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Predictive value of control of COPD for risk of exacerbations:

An international, prospective study

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Summary at a glance

The concept of control has been well defined in asthma. We have validated the proposal of control status in COPD consisting of easy to obtain clinical variables. Patients controlled had a reduced risk of exacerbations compared to uncontrolled patients.

ABSTRACT

Background and objective: The concept of clinical control in COPD has been developed to help in treatment decisions, but it requires validation in prospective studies.

Method: This international multicentre prospective study aimed to validate the concept of control in COPD. Patients with COPD were classified as controlled/uncontrolled by clinical criteria or CAT scores at baseline and followed-up for 18 months. The main outcome was the difference in rate of a composite endpoint of moderate and severe exacerbations or death over the 18 months followp.

Results: A total of 307 patients were analysed (mean age 68.6 years and mean FEV1%= 52.5%). Up to 65% and 37.9% of patients were classified as controlled by clinical criteria or CAT respectively. Controlled patients had significantly less exacerbations during follow up (by clinical criteria: 1.1 versus 2.6; $p<0.001$, by CAT: 1.1 versus 1.9; $p=0.014$). Time to first exacerbation was significantly prolonged for patients controlled by clinical criteria only (median 93 days, IQR: 63; 242 days versus 274 days, IQR: 221; 497 days; $p<0.001$). Control status by clinical criteria was a better predictor of exacerbations compared to CAT criteria (area under the ROC curve 0.67 versus 0.57).

Conclusion: Control status, defined by easy-to-obtain clinical criteria, is predictive of future exacerbation risk and time to the next exacerbation. The concept of control can be used in clinical practice at each clinical visit as a complement to the current recommendations of initial treatment proposed by guidelines.

Key words: chronic obstructive pulmonary disease; clinical control status; COPD Assessment Test; dyspnoea; exacerbations, prevention

Short title: COPD control and exacerbations

INTRODUCTION

The main objectives of treatment of chronic obstructive pulmonary disease (COPD) are the control of symptoms and the prevention of exacerbations (1,2). However, the definition of control of symptoms is not yet established (3). The Global Initiative for Obstructive Lung Disease (GOLD) strategy recommends more intensified treatment in patients with a COPD Assessment Test (CAT) score 10 or higher or a modified Medical Research Council (mMRC) dyspnea degree 2 or higher, but it does not mention which the goal of therapy should be (1).

The most recent update of the GOLD strategy recommends reassessing COPD patients after initial treatment based on symptoms and exacerbations (4). In this context, the concept of control in COPD has been proposed as a guide to complement treatment recommendations of current guidelines (3,5). It has been well documented that patients with the same impairment in lung function may have very different outcomes in terms of frequency of exacerbations or quality of life (6); therefore, other clinical criteria may help the clinician to make decision as to step up or down therapy according to the level of "control". A set of initial clinical criteria of control was proposed by Soler-Cataluña et al (3,5), but a retrospective database study in the UK (7) and a single center prospective study (8) demonstrated that, although these initial criteria were useful to predict outcomes, they were too restrictive and the predictive value was not optimal. In fact, the later study developed a new set of simplified clinical criteria with new thresholds, that provided a better prognostic value for exacerbations (8).

The current study is the first international, multicenter, prospective study designed with the objective to validate the concept of control of COPD long-term. In this article we describe the main results of the prospective validation of the new clinical and CAT control criteria (8) as a useful predictor for poor outcomes.

METHOD

Study design

This international multicentre prospective study of a cohort of patients with COPD aimed to validate the concept of clinical control in COPD. The design of the study and the evaluation of the control status at baseline have been published previously (9,10). Briefly, this was a 21-month prospective observational study, comprising 5 evaluation points: one screening evaluation (V-1), one baseline visit after 3 months (V0) and 3 follow-up visits at 6 months intervals (V1-V3).

The primary study outcome was the difference in rates of a composite endpoint for patients controlled versus uncontrolled at baseline and was measured over the 18-month follow-up period. The composite endpoint is defined as occurrence of any of the following: an ambulatory exacerbation, an emergency room attendance or hospital admission due to an exacerbation, or death.

The study was approved by the local Research and Ethics Committees of each participating research site and all patients provided written informed consent. The data for UK was obtained from the Optimum Patient Care Research Database (OPCRD) and permission to access and link UK data to anonymous electronic medical records was obtained from the Health Research Authority for clinical research use (Anonymised Data Ethics & Protocol Transparency (ADEPT) approval number ADEPT0115). This study was registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), Register Number EUPAS10679.

Population

Eligible patients had to have spirometry-defined COPD (i.e. post-bronchodilator FEV1/FVC<0.7), be over 40 years of age, be current or ex-smokers with at least 10 pack-years of smoking exposure and be in a stable clinical state at the screening visit. Patients were excluded from the trial if they: 1) had any chronic concomitant respiratory condition other than asthma or bronchiectasis; 2) had severe comorbidity with a life expectancy shorter than 2 years; 3) were unable to understand the instructions of the study or to fill in the questionnaires; 4) Were participating in another clinical study or clinical trial.

