

Geographic differences in clinical characteristics and management of COPD: the EPOCA study

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Aims: Data on differences in clinical characteristics and management of COPD in different countries and settings are limited. We aimed to characterize the profile of patients with COPD in a number of countries and their treatment in order to evaluate adherence to recommendations of international guidelines.

Method: This was an observational, international, cross-sectional study on patients with physician-diagnosed COPD. Demographic and clinical characteristics, risk factors, and treatment were collected by their physician via an internet web-based questionnaire developed for the study.

Results: A total of 77 investigators from 17 countries provided data on 833 patients. The countries with the highest number of patients included were: Argentina (128), Ecuador (134), Spain (162), and Hong Kong (153). Overall, 79.3% were men and 81% former smokers, with a mean FEV₁ = 42.7%, ranging from 34.3% in Hong Kong to 58.8% in Ecuador. Patients reported a mean of 1.6 exacerbations the previous year, with this frequency being significantly and negatively correlated with FEV₁(%) ($r = -0.256$; $p < 0.0001$). Treatment with short-acting bronchodilators and theophyllines was more frequent in Ecuador and Hong Kong compared with Spain and Argentina, and in patients belonging to lower socioeconomic levels ($p < 0.0001$ for all comparisons). Inadequacy of treatment with inhaled corticosteroids and theophyllines was high, with significant differences among countries.

Conclusions: Differences in the clinical characteristics and management of COPD were significant across countries. Adherence to international guidelines appears to be low. Efforts should be made to disseminate and adapt guidelines to the socioeconomic reality of different settings.

Keywords: COPD, epidemiology, EPOCA, socioeconomics

Introduction

Chronic obstructive pulmonary disease (COPD) is an important public healthcare problem throughout the world. Despite anti-smoking campaigns, its prevalence and mortality rate continue rising every year (Jemal et al 2005). By 2020 it is estimated that COPD will be the fifth cause of disability and the third cause of death (Pauwels et al 2001).

A previous epidemiologic study demonstrated the prevalence of COPD in the general Spanish population between 40 and 70 years of age to be of 9.1% (Sobradillo et al 2000). However, more importantly, it was observed that 78% of the patients identified with COPD had not been previously diagnosed with the disease, and 60% of these patients were not being treated according to the current guidelines (Sobradillo et al 2000; Miravittles et al 2005). Worldwide, the prevalence of COPD in the general population is estimated to be 1% across all ages, rising steeply to 8% to 10% or higher among those aged 40 years and with nearly 80% of COPD cases remaining undiagnosed (Chapman et al 2006; Halbert et al 2006). Most of the information on the characteristics of patients with COPD and the patterns of treatment derive from a series of studies

conducted in North America and Europe (Jackevicius et al 1997; Miravittles et al 1999; Roche et al 2001; De Miguel et al 2003; Esteban et al 2006). Few studies have provided data from countries from other parts of the world, although the prevalence of COPD is also high in Latin America (Menezes et al 2005), Korea (Kim et al 2005), Taiwan (Wang et al 2007), China (Zhong et al 2007), and Japan (Fukuchi et al 2004). Exposure to respiratory risk factors also differ between geographic areas (Menezes et al 2005; Zhong et al 2007) and these, together with genetic determinants and patterns of smoking, may be the reason for the different characteristics and severity of COPD across countries (Buist et al 2007).

In recent years, epidemiological studies have demonstrated a high and increasing burden of COPD worldwide (Chapman et al 2006; Halbert et al 2006). Moreover, the adherence of treatment to currently accepted guidelines is poor in many countries (Miravittles et al 1999; Roche et al 2001; Rennard et al 2002; De Miguel et al 2003).

The EPOCA (Enfermedad Pulmonar Obstructiva Crónica en Acción) project is an international web-based survey of doctors and their COPD patients, aimed at comparing the clinical and demographic characteristics, risk factors, and treatment of patients with COPD in different areas of the world using a common protocol through the internet.

Method

Design

This was a prospective, international, cross-sectional, observational survey of outpatients diagnosed with COPD. The full data collection period included one year, from December 2005 to December 2006. Data were collected through a web-enabled database developed in two languages, English and Spanish. Physicians interested in COPD were recruited using email addresses retrieved from their publications in the field and were invited to participate by email. We aimed to have a representation of different geographic areas by contacting leading investigators who could invite colleagues in their area to join the study. Each investigator was provided with a username and a password to access an online study questionnaire. They were allowed to visualize and modify data of only their own patients. None of the investigators received any payment for participating in the study. Since the main study objectives were descriptive and group comparisons analyses were not planned, we did not make a pre-specified calculation of sample size.

