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Chronic Cough and Dyspnea as Basic Indices for Phenotyping COPD in Primary Care

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Abstract

Introduction: Chronic Obstructive Pulmonary Disease (COPD) is a progressive respiratory condition characterized by heterogeneous clinical presentations and by chronic cough and dyspnea as the major symptoms.

Aim: To correlate the prevalence of chronic cough and dyspnea to corresponding clinical and lung function profiles in COPD patients.

Materials and Methods: COPD patients were recruited from twenty-four national sites. Patients were grouped by Chronic Cough (COPD-CC) or Dyspnea (COPD-Dy) as their prevailing symptom. Variables collected were: anagraphics; smoking habit; n. exacerbations in the previous year; alpha1 Anti-Trypsin (α1-AT) levels; complete lung function, and the chest X-ray report, mMRC, CAT, BCS, EQ5d-5L were also used. The association between variables and chronic cough or dyspnea was checked by Chi-square test and multinomial logistic regression.

Results: 877 patients were recruited. COPD-CC was the prevailing clinical presentation (55.4%). Lung function proved more preserved in the COPD-CC patients. Smoke; n. exacerbations/year; VR, and BODE index were positively correlated with the COPD-Dy presentation. Lower DLco values were highly probative for the COPD-Dy presentation ($p<0.001$). The probability to have some extent of emphysema was 3.40 times higher in COPD-Dy patients. Multiparametrical scores also contributed to discriminate COPD-Dy patients.

Conclusion: Chronic cough and dyspnea represent the major clinical symptoms claimed by COPD patients. As confirmed by proper lung function indices and multiparamerical scores, these symptoms provide relevant information that can contribute to easily suggest the occurrence of different pathological determinants in COPD in primary care.

Keywords: COPD; Chronic cough; Dyspnea; Emphysema; Lung function

Abbreviations

BCS: Borg Category Scale; BMI: Body Mass Index; BODE index: BMI Obstruction, Dyspnea and Exercise Performance Index; CAT: OPD Assessment Test; COPD: Chronic Obstructive Pulmonary Disease; DLCO: Diffusing Capacity; EQ5D-5L: Quality of Life Questionnaire 5-Level; FVC: Forced Vital Capacity; FEV1: Forced Expiratory Volume in 1 second; GCP: Good Clinical Practice; GP: General Practitioner; mMRC: Modified Questionnaire of British Medical Research Council; 6MWT: Six Minute Walking Test; RV: Residual Volume; SpO2: Oxygen % Saturation; VC: Vital Capacity; α1-AT: Alpha1 Anti-Trypsin

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a pathological condition characterized by a significant progression, a huge epidemiological, and a socio-economic impact worldwide [1-4]. The pathogenetic mechanisms underlying the current airflow limitation are variably mixed and lead to different clinical presentations of COPD, usually defined as "clinical phenotypes of COPD" [5-24].

In clinical practice, chronic cough and dyspnea are the major symptoms usually claimed by COPD patients, though occurring with variable severity. The careful assessment of these two major symptoms and their implementation with clinical indices and proper lung function can contribute to discriminate the prevailing obstructive chronic bronchitis from those conditions where some emphysema components are complicating COPD.

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Aim

To assess the prevalence of chronic cough and dyspnea in COPD patients, and to correlate their prevalence to corresponding clinical and lung function profiles.

Materials and Methods

The study was an observational investigation and consisted of a single visit at the referring site. During the visit, cough and dyspnea were checked together to the anagraphics of patients, their clinical history, some biological data, and their extensive lung function.

Inclusion criteria were: 1) COPD patients of both genders, aged ≥ 40 years, with airway flow limitation (post-bronchodilator FEV1/FVC ratio <0.7) in stable clinical condition; 2) subjects who provided their informed consent.

Exclusion criteria were: 1) Patients who did not meet the inclusion criteria; 2) patients who refused their informed consent; 3) subjects with severe cognitive and/or physical limitations that could interfere with the protocol procedures or make impossible any collection of anamnestic data or instrumental procedures; 4) asthma patients.