Measurements

At screening visit, eligible patients had a full clinical assessment, including socioeconomic variables, evaluation of current smoking status, respiratory symptoms, current treatment, presence of comorbidities, lung function measured by spirometry and questionnaires. At baseline visit, the control status of the patients was assessed as indicated below.

The CAT (11) and the mMRC dyspnea scale (12) were administered at each clinical visit. Physical activity was quantified by self-declared minutes walking per day, as previously described (13) and comorbidities were assessed with the age-adjusted Charlson index (14).

A COPD exacerbation was defined as an increase in respiratory symptoms that required the use of systemic corticosteroids and/or a course of antibiotics. When the patient required hospital treatment the exacerbations were considered severe (15).

Definition of control

A patient was considered controlled when disease was clinically stable and of low impact, when adjusted for the level of disease severity (8). Two different approaches to control were compared for their predictive value for future events: a) clinical control by using only clinical variables and b) CAT control by using CAT scores and changes in CAT scores between consecutive visits.

In the clinical approach to control, stability was defined by the absence of exacerbations in the previous 3 months and impact was classified as low or high according to the information collected on sputum (presence and colour), breathlessness, daily physical activity and rescue medication use. On the other hand the CAT control was defined by a CAT score below the prespecified threshold (low impact) and any change that was less than a 3 unit increase between visits (stability).

Evaluation of impact was adjusted by disease severity according to the forced expiratory volume in the first second (FEV1). Patients with FEV1(%) $\geq$ 50% predicted were classified as mild/moderate and those with FEV1(%) < 50% as severe.

The control status of the patients was established according to the clinical and CAT data obtained at baseline visit (V0) and the history of exacerbations and changes in CAT scores between screening visit (V-1) and V0 (Supplementary Table S1).

Statistical analysis

The sample size calculation was described previously and indicated that 328 patients should be enrolled in the study, including an expected drop-out rate of 15%.

Absolute frequencies and percentages were used for comparisons of qualitative variables. The description of quantitative variables was performed using the mean and standard deviation (SD). The Kolmogorov-Smirnov test was used to assess the normality of distributions. In the case of quantitative variables, the comparison of the characteristics between controlled versus uncontrolled patients was carried out using the Student t-test (Mann-Whitney U-test if normality was not assumed). The Chi-squared test (Fisher test for frequencies <5) was employed for the comparison of categorical variables. The Kappa coefficient was calculated to evaluate the concordance between the classification by clinical criteria or CAT.

Kaplan Meier analysis were used in order to compared time to the first exacerbation between control and uncontrolled patients according to the clinical and CAT criteria of control. Predictive values of both criteria of control for the main outcome were also evaluated using Receiver Operating Characteristic (ROC) curves. For all the tests *p*-values <0.05 were considered statistically significant. The statistical package R Studio (V2.5.1) was used for the statistical analyses.

RESULTS

Population

A total of 349 patients were consecutively recruited, of which 307 (88%) fulfilled all inclusion and exclusion criteria, completed the baseline visit (V0), could be evaluated for control status either by clinical or CAT criteria and constitute the population of this study. The mean age was 68.6 years [standard deviation (SD)= 8.7], 73.9% were male and mean FEV1(%) was 52.5% (18.1%). A total of 172 (56%) were classified as having mild/moderate COPD and 135 (44%) as severe (Table 1).

Control status by clinical and CAT criteria

A total of 303 patients had complete information to evaluate control by clinical criteria, 197 (65%) of them were classified as controlled. The proportion of controlled patients was 68.5% of mild/moderate and 59.3% of severe COPD patients. The presence of dyspnea (32.2% of cases), followed by rescue medication use (24.8%) were the most common clinical criterion that meant that patients were not considered low impact. Only 21.8% of patients were classified as unstable due to at least one exacerbation in the previous 3 months (Supplementary Table S2). Regarding CAT, data were available for 306 patients and of these 116 (37.9%) were classified as controlled; 41.5% among the mild/moderate and 34.5% of severe COPD patients. The index of overall concordance between the clinical criteria and the CAT scores in defining control status

was low (K=0.253). Comparison of characteristics of controlled versus uncontrolled patients by clinical and CAT criteria are presented in Table 1.

The rates of control status by severity according to the different criteria of control and the percentage of patients with low impact and stability in the different subgroups are presented in Supplementary Table S3.

Clinical evolution during follow-up

From the initial population of 303 valid patients for clinical control, a total of 268 (88.4%) patients completed the 18 months follow-up (Figure 1). Among the 197 controlled patients 4 patients died (2%) and 13 were lost to follow-up (6.6%) and among the 106 non controlled 6 died (5.7%) and 12 were lost (11.3%) (p=0.092 for mortality and p=0.04 for lost to follow-up).

