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Characteristics of patients admitted for the first time for COPD exacerbation

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Summary
Background: This study describes the characteristics of a large sample of patients hospitalised for the first time for a chronic obstructive pulmonary disease (COPD) exacerbation.
Methods: All subjects first admitted for a COPD exacerbation to nine teaching Spanish hospitals during January 2004—March 2006, were eligible. COPD diagnosis was confirmed by spirometry under stability. At admission, sociodemographic data, lifestyle, previous treatment and diagnosis of respiratory disease, lung function and Charlson index of co-morbidity were collected. A comprehensive assessment, including dyspnea, lung function, six-minute walking test, and St. George's Respiratory Questionnaire (SGRQ), was completed 3 months after admission, during a clinically stable disease period.
Results: Three-hundred and forty-two patients (57% of the eligible) participated in the study: 93% males, mean (SD) age 68 (9) years, 42% current smokers, 50% two or more co-morbidities, 54% mild-to-moderate dyspnea, post-bronchodilator FEV_1 52 (16)% of predicted (54% mild-to-moderate COPD in ATS/ERS stages), 6-min walking distance 440 m, total SGRQ score 37 (18), and 36% not report respiratory disease. The absence of a previous COPD diagnosis, positive bronchodilator test, female gender, older age, higher DLco and higher BMI were independently associated with less severe COPD.
Conclusions: We show that the patients admitted after presenting with their first COPD exacerbation have a wide range of severity, with a large proportion of patients in the less advanced COPD stages.

Introduction

Chronic obstructive pulmonary disease (COPD) is associated with a significant and increasing burden worldwide. It has been estimated that it will become the third most common cause of death and the fifth leading cause of disability-adjusted life years by 2020.[1,2] Hospitalisations due to a COPD exacerbation have a significant impact on the natural history of the disease and represent the most important direct healthcare costs associated with COPD.[1,2] Several studies highlighted the fact that COPD is frequently underdiagnosed in the community and, as a consequence, a substantial proportion of patients do not receive appropriate treatment or adequate follow-up,[3—5] which may increase the risk of exacerbations and the need for hospitalisation. The first hospital admission for a COPD exacerbation may provide a window of opportunity for the diagnosis of COPD, assessment of its severity and the initiation of appropriate therapy, including modifications to lifestyle.[6] In addition, there is evidence that even after a first admission for an exacerbation, the prognosis of COPD patients is poor. Information about the degree of airflow limitation or other severity markers, as well as other organ alterations, could all contribute to explain the significant mortality that has been previously reported concerning COPD patients after the first hospital admission.[7—9] However, most published studies of patients admitted for an exacerbation of COPD include a large proportion of patients with previous admissions, so those published conclusions may not be applicable to patients admitted for the first time.[10,11] Therefore, the clinical and functional characteristics of the patients admitted to hospital for the first time presenting with COPD exacerbation are not known.

The PAC-COPD project is a prospective multicentre study aimed at both investigating the phenotype heterogeneity of COPD patients at the time of first admission for an exacerbation and assessing the relationship between the described phenotypes and COPD course.[12] The present paper aims to describe the sociodemographic characteristics, lifestyle, clinical-functional characteristics and co-morbidities of patients admitted for the first time for a COPD exacerbation, both at the time of admission and after reaching clinical stability.

Methods

Design

The PAC-COPD project includes a cross-sectional design and a follow-up of 5 years. The present paper is based on the cross-sectional phase of the PAC-COPD, which included a recruitment visit (during the hospital admission) and a subsequent hospital visit after reaching clinical stability.

Subjects

All subjects admitted for the first time, because of a COPD exacerbation episode, between January 2004 and March 2006 to nine teaching hospitals in Spain, were recruited. Any hospital stay or time spent in the emergency room for at least 18 h with a clinical diagnosis of COPD exacerbation, was considered an admission. A COPD exacerbation was defined as ''a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD''.[13] The criteria for a first admission definition were established by means of a questionnaire, the patient's clinical record and a search of the hospital records. The exclusion criteria were: (1) patients under 45 years of age; (2) severe co-morbidity, *i.e.* tuberculosis with residual lesion affecting more than 1/3 of parenchyma, pneumectomy or diagnosed pneumoconiosis ($n = 38$), advanced cancer ($n = 74$), psychiatric disorder ($n = 33$), severe cardiovascular or neurological disease ($n = 39$), and other ($n = 74$); (3) mental incapacity ($n = 75$); (4) frail or elderly patients with any disability that would hinder participation in the study ($n = 99$); (5) not living in the healthcare area of that particular hospital ($n = 17$); and (6) not understanding the language. The diagnosis of COPD was confirmed by spirometry when the patient had reached clinical stability (at least 3 months after discharge), according to a post-bronchodilator $FEV_1/FVC \leq 0.7$.[14] COPD severity was defined according to the criteria of the European Respiratory Society and the American Thoracic Society (ERS/ATS).[14]

The protocol was approved by the Ethics Committees of all the participating hospitals and written informed consent was obtained from all subjects.