Two clusters of COPD patients were identified, independently of any comorbidity:

a. Patients with chronic productive chronic cough as their prevailing symptom (COPD-CC);

b. Patients with dyspnea as their prevailing symptom, in the absence of any history of bronchial asthma (COPD-Dy).

As the study was planned "per normal clinical practice" and CT was then not performed in the great majority of patients, the concomitant presence of bronchiectasis was not considered as a particular phenotype to investigate in the present study.

Variables considered were: Age; gender, BMI; smoking habit; >1 exacerbation in the previous 12 months; degree of dyspnea; recurrence of wheezing; alpha1 Anti-Trypsin (α1-AT) levels <100 mg/dl. Lung function consisted of: FEV1, FVC, and VC % predicted; FEV1/FVC and FEV1/VC ratio; RV % predicted; % short-term FEV1 reversibility from baseline (FEV1 increase ≥ 12% and 200 ml 30' after salbutamol 400 mcg); DLco % predicted; SpO2, and BODE Index (which consists per sé of BMI, FEV1, dyspnea, 6 min walking test). The description of the chest X-ray was also recorded, paying attention to the clear mention of "emphysema" in the radiological report. When already available, data should not precede of >6 months the date of patients' recruitment.

Patients were also provided of some questionnaires to fill:

- The Modified Questionnaire of British Medical Research Council (mMRC), in order to associate the degree of dyspnea with the level of physical exercise;
- The COPD Assessment Test (CAT): Aimed to assess the impact of COPD on patients' quality of life;
- The Borg Category Scale (BCS): To assess symptoms of breathlessness;
- The Quality of Life Questionnaire (EQ5D-5L): for assessing the generic health status.

Statistics

Calculations were performed on a single population by Full Analysis Set (FAS). The sample size needed for the evaluation of the endpoint was pre-calculated and estimated in 384 patients (95% confidence interval).

Continuous variables were expressed as mean and Standard Deviation (SD), while categorical variables were calculated as absolute number (n) and percentage (%). ANOVA model or Kruskal-Wallis test were used to compare quantitative variables, while Chi-square test was applied to compare categorical variables.

The multinomial logistic regression was used for identifying the variables associated with each clinical presentation (i.e.: COPD-CC or COPD-Dy patients). In the multivariable analysis, the Stepwise selection method was applied considering all variables with a p value ≤ 0.1 in the univariable analysis.

Moreover, the Chi square test was applied to evaluate any difference in MMRC score. Relationships between CAT tests, EQ5D-5L dimensions and BCS with each phenotype were evaluated by ANOVA, or by the nonparametric Kruskal Wallis test, while the Wilcoxon test was used for post hoc comparisons, and the Bonferroni correction for multiple comparisons.

For all statistical calculations the software SAS 9.4 was used. A p value <0.05 was considered statistically significant.

Ethics

The study was conducted according to the Good Clinical Practices (GCP) and approved by the Ethical Committee on June 15th, 2017.

The patients' informed consent was also requested for the possible anonymous use of their own data for research purposes.

Results

A total of 877 patients were recruited: 486 COPD-CC patients (55.4%) and 391 COPD-Dy patients (44.6%), respectively. They were comparable for age, gender, and BMI distribution (Table 1).

The distribution of all independent variables is reported in Table 2. Around 20% of patients still were current smokers. The never smokers were slightly more represented in COPD-CC patients, while the ex-smoker in COPD-Dy ones.

Differently from wheezing (that was equally distributed within the two groups), patients referring >1 exacerbations in the previous 12 months and those with α1-AT levels ≤ 100 mg/dl (even if measured in a limited number of patients) were more prevalent in COPD-Dy group.

As concerning lung function, the FEV1/VC ratio generally seemed more sensitive than the corresponding FEV1/FVC ratio in grading the severity of current airflow limitation. In COPD-CC patients, lung function proved more preserved, and their short-term reversibility of airway obstruction more effective. On the contrary, RV % predicted proved higher and DLco % predicted significantly lower in COPD-Dy patients, regardless their SpO_2 values that were not significantly different in the two groups. The BODE score showed lower values in COPD-CC subjects than in COPD-Dy ones. Finally, the explicit mention of emphysema in the chest X-ray reports was comparable in both groups of patients.