Regarding the main outcome of the study, patients classified as controlled had significantly less exacerbations during follow-up, and especially when classified as controlled by clinical criteria (1.1 (2.1) versus 2.6 (3.1); p<0.001). Differences were lower, although still significant, when using CAT criteria of control (1.1 (2) exacerbations in controlled versus 1.9 (2.9) in uncontrolled patients; p=0.014) (Table 2). Results were the sae when ACO patients were excluded from the analysis (data not shown)

Time to combined event in patients controlled or uncontrolled at baseline

The accumulated probability of combined event was significantly higher in patients uncontrolled by either clinical or CAT criteria (Figure 2). However, only patients controlled by clinical criteria showed a significantly increased time to the first exacerbation compared to uncontrolled (median 93 days, interquartile range (IQR): 63; 242 days versus 274 days, IQR: 221; 497 days; p<0.001). Differences were not significant when classifying the patients by CAT criteria of control (222 days, IQR: 83; 436 days versus 240 days, IQR: 176; 337 days; p=0.54).

Predictive value of the control status

Patients classified as controlled by clinical criteria had a reduced risk of having an exacerbation during follow-up (HR= 0.47; 95%CI 0.35 to 0.65). Interestingly, the HR for any exacerbation by CAT criteria was not significant (HR= 0.82; 95%CI 0.60 to 1.14). CAT classification of control was only significant for a reduced risk of ambulatory exacerbations (HR= 0.68; 95%CI 0.48 to 0.97) (Table 3).

The receive operating characteristic (ROC) curves demonstrated that control status measured with clinical criteria was a better predictor of combined event (area under the receiver operating characteristics (ROC) curve (AUC)= 0.67) compared with the control status measured by CAT criteria (AUC= 0.57) (Figure 3).

DISCUSSION

Our study is the first international, multicentre, prospective study specifically designed to test the long-term predictive value of the concept of clinical control in COPD. In addition, two different definitions of clinical control were evaluated, one using easy to obtain clinical variables and another using only the CAT questionnaire.

Our results have shown that patients classified as controlled at the beginning of the study had a reduced risk of a combined event over a period of 18 months; and when the clinical criteria were used, controlled patients had a significantly prolonged time to the first exacerbation. These results suggest that control status, especially when evaluated by clinical criteria, may be a valid tool to evaluate future risks and direct therapy in patients with COPD. After establishing initial therapy based on GOLD A-D classification (1,4) or phenotypes and level of risk (16,17), the control status may be a dynamic tool to be easily incorporated at every clinical visit in order to make informed decisions about step-up or down therapy in COPD (18).

Current treatment recommendations for COPD have emphasised initial classification and treatment, but recommendations about follow-up are less precise. Only in the last reviews, the GOLD initiative has proposed two different algorithms for stepping up or down therapy during follow-up according to the persistence of symptoms (dyspnea) or exacerbations (4). In this context, the control status may be an adequate complemenby easily indicating the patient and the physician that something is not going as expected. The uncontrolled status may prompt investigation and possibly stepping up in therapy (19,20); it is not a diagnosis by itself, but a sign of alarm.

The concept of clinical control of COPD was initially tested retrospectively in the Optimum Patient Care Research database (OPCRD) in the UK (7). The analysis showed that patients who fulfilled the initially proposed control criteria had a reduced frequency of exacerbations over a period of one year (7). However, the proportion of controlled patients was very small indicating that the tool was too sensitive and had poor specificity. In a single center study, Soler-Cataluña et al (8) confirmed the predictive value of the control status and identified the control criteria which provided the best sensitivity and specificity (8). The current study has evaluated prospectively these new modified control criteria and has observed a similar proportion of controlled patients (65%) in comparison with the previous study (61.5%) (8). Interestingly, the clinical criteria of control provided an improved predictive classification of controlled or uncontrolled patients compared with the CAT and the concordance between control status by clinical criteria or CAT was poor. Therefore, the use of these easy-to-obtain variables (i.e. dyspnea degree, use of rescue medication, sputum color, minutes walked a day and previous exacerbations), must be encouraged at each clinical visit of patients with COPD (21).

In COPD, as opposed to asthma, control does not mean absence of symptoms or return to normal lung function, but the achievement of the best health status possible according to the level of severity (3,5,19). Due to these differences between COPD and asthma, the definition of control in COPD has been elusive to researchers and clinicians (22), but the current definition is easy to apply and has demonstrated its predictive value, making it suitable for clinical practice both in primary andin secondary care.

Our study has some limitations, since it was not an interventional study, we could not investigate whether the change in treatment could modify the control status and influence the outcomes. It is likely that a step up in treatment in non-controlled patients may change their status to controlled and reduce the future risks, but this has to be demonstrated in future interventional studies. Among the strengths, it includes a large population of patients with different degrees of severity recruited in several countries from Europe and Asia (10) and with a wide range of comorbidities, likely reflecting the real population of patients with COPD attended in specialised centers (23).