Measurements

Upon first time admission (recruitment), patients were asked to complete an epidemiological questionnaire, which included: (1) sociodemographic data: age, gender, marital status, working activity, level of education and socioeconomic status (questions from the EFRAM study);[11] (2) lifestyle information: smoking [11] and physical activity; and (3) previous treatment (any pharmacologic treatment the patient was taken regularly for chronic diseases: name of the drug, dosage, and mode of delivery) and diagnosis of respiratory disease. Additionally, the Charlson index of co-morbidity[15] was obtained by a pulmonologist from archived medical records. Lung function at admission was also recorded from medical records. Length of stay, need for non-invasive mechanical ventilation and intensive care unit (ICU) admission were obtained from the hospital discharge report. The causes of the COPD exacerbation were obtained from the list of discharge diagnosis. Available information about the non-participants was collected from their medical records.

When clinically stable, at least 3 months after hospital discharge, patients performed the following tests. To assess pulmonary function, the following analyses were performed: forced spirometry and bronchodilator test, static lung volumes by whole-body plethysmography, diffusing capacity for carbon monoxide (DLco) and arterial blood gases analysis while breathing room air at rest. All procedures were standardised according to the Manual of Procedures for the Evaluation of Lung Function from the Spanish Society of Pneumology and Thoracic Surgery.[16,17] The bronchodilator test involved the administration of 400 μg of salbutamol through a holding chamber and an increase in FEV_1 that was both greater than 200 ml and 12% above the pre-bronchodilator FEV_1 was considered significant, according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations.[18] Six minutes walking distance (6MWD) was obtained, all participating hospitals following the same protocol adapted from published recommendations,[19,20] and expressed as absolute and percentage of predicted values.[21] This consisted of two attempts (with at least a 30-min rest between them) in 30-m corridors. Encouragement was given every 1 min and the test was interrupted if symptoms of exhaustion appeared. Patients also answered an epidemiological questionnaire, including the dyspnea assessment using the Modified Medical Research Council (MMRC) scale[22] and a health status measurement (the validated Spanish version of St. George's Respiratory Questionnaire (SGRQ)).[23] Body mass index (BMI, kg/m^2) and the BODE index were calculated for each patient.[24]

A quality control protocol was applied in the different phases of the study. During preparation of the protocol and before data collection, test protocols were homogenised according to local and international guidelines, qualified staff was selected and trained, and questionnaires and forms were designed allowing to automation of filter variables and definition of intervals. Throughout the data collection process, periodic telephone conversations with data collection managers were held to comment on doubts and problems, follow-up forms for patient selection and performance of tests were dispatched weekly to draw up summary tables and detect delays or errors, results of tests were dispatched monthly to detect and resolve errors or protocol deviations, interviews were taped for later evaluation at the coordinating site using a standard form, and annual visit to sites were done to observe the interviews and test processes and to detect possible errors or protocol deviations. After data collection, data were double entered calculating the number and percentage of inconsistent data entries per test, per site, and per data input clerk, data were checked searching for improbable data, inconsistencies, and lost data, and distribution of data and of lost data was analysed by trend over time, by hospital, and by interviewer.

Statistical analysis

The results are expressed as mean ± SD or median (IQR, 25th to 75th percentiles), depending on their distribution for quantitative variables, and as frequencies and percentages for qualitative variables. Comparison between the participant and non-participant groups was performed by means of an unpaired *t*-test for quantitative variables with normal distribution, a Mann–Whitney *U*-rank test for quantitative variables without normal distribution and a chi-square or Fischer's exact test for qualitative variables. All sociodemographic, lifestyle,

