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ORIGINAL RESEARCH ARTICLE

Monitoring daily symptoms and (self-reported) exacerbations in patients with bronchiectasis: a prospective study

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ABSTRACT

Background: Exacerbations are pivotal events in the natural history of patients with non-cystic fibrosis bronchiectasis (NCFB), since they have a negative impact on the functional evolution of these individuals. The daily symptoms of patients with NCFB show great variability, which negatively affects their self-perception of symptoms and exacerbations. The aim of this study was to identify daily symptoms in patients with NCFB, and to investigate whether there is a correlation between the frequency of self-reported exacerbations and events defined according to the criteria established in the literature to define exacerbation in bronchiectasis.

Methods: This observational and prospective study was carried out in outpatient clinics of a Brazilian public university hospital. Over 24 weeks, patients completed a diary in which daily symptoms, self-reported exacerbations, and demands for medical care for respiratory symptoms were recorded. The instruments used (diary and symptom scores ranging from 0 to 12) were developed by the researchers. The participants also answered questionnaires mMRC, Leicester's, and St. George's Respiratory (SGRQ).

Results: Twenty-eight patients returned the diary, their mean age was 54 years, and 50% out of them were classified as mild by the FACED score. Cough (64%) and expectoration (62%) were the most frequent symptoms. Correlations were found between the stability score and the mMRC ($r=0.4727$, $p=0.011$) and SGRQ ($r=0.6748$, $p<0.0001$) questionnaires. The number of self-perceived exacerbations (24) was significantly lower than exacerbations using the exacerbation consensus (63) ($p<0.01$). Additionally, no correlation was found between these two criteria.

Conclusions: There was great variability of symptoms among the individuals sampled, and even for the same individual, over time. Patients had low self-perception of exacerbations, which suggests that strategies aimed at improving this self-perception may contribute to the early detection of exacerbations.

Key words: Bronchiectasis; exacerbations; symptom diary.

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Ethics approval and consent to participate: The study has been approved by the Research Ethics Committee of the School of Medical Sciences, University of Campinas (ruling no. 79768617.9.0000.5404).

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Introduction

Bronchiectasis is persistently dilated bronchi that usually results from recurrent infections and chronic airway inflammation. Clinically, patients with bronchiectasis constitute a heterogeneous group; however, coughing, phlegm production, and exacerbations are typical hallmarks of the condition [1].

The recurrence of exacerbations characterizes the natural history of the disease and is associated with the clinical and functional deterioration of patients [2]. Additionally, exacerbations are associated with higher mortality in this population, causing higher costs for the health system [2]. Reducing the frequency, as well as diagnosing and treating exacerbations early, are actions that can have a positive impact on the quality of life and clinical evolution of patients. For this reason, the reduction of exacerbations has been used as an outcome in clinical studies [1,2].

Patients with noncystic fibrosis bronchiectasis (NCFB) present respiratory symptoms chronically. As observed in patients with chronic obstructive pulmonary disease (COPD), there is variation in the intensity of symptoms in patients with NCFB over the days, without this necessarily meaning a new exacerbation. Our hypothesis is that this variability may contribute to a low self-perception of symptoms, making it difficult in some cases to recognize early signs of exacerbations. The aim of this study was to characterize the daily symptoms of patients with NCFB and the self-reported exacerbations over 6 months. In addition, we investigated whether there is a correlation between self-reported exacerbations and those defined on the basis of the criteria of the European consensus [3].

Methods

This was an observational prospective study with a convenience sample of patients over 18 years old diagnosed with NCFB using high resolution computed tomography (CT). The study was conducted in a specialist bronchiectasis center at the Clinic Hospital of State University of Campinas (UNICAMP), and was approved by the Research Ethics Committee of the School of Medical Sciences (ruling no. 79768617.9.0000.5404). All participants signed the informed consent form. The selection, inclusion and patient follow up occurred between 2018 and 2020. Demographic, clinical and laboratory data were collected at the first visit, and spirometry data were collected from medical records. This information was gathered to draw a clinical and functional profile of the individual. At their first visit, the patients also answered questionnaires: mMRC, Leicester, and St. George's Respiratory Questionnaire (SGRQ).