In conclusion, the current study has demonstrated that the proposed definition of control in COPD is useful in clinical practice. When defined using easy-to-obtain clinical criteria, control status is predictive of future exacerbations and time to the next exacerbation. The concept of control can be used in clinical practice at each clinical visit as a complement to the current recommendations of initial treatment proposed by guidelines.

Data availability statement:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

Conceptualization: MM, VC, AK, DBP. Data curation: MM, CE, AK. Data Acquisition: MM, PS, CKR, RWC, VC, JHYT, TSL, BA, CG, JLG-R, AT, MR-R. Formal analysis: MM, CE, AK. Funding acquisition: MM, DBP. Investigation: MM, PS, CKR, RWC, VC, JHYT, TSL, BA, CG, JLG-R, AT, MR-R, JJS-C, DBP. Project administration: MM, AK, DBP. Writing—original draft: MM. Writing—review and editing: PS, CKR, RC, VC, JHYT, TSL, BA, CG, JLG-R, AT, MR-R, JJS-C, DBP

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Table 1. Demographic and clinical characteristics of the population and comparison between controlled and uncontrolled patients using either clinical criteria or CAT scores.

	All (n=307)	Clinical Criteria (n=303)		P value	CAT Scores (n=306)		P value
		Controlled (n=197)	Uncontrolled (n=106)		Controlled (n=116)	Uncontrolled (n=190)	
Age, years	68.6 (8.7)	68.5 (8.9)	68.4 (8.3)	0.976	68.9 (9.3)	68.3 (8.3)	0.438

Sex, men, n (%)	224 (73.9)	155 (78.7)	69 (65.1)	0.010	97 (83.6)	129 (67.9)	0.002
Active smokers, n (%)	81 (26.7)	52 (26.4)	29 (27.4)	0.857	30 (25.9)	52 (27.4)	0.773
Pack-years	47.5 (31.6)	45.4 (29.1)	51.5 (35.6)	0.242	44.5 (28.2)	50.1 (34)	0.207
BMI (Kg/m^2)	26.5 (5.4)	26.4 (5.4)	26.8 (5.3)	0.536	25.9 (5.2)	26.8 (5.5)	0.132
Chronic bronchitis, n (%)	155 (59.2)	99 (59.3)	56 (58.9)	0.958	58 (55.8)	100 (62.5)	0.276
Emphysema, n (%)	201 (76.7)	132 (79)	69 (72.6)	0.238	87 (83.7)	114 (71.3)	0.021
ACO, n (%)	29 (9.6)	20 (10.2)	9 (8.5)	0.639	9 (7.8)	20 (10.5)	0.423
Bronchiectasis, n (%)	40 (13.2)	26 (13.2)	14 (13.2)	0.998	13 (11.2)	28 (14.7)	0.379
Charlson index	4.3 (1.7)	4.2 (1.0)	4.5 (1.9)	0.213	4.1 (1.6)	4.4 (1.8)	0.245
mMRC	1.5 (1)	1.3 (0.9)	2 (1)	<0.001	1.3 (0.9)	1.7 (1)	0.008
FVC, mL	2898.5 (888.5)	3062 (897.7)	2592.3 (788)	<0.001	2911.3 (878.6)	2892.3 (891.4)	0.877
FVC (%)	67.5 (14.3)	71.6 (16.1)	65.6 (14.2)	0.019	68.2 (14.5)	66.7 (13.5)	0.523
FEV1, mL	1488.5 (581.0)	1578.2 (604.2)	1321.0 (497.6)	<0.001	1498.2 (575.2)	1479.3 (584.9)	0.733
FEV1 (%)	52.5 (18.1)	54.9 (19.1)	47.9 (15.5)	<0.001	50.9 (17.5)	53.5 (17.3)	0.230
Exacerbations in the previous year	1.5 (2.8)	0.7 (1.4)	2.9 (4)	<0.001	0.9 (1.6)	1.8 (3.3)	0.019
BODEx index	2.3 (1.8)	1.8 (1.5)	3.3 (1.8)	<0.001	2.2 (1.5)	2.4 (1.4)	0.294
CAT score	14.4 (8.6)	12.1 (7.6)	18.5 (8.9)	<0.001	11.7 (6.7)	16 (9.2)	<0.001
Minutes walked/day	87.7 (75.5)	99.5 (75.7)	65.6 (70.2)	<0.001	81.7 (66.9)	91.0 (79.9)	0.738
LABA alone	32 (10.4%)	24 (12.2%)	8 (7.5%)	0.211	11 (9.5%)	21 (11.1%)	0.663
LAMA alone	39 (12.7%)	32 (16.2%)	7 (6.6%)	0.017	20 (17.2%)	20 (10.5%)	0.091
LABA/LAMA	75 (24.2%)	55 (27.9%)	23 (21.7%)	0.238	36 (31%)	43 (22.6%)	0.103
LABA/ICS	50 (16.3%)	23 (11.7%)	17 (16%)	0.285	15 (12.9%)	25 (13.2%)	0.954
LAMA/ICS	6 (1.9%)	4 (2%)	2 (2%)	0.932	0 (0%)	6 (3.2%)	0.053
LABA/LAMA/ICS	94 (30.6%)	49 (24.9%)	45 (42.5%)	0.002	29 (25%)	66 (34.7%)	0.074
LTOT	20 (6.5%)	12 (6.1%)	8 (7.5%)	0.626	6 (5.2)	14 (7.3%)	0.713