In order to investigate which variables might characterize each clinical presentation specifically, the COPD-CC was used as the

Table 1: Demographics by clinical presentation.

	Summary statistics	COPD-CC (n=486)	COPD-Dy (n=391)	p value
Male	%	74.50%	80.30%	ns
Age	mean ± SD	72.1 ± 8.6	71.1 ± 8.9	ns
	median (IQR)	73.0 (68- 78)	72.0 (65- 78)	
	min-max	41 - 92	42 - 91	
	min-max	38.0 - 140.0	38.0 - 120.0	
BMI	mean ± SD	27.60 ± 5.14	27.00 ± 5.58	ns
	median (IQR)	27.20 (24.0- 30.9)	26.60 (23.1- 30.7)	
	min-max	16.0 - 47.9	15.6 - 44.4	

*Chi square; **Non parametric Kruskal Wallis ***Anova test

Table 2: Description of independent variables in the two groups.

	Summary statistics	COPD-CC (n=486)	COPD-Dy (n=391)
Never smoking	%	11.4	6.6
current smoker	%	21.3	22.3
Ex smoker	%	67.3	71.1
>1 exacerbations	%	35.4	44
in the last 12 months			
Wheezing	%	25.5	23.7
α1-AT level ≤ 100 mg/dl	%	2.4	4.5
FEV1% predicted	mean ± SD	73.2 ±20.8	45.6±19.4
FEV1/VC %	mean ± SD	57.9 ± 20.7	44.6 ± 19.4
FEV1/FVC %	mean ± SD	62.5 ± 18.1	55.2 ± 33.1
RV % predicted	mean ± SD	132.8 ± 51.3	163.3 ± 61.9
FEV1 % Reversibility	Mean ± SD	14.5 ± 14.9	11.1 ± 10.7
DLco % predicted	mean ± SD	66.9 ± 28.4	45.7 ± 20.6
Chest X-ray mentioning emphysema	%	25.4	31.2
SpO_2 %	mean ± SD	94.9 ± 4.9	93.4 ± 5.5
Bode index (score)			
0-2	%	62.9	28.4
3-4	%	26.8	34.3
5-6	%	6.4	23.5
7-10	%	3.9	13.8

reference condition 1 (Table 3). In COPD-CC patients, smoke; n. exacerbations/year; VR % predicted, and BODE index proved positively correlated with the COPD-Dy phenotype, while DLco % predicted, SpO_2, FEV1/VC and FEV1/FVC ratio, and short-term FEV1 % reversibility proved negatively correlated (Table 3). Based on lung function data, COPD-Dy patients had 3.40 times higher probability to have some emphysema components in their respiratory condition (95% CI=1.89-6.10; p<0.001). The sole mention of "emphysema" in the chest X-ray report did not prove any significant relationship with lung function indices suggesting the presence of some effective emphysema components (Table 3).

The scores of all the Questionnaires used for checking the impact of COPD showed significant differences in the two groups of patients. In particular, the CAT score allowed to discriminate the COPD-CC from the COPD-Dy condition (Wilcoxon test p<0.001) (Table 4). A significant difference was also found by the MMRC score (Table 4). When using the BCS, the COPD-Dy patients showed higher mean scores comparing to those of COPD-CC patients (Wilcoxon test p=0.006) (Table 4).

Table 3: The multinomial logistic regression model (n=877). (Variables significantly related in bold).

