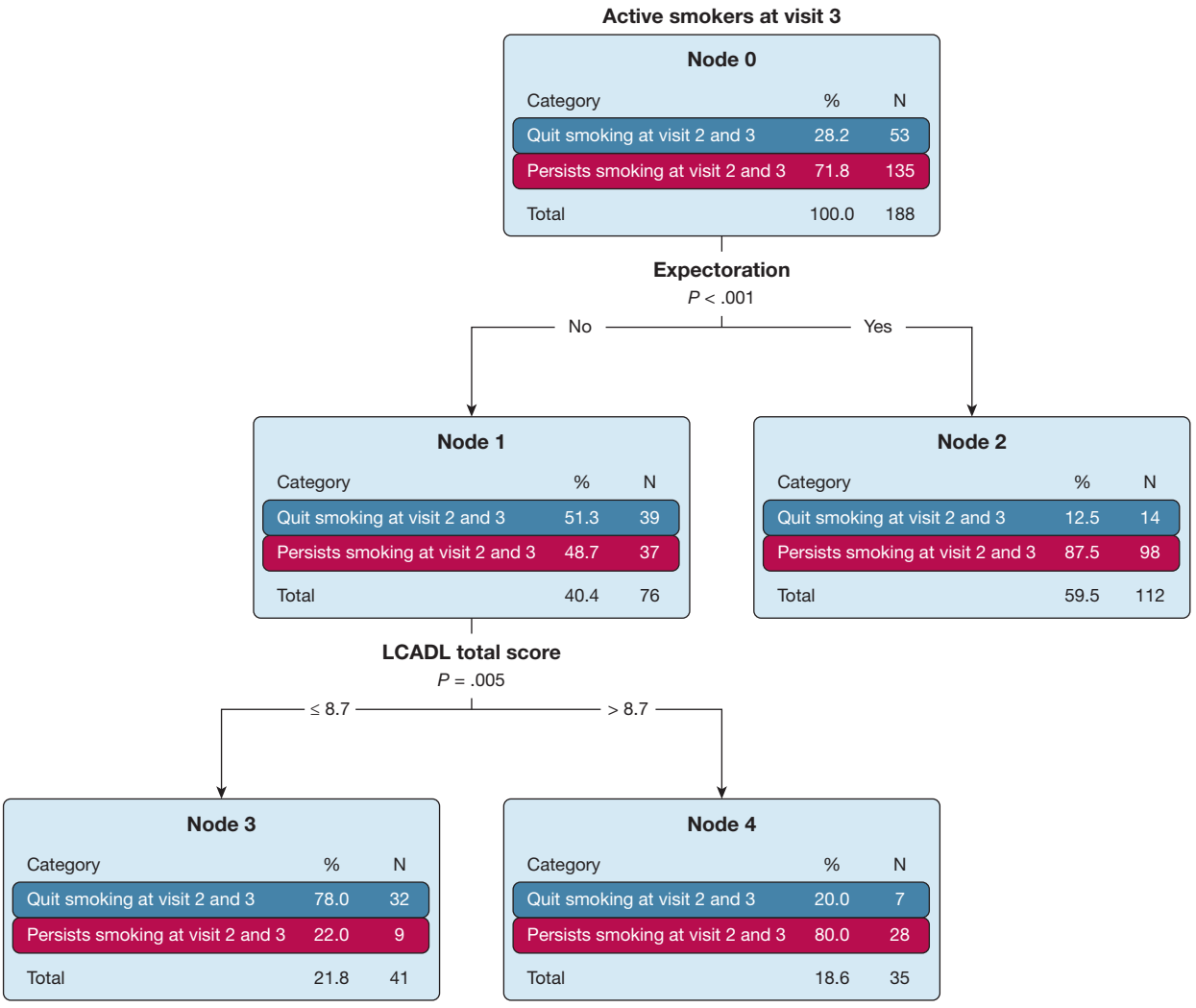

Figure 2 – *Classification of patents who quit smoking during the three visits vs persistent smokers. LCADL = London Chest Activity of Daily Living.*

Discussion

The present study provides novel information regarding the longitudinal evolution of smoking in a large cohort of patients with COPD, in which the determinants are associated with smoking cessation and their clinical consequences. The main results of our study indicate that (1) if there is no therapeutic intervention other than minimal counseling, the majority of the patients remain in their smoking habit state in the following 2 years; (2) the main variables associated with smoking cessation are lung function, the presence of chronic expectoration, and daily activities; and (3) the clinical consequences of smoking cessation are observed at 1 year in sputum production and disease impact, while a long-term improvement in disease impact evaluated by anxiety and daily living activities questionnaires is even more important.