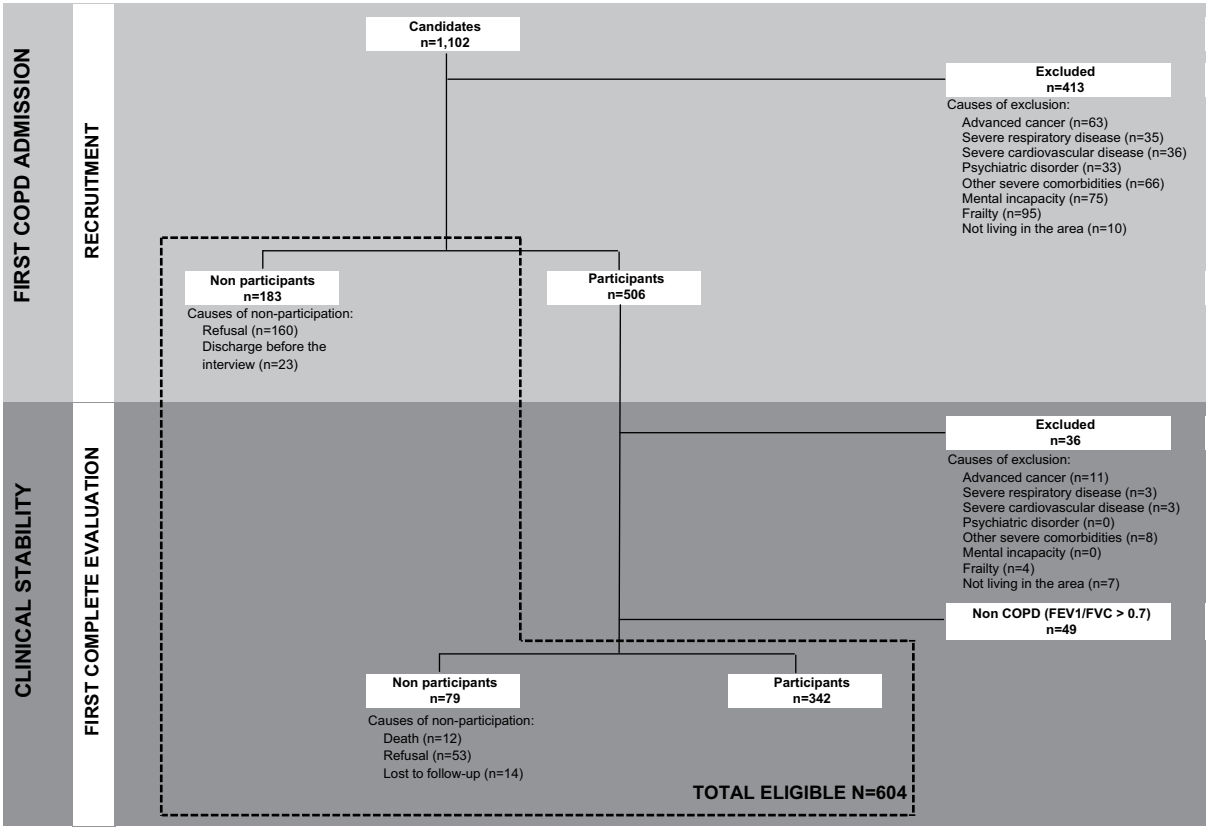

Figure 1 Flow chart of candidate patients from the first COPD admission to clinical stability, specifying their eligibility and willingness to participate, as well as exclusion or non-participation reasons.

medical care-related, clinical and functional variables of patients were compared between severity stages of COPD using ANOVA or Kruskall Wallis (for quantitative variables) and chi-square or Fisher's exact test (for qualitative variables). To identify the variables independently associated with being in a mild-to-moderate COPD stage, with severe and very severe stages as the reference groups, we built a multivariate logistic regression model. First, all variables that were associated with COPD severity in the bivariate analysis were included. Finally, a model with only independently statistically associated variables was obtained. Results were considered statistically significant at $p < 0.05$. The analyses were performed with SPSS version 11.5 (2002, SPSS Inc., Chicago, IL, USA).

Results

A total of 604 eligible subjects were identified and 342 (56.6% of them) accepted to participate. (Fig. 1). The most frequent cause of the COPD exacerbation was infection, usually tracheobronchial infection in 172 patients (50.3%), or pneumonia in 79 patients (23.1%); in the remaining 91 (26.6%) the cause was not identified. Table 1 shows that the parameters obtained during hospitalisation, including age, gender, marital status, Charlson index score, length of hospital stay and the mean of the predicted FEV_1 (%), were similar between participants and non-participants. Non-participants were more likely to have never been smokers and to have congestive heart failure. Table 1 shows the sociodemographic characteristics, lifestyle and co-morbidities of the study sample at admission. Mean (SD) age was 67.5 (8.5) years and 318 patients (93%) were males. Up to 42.4% of the patients were current smokers. At least two co-morbidities were found in 172 patients (50.3%). Two hundred and nineteen patients (64%) reported a previous diagnosis of respiratory illness and 193 patients (56.4%) were receiving some pharmacological treatment for respiratory disease before exacerbation. The comparison between males ($n = 318$) and females ($n = 24$) (not presented in tables) showed that the females were younger (58.7 (7.7) vs. 68.1 (8.2) years, $p < 0.001$), with a higher proportion of those who reported being current smokers (79.2% vs. 39.6%, $p < 0.001$) being unmarried (41.7% vs. 18.2%, $p = 0.013$) and of a high socioeconomic status (52.4% vs. 15.9%, $p < 0.001$). No statistically significant differences were found in the percentage of patients with more than one co-morbidity between females and males (37.5% vs. 51.3%, respectively, $p = 0.194$).