At inclusion, participants had to be clinically stable for the previous 4 weeks, without having used antibiotics or corticosteroids. Patients with cystic fibrosis were not included. The participants must be able to come for scheduled visits and to complete a diary and answer the questionnaires. At the first visit, the patient received a diary where to record his/her symptoms daily for 6 months (24 weeks). The instruments used (diary and symptom scores ranging from 0 to 12) were developed by the researchers, based on the symptoms most frequently reported by patients with cystic non fibrosis bronchiectasis. In the diary, the patient signed the symptoms each day (cough, dyspnea, sputum, sputum color, asthenia, fatigue, malaise), indicating the presence (yes/no) and quantity/intensity/characteristic of each one of them; thus, a score was generated for each item, as well as a final score. For example, cough intensity was graded as none = 0, mild = 1, and severe = 2. Regarding the production of sputum, the quantity (none = 0, little = 1, average = 2 and much = 3) and color (none = 0, white = 1, yellow = 2, green = 3 and hemoptoic = 4) were graded. The other items (shortness of breath, tiredness, malaise) were also graded, and together they were called symptoms (A) with a score ranging from 0 to 12. Symptoms (B) included seeking medical attention due to worsening symptoms and exacerbation (Table 1).

During the 24-week follow up, the researcher called the patient once a month to remind him/her to complete the diary and ask him/her if he/she had to seek medical attention due to the worsening of symptoms. In each contact with the patient, the researcher reminded him/her of warning signs for exacerbations; in addition, patients were instructed to attend outpatient consultation on the next available date or to seek emergency medical care, if necessary. After six months, the patient returned the diary.

Important definitions

a) Exacerbation criterion 1: self-reported exacerbations characterized by the presence of a change in baseline symptoms that compel the patient to seek medical attention, use cortisone, or use antibiotics;
b) Exacerbation criterion 2: exacerbation defined according to the literature [3], that is, by the presence of deterioration of three or more respiratory symptoms, such as cough, increased sputum volume and consistency, sputum purulence, increased dyspnea and exercise intolerance, fatigue, malaise and hemoptysis, which last for more than 48 h with need for a change in treatment decided by a specialist doctor; this definition of exacerbation was made by the researchers and considered when there was evidence of an increase of 3 points or more in the symptom scores for at least 48 h.
c) The stability score: this score was the mean score of the first week of follow up, since, for inclusion in the study, the patient should be clinically stable for 4 weeks;
d) The exacerbation score: this score was calculated based on the scores of the days in which the patient presented with an exacerbation for any of the criteria (1 or 2).

Statistical analysis

Continuous variables are presented as the mean ± SD, and categorical variables are presented with frequency measures (absolute values and percentage). For comparing tests, the Mann-Whitney test was used (numerical variables). For comparison between stability and exacerbation scores and for the occurrence and characteristics of exacerbations according to criteria 1 and 2, the

Table 1. Symptoms score.

Group of symptoms (A) (0-12)	
Cough (0-2)	
None / mild / severe	0/1/2
Sputum volume (0-3)	
None / little / average / much	0/1/2/3
Sputum color (0-4)	
None / white (mucoid) / yellow / green / hemoptoic	0/1/2/3/4
Dyspnea	
Absence / presence	0/1
Fatigue	
Absence / presence	0/1
Malaise	
Absence / presence	0/1
Group of symptoms (B) (0-2)	
Exacerbation (0-1)	
Absence / presence	0/1
Medical care (0-1)	
Absence / presence	0/1

Wilcoxon test for related samples was used. The Spearman test was used for linear correlation analysis. Probability values of <0.05 were considered to be statistically significant. Analyses were performed with the SAS System for Windows (version 9.4, SAS Institute, 2002-2012; Cary, NC, USA).