The current analysis describes the progression of smoking habit in a well-characterized COPD cohort over time. Our data indicate that the majority of patients maintain the same smoking status. Only a few studies have shown some data on progression of smoking status in COPD. A recent randomized trial showed that 89.8% of smokers continued with the same habit after 1 year despite an antitobacco intervention.[9] A nationwide hospital-based prospective follow-up study in Denmark showed that the probability of stopping smoking was 45% at 5 years.[7] Another randomized trial studied telephone-based chronic disease treatment and showed that 30.2% of participants reported a 6-month abstinence from smoking during an 18-month follow-up.[23] These studies together with the results of our cohort strengthen the concept of smoking cessation challenges in real life.[24] There is potential for

TABLE 3] Variables Not Significantly Different Between Smokers and Ex-Smokers During Visit 1 but Significantly Different at Visit 2 After Quitting Tobacco

Variable	Visit	Stopped Smoking (n = 80)	Continued Smoking (n = 198)	*P* Value
Cough	1	44 (55.0%)	126 (63.6%)	.115
	2	13 (16.3%)	105 (53.0%)	< .001
Expectoration	1	52 (65.0%)	137 (69.2%)	.294
	2	20 (25.0%)	141 (71.2%)	< .001
Neoplasms	1	2 (2.5%)	16 (8.1%)	.067
	2	1 (1.3%)	17 (8.6%)	.016
Previous bronchodilator therapy	1	50 (62.5%)	125 (63.1%)	.513
	2	26 (32.5%)	126 (63.6%)	< .001
Previous ICS treatment	1	5 (6.3%)	21 (10.6%)	.185
	2	0 (0.0%)	19 (9.6%)	.001
Previous ICS-LABA treatment	1	28 (35.0%)	85 (42.9%)	.139
	2	17 (21.3%)	71 (35.9%)	.012
Previous psychiatric treatment	1	18 (22.5%)	42 (21.2%)	.465
	2	3 (3.8%)	26 (13.1%)	.013
Number of exacerbations	1	1.1 (1.7)	1.6 (3.8)	.758
	2	0.9 (2.9)	0.8 (1.7)	.018
Post-bronchodilator FEV_1, %	1	60.1 (20.4)	65.3 (19.8)	.053
	2	58.3 (20.6)	65.5 (19.6)	.043
COPD Assessment Test	1	12.5 (7.6)	13.2 (8.0)	.596
	2	5.3 (7.3)	11.2 (7.7)	< .001
London Chest Activity of Daily Living scale	1	13.3 (11.3)	14.1 (12.6)	.771
	2	7.7 (11.9)	15.4 (11.2)	< .001
Total anxiety, HDAS scale	1	10.2 (6.1)	11.2 (5.1)	.351
	2	4.2 (6.0)	9.3 (6.2)	< .001
Total depression, HDAS scale	1	7.6 (5.2)	8.6 (5.1)	.158
	2	2.8 (4.7)	6.6 (5.8)	< .001
Charlson Comorbidity Index	1	1.1 (1.3)	1.2 (1.4)	.248
	2	0.8 (1.6)	1.2 (1.5)	.007

Data expressed as mean (SD) or absolute (relative) frequency as appropriate. HDAS = Hospital Anxiety and Depression Scale; ICS = inhaled corticosteroid; LABA = long-acting β-agonist.

information and communication technology to assist with smoking cessation over time, which should be further explored in the future.[25]