The characteristics of the study sample at stability are summarised in Table 2. A wide range of severity was found, although the majority of patients had moderate-to-severe COPD. The mean (SD) post-bronchodilator FEV_1 was 52.4% (16.2) of predicted. Most patients showed air trapping (measured by residual volume/total lung capacity, RV/TLC) and a mild decrease of DLco. Twenty-one patients (6.3%) had respiratory failure (PaO_2 <60 mmHg) and of those, 15 (4.5%) were also hypercapnic ($PaCO_2$ >45 mmHg). The mean (SD) BMI was 28.2 (4.7) (kg/m^2). Quality of life was moderately affected, mostly in the symptoms and activity score. There

Table 1 Sociodemographic characteristics, lifestyle and co-morbidities of COPD patients at the time of their first admission presenting with an exacerbation. Comparison between participants and non-participants.

Characteristics	Participants ($n = 342$)[a]	Non-participants ($n = 262$)[a]	p
Sociodemographic factors			
Males, *n* (%)	318 (93.0)	233 (89.3)	0.108
Age (years), mean (SD)	67.5 (8.5)	68.8 (9.2)	0.065
Married, *n* (%)	274 (80.1)	195 (75.0)	0.134
Less than primary education, *n* (%)	142 (41.5)	—	—
Low socioeconomic status (IV-V), *n* (%)[b]	259 (81.7)	—	—
Current workers, *n* (%)	61 (17.8)	—	—
Lifestyle			
Smoking, *n* (%)			
Current smoker	145 (42.4)	119 (46.1)	0.028
Ex-smoker	195 (57.0)	131 (50.8)	
Never smoker	2 (0.6)	8 (3.1)	
Pack-years, mean (SD)	65.9 (41.2)	63.3 (55.5)	0.651
Usual physical activity (h/week), median(P_{25}—P_{75})	28.5 (13.9—45.8)	—	—
Co-morbidities[c]			
Myocardial infarction, *n* (%)	34 (9.9)	20 (7.6)	0.325
Congestive heart failure, *n* (%)	17 (5.0)	24 (9.2)	0.042
Peripheral vascular disease, *n* (%)	32 (9.4)	28 (10.7)	0.588
Cerebrovascular disease, *n* (%)	12 (3.5)	18 (6.9)	0.059
Connective tissue disease, *n* (%)	6 (1.8)	4 (1.5)	1.000
Ulcer disease, *n* (%)	37 (10.8)	33 (12.6)	0.499
Mild liver disease, *n* (%)	14 (4.1)	13 (5.0)	0.609
Diabetes, *n* (%)	61 (17.8)	52 (19.8)	0.530
Hemiplegia, *n* (%)	2 (0.6)	1 (0.4)	1.000
Moderate or severe renal disease, *n* (%)	20 (5.8)	11 (4.2)	0.363
Diabetes with end organ damage, *n* (%)	6 (1.8)	7 (2.7)	0.441
Any malignancy, *n* (%)	33 (9.6)	18 (6.9)	0.223
Moderate or severe liver disease, *n* (%)	2 (0.6)	4 (1.5)	0.411
Charlson index, mean (SD)	2.0 (1.3)	2.0 (1.3)	0.602
Number Charlson co-morbidities, *n* (%)			
1	170 (49.7)	123 (46.9)	0.501
≥2	172 (50.3)	139 (53.1)	
Other			
Length of hospital stay (days), median (P_{25}—P_{75})	7 (4—10)	6 (4—10)	0.972
ICU admission, *n* (%)	16 (4.7)	—	—
Non-invasive mechanical ventilation, *n* (%)	15 (4.4)	—	—
FEV_1 (% pred.) during admission, mean (SD)	47.0 (16.5)	47.8 (17.5)	0.725
Previous diagnosis of respiratory illness (self-reported), *n* (%)	219 (65.0)	48 (61.5)	0.703
Any respiratory drug treatment, *n* (%)	193 (56.4)	145 (55.3)	0.789

[a] Some variables had missing values: two in marital status, four in smoking status, 183 in pack-years of smoking, 164 in % FEV_1 and 184 in previous diagnosis of respiratory illness (non-participants), 25 in socioeconomic status, one in pack-years of smoking, one in physical activity and 220 in % FEV_1 (participants).

[b] According to the International Standard Classification of Occupations (ISCO).

[c] Other co-morbidities included in the Charlson index (dementia, metastatic malignancies or AIDS) are not shown because of the lack of patients with such diseases.

were no significant differences between genders in air trapping and DLco, dyspnea score, 6MWD and BMI. However, females reported a previous diagnosis of respiratory illness in a lower proportion than males, showed less severe airflow obstruction and scored better in the SGRQ activity index.