Ethics

The design of the EPOCA website fulfilled all standards of data protection. Since the server was located in Barcelona

(Spain), the database was declared to the Spanish authorities. No data were collected that could help to identify any single patient in the database. The study was approved by a central ethics committee of the Hospital Clínic of Barcelona, Spain. Informed consent forms were available in the website for downloading in English and Spanish. Written or oral informed consent was obtained for the patients to be included in the study, according to local legislation for observational, non-interventional studies in each country.

Study population

This was an international, multicenter study in real life practice with a large number of investigators in different settings; therefore we wanted to minimize the risk of misclassification or misdiagnosis as much as possible by not including life-long never smokers. The inclusion criteria were: a) aged older than 40 years; b) smokers or former smokers of at least 10 pack-years; and c) had forced spirometry with a post-bronchodilator $FEV_1/FVC < 70\%$.

Exclusion criteria were diagnoses of: a) bronchial asthma; b) severe bronchiectasis; c) active tuberculosis and any other chronic infectious disease.

Study variables

The data collected included age, sex, race, socioeconomic and educational level, and risk factors and clinical characteristics of COPD. Socioeconomic level was categorized by the investigators into high, intermediate, or low according to the gross national income and related to the values for their country. Clinical characteristics of COPD included spirometric results as well as the number of previous exacerbations, emergency visits and hospitalizations due to exacerbations in the previous 12 months and healthcare utilization. Owing to the characteristics of the study, standardization of the spirometric measurements was not possible and each investigator was requested to observe American Thoracic Society criteria for standardization of spirometric procedures (American Thoracic Society 1995). Post-bronchodilator values were used for the analysis whenever available.

The treatment patterns identified included drug treatments, vaccination, rehabilitation, and long-term oxygen therapy. Adherence of prescribed treatments to the current guidelines was assessed for inhaled corticosteroids (ICS) and theophyllines. According to the GOLD guidelines existent at the time of data collection (Pauwels et al 2001), ICS were indicated in patients with FEV_1 less than 50% predicted and with one or more exacerbations and/or visits to emergency rooms and/or admissions. Theophyllines were indicated

as a second-line treatment after long-acting beta2-agonists (LABAs) and tiotropium in severe patients. To be restrictive in the indication for severe patients, we decided to use a cut off level of FEV₁ less than 30% predicted in patients already treated with LABAs and/or tiotropium. For both groups of drugs the percentages of not indicated drugs among the prescribed and the percentage of not prescribed over the indicated was calculated.

Statistical analysis

Main variables are presented as percentages. Countries with the largest participation were identified and clinical and treatment characteristics of COPD among the patients recruited in these countries were compared. We used a parametric test (Student's t-test) for variables with a normal distribution and non-parametric test (Mann-Whitney test) for non normally distributed variables. Percentages were compared by means of the chi-squared test. A p value less than 0.05 was considered significant.

Factors potentially associated with exacerbations, prescription of ICS, combination therapy of LABA + ICS, and tiotropium were studied using stepwise logistic regression analysis with the statistical package SAS version 8.02.

Results

Patient demographic characteristics

A total of 77 investigators from 17 countries included data from at least one patient in the database. The total number of patients included was 833, representing a mean of 10.8 patients per investigator. The countries/areas with the highest number of recruited patients were: Spain (n = 162), Hong-Kong (n = 153), Ecuador (n = 134), and Argentina (n = 128); these were further analyzed.

Patient demographic characteristics are summarized in Table 1. Mean age was 69.5 (SD = 10.2) years, 78.2% of participants were men, and only 19.4% were active smokers. Mean tobacco consumption for both smokers and ex-smokers was 47.7 pack-years (SD = 34 pack-years). Most of the patients had attended, either finished (24.5%) or unfinished (29.3%), only primary school, and only 8.3% had a university degree. Most individuals were retired (59.4%) and only 23.2% were active, either part- or full-time, workers. According to the investigator's perception, 38.2% of patients belonged to a lower socioeconomic class, 54.4% to a middle class, and 7.2% were ranked as upper class.