Results

Out of the 150 patients diagnosed with NCFB followed at the clinic, 97 were not included because they were not clinically stable in the 4 weeks prior to the approach, or they said they would have difficulty filling in the diary, or they were illiterate, and 16 patients did not wish to participate. Therefore, 37 patients agreed to participate and remained active until the sixth month; however, only 28 patients returned the diary fully completed over the proposed period (6 months) (Figure 1).

The baseline characteristics of the 28 patients who participated in the study are summarized in Table 2. More than half of the patients had only elementary education. Fifty percent of the group had mild disease according to the FACED score. The SGRQ showed a moderate impact on quality of life (QoL), and the Leicester questionnaire showed a mild impact of cough on QoL, with average scores of 38.6% and 17.5 points, respectively. *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Haemophilus influenzae* were the most isolated microorganisms in the sputum culture. The most frequent symptoms were cough, which was present at 15.3±9.9 weeks (64%), and sputum production, which was present at 14.8±10.5 weeks (62%); at 35% of the time, the patients described the secretion as white, and at 15% described it as yellowish. The great intra- and interindividual variability in the symptoms' scores can be appreciated in Figure 2.

Comparing the symptom stability score with the exacerbation score, we found no difference between them (2.83±2.62 *versus* 3.32±2.80, respectively, p=0.26).

The analysis of linear correlation between the mean stability score and some variables of interest showed a moderate and strong correlation with the mMRC (ρ=0.4727, p=0.0111) and SGRQ (ρ=0.6748, p<0.0001) questionnaires (Table 3 and Figure 3) but

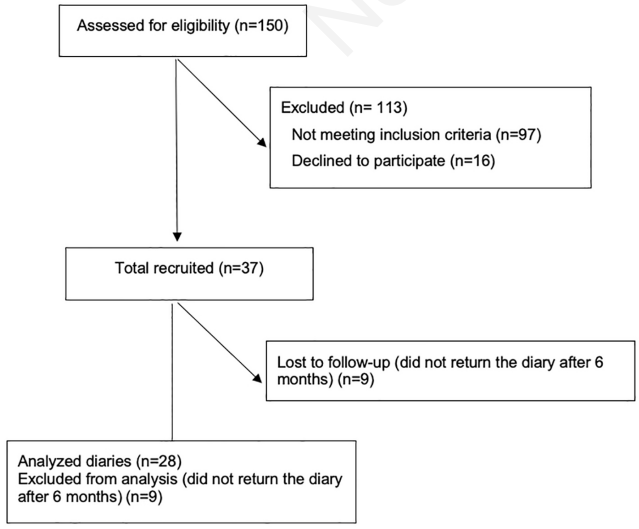

Figure 1. Flow diagram.

Table 2. Baseline data of patients (n=28).