Concordance between self-reported smoking status and CO testing was close to 0.7. In research studies of people who smoke, CO levels > 10 ppm in expired breath indicate current smoking.[26-28] However, CO has a half-life of 5 to 6 h in the body, and CO levels return to normal after 24 to 48 h of not smoking. In addition, CO levels are also determined by several endogenous, environmental, product-related, medical, and individual factors. For instance, patients with COPD or asthma and those who live in heavily urbanized areas have higher CO levels, even if they do not smoke.[29] Accordingly, CO levels may be elevated in people with very high levels of secondhand smoke exposure (eg, exhaust from combustible materials), including those who spend time along roads or in heavily polluted urban areas.[30] Consequently, although CO levels in expired air are correlated with levels of self-reported cigarette or cigar smoking, kappa coefficients have not been thoroughly reported and current available information suggests this kappa value may be at 0.7.[31]

The main variables associated with smoking cessation in our study were expectoration and activities of daily living measured by the LCADL questionnaire. This relationship with LCADL has not been studied so far. In a hospital-based prospective follow-up registry in

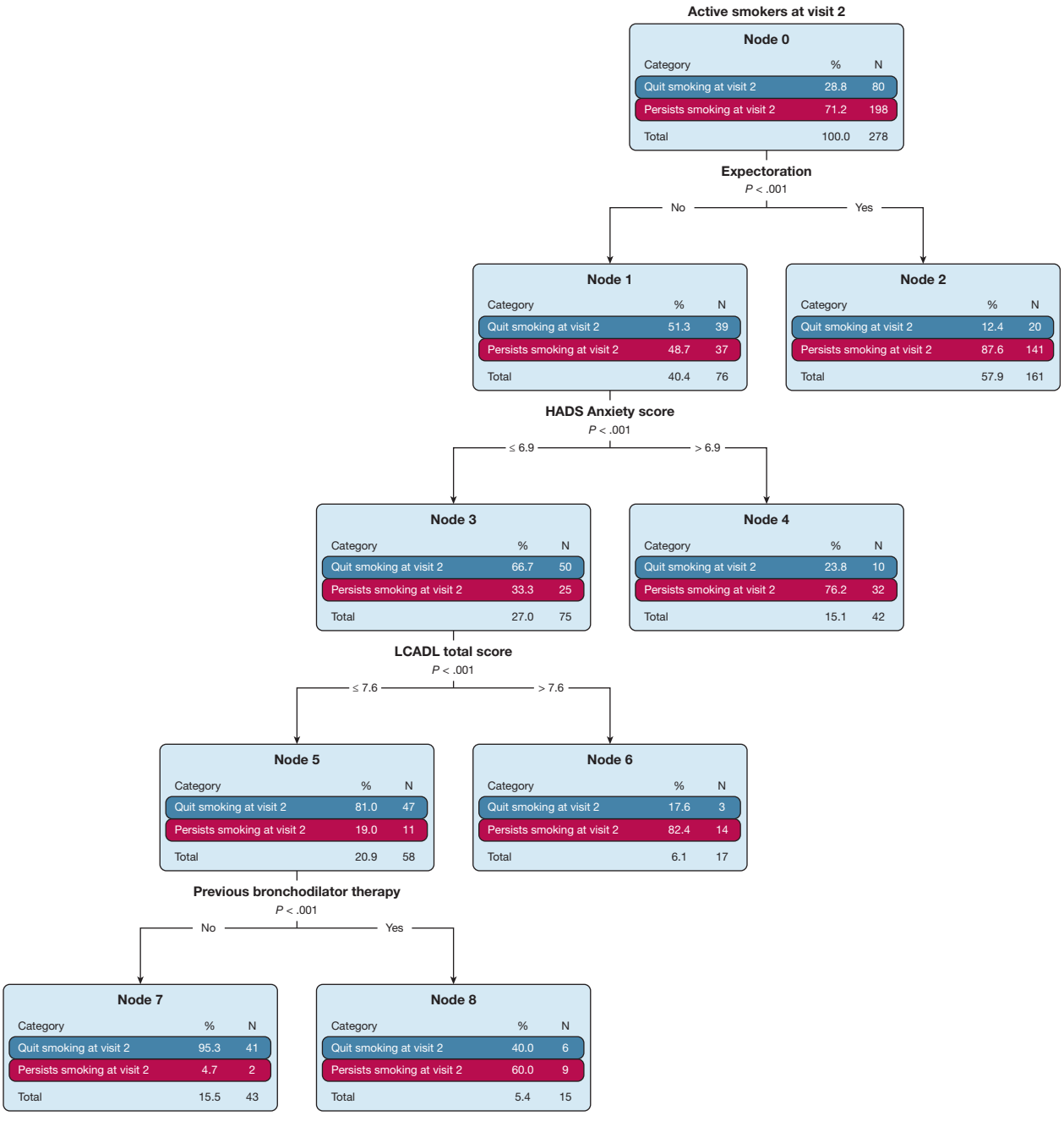

Figure 3 – *Classification of variables affected by quitting tobacco in the first year. HADS = Hospital Anxiety and Depression Scale. See Figure 2 legend for expansion of other abbreviation.*

Denmark, the authors studied over 5 years the clinical and sociodemographic determinants of smoking cessation in 3,233 patients with COPD with no specific reported antitobacco intervention. In adjusted analyses, patients were less likely to stop smoking if they were younger, had lower income, lived alone, were unemployed, had milder COPD, had milder dyspnea perception, or no history of exacerbations treated on an outpatient basis.