Values are mean (SD, except otherwise indicated. BMI: Body mass index; ACO: Asthma-COPD overlap; mMRC: modified Medical Research Council; CAT: COPD assessment test; CCQ: clinical COPD questionnaire; FVC: Forced vital capacity; FEV1: Forced expiratory volume in 1 second; LABA: long-acting beta-2 agonist; LAMA: Long-acting anticholinergic agent; ICS: inhaled corticosteroid; LTOT: Long-term oxygen therapy.

Table 2. Outcomes during 18 months follow-up of patients according to control status at baseline defined by either clinical or CAT criteria

	Clinical Criteria (n=303)		**P value**	**CAT Scores (n=306)**		**P value**
	Controlled (n=197)	**Uncontrolled (n=106)**		**Controlled (n=116)**	**Uncontrolled (n=190)**	
Combined event, n (%)	1.1 (2.1)	2.6 (3.1)	<0.001	1.1 (2)	1.9 (2.9)	0.015
Hospitalisation	0.2 (0.8)	0.6 (1)	<0.001	0.2 (0.8)	0.4 (0.9)	0.039
Emergency visits	0.2 (0.7)	0.5 (1)	<0.001	0 2 (0.7)	0.3 (0.9)	0.075
Ambulatory exacerbations	0.7 (1.2)	1.5 (2)	<0.001	0.7 (1.1)	1.2 (1.8)	0.016

CAT indicates COPD assessment test.

Table 3. Hazard ratios of controlled compared to non-controlled patients according to the different criteria used.

Control by clinical criteria	**HR**	**CI95%**
- Time to combined event	0.49	0.36 to 0.66
- Time to exacerbation requiring hospitalisation	0.27	0.15 to 0.47
- Time to emergency department exacerbation	0.42	0.23 to 0.77
- Time to ambulatory exacerbation	0.53	0.38 to 0.73
Control by CAT criteria	**HR**	**CI95%**

- Time to combined event	0.82	0.60 to 1.14
- Time to exacerbation requiring hospitalisation	0.61	0.33 to 1.12
- Time to emergency department exacerbation	0.72	0.37 to 1.42
- Time to ambulatory exacerbation	0.68	0.48 to 0.97

HR: Risk attributable to presenting an event in controlled patients versus non-controlled patients. Values in grey are statistically significant.

Figure legends

Figure 1. Flow chart of the study participants

Figure 2. Accumulated probability of combined event in patients controlled or noncontrolled according to either clinical (2a) or CAT (2b) criteria of control.

Figure 3. Receiver operating characteristic analysis of control status defined by clinical criteria (3a) or CAT scores (3b) and their capacity to predict the composite outcome.