There were significant differences in most of the demographic characteristics across countries. For instance, patients in Hong Kong showed the lowest body mass index

Table 1 Demographic and socioeconomic characteristics of the study population

Variable	Global N = 833	Argentina N = 128	Ecuador N = 134	Spain N = 162	Hong Kong N = 153	p value
Sex, men, %	79.3	71.1	70.9	90.7	90.8	<0.0001
Age, years	69.5 (10.2)	66.8 (8.9)	71.7 (12.0)	69.0 (10.2)	74.9 (7.1)	<0.0001
BMI, kg/m ²	25.0 (5)	25.5 (4.3)	25.6 (5.2)	26.4 (4.8)	21.7 (3.9)	<0.0001
Active smokers, %	19	14	18.1	20.1	20	0.53
Pack-years	46.9 (33.1)	58.1 (31.1)	33.4 (31.7)	46.9 (29.9)	45.2 (33.8)	<0.0001
Biomass exposure, %	22.9	15.7	32.3	8.1	43	<0.0001
Comorbidity, %	42.5	38.1	41.4	63.4	42.1	<0.0001
Socioeconomic, %						
High	7.2	7.9	12.5	6.3	1.3	<0.0001
Intermediate	53.2	62.2	50.8	67.1	21.0	
Low	39.6	29.9	36.7	26.6	77.7	
Residence, %						
Rural	11.5	7.1	12.7	18.1	6.0	<0.0001
Intermediate	6.9	1.6	11.2	16.9	0	
Urban	81.6	91.3	76.1	65.0	94.0	
Education, %						
Up to primary	53.5	39.1	46.3	65.0	86.7	<0.0001
Up to secondary	27.7	45.3	32.8	26.1	10.6	
Up to postgraduate	18.7	15.6	20.9	8.9	2.6	

Abbreviations: BMI, body mass index.

(21.7), the oldest mean age (74.9 years), and the highest proportion of males (90.8%). Mean tobacco consumption was highest in Argentina (58.1 pack-years) and highest exposure to biomass smoke was in Hong Kong and Ecuador (43% and 32.3%, respectively) ($p < 0.0001$ for all comparisons) (Table 1).

Characteristics of COPD

Dyspnea on exertion was the most frequent symptom (97.8%), with 54.8% of patients presenting dyspnea MRC degree III or IV. Mean FEV_1 % predicted was 42.7% (SD = 17.8%). The patients presented a mean of 1.6 (SD = 2) exacerbations, 1.5 (SD = 2.5) visits to the general practitioner and 2.4 (SD = 2.6) visits to the chest specialist in the previous 12 months (Table 2). The frequency of exacerbations was significantly, albeit weakly, correlated with COPD severity, as measured by FEV_1 (%), giving a correlation factor (r) of -0.256 ($p < 0.0001$) (Figure 1).

Analysis of differences among countries showed several highly significant items. Chronic respiratory symptoms, cough and sputum, were most frequent in Ecuador (87.4% and 92.1%, respectively). Mean FEV_1 ranged from 34.3% in Hong Kong to 58.8% in Ecuador. Use of healthcare resources also differed by country. The mean number of admissions ranged from 1 per patient per year in Hong Kong to 0.4 in Ecuador and the mean number of visits to a chest specialist from 1.8 in Spain and Hong Kong to 4.6 in Argentina ($p < 0.0001$ for all comparisons) (Table 2).

Treatment of COPD

The most frequently prescribed treatment for COPD was short-acting beta-agonists (SABA) (74.8%) followed by ipratropium (48.3%), with large differences between countries. SABAs were prescribed in a range from 90.1% in Hong Kong to 21.1% in Spain. Tiotropium was used by 73.9% of patients in Spain and only 1.9% in Hong Kong. Combined treatment of LABA and ICS was used by 45.9% of patients, ranging from 12.5% in Hong Kong to 72.8% in Argentina (all differences were statistically significant, Table 3). Oral treatment was prescribed less frequently; theophyllines were used by 25.3% of the sample, with maximum frequency in Hong Kong (46.6%). Only 15.6% of patients were following a rehabilitation program, mostly in Argentina (30.5%). Interestingly, 58.6% had received the anti-influenza vaccine the previous year, with the lowest percentage in Ecuador (22.6%). Antipneumococcal vaccine was administered to 32.5%, with almost no use in Hong Kong (0.7%) and a maximum in Argentina (64.4%).