[7] A more recent smaller study, including 296 smokers with mild-to-moderate COPD and face-to-face counseling with a nurse and administration of nortriptyline for smoking cessation over 1 year, found that patients with COPD with a high level of education, more favorable general health perception, and those living without a partner, appeared to be more likely to successfully stop smoking in the long term.[9] In our study, however, although the multivariate analysis did not show this, the decision tree analysis identified

TABLE 4] Variables Not Significantly Different Between Smokers and Ex-Smokers During Visit 1 but Significantly Different at Subsequent Visits After Quitting Tobacco

Variable	Visit	Stopped Smoking (n = 53)	Continued Smoking (n = 135)	*P* Value
Cough	1	31 (41.5%)	78 (57.8%)	.531
	2	9 (17.0%)	69 (51.1%)	< .001
	3	9 (17.0%)	75 (55.6%)	< .001
Expectoration	1	38 (71.7%)	96 (71.1%)	.544
	2	14 (26.4%)	98 (72.6%)	< .001
	3	13 (24.5%)	89 (65.9%)	< .001
Previous bronchodilator treatment	1	30 (56.6%)	85 (63.0%)	.261
	2	18 (34.0%)	85 (63.0%)	< .001
	3	18 (34.0%)	89 (65.9%)	< .001
Previous ICS-LABA treatment	1	16 (30.2%)	59 (43.7%)	.061
	2	11 (20.8%)	47 (34.8%)	.042
	3	8 (15.1%)	53 (39.3%)	.001
COPD Assessment Test	1	12.3 (7.9)	13.0 (8.3)	.838
	2	6.1 (8.1)	10.6 (7.6)	< .001
	3	5.9 (8.6)	11.3 (7.8)	< .001
London Chest Activity of Daily Living scale	1	13.3 (11.3)	12.0 (13.4)	.608
	2	7.8 (13.2)	14.7 (10.3)	< .001
	3	8.1 (12.6)	16.9 (11.2)	< .001
Total anxiety, HDAS scale	1	9.4 (7.6)	11.3 (5.2)	.117
	2	4.4 (6.5)	9.5 (6.4)	< .001
	3	3.5 (6.2)	10.1 (6.3)	< .001
Total depression, HDAS scale	1	7.6 (5.6)	8.8 (5.0)	.170
	2	3.4 (5.3)	6.5 (5.8)	< .001
	3	2.8 (5.5)	7.8 (6.1)	< .001
Charlson Comorbidity Index	1	0.9 (1.1)	1.3 (1.5)	.076
	2	0.6 (1.6)	1.1 (1.5)	< .001
	3	0.7 (1.7)	1.2 (1.5)	< .001

Data expressed as mean (SD) or absolute (relative) frequency as appropriate. See Table 3 legend for expansion of abbreviations.