[AVE1]**For the typesetters:**
Collaborators should be listed in a drop menu display under the author list in PubMed.
Collaborators are not authors and they require a different @creatorRole in the XML mark-up.
Please use creatorRole="investigator" for each collaborator. The group name should be marked up as “author” as standard.
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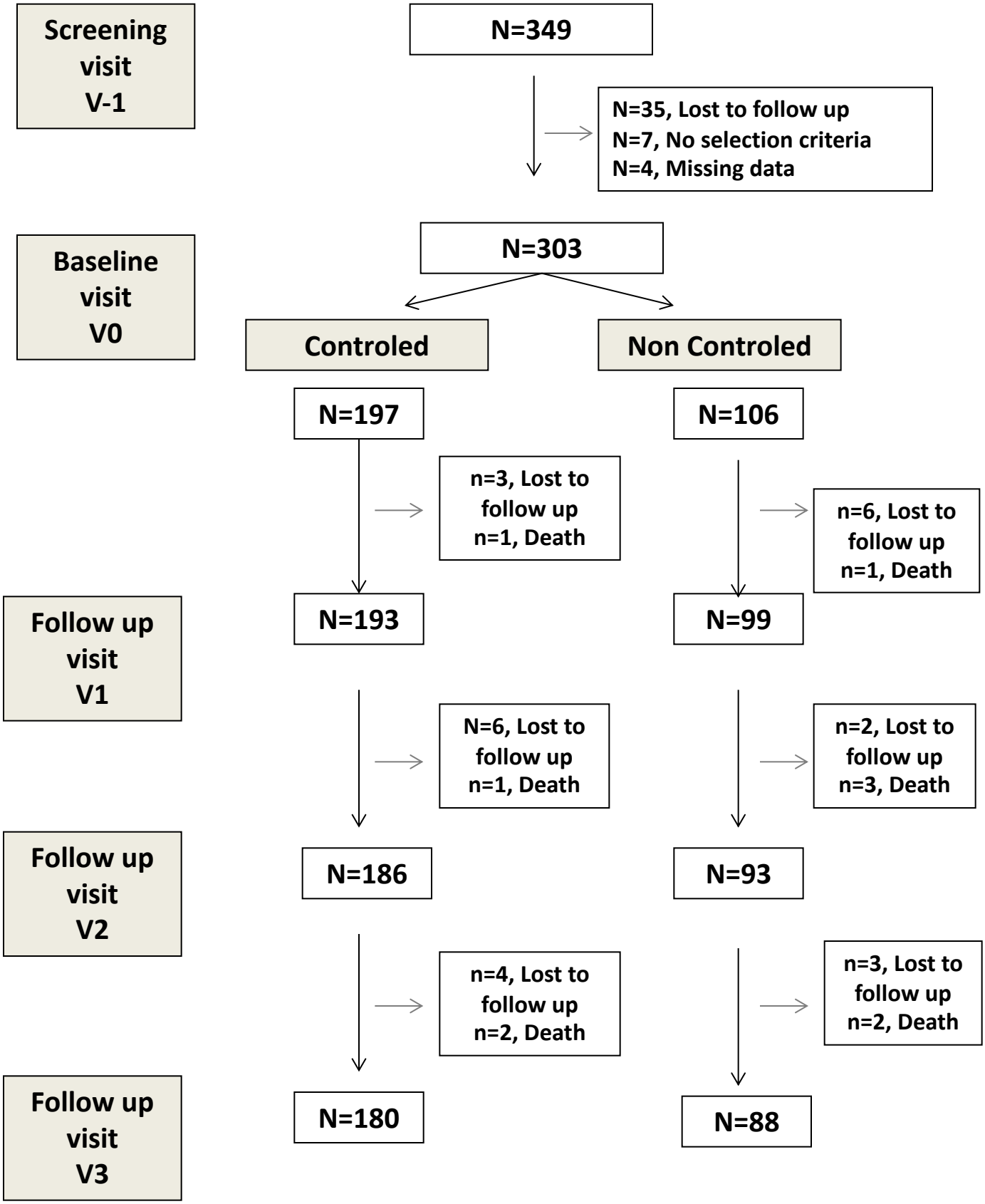
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Controled
Non Controled
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N=106
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n=1, Death
n=6, Lost to follow up
n=1, Death
Follow up visit V1
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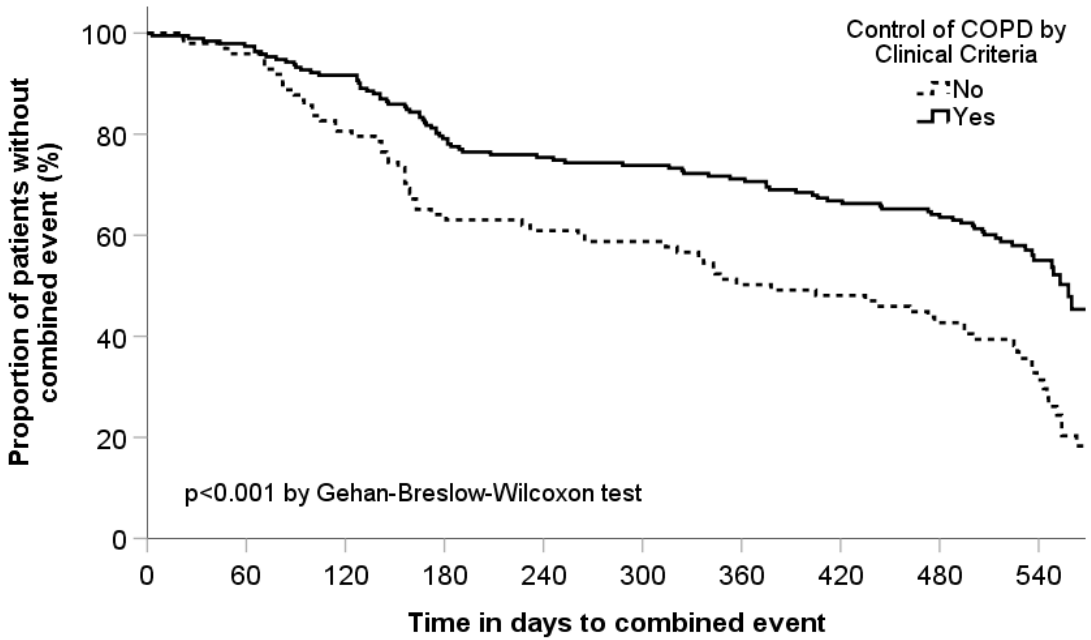
2a