Variables	n (%) or mean ± SD
Female/ male	17 (61%) / 11 (39%)
Age, years*	54± 13
BMI, kg/m²*	26 ± 5
Smoking history	7(25%)
Schooling, n (%)	
Elementary school	17 (60.7%)
High school	10 (35.7%)
Higher education	1 (3.6%)
Causes, n (%)	
Postinfectious	10 (36%)
Ciliary dyskinesia	4 (14%)
COPD	6 (21%)
Idiopathic	5 (18%)
Others°	10 (36%)
Medicine in use, n (%)	
Inhaled corticosteroid	26 (93%)
Long action Beta 2 agonist	27 (96%)
Short action Beta 2 agonist	5 (18%)
Macrolides	9 (32%)
Pulmonary function*	
FVC (L)	2.3 ± 0.7
FVC (% predicted)	64.3 ± 14.9
FEV_1 (L)	1.6 ± 0.6
FEV_1, (% predicted)	54.4 ± 20.0
FEV_1 / FVC	0.7± 0.1
Oxygen saturation (%)	94± 4
Computed tomography, affected lung lobes#, n (%)	
1 to 3 lobes	10 (38%)
4 to 6 lobes	16 (61%)
FACED score#, n (%)	
Mild (0-2 points)	13 (50%)
Moderate (3-4 points)	10 (38%)
Severe (5-7 points)	3 (11%)
Questionnaires*	
St. Georges score (%)	38 ± 20
Leicester score (3 - 21)	18 ± 4
mMRC (0-1)	17 (60%)
mMRC (2 or more)	11 (39%)
Bacterial isolates, n (%)	
Pseudomonas aeruginosa	11 (39%)
Staphylococcus aureus	11 (39%)
Haemophilus influenzae	7 (25%)
Acinetobacter sp.	2 (0%)
Patients with exacerbations in the last year#, n (%)	15 (58%)
Laboratory data*	
Leukocytes (x 103/µl)	8 ± 3
Hemoglobin (g/dl)	14 ± 1
Hematocrit (%)	43 ± 5
Platelets (x 10^3/µl)	280 ± 92
Erythrocyte sedimentation rate (mm/h) ^	29 ± 22
C-reactive protein (CRP)#	9±10

*Values expressed as mean and standard deviation; °primary malformations, Graft-versus-host disease, allergic bronchopulmonary aspergillosis, asthma, Swyer-James syndrome, bronchiolitis obliterans after bone marrow transplantation, common variable immunodeficiency; BMI, body mass index; FVC, forced vital capacity; FEV_1, forced expiratory volume in the first second; COPD, chronic obstructive pulmonary disease; St. Georges score, the higher score, the greater impact on quality of life; Leicester score, the higher score, the lower impact of cough on quality of life; #n=26, ^ n=25.

not with the other variables investigated (SpO_2, FEV_1, FVC and FACED score). The occurrence of self-reported exacerbations (criterion 1) was significantly lower than the exacerbations defined according to the consensus (criterion 2) ($p<0.01$). Furthermore, there was no agreement between exacerbations defined by criteria 1 and by criterion 2 ($\rho=0.32946$ and $p=0.0869$). The most frequent symptoms before and during exacerbations were increased sputum volume, change in sputum color and cough, and there was no difference concerning the type of symptom between the 2 criteria. All these data are shown in Table 4.