LCADL as one potential variable to identify patients who are prone to stop smoking in the long term, with a cutoff value of 9 points.

Smoking cessation has been shown to provide more important prognostic benefits in patients with COPD than those demonstrated with pharmacologic treatments, although it is less studied. The present work expands on those findings. The main clinical outcomes associated with smoking cessation have also been described. Previous studies already indicated an impact of smoking cessation on clinically relevant outcomes including lung function decline and overall prognosis.[3,32] More recently, a study including 16,479 patients with COPD found that compared with active smokers, former smokers had significantly reduced risk of death, hospitalization, and ED visits, emphasizing the importance of effective smoking cessation support, regardless of age or lung function.[33] In the present work, we found a significant association with expectoration, lung function, HADS anxiety scale, and LCADL scale during the first year of follow-up, which was also confirmed during the second year of follow-up. Interestingly, after considering all these variables, exacerbations did not have any impact in the model, probably influenced by the low number of exacerbations in our cohort.

Although the relationship between tobacco cessation with lung function and expectoration has been previously described, the association with anxiety and daily activities deserves a comment. Anxiety is a very important comorbidity in COPD. In addition to the already existing relationship between anxiety and

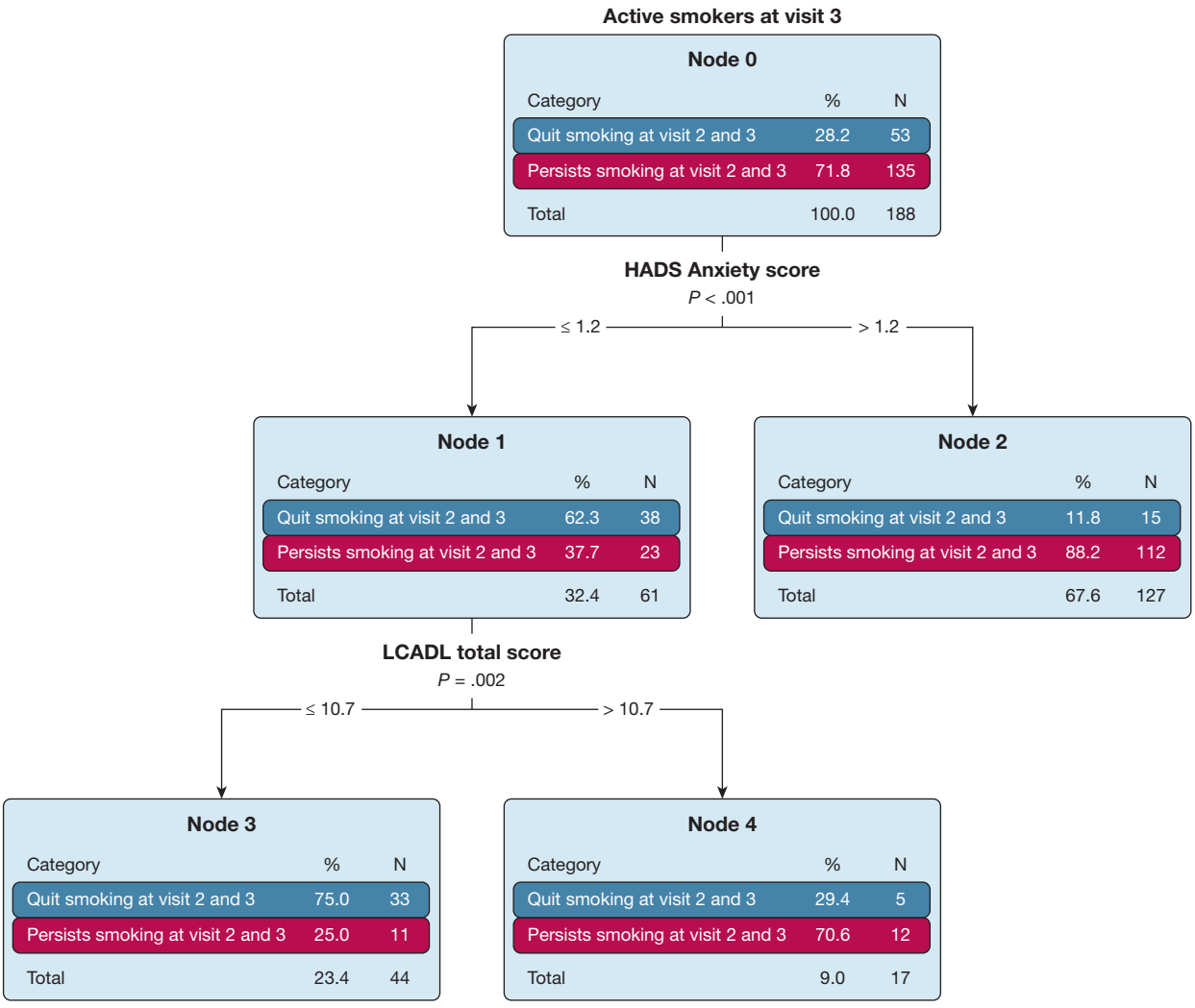

Figure 4 – *Classification of variables affected by quitting tobacco in the third visit. See Figure 2 and 3 legends for expansion of abbreviations.*

smoking cessation, patients with COPD frequently suffer from different degrees of anxiety with a profound impact on disease perception and prognosis.[34] Therefore, the evaluation of anxiety in these patients is extremely important for disease treatment. In the present analysis, we have used the HADS. More recently, new scales have been reported[35] that should be further explored to determine their impact on smoking cessation. In addition, a multidisciplinary approach should also be considered in smoking cessation clinics to achieve a potential impact in the treatment.