When compared with recommendations based on international guidelines (Pauwels et al 2001), we observed non-compliance with these recommendations in a significant number of patients. Specifically, 306 patients fulfilled indications for chronic treatment with ICS and 527 were regularly treated with ICS. Up to 27.8% of those with an indication for ICS treatment were not receiving them, and, according to the guidelines, 41.9% of patients treated with ICS did not fulfil the indications for treatment. This inadequacy varied

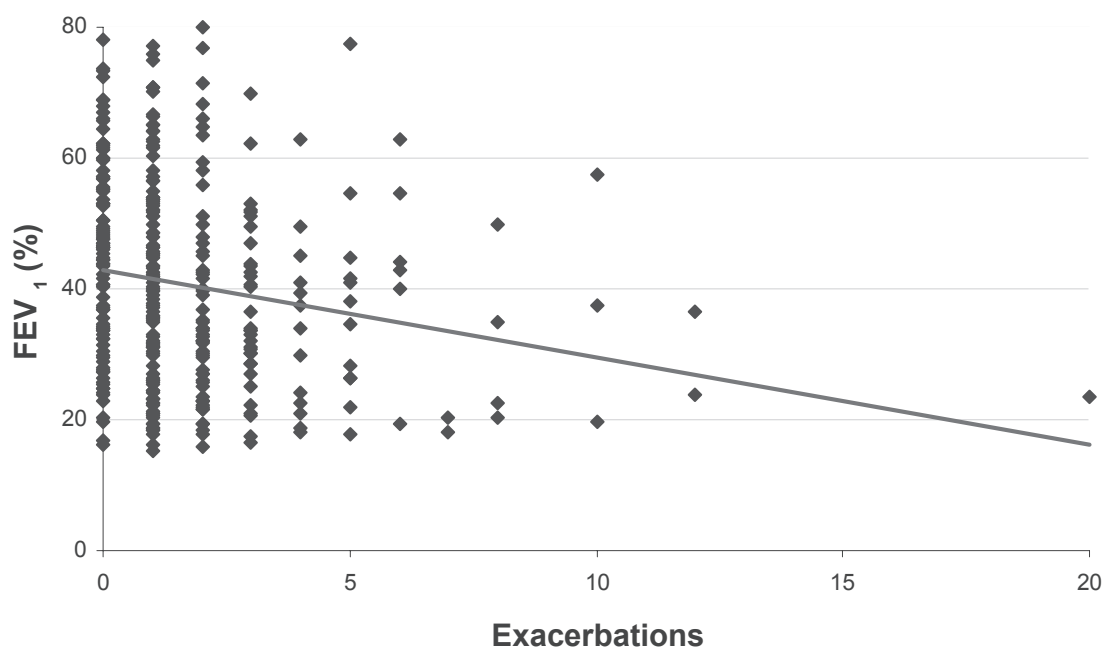


Figure 1 Correlation between lung function (FEV_1 (%)) and the frequency of exacerbations the previous year ($r = -0.256$; $p < 0.0001$).

Table 2 Characteristics of COPD

Variable	Global N = 833	Argentina N = 128	Ecuador N = 134	Spain N = 162	Hong Kong N = 153	p value
Years of evolution	10.1	11.1	8.1	14.3	8.8	<0.0001
Symptoms, %						
Dyspnea Degree 0	2.2	0	5.9	1.5	0	<0.0001
Degree 1	11.5	2.6	16.8	10.3	3.7	
Degree 2	31.4	36.2	32.8	30.1	28.3	
Degree 3	34.3	36.2	26.9	32.3	47.8	
Degree 4	20.5	25.0	17.6	25.0	20.1	
Chronic cough, %	69.6	71.2	87.4	76.6	52.3	<0.0001
Sputum, %	70.5	75.4	92.1	59.4	63.8	<0.0001
Lung function						
FVC, ml	2312.2 (920.5)	2472.5 (804.9)	2295.1 (750.2)	2709.9 (1016.9)	1448.9 (602.5)	<0.0001
FVC, % predicted	59.7 (19.4)	62.2 (16.0)	65.4 (17.7)	66.8 (19.5)	40.3 (14.8)	<0.0001
FEV ₁ , mL	1143.8 (518.7)	1147.2 (465.4)	1406.0 (627.1)	1279.5 (547.0)	841.6 (391.4)	<0.0001
FEV ₁ , % predicted	42.7 (17.8)	41.1 (15.4)	58.8 (23.5)	44.3 (17.3)	34.3 (13.9)	<0.0001
FEV ₁ /FVC	50.6 (14.5)	47.0 (13.7)	60.9 (15.9)	48.0 (13.1)	59.0 (14.2)	<0.0001
During the last year						
Number of exacerbations	1.6 (2.0)	2.0 (1.9)	0.9 (1.4)	1.8 (1.9)	1.9 (3.0)	<0.0001
Emergency visits	0.9 (1.5)	1.3 (1.8)	0.3 (0.7)	0.9 (1.5)	1.3 (2.1)	<0.0001
Admissions	0.6 (1.0)	0.5 (1.1)	0.4 (0.8)	0.6 (1.0)	1.0 (1.3)	<0.0001
IC admissions	0.1 (0.3)	0.2 (0.5)	0.0 (0.3)	0.1 (0.4)	0.0 (0.3)	<0.0001
Visits to GP	1.5 (2.5)	2.6 (3.7)	1.6 (3.2)	2.0 (3.2)	1.2 (2.5)	<0.0001
Visits to chest specialist	2.4 (2.6)	4.6 (3.8)	2.8 (2.7)	1.8 (1.8)	1.8 (2.0)	<0.0001