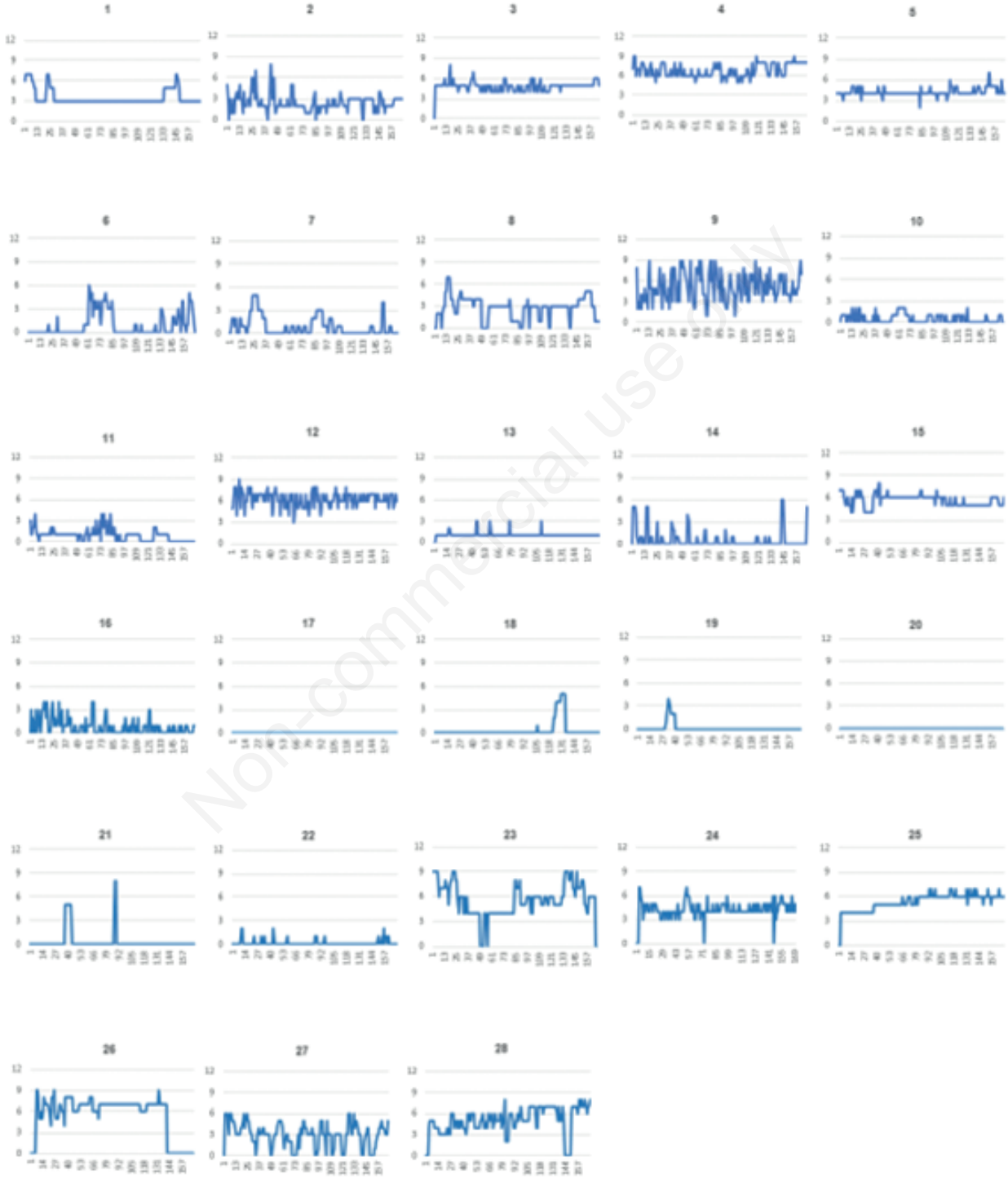

Figure 2. Graphs of the 28 patients with X axis = time (days), Y axis = symptom score (0-12). Note the great intra- and inter-individual variability in the symptom's score.

Discussion

The evaluated patients showed great intra- and interindividual variability regarding the frequency and intensity of symptoms. Intra-individual variability concerns how symptoms fluctuate and vary over time for each individual. Inter-individual variability refers to the fact that each patient has a profile of symptoms, and there is variation among patients: some individuals are oligosymptomatic, others asymptomatic and others very symptomatic. This great variability is due, at least partially, to the clinical heterogeneity of patients with NCFB. It is important to remember that the term non-cystic fibrosis bronchiectasis encompasses several causes and diseases that can cause bronchiectasis, through different triggering factors. This can lead to a clinically heterogeneous group of patients. Although it is a potential limitation of the study, we believe it is important to present this great inter-variability, which highlights the difficulty imposed by the comprehensive NCFB denomination. As a consequence, it is difficult to describe a symptom profile that applies to all patients with NCFB.

Despite this great variability, some observations deserve to be highlighted. Considering the symptomatic patients, cough and sputum production were the most common symptoms in 64% and 62%, respectively. Shashidhar *et al*. [4] identified a productive cough in 100% of patients with NCFB. Indeed, these symptoms seem to be the most frequent in individuals with NCFB [5,6]. Palwatwichai *et al*. [7] also identified cough and secretion production as the most frequent symptoms, but additionally, the authors reported dyspnea in 68% of the patients. In our study, 35% of the patients mentioned dyspnea, and the other symptoms - malaise, fever, hemoptysis, dyspnea and respiratory pain - were not fre-