The characteristics of patients, according to COPD severity, are reported in Table 3. The proportion of males was lower in mild COPD, but there were no differences in the remaining sociodemographic characteristics, lifestyle and Charlson co-morbidities. The proportion of patients who were using respiratory drug treatment and reported a previous diagnosis of respiratory disease was higher in more severe COPD individuals. There were relevant differences between the stages of severity in the majority of the clinical and functional variables. Among the patients with a first admission due to a COPD exacerbation, the

Table 2 Clinical and functional characteristics of the 342 COPD patients under stable conditions following their first admission for a COPD exacerbation.

Characteristics[a]	Total ($n = 342$)	Males ($n = 318$)	Females ($n = 24$)	p
Previous diagnosis of respiratory illness (self-reported), *n* (%)	219 (64.0)	208 (65.4)	11 (45.8)	0.046
Any respiratory drug treatment, *n* (%)	193 (56.4)	182 (57.2)	11 (45.8)	0.277
MMRC dyspnea scale, mean (SD)	2.60 (1.35)	2.64 (1.34)	2.08 (1.41)	0.055
Grade 0, *n* (%)	27 (8.0)	24 (7.6)	3 (13.0)	
Grade 1, *n* (%)	15 (4.4)	12 (3.8)	3 (13.0)	
Grade 2, *n* (%)	142 (42.0)	130 (41.3)	12 (52.2)	
Grade 3, *n* (%)	85 (25.1)	83 (26.3)	2 (8.7)	
Grade 4, *n* (%)	17 (5.0)	17 (5.4)	–	
Grade 5, *n* (%)	52 (15.4)	49 (15.6)	3 (13.0)	
FVC (l), mean (SD)	2.75 (0.73)	2.78 (0.73)	2.39 (0.64)	0.013
FVC (% pred), mean (SD)	68.7 (16.2)	67.9 (15.6)	78.7 (20.3)	0.002
FEV_1 (l), mean (SD)	1.44 (0.52)	1.46 (0.52)	1.30 (0.46)	0.162
FEV_1 (% pred), mean (SD)	48.7 (15.6)	48.1 (15.2)	56.2 (18.6)	0.015
PostBD FEV_1 (% pred), mean (SD)	52.4 (16.2)	51.7 (15.9)	61.8 (17.9)	0.003
PostBD FEV_1/FVC (%), mean (SD)	53.4 (11.9)	53.3 (12.1)	54.9 (10.5)	0.524
COPD severity, *n* (%)[b]				
I: Mild ($FEV_1 \geq 80\%$), *n* (%)	19 (5.6)	15 (4.7)	4 (16.7)	0.015
II: Moderate ($FEV_1 \geq 50\%$, $<80\%$), *n* (%)	164 (48.0)	149 (46.9)	15 (62.5)	
III: Severe ($FEV_1 \geq 30\%$, $<50\%$), *n* (%)	132 (38.6)	128 (40.3)	4 (16.7)	
IV: Very severe ($FEV_1 < 30\%$), *n* (%)	27 (7.9)	26 (8.2)	1 (4.2)	
RV/TLC (%), mean (SD)	55.5 (10.0)	55.5 (10.0)	56.0 (11.2)	0.814
DLco (% pred), mean (SD)	65.2 (20.7)	65.4 (20.8)	63.1 (19.1)	0.627
Bronchodilator test, *n* (%)[c]	69 (21.0)	63 (20.7)	6 (25.0)	0.621
PaO_2 (mmHg), mean (SD)	74.3 (10.6)	74.5 (10.8)	72.1 (8.4)	0.300
$PaCO_2$ (mmHg), mean (SD)	41.8 (5.3)	41.8 (5.5)	42.1 (3.5)	0.618
Body mass index (kg/m^2), mean (SD)	28.2 (4.7)	28.3 (4.5)	26.5 (6.5)	0.204
6MWD (m), median (P_{25}—P_{75})[d]	440.0 (390.0—509.2)	441.4 (390.0—509.6)	428.0 (378.4—510.2)	0.526
6MWD (% pred), median (P_{25}—P_{75})	90.0 (79.8—103.0)	90.7 (79.8—103.2)	86.1 (75.8—96.1)	0.221
SGRQ score (0, no health impairment to 100, maximum impairment), m(SD)				
Symptoms, mean (SD)	48.5 (17.6)	48.4 (17.7)	49.8 (17.3)	0.718
Activity, mean (SD)	47.3 (24.5)	48.3 (24.0)	33.7 (27.8)	0.006
Impacts, mean (SD)	26.5 (18.5)	26.7 (18.6)	22.8 (18.1)	0.331
Total, mean (SD)	36.5 (17.8)	36.9 (17.7)	30.7 (18.3)	0.105
BODE index score (from 0 to 10), median (P_{25}—P_{75})	2 (1—3)	2 (1—3)	1 (0—2)	0.011