The relationship with daily activities is also worth comment. The direct impact of tobacco use beyond the respiratory system has been scarcely studied. Although the systemic consequences of smoking have been well described,[36] the systemic impact of smoking cessation represents a current area for research. Apart from cardiovascular diseases,[37] the systemic consequences of smoking cessation have not been profoundly addressed. The present analysis advances our understanding of these systemic impacts of smoking cessation by including daily activities as one clinical outcome with a significant association. The rationale behind needs further scrutiny in the future. Interestingly, it has been hypothesized that oxidants contained in cigarettes induce adverse effects on tissues through oxidative phenomena. One study investigated the effect of tobacco on peripheral muscle, concluding that cigarette smoking exerts direct oxidative modifications on muscle proteins, without inducing any significant rise in muscle inflammation.[38]

The main strengths of the CHAIN cohort lie in its large number of patients with long-term follow-up and the

large number of variables evaluated, which provide a thorough evaluation and a multidimensional view of the patients. However, from the methodologic point of view, it is necessary to keep in mind some characteristics of the cohort in order to correctly interpret our results. First, the CHAIN cohort was obtained from an observational study of patients attending pulmonary clinics and not from a general medical practice or population-based study. Therefore, the cohort might not represent the true distribution of COPD severity in the general population or in a different setting such as primary care. However, our cohort included a broad range of disease severity, including patients in GOLD (Global Initiative for Chronic Obstructive Lung Disease) stages 1 to 4. Second, few women were included in the cohort, and the findings reported here cannot be directly extended to include sex as a variable. Therefore, they must be interpreted with caution. Third, it was only a 2-year follow-up assessment, and there was a loss of patients during follow-up that could result in measurement bias; therefore, serial measurements for a longer period would likely show a reliable trend of variability. Fourth, as a consequence we have not described outcomes, such as mortality; we still require longer follow-up times to be able to perform that analysis. Finally, it is important to highlight that there was no antitobacco intervention except for minimal interventions such as smoking cessation counseling during yearly visits. Accordingly, we are describing here the relation between different clinical variables with smoking cessation without the influence of more intense tobacco interventions.