Control of COPD by Clinical Criteria
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Yes
Proportion of patients without combined event (%)
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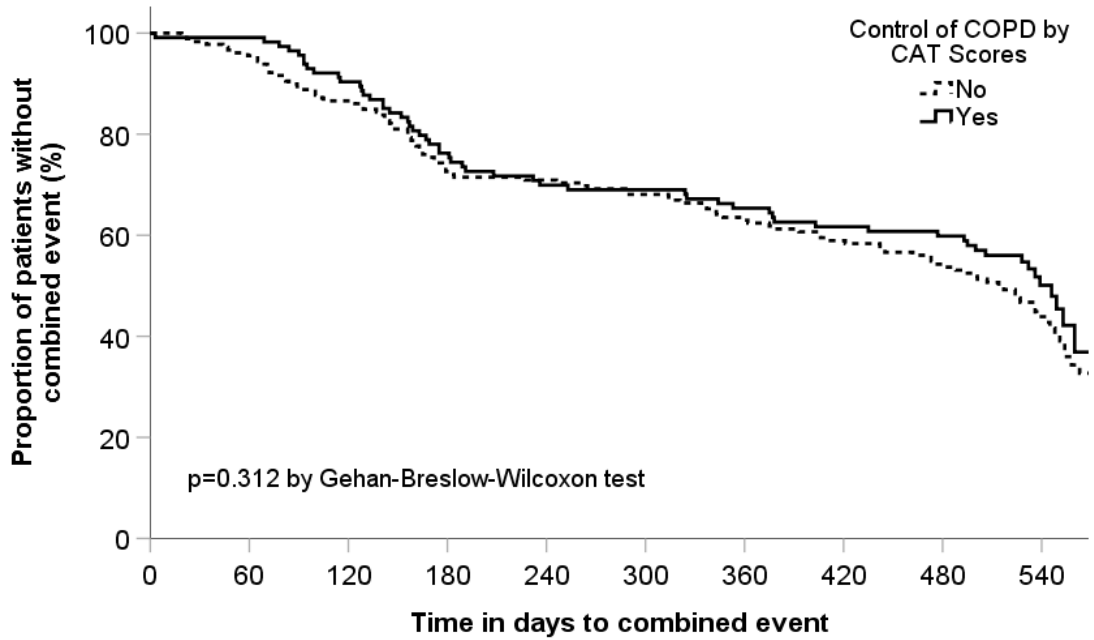
80
60
40
20
0
p<0.001 by Gehan-Breslow-Wilcoxon test
0
60
120
180
240
300
360
420
480
540
Time in days to combined event

2b


Control of COPD by CAT Scores
No
Yes
Proportion of patients without combined event (%)
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80
60
40
20
0
p=0.312 by Gehan-Breslow-Wilcoxon test
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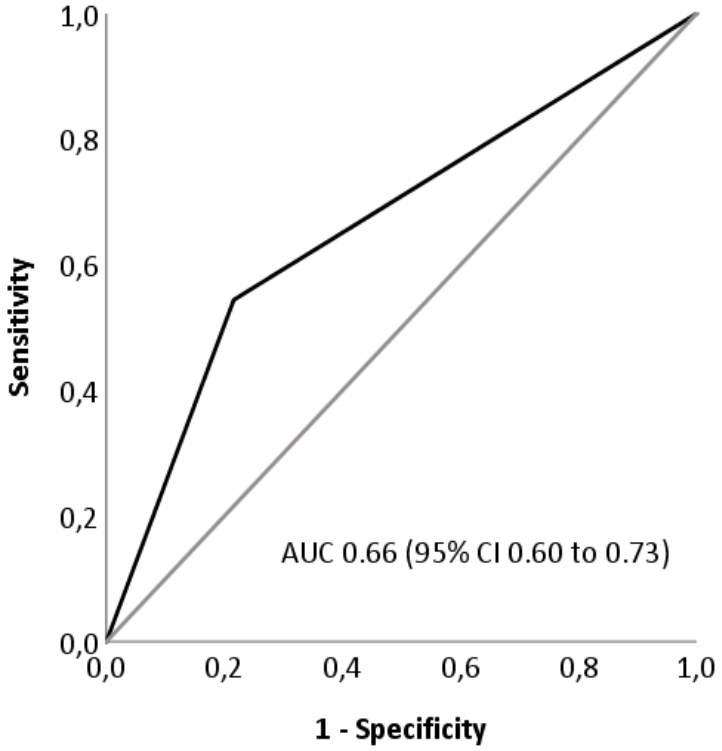
60
120
180
240
300
360
420
480
540
Time in days to combined event