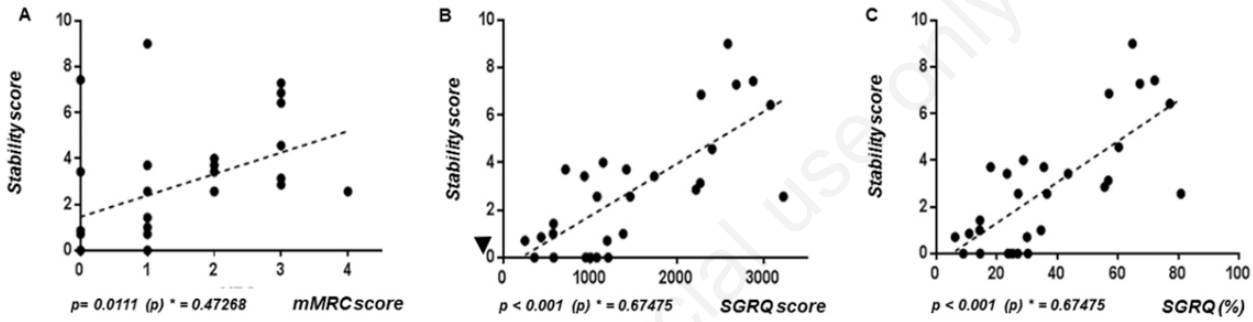

Figure 3. **Comparison between mean stability score and variables A) mMRC, B) St. Georges score, and C) St. Georges score %. (ρ)* Spearman's linear correlation coefficient.**

Table 3. **Correlation of the mean stability score and questionnaires.**

Mean stability score (0-12) (first week of inclusion)	Questionnaires	ρ*	p
2.83 ± 2.62	SGRQ	0.67475	<0.001
	SGRQ (%)	0.67475	<0.001
	Leicester	-0.35884	0.0608
	mMRC	0.47268	0.0111

*Spearman's linear correlation coefficient.

Table 4. **Comparison of frequency and characteristics of exacerbations according to criteria 1 and 2.**

	Criterion 1 (self-reported exacerbation)		Criterion 2 (exacerbation defined by consensus)	p*
Events (n)	24		63	0.007
Mean ± SD	0.9±1.2		2.3±2.6	
Spearman's Linear Coefficient (ρ)#		0.3295		0.087
Changed symptoms, n (%)				p° ****
Cough	11(46 %)		51 (81 %)	0.395
Sputum volume	14 (58 %)		54 (86 %)	0.903
Sputum color	7 (29 %)		52 (83 %)	0.979
Dyspnea	4 (17 %)		27 (43 %)	0.892
Fatigue	6 (25 %)		21 (33 %)	0.506
Malaise	5 (21 %)		12 (19 %)	0.057

*Wilcoxon test for related samples assessed correlation on the number of events between criteria; #the correlation coefficient (ρ) can vary from -1 (indicating a strong negative correlation between the two variables, that is, when one grows the other decreases) to 1 (indicating a strong positive correlation between the two variables); °comparison of each symptom between the criteria (Generalized Estimating Equations-GEE).

quent. Patients showed moderate and mild impairment of QoL by the two questionnaires applied, SGRQ and Leicester. A very interesting finding was the evidence of a correlation between SGRQ scores and stability scores. A meta-analysis by Spinou *et al*. [8] showed that the SGRQ and Leicester questionnaires are the most used questionnaires with NCFB patients, and they have strong correlations with the measured metrics (physical, psychological and social impact). These correlations, similar to our results, reinforce a possible role for these questionnaires in assessing personal and meaningful outcomes for patients with NCFB.

In addition to the correlations observed with the SGRQ, there was a correlation between the stability score and the mMRC scale. The mMRC scale, although simple, has been shown to be sensitive to assess one of the dimensions involved in the severity of NCFB patients [8-10].