Abbreviations: FVC, forced vital capacity; FEV₁, forced expiratory volume in the first second; IC, intensive care; GP, general practitioner.

significantly among countries (Table 4). Theophyllines were administered to 222 patients while 123 had indications for treatment with this drug. However, up to 79.6% of the patients with indication for theophyllines were not receiving them, and, according to the guidelines, 26.6% of patients treated with theophyllines had no indication. Differences were, again, large and significant among countries (Table 4).

Differences according to estimated social class

Patients of a lower socioeconomic class were older and had a more severe impairment of FEV₁(%) than patients belonging to an upper class. They were also more exposed to biomass smoke (36.1% vs 13.5% and 18.6% for low, middle, and high class, respectively, $p < 0.0001$). Lower class patients tended to require more visits to emergency rooms and admissions for exacerbations ($p = 0.058$ and $p = 0.083$, respectively) (Table 5).

Treatments differed according to the class; SABAs, LABAs, ipratropium, and theophyllines were more frequently prescribed to lower class patients and tiotropium and combination therapy LABA + ICS were less frequently used by lower class patients (all comparisons $p < 0.0001$).

Rehabilitation was more frequent in upper class patients (31.5% compared with 15.7% and 13.4% in middle and lower classes, respectively; $p = 0.0036$) (Table 5).

Analysis of factors associated with exacerbations and prescribed drugs

Stepwise regression analysis identified the variables significantly associated with the frequency of exacerbations categorized as 0–1 versus more than 1. Older age, increasing baseline dyspnea, and use of ICS were associated with an increased frequency of exacerbations in the model (Table 6a).

In terms of pharmacologic treatment, use of ICS was significantly associated with more impaired lung function and the presence of expectoration. Patients belonging to the upper class, active smokers, and Spanish were less likely to use ICS alone compared with lower classes, former smokers, and patients from Argentina, Ecuador, and Hong Kong (Table 6b). In contrast, Spanish patients were more likely to use combination therapy with LABA + ICS than patients from Ecuador or Hong Kong, and patients with secondary schooling, former smokers, or with chronic cough were more likely to be prescribed the combination of LABA + ICS

Table 3 Treatment administered for stable COPD

Variable	Global N = 833	Argentina N = 128	Ecuador N = 134	Spain N = 162	Hong Kong N = 153	p value
Inhaled treatment, %						
SABA	74.8	85.6	69.5	75.3	97.4	<0.0001
Ipratropium	48.3	52.5	30.4	21.1	90.1	<0.0001
Tiotropium	35.5	33.9	40.6	73.9	1.9	<0.0001
LABA	9	2.5	13.3	9.1	2.6	0.0007
ICS	21.8	12.7	31.2	5.6	44.7	<0.0001
LABA/ICS	45.9	72.8	35.9	68.3	12.5	<0.0001
Oral treatment, %						
Teophyllines	25.3	18.6	26.6	7.1	46.6	<0.0001
Mucolytics	10.1	5.9	13.2	20.4	1.3	<0.0001
Oral corticosteroids	4.4	3.4	11.7	3.5	0	<0.0001
Other, %						
LTOT	21.1	14.4	17.9	24.6	17.7	0.18
Rehabilitation	15.6	30.5	3.1	4.9	7.9	<0.0001
Antiinfluenza vaccine	58.6	72.0	22.6	80.3	48.7	<0.0001
Antipneumococcal vaccine	32.5	64.4	18.7	43.6	0.7	<0.0001

Abbreviations: SABA, short-acting beta2 agonist; LABA, long-acting beta2-agonist; ICS, inhaled corticosteroid; LTOT, long-term oxygen therapy.