3a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0,2
0,0
Sensitivity
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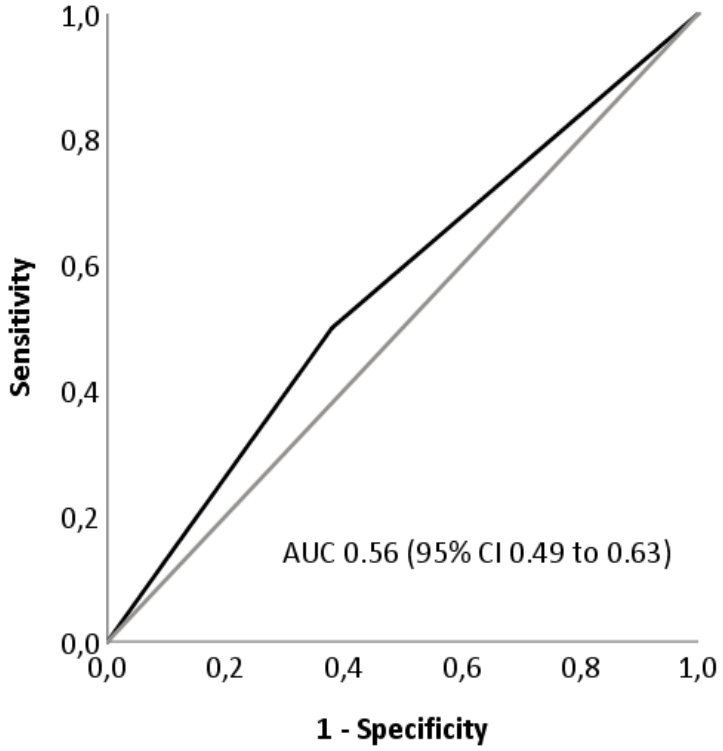
0,2
0,4
0,6
0,8
1,0
1 - Specificity

3b


1,0
0,8
0,6
0,4
0,2
0,0
Sensitivity
AUC 0.56 (95% CI 0.49 to 0.63)
0,0
0,2
0,4
0,6
0,8
1,0
1 - Specificity

SUPPLEMENTARY INFORMATION

Predictive value of control of COPD for risk of exacerbations: An international, prospective study.

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Table S1: Modified control criteria, with adjustment for severity according to the FEV_1%.

CLINICAL EVALUATION	**Criteria of control stratified by severity (FEV1(%))**	
Low impact by clinical criteria (at least three of the four criteria should be fulfilled)		
	$FEV_1 \geq 50\%$	$FEV_1 < 50\%$
- Dyspnoea (mMRC)	0-1	0-2
- Rescue medication	≤ 3 times / week	
- Sputum colour	White or no sputum	
- Physical activity	≥ 30 min/day	

Clinical stability by clinical criteria		
- Exacerbations in the last 3 months	None	
Control by clinical criteria	Low impact + Stability	
EVALUATION BY CAT	**Criteria of control stratified by severity (FEV1(%))**	
Low impact by CAT		
	$FEV_1 \geq 50\%$	$FEV_1 < 50\%$
- CAT	0-10	0-16
Stability by CAT		
- CAT changes	≤ 2 points	
Control by CAT	Low impact + Stability	

Footnote: CAT: COPD Assessment Test; FEV1(%): Forced expiratory volume in the first second in percent predicted; mMRC: modified Medical Research Council dyspnea scale.

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Table S2. Number (and percentage) of patients not fulfilling any of the impact or stability criteria required for the control status, according to either clinical of CAT definitions.

	Clinical Criteria	**CAT criteria**
High impact		
Dyspnea (mMRC)	98 (32.2)	
Rescue medication	77 (24.8)	
Sputum	50 (16.6)	
Physical activity	48 (16)	
Two or more criteria (high impact)	72 (23.5)	
CAT score		159 (51.8)
Instability		
Exacerbations previous 3 months	67 (21.8)	
Changes in CAT scores >2		98 (31.9)
Uncontrolled (High impact or instability or both)	106 (35)	190 (57.5)

Values are n (%). Percentages calculated on non-missing data. CAT indicates COPD assessment test; mMRC modified Medical Research Council.

Table S3. Number (and percentage) of controlled patients according to the criteria used: clinical or CAT scores, adjusted for severity by the FEV1(%)

	Clinical Criteria		**CAT Scores**	
	FEV1(%) <50% (n=135)	**FEV1(%) ≥ 50% (n=168)**	**FEV1(%) < 50% (n=135)**	**FEV1(%) ≥ 50% (n=171)**
Low impact	96 (71.1)	131 (78)	72 (53.3)	73 (43.5)
Stability	98 (72.6)	139 (82.7)	89 (65.9)	113 (67.3)
Control (low impact and stability)	80 (59.3)	115 (68.5)	56 (41.5)	58 (34.5)

Data are expressed as n (%); FEV1(%): Forced expiratory volume in the first second in percentage predicted.