[a] Some variables had missing values: four in dyspnea, 27 in RV/TLC, 46 in DLco, 11 in PaO_2, 10 in $PaCO_2$, 33 in 6MWD, four in SGRQ score, 14 in bronchodilator test and 34 in BODE index.
[b] According to the criteria of the ERS/ATS (14).
[c] Change in $FEV_1 \geq 200$ ml and $\geq 12\%$.
[d] 6-minute walking distance; the best of two 6-minute-walk tests separated by ≥ 30 min.

following variables showed significant and independent association with a mild-to-moderate stage of COPD: female gender, a significant bronchodilator test, no report of previous diagnosis of respiratory illness, higher DLco (% predicted), higher BMI and older age (Table 4).

Discussion

This is the first study that characterises a large and representative sample of the patients admitted after presenting with an exacerbation of COPD for the first time. In general, the patients in our sample population were relatively old, had more than one chronic co-morbid condition, a high proportion were current smokers and more than one third did not report a previous diagnosis of respiratory illness. At a period of COPD stability, these patients demonstrated a wide range of disease severity, with a mean post-bronchodilator FEV_1 value of about 50% of that predicted, and they reported a moderate degree of dyspnea and moderate impairment in quality of life. Multivariate analysis

Table 3 General characteristics of the 342 COPD patients admitted for the first time following an exacerbation, according to disease severity.

Characteristics	Stage I ($n = 19$)	Stage II ($n = 164$)	Stage III ($n = 132$)	Stage IV ($n = 27$)	p
Age (years), mean (SD)	67.4 (8.5)	67.6 (8.9)	68.1 (8.0)	64.0 (8.6)	0.154
Males, *n* (%)	15 (78.9)	149 (90.9)	128 (97.0)	26 (96.3)	0.015
Married, *n* (%)	19 (100.0)	131 (79.9)	105 (79.5)	19 (70.4)	0.060
Less than primary education, *n* (%)	10 (52.6)	64 (39.0)	56 (42.4)	12 (44.4)	0.676
Low socioeconomic status, *n* (%)	16 (84.2)	123 (83.1)	100 (80.6)	20 (76.9)	0.842
Current workers, *n* (%)	2 (10.5)	32 (19.5)	22 (16.7)	5 (18.5)	0.822
Smoking, *n* (%)					
Current smoker	7 (36.8)	70 (42.7)	54 (40.9)	14 (51.9)	0.354
Ex-smoker	11 (57.9)	93 (56.7)	78 (59.1)	13 (48.1)	
Never smoker	1 (5.3)	1 (0.6)	–	–	
Usual physical activity (hours/week), median (P_{25}–P_{75})	34.0 (11.3–58.0)	32.0 (16.7–49.3)	22.6 (11.1–42.4)	23.5 (14.0–46.7)	0.134
Previous diagnosis of respiratory illness (self-reported), *n* (%)	6 (31.6)	98 (59.8)	96 (72.7)	19 (70.4)	0.009
Any respiratory drug treatment, *n* (%)	5 (26.3)	82 (50.0)	88 (66.7)	18 (66.7)	0.001
Charlson index, mean (SD)	2.0 (1.7)	2.0 (1.3)	2.0 (1.4)	1.9 (1.3)	0.989
MMRC dyspnea score, mean (SD)	1.73 (1.36)	2.29 (1.25)	2.88 (1.29)	3.74 (1.19)	<0.001
RV/TLC (%), mean (SD)	44.5 (9.4)	51.5 (8.5)	60.3 (8.0)	67.7 (7.7)	<0.001
DLco (%pred), mean (SD)	90.7 (18.4)	70.2 (17.9)	59.4 (18.4)	41.4 (21.1)	<0.001
PaO_2 (mmHg), mean (SD)	82.1 (10.9)	76.5 (10.8)	71.9 (9.5)	67.3 (7.6)	<0.001
$PaCO_2$ (mmHg), mean (SD)	39.8 (4.3)	40.4 (4.8)	42.8 (5.4)	46.2 (5.2)	<0.001
Bronchodilator test, *n* (%)	9 (50.0)	36 (22.9)	23 (18.0)	1 (4.0)	0.003
6MWD (m), median (P_{25}–P_{75})	460.0 (389.9–540.0)	442.6 (390.0–510.0)	441.0 (396.5–504.3)	417.5 (337.0–466.8)	0.119
6MWD (% pred), median (P_{25}–P_{75})	94.4 (86.4–107.1)	92.5 (82.0–103.3)	88.0 (79.7–103.1)	77.0 (59.4–91.1)	<0.001
Body mass index (kg/m^2), mean (SD)	29.1 (5.2)	29.2 (4.4)	27.7 (4.5)	23.9 (4.3)	<0.001
SGRQ score, mean (SD)					
Symptoms, mean (SD)	47.2 (13.8)	45.4 (16.5)	50.5 (18.4)	58.3 (18.7)	0.002
Activity, mean (SD)	27.5 (21.5)	39.8 (21.3)	54.4 (23.5)	71.2 (21.4)	<0.001
Impacts, mean (SD)	13.4 (10.3)	22.0 (16.4)	30.5 (18.2)	43.2 (21.2)	<0.001
Total, mean (SD)	23.5 (11.5)	31.4 (15.1)	41.1 (17.4)	54.2 (18.8)	<0.001
BODE index, median (P_{25}–P_{75})	0 (0–1)	1 (1–2)	3 (2–5)	5 (4–7)	<0.001