(Table 6c). Finally, use of tiotropium was associated only with geographic variables, with patients from Argentina, Ecuador, or Hong Kong being less likely to be treated with this drug than patients from Spain (Table 6).

Discussion

This study shows that there are significant and relevant differences in the clinical characteristics, exposure to risk factors, and patterns of management of patients with COPD in different areas of the world. Differences in genetic background may account for part of the variations shown by the results. However, different toxic exposures, differences in socioeconomic and living conditions, and differences in education levels also exist and may be responsible, at least

in part, for the variations observed in the manifestations of COPD. Epidemiological studies have demonstrated important variations in the prevalence of smoking in young adults across countries and, as a consequence, a large variation in the prevalence of chronic bronchitis (Cerveri et al 2001) and COPD (De Marco et al 2004). However, the same authors indicated that only 30% of the geographical variability in prevalence could be explained by differences in smoking habits, suggesting other factors such as environmental exposure or genetic background as contributors to this variability (Cerveri et al 2001).

The clinical characteristics of patients with COPD have been carefully studied in clinical trials (Calverley et al 2007). However, due to the restrictive inclusion and

Table 4 Inadequate treatment for stable COPD

Variable	Global N = 833	Argentina N = 128	Ecuador N = 134	Spain N = 162	Hong Kong N = 153	P value
Inhaled corticosteroids						
Indicated (n = 306)						
Prescribed (n = 527)						
Indicated, not prescribed	27.8	11.3	18.7	17.4	49	<0.0001
Prescribed, not indicated	41.9	38.6	65.1	33.3	33.3	<0.0001
Theophyllines						
Indicated (n = 123)						
Prescribed (n = 222)						
Indicated, not prescribed	79.6	85	72.2	92.9	0	0.008
Prescribed, not indicated	26.6	4.5	26.4	0	33.8	0.0016

Table 5 Demographic and clinical characteristics of patients according to estimated social class

Variables	Low N = 324	Intermediate N = 436	High N = 59	p value
Sex, men	76.5	81.9	72.8	0.091
Age, years	71.3 (9.6)	68.8 (10.2)	63.4 (10.5)	<0.0001
Active smoker	16.9	20.2	24.1	0.34
Pack-years	45.6 (33.2)	46.7 (31.6)	53.3 (39.6)	0.49
Biomass exposure	36.1	13.5	18.6	<0.0001
Years of evolution	9.3 (8.5)	10.7 (10.3)	10 (9.1)	0.34
Comorbidity	40.2	44.8	37	0.32
Baseline dyspnea				0.007
Degree 0	2.4	2	2	
Degree 1	6.3	13.7	26	
Degree 2	30.5	32.1	26	
Degree 3	37.5	32.6	30	
Degree 4	23.1	19.4	16	
Lung function				
FVC, mL	2012.5 (829.2)	2442.4 (885.3)	3033.5 (1116.5)	<0.0001
FVC, %	55.5 (19.5)	61.5 (18.4)	69.2 (19.9)	<0.0001
FEV ₁ , mL	1053.2 (485.8)	1164.4 (515.5)	1487.8 (587.1)	<0.0001
FEV ₁ , %	42.1 (18.4)	42.1 (17.0)	47.4 (18.1)	0.1311*
FEV ₁ /FVC, %	53.8 (15.2)	48.2 (13.7)	50.5 (13.3)	0.0002
Previous 12 months				
Medical visits GP	1.5 (2.4)	1.6 (2.8)	1.1 (1.5)	0.47
Medical visits specialist	2.4 (2.2)	2.5 (2.9)	2.2 (2.6)	0.43
Exacerbations	1.7 (2.4)	1.5 (1.7)	1.4 (1.5)	0.74
Emergency visits	1.1 (1.8)	0.8 (1.3)	0.6 (1.3)	0.058
Admissions	0.7 (1.2)	0.5 (0.8)	0.5 (0.8)	0.083
Treatment				
SABA	83.6	71.1	53.7	<0.0001
Ipratropium	64	39.4	24.1	<0.0001
Tiotropium	22.5	42.4	57.4	<0.0001
LABA	7.5	7.6	29.6	<0.0001
ICS	34.3	13.7	9.2	<0.0001
LABA/ICS	34.3	54.6	44.4	<0.0001
Theophyllines	35.6	23.7	22.2	0.0014
Mucolytics	6.5	14.4	9.2	0.0033
Rehabilitation	13.4	15.7	31.5	0.0036
LTOT	21.9	20.6	22.2	0.8988
Antiinfluenza vaccination	56.2	62.2	48.1	0.067
Antipneumococcal vaccination	23.8	38.9	35.1	<0.0001