In line with our findings, Artaraz *et al*. [11], in a study to develop a symptom diary to detect exacerbation in individuals with bronchiectasis, found that the baseline score, which included cough, dyspnea, fatigue, color of the sputum and fever, had a good correlation with the CAT variables, Leicester questionnaire and SGRQ. These observations allow us to hypothesize that the symptom scores objectively capture the individual's uniqueness and may eventually be useful for the patient to improve his/her self-perception, thus contributing to the self-management of the disease.

The low number of self-reported exacerbations compared to those defined from diary analysis was a surprising and unprecedented finding in patients with NCFB. To the best of our knowledge, there are few studies on self-reported exacerbations in patients with NCFB. In a large study with COPD patients aiming to determine the incidence of reported and unreported exacerbations and to compare their impact on health status, Langsetmo *et al*. have shown that less than one-third of the exacerbations were reported. Reported exacerbations were events that led to contact the study center or health care visit, and unreported were those captured by analyzing the diary. It is noteworthy that both reported and unreported exacerbations had an impact on health status [12].

The individual's self-perception regarding the worsening of symptoms may be related to what is called "functional health literacy". This term refers to the ability to process, understand and use health information that can contribute to appropriate decision-making. Low functional health literacy can predispose the individual to poor self-management and lead to worse outcomes in the disease. Sociodemographic factors such as education level, age and income influence the level of health literacy [13-15].

In our study, the majority of the patients had only completed elementary school. It is plausible to assume that the low level of education associated with low health literacy are factors that may have contributed to the reduced self-perception of exacerbations, when compared with those derived from the analysis of the diaries.

One could argue that the low educational level of the patients could have made it difficult to fill in the diaries, so that the information collected would not have been reliable. In this sense, it is important to emphasize that all patients included were literate, and that in the first interview, we shared the diary with the patient, with the aim of ensuring that the patient understood what was requested and that he/she would be able to complete it. The telephone calls and contacts made by the researcher were monthly, occasions in which any doubts regarding understanding or filling in the diary were checked. Therefore, we do believe that the information collected is reliable.

Another factor that may have contributed to the low self-perception was the daily variability of the symptoms, making it difficult to distinguish symptoms that characterize the occurrence of mild exacerbations. Figure 3 illustrates the fluctuation of symptoms (scores) over time, clearly demonstrating that some patients have symptoms every day (patients 2,3,4,5,6,7,8,9, 10,11,12,14,15,16,22,23,24,25,26,27,28), while others are mostly asymptomatic (patients 5,17,18,19,20,21). Patients who have a productive cough and dyspnea every day will find it more difficult to notice changes in the intensity of these symptoms. On the other hand, those who are basically asymptomatic or oligosymptomatic will possibly have a greater sensitivity to changes in the pattern or intensity of baseline symptoms.

Patients with COPD with increased knowledge about the disease and its impacts also showed better perception of exacerbations [16]. Low knowledge and poor self-perception of symptom deterioration in chronic patients can delay the search for help and result in suboptimal therapeutic management of exacerbation.

Our findings reinforce the importance of personalized assessment of patients with NCFB so that they can recognize their "profile" of baseline symptoms. This self-knowledge can improve individuals' sensitivity to even subtle changes in symptoms, potentially leading to an improvement in self-perception of signs of exacerbation. It is important to emphasize that frequent exacerbations directly impact costs in the health system. In addition, these events strongly contribute to the decline in lung function and increased morbidity and mortality in these patients.

One of the limitations of this study is the low number of patients, and one of the strengths is having assessed the daily symptoms over a period of 6 months. Patients' low perception of what they consider an exacerbation should be better evaluated in a study with a larger number of patients. The use of electronic devices for capturing daily symptoms may increase adherence to this type of self-monitoring. It is important to highlight that our findings point to the urgent need to increase the level of knowledge of the disease by patients with NCFB, as well as to propose strategies to improve their self-perception of symptoms.

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