Table 4 Variables that were independently related to being in a mild-to-moderate stage of COPD in a sample population of 342 patients admitted for the first time for COPD exacerbation.

Variables	OR (95% CI)	*p*
Age (years)	1.07 (1.02–1.13)	0.002
Gender: females	16.80 (2.89–97.46)	0.002
No previous diagnosis of respiratory illness	2.29 (1.03–5.08)	0.042
Degree of dyspnea (score from 0 to 5)	0.68 (0.50–0.91)	0.011
Significant bronchodilator test		
Change in FEV_1 $\geq$200 ml and $\geq$12%	3.37 (1.35–8.40)	0.009
DLco (%pred)	1.03 (1.01–1.06)	0.001
RV/TLC (%)	0.84 (0.79–0.88)	<0.001
$PaCO_2$ (mmHg)	0.89 (0.83–0.96)	0.003
BMI (kg/m^2)	1.11 (1.01–1.21)	0.028

OR, odds ratio; CI, confidence interval.

identified that female gender, older age, a significant bronchodilator response, no report of previous diagnosis of respiratory illness, a higher percentage of predicted DLco and a higher value of BMI were significantly and independently associated with being in the early stages of the disease at the first hospitalisation.

Prognosis is poor for patients after the first hospital admission for a COPD exacerbation. For example, a recent study of compiled data from both hospital and mortality registers reported that about 20% of patients have a 1-year mortality rate following the first COPD-associated hospital admission.[9] Similar mortality rates were reported for 49 patients from a cohort of 205 patients that had been recruited for COPD exacerbation-associated first time hospitalisation.[10] Likewise, a prospective study involving 304 COPD patients followed up for 5 years demonstrated that patients with only one COPD-related hospital admission had a poorer survival rate than those patients who were not hospitalised following an emergency room visit.[25] Surprisingly, only two previous studies provide any information on the characteristics of the few patients, admitted for the first time for a COPD exacerbation, and those studies were focused on the prevalence of modifiable risk factors of exacerbation[26] and the implementation of the British Thoracic Society guidelines.[27]

In general, the studies investigating patients admitted for COPD exacerbation are predominantly focused on patients with severe and very severe airflow obstructions.[10,26,28] By contrast, more than 50% of our sample population of first-time hospitalised COPD patients had mild-to-moderate disease. It is unlikely that the first hospital admission of COPD patients with less advanced disease was precipitated by sociodemographic factors or co-morbidities, because only older age and female gender were significantly associated with mild-to-moderate stage and there were no differences between patients with different degrees of airflow limitation within the remaining sociodemographic factor subgroups (socioeconomic status, education level or marital status) or co-morbidities. Interestingly, we have observed a strong association between having mild-to-moderate disease and the absence of a previous diagnosis of respiratory disease, which was similarly reported in a population-based study.[29] It is more likely that the absence of COPD diagnosis, and therefore, a lack of appropriate treatment, may have facilitated the admission. In fact, it has been observed that the lack of awareness of respiratory disease in mild COPD (68%) is similar to the proportion of COPD under-diagnosis reported in a Spanish population-based study.[3] It is noteworthy that the percentage of under-diagnosis is still high (up to 30%) in the severe and very severe COPD patients. These observations reinforce the importance of accurate COPD diagnosis and the implementation of appropriate therapeutic measures at the first hospital admission so that the disease can be properly managed at the earlier stages, which is more likely to halt or reduce the progression of the disease. It is of particular interest that about 40% of patients were current smokers.