The present study has used two different statistical techniques to evaluate the association: a traditional binomial multivariate logistic regression analysis and the construction of decision trees. These two techniques have different methodology and objectives, so, although they are expected to provide similar results, they may not be identical but, rather, complementary. On the one hand, regression analysis reports on the variables associated with a particular clinical event under study, in our case smoking cessation. On the other hand, the decision tree is a technique that helps to identify groups rather than discover relationships between them and predict future events.[39] This technique presents a very visual decision, and classification trees help to explain better the analyses on a more clinical basis, by creating classification models for the segmentation of the cohort according to the results found.

In summary, the current analysis provides new insights in the understanding of the relationship between tobacco and COPD-related clinical evaluation. The present study highlights for the first time the importance of activities of daily living, and different scores in the evaluation of the patient with active smoking. Our data reinforce the importance of effective smoking cessation support and open a window of opportunity to use these questionnaires as a tool to evaluate candidates for initiation of a more intense tobacco treatment.

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References

1. GBD 2015 Tobacco Collaborators. Smoking prevalence and attributable disease burden in 195 countries and territories, 1990-2015: a systematic analysis from the Global Burden of Disease Study 2015. *Lancet*. 2017;389(10082):1885-1906.
2. Riesco JA, Alcazar B, Trigueros JA, Campuzano A, Perez J, Lorenzo JL. Active smoking and COPD phenotype: distribution and impact on prognostic factors. *Int J Chron Obstruct Pulmon Dis*. 2017;12:1989-1999.
3. Anthonisen NR, Skeans MA, Wise RA, et al. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med*. 2005;142(4):233-239.
4. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report: GOLD executive summary. *Arch Bronconeumol*. 2017;53(3):128-149.
5. Miravitlles M, Soler-Cataluna JJ, Calle M, et al. Spanish guidelines for management of chronic obstructive pulmonary disease (GesEPOC) 2017: pharmacological treatment of stable phase. *Arch Bronconeumol*. 2017;53(6):324-335.
6. van Eerd EA, van der Meer RM, van Schayck OC, Kotz D. Smoking cessation for people with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2016;8:CD010744.