*p = 0.0447 between high and low social class.

Abbreviations: FVC, forced vital capacity; FEV₁, forced expiratory volume in the first second; GP, general practitioner; SABA, short-acting beta2-agonist; LABA, long-acting beta2-agonist; ICS, inhaled corticosteroid; LTOT, long-term oxygen therapy.

exclusion criteria, these characteristics differ significantly from those of COPD patients in general practice. In fact, a Swedish study demonstrated that less than 20% of patients with COPD attended by general practitioners share characteristics with patients included in clinical

trials (Herland et al 2005). Therefore, surveys conducted in real clinical practice in different areas of the world with broad inclusion criteria are required to identify the characteristics, risk factors, and patterns of management of COPD in real life.

Table 6 Multivariate stepwise regression models of dependent variables significantly and independently associated with the following independent variables: frequency of exacerbations (0–I versus > I), treatment with ICS, combination therapy LABA + ICS and tiotropium (all presented as yes versus no)**a) Frequency of exacerbations**

Variable	Point estimate	95% confidence limits	p value
Age >75 vs 65–75 yrs	0.948	0.596–1.508	0.8223
Age >75 vs <65 yrs	2.088	1.280–3.406	0.0032
Dyspnea II vs 0–I	4.399	1.618–11.962	0.0037
Dyspnea III vs 0–I	6.223	2.308–16.782	0.0003
Dyspnea IV vs 0–I	14.249	5.110–39.735	<0.0001
Inhaled corticosteroids	2.535	1.611–3.991	<0.0001

b) Treatment with inhaled corticosteroids

Variable	Point estimate	95% confidence limits	p value
FEV1 <50% vs >50%	1.994	1.059–3.754	0.0326
Expectoration	2.595	1.457–4.619	0.0012
Low class vs high class	5.875	1.907–18.098	0.0020
Middle class vs high class	4.667	1.620–13.448	0.0043
Former vs active smoker	4.663	2.386–9.113	<0.0001
Argentina vs Spain	1.599	0.762–3.358	0.2148
Ecuador vs Spain	1.484	0.447–4.923	0.5193
Hong Kong vs Spain	0.185	0.088–0.388	<0.0001

c) Treatment with combination LABA + ICSs

Variable	Point estimate	95% confidence limits	P value
Education secondary vs primary	1.689	1.031–2.766	0.0373
Education postgraduate vs primary	0.925	0.482–1.778	0.8160
Cough	1.756	1.073–2.875	0.0252
Former vs active smoker	3.139	1.754–5.617	0.0001
Argentina vs Spain	1.110	0.628–1.962	0.7203
Ecuador vs Spain	0.181	0.101–0.326	<0.0001
Hong Kong vs Spain	0.073	0.039–0.137	<0.0001

d) Treatment with tiotropium

Variable	Point estimate	95% confidence limits	P value
Former vs active smoker	1.442	0.803–2.590	0.2198
Argentina vs Spain	0.166	0.096–0.286	<0.0001
Ecuador vs Spain	0.234	0.135–0.403	<0.0001
Hong Kong vs Spain	0.007	0.002–0.22	<0.0001

Data from international surveys of patients with COPD in real life are scarce. Two previous surveys identified patients through random telephone calls (Rennard et al 2002; Miravittles et al 2007). The Confronting Survey performed in 6 European countries, the US, and Canada demonstrated

the significant impact of COPD on daily life activities and how patients underestimate disease severity. Furthermore, only 45% of patients had undergone spirometry