Parameters	Phenotypes*	OR (95% CI)	P value
History of smoke			
Current smoker *vs.* never	COPD-Dy	1.8 (1.0 - 3.2)	0.035
Ex smoker vs never	COPD-Dy	1.8 (1.1 - 3.0)	0.018
>1 exacerbations/last 1yr Yes vs no	COPD-Dy	1.4 (1.1 - 1.9)	0.01
Wheezing Yes *vs.* No	COPD-Dy	0.9 (0.7 - 1.2)	0.537
Chest x-ray mentioning emphysema Yes vs No	COPD-Dy	1.3 (0.9 - 2.1)	0.199
FEV1/VC %	COPD-Dy	0.97 (0.9 - 1.0)	<0.001
FEV1/FVC %	COPD-Dy	0.98 (0.9 - 1.0)	<0.001
RV % predicted	COPD-Dy	1.0 (1.0 - 1.01)	<0.001
% FEV1 Reversibility	COPD-Dy	1.0 (1.00 - 1.3)	0.015
DLco % predicted	COPD-Dy	1	0.044
		1.0 (1.00 - 1.02)	
SpO_2	COPD-Dy	1.0	0.024
		1.0	
BODE Index			
3-4 *vs.* 0-2	COPD-Dy	2.83 (1.8 - 4.5	<0.001
5-6 *vs.* 0-2	COPD-Dy	8.21 (4.1-16.3)	<0.001
6-10 *vs.* 0-2	COPD-Dy	7.78 (3.3 - 8.1)	<0.001

*The COPD-CC presentation was the reference condition in the multinomial model

A part the Anxiety/Depression score, all the other sub-scores of the EQ5d-5L questionnaire showed a lower impact in COPD-CC than in COPD-Dy condition, particularly as concerning the Mobility, the Self Care, the Usual activities, and the VAS scores (Table 5).

Discussion

Chronic Obstructive Pulmonary Disease (COPD) is progressive respiratory condition characterized by heterogeneous clinical presentations [1,5-8]. What is currently defined "COPD" is in fact corresponding to various respiratory conditions variably characterized in clinical, biological, and lung function terms: The COPD phenotypes [10-12,14,15,24-26]. Their identification would be of great value in clinical practice as it would substantially affect the therapeutic strategy, the short- and long-term outcomes, and the overall impact of COPD.

The use of the most frequent clinical signs would also be quite important for quickly presuming the presence of some emphysema components of COPD, such as the evaluation of chronic cough and dyspnea as the prevailing symptoms claimed by COPD patients.

Actually, each of these two major symptoms proved characterized by a different discriminating power from this point of view and differently correlated to peculiar changes in some biological and lung function indices.

Simply stemming from the prevalence of these two major clinical signs, two distinct COPD conditions can be recognized in the present study: 1) The first one, characterized by chronic cough, proved related to the clinical picture of simple obstructive chronic bronchitis; 2) the second one, largely characterized by the presence of dyspnea, was characterized by a lung function profile suggesting the presence

Table 4: CAT, BCS, and MRC questionnaires in the two groups.

	Summary statistics	COPD-CC (n=486)	COPD-Dy (n=391)	p value
COPD Assessment Test (CAT)	Mean ± SD	14.6 ± 7.6	17.8 ± 7.6	<0.001
	Median (IQR)	14.0 (9-20)	18.0 (13-23)	
Low impact on life (CAT<10)	%,	33.3	23	<0.001
Medium impact on life (10 ≤ CAT ≤ 20)	%,	50.00%	44	
High impact on life (20<CAT ≤ 30)	%,	14.2	29.7	
Very High impact on life (CAT>30)	%,	2.5	3.3	
MMRC score				
no breathlessness except on strenuous exercise	%,	7.5	2.9	<0.001
shortness of breath when hurrying on the level or walking up a slight hill	%,	34.5	26.5	
walks slower than people of same age on the level because of breathlessness or has to stop to catch breath when walking at their own pace on the level	%,	36.5	36.0	
stops for breath after walking ~100 m or after few minutes on the level	%,	15.6	23.9	
too breathless to leave the house, or breathless when dressing or undressing	%,	5.8	10.6	
BCS	Mean ± SD	4.2 ± 2.6	4.7 ± 2.4	<0.001
	Median (IQR)	3.0 (2.0- 6.0)	4.0 (3.0- 6.0)	

Table 5: The EQ5d-5L questionnaire scores in the two groups.

	Summary statistics	COPD-CC (n=486)	COPD-Dy (n=391)	p value
EQ-5D-5L Questionnaire				
Mobility	Mean ± SD	1.9 ± 0.9	2.2 ± 1.0	<0.001
	Median (IQR)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	
1-2	%	73.8	59	
3	%	20.8	28.8	
4-5	%	5.5	12.2	
Self Care	Mean ± SD	1.5 ± 0.8	1.8 ± 1.0	<0.001
	Median (IQR)	1.0 (1- 2)	2.0 (1- 2)	
1-2	%	85.8	78.3	
3	%	11.5	14.2	
4-5	%	2.7	7.5	
Usual Activities	Mean ± SD	1.8 ± 0.9	2.1 ± 1.0	<0.001
	Median (IQR)	2.0(1.0-2.0)	2.0(1.0-3.0)	
	1-2%	78.1	67.8	
	3%	16.9	21.7	
	4-5%	4.9	10.5	
Pain/Discomfort	Mean ± SD	1.8 ± 0.9	1.7 ± 0.9	0.049
	Median (IQR)	2.0 (1.0-2.0)	1.0 (1.0-2.0)	
1-2	%,	78.4	79.3	
3	%,	17.8	18	
4-5	%,	3.8	2.7	
Anxiety/Depression	Mean ± SD	1.8 ± 0.9	1.8 ± 0.91	0.795
	Median (IQR)	2.0 (1.0-2.0)	2.0 (1.0-2.0)	
1-2	%,	80.90%	78.6	
3	%,	14.5	16.9	
4-5	%,	4.6	4.4	
VAS Score	Mean ± SD	63.2 ± 19.0	58.5 ± 17.5	<0.001
	Median (IQR)	65.0 (50.0-78.0)	60.0 (50.0-70.0)	

of emphysema components with high probability, even though at variable extent. In particular, if COPD-CC patients confirmed their higher prevalence in clinical practice, COPD-Dy patients proved to be the most frequent exacerbators, those characterized by the poorest lung function profile, by the lowest quality of life, and by the highest impact on health status. Recent studies carried out in Central-Eastern Europe and in Far East regions are in concordance with data of the present investigation [27,28].

This evidence tends to emphasize the discriminating power of dyspnea when it represents the prevailing respiratory symptom in COPD.

On the other hand, the identification of a peculiar lung function profile for each one of the two conditions investigated still represents a challenging issue in clinical practice [29,30]. The current assumption from the literature is that the spirometrical staging merely based on a sole parameter (usually the FEV1) is not sensitive enough for describing the complexity and the heterogeneity of structural events occurring in COPD [8,9,31,32].

It is in fact well known that FEV1 reflects all the different factors underlying the COPD airflow limitation, and then it is not effective enough for mirroring each airway or parenchymal pathogenetic mechanism contributing to different COPD presentations [13]. Also the extent of the short-term FEV1 reversibility confirmed of limited value [33]. Moreover, when compared to FEV1/FVC ratio, the FEV1/VC ratio (a measure that is more related to the elastic recoil) proved more sensitive from this point of view [34-36].

The measure of DLco contributed to discriminate COPD-Dy patients from COPD-CC ones. In other words, the existence of a substantial damage of alveolar structures can be easily presumed when dyspnea is the prevailing symptom, independently of the too frequently recurring mention of "emphysema" recorded in the chest X-ray reports of these patients.

The use of multiparametrical scores also contributed to discriminate COPD-CC from COPD-Dy patients. In particular, severe BODE scores were much more frequently recorded in COPD-Dy patients of the present study [37]. Also data from the Questionnaires used for checking any difference in Quality of Life, health status and impact for each COPD presentation confirmed their significant high sensitivity in identifying COPD-Dy patients peculiarly [38].

Conclusion

COPD is a complex, multifaceted chronic disorder that can be declined by different clinical presentations, even if their recognition still is not sufficiently pursued in clinical practice. Though at variable extent, chronic cough and dyspnea represents the major clinical symptoms claimed by COPD patients. As confirmed by proper lung function indices and multiparamerical scores, these symptoms enclose relevant information that can contribute to easily presume the occurrence of different pathological determinants in COPD, and then to optimize the most appropriate therapeutic approach even in daily clinical practice.

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