An important observation from our study is that a considerable proportion of patients had a significant bronchodilator response, which is associated with mild-to-moderate airflow obstruction. In fact, bronchodilator reversibility has already been detected in COPD patients with a wide spectrum of disease severity.[30,31] In the Lung Health Study, large bronchodilator responses were uncommon in COPD patients with FEV_1 values above 55% of the predicted.[30] However, more recently, another large study has reported a substantial percentage of bronchodilator reversibility in COPD patients that decreased progressively with increasing disease severity,[31] which is consistent with our results. We speculate that the presence of a significant bronchodilator response could be a factor that contributes to first time hospitalisation in patients with less advanced disease and may increase the probability of being admitted with less severe disease.

Our results describe the distribution of relevant prognostic factors in COPD, such as airflow limitation, dyspnea, exercise capacity, nutritional depletion and health status.[32] We have already discussed that the airflow limitation was only mild-to-moderate in more than 50% of the studied patients. Although the vast majority of patients had a dyspnea of grade two to three, a large percentage of the patients reported very severe dyspnea at the stability assessment. In contrast, exercise capacity (as measured by the 6MWD) was only significantly affected in the very severe stage of disease. In fact, data from the original BODE cohort suggests that COPD patients from Spain walk more than the group from the United States.[33] Likewise, we found that the prevalence of a low body weight (defined by a BMI<20 kg/m^2) in the studied patients was only 2.9%, a substantially lower percentage than reported in other studies,[34] but consistent with previous studies that included patients with moderate-to-severe COPD from a Mediterranean population.[35] Finally, our patients exhibited higher scores in all the domains of the SGRQ (worse health-related quality of life), compared with the reference values for COPD provided by the IBERPOC study of the general population of 40–69-year old patients.[36]

The prevalence of COPD in females is increasing worldwide, which is likely the result of changing trends in cigarette consumption, with increased smoking among females. Despite this trend, most studies that recruited COPD

patients presenting with exacerbation have tended to focus on males. Only recently have some studies found gender differences in quality of life, symptoms, exercise capacity and health care use, while other studies have shown a gender bias in the diagnosis of COPD.[37,38] Our cohort included only 24 females with COPD (7% of the sample), which is a percentage slightly higher than the 4% described in a general population Spanish study in 1997,[3] although still much lower than the observed in other European countries.[18] Such a small number of women makes it difficult to draw conclusions about gender differences in patients admitted for the first time for COPD exacerbation. It is worth mentioning that there were differences in sociodemographic profile and lower degree of airflow obstruction in females, with a male:female ratio of 4:1 in the mild stage. It is likely that this difference observed in COPD severity could be explained, in part, by the younger ages of the included women.

Our study does have some limitations worth noting. First, non-participation could have lead to selection bias, since the studied sample population only included 56.6% of the total number of patients, presenting with COPD exacerbation, admitted for the first time. Most likely the non-participation was, in part, the result of the large number of tests performed during the study. The lack of difference between the non-participants and participants suggests that any selection bias, if present, is small. Second, co-morbidities may have been underestimated, since COPD patients with cardiovascular and cerebrovascular diseases and cancer were excluded, as typically occurs in studies with similar characteristics. However, a strength of the design, in contrast to other studies, is that the patients were recruited not only from the pulmonology ward, but also from all other clinical wards, which provides more reliable information regarding co-morbidities. Third, our study could possibly be criticized for the large range of inclusion criteria, without excluding non-smokers or patients with significant bronchodilator response. We chose these inclusion and exclusion criteria so that the PAC-COPD project would be aimed at investigating the phenotype heterogeneity of COPD at the time of first admission for an exacerbation. Thus, the use of more restrictive criteria could possibly have resulted in some phenotype or clinical expression of COPD being omitted. It is well known that a differential diagnosis from asthma can be difficult in some subjects and that the two diseases can overlap. In our study, the differential diagnosis from asthma was based on medical history; all patients recruited were carefully clinically evaluated by a pulmonologist participating in the study, with the clear objective to include patients without other features of asthma.

Finally, our findings might not be applicable to the first-time hospitalised COPD patients with an exacerbation from other countries that have different social and sanitary organisations. However, since there is currently a lack of relevant COPD patient characteristics information at their first admission, the results presented in this study provide a good reference point for similar studies in other countries.

In conclusion, we show that the patients admitted after presenting with their first COPD exacerbation have a wide range of severity, with a large proportion of patients in the less advanced COPD stages. We found that the patients admitted for the first time are likely to have mild-to-moderate COPD if they are females, have a significant bronchodilator response and do not report a previous diagnosis of respiratory illness. A detailed and systematic assessment of COPD patients admitted after presenting with their first exacerbation would allow for an earlier and better-planned therapeutic treatment strategy that has the potential to be tailored to each COPD patient.

Conflict of interest statement

None of the authors have a conflict of interest to declare in relation to this manuscript.

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