7. Tottenborg SS, Thomsen RW, Johnsen SP, Nielsen H, Lange P. Determinants of smoking cessation in patients with COPD treated in the outpatient setting. *Chest*. 2016;150(3):554-562.
8. Gilkes A, Hull S, Durbaba S, et al. Ethnic differences in smoking intensity and COPD risk: an observational study in primary care. *NPJ Prim Care Respir Med*. 2017;27(1):50.
9. van Eerd EAM, van Schayck OCP, Wesseling G, Kotz D. Predictors of long-term smoking cessation in patients with COPD: results from a randomised controlled trial. *Eur Respir J*. 2017;49(6):1700561.
10. Bai JW, Chen XX, Liu S, Yu L, Xu JF. Smoking cessation affects the natural history of COPD. *Int J Chron Obstruct Pulmon Dis*. 2017;12:3323-3328.
11. Casanova C, Marin JM, Martinez-Gonzalez C, et al. New GOLD classification: longitudinal data on group assignment. *Respir Res*. 2014;15:3.
12. de Torres JP, Marin JM, Martinez-Gonzalez C, et al. Clinical application of the COPD assessment test: longitudinal data from the COPD History Assessment in Spain (CHAIN) cohort. *Chest*. 2014;146(1):111-122.
13. Cosio BG, Soriano JB, Lopez-Campos JL, et al. Defining the asthma-COPD overlap syndrome in a COPD cohort. *Chest*. 2016;149(1):45-52.
14. Casanova C, Marin JM, Martinez-Gonzalez C, et al. Differential effect of Modified Medical Research Council Dyspnea, COPD Assessment Test, and Clinical COPD Questionnaire for symptoms evaluation within the new GOLD staging and mortality in COPD. *Chest*. 2015;148(1):159-168.
15. Lopez-Campos JL, Peces-Barba G, Soler-Cataluna JJ, et al. Chronic obstructive pulmonary disease history assessment in Spain: a multidimensional chronic obstructive pulmonary disease evaluation: study methods and organization. *Arch Bronconeumol*. 2012;48(12):453-459.
16. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;350(10):1005-1012.
17. American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. *Am Rev Respir Dis*. 1991;144(5):1202-1218.
18. American Thoracic Society. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166(1):111-117.
19. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. *Chest*. 1988;93(3):580-586.
20. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. *Eur Respir J*. 2009;34(3):648-654.
21. Garrod R, Bestall JC, Paul EA, Wedzicha JA, Jones PW. Development and validation of a standardized measure of activity of daily living in patients with severe COPD: the London Chest Activity of Daily Living scale (LCADL). *Respir Med*. 2000;94(6):589-596.
22. Bisca GW, Proenca M, Salomao A, Hernandes NA, Pitta F. Minimal detectable change of the London Chest Activity of Daily Living scale in patients with COPD. *J Cardiopulm Rehabil Prev*. 2014;34(3):213-216.
23. Joseph AM, Fu SS, Lindgren B, et al. Chronic disease management for tobacco dependence: a randomized, controlled trial. *Arch Intern Med*. 2011;171(21):1894-1900.
24. Carrion Valero F, Paulos Dos Santos S, Celli BR. Smoking in COPD patients: a new clinical phenotype? *Arch Bronconeumol*. In press. https://doi.org/10.1016/j.arbres.2017.10.021.
25. Mussener U, Bendtsen M, Karlsson N, White IR, McCambridge J, Bendtsen P. Effectiveness of short message service text-based smoking cessation intervention among university students: a randomized clinical trial. *JAMA Intern Med*. 2016;176(3):321-328.
26. Goldstein AO, Gans SP, Ripley-Moffitt C, Kotsen C, Bars M. Use of expired air carbon monoxide testing in clinical tobacco treatment settings. *Chest*. 2018;153(2):554-562.
27. Sandberg A, Skold CM, Grunewald J, Eklund A, Wheelock AM. Assessing recent smoking status by measuring exhaled carbon monoxide levels. *PLoS One*. 2011;6(12):e28864.
28. SRNT Subcommittee on Biochemical Verification. Biochemical verification of tobacco use and cessation. *Nicotine Tob Res*. 2002;4(2):149-159.
29. Ryter SW, Choi AM. Carbon monoxide in exhaled breath testing and therapeutics. *J Breath Res*. 2013;7(1):017111.
30. Kotz D. Possible reasons for elevated carbon monoxide levels in self-reported ex-smokers. *Nicotine Tob Res*. 2012;14(8):900-901.
31. Frei M, Engel Brugger O, Sendi P, Reichart PA, Ramseier CA, Bornstein MM. Assessment of smoking behaviour in the dental setting: a study comparing self-reported questionnaire data and exhaled carbon monoxide levels. *Clin Oral Investig*. 2012;16(3):755-760.
32. Scanlon PD, Connett JE, Waller LA, et al. Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease: the Lung Health Study. *Am J Respir Crit Care Med*. 2000;161(2 Pt 1):381-390.
33. Josephs L, Culliford D, Johnson M, Thomas M. Improved outcomes in ex-smokers with COPD: a UK primary care observational cohort study. *Eur Respir J*. 2017;49(5).
34. Divo M, Cote C, de Torres JP, et al. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2012;186(2):155-161.
35. Dong XY, Wang L, Tao YX, et al. Psychometric properties of the Anxiety Inventory for Respiratory Disease in patients with COPD in China. *Int J Chron Obstruct Pulmon Dis*. 2017;12:49-58.
36. Rostron BL, Chang CM, Pechacek TF. Estimation of cigarette smoking-attributable morbidity in the United States. *JAMA Intern Med*. 2014;174(12):1922-1928.
37. Prochaska JJ, Benowitz NL. Smoking cessation and the cardiovascular patient. *Curr Opin Cardiol*. 2015;30(5):506-511.
38. Barreiro E, Peinado VI, Galdiz JB, et al. Cigarette smoke-induced oxidative stress: a role in chronic obstructive pulmonary disease skeletal muscle dysfunction. *Am J Respir Crit Care Med*. 2010;182(4):477-488.
39. Weber RM, Fajen BR. Decision-tree analysis of control strategies. *Psychon Bull Rev*. 2015;22(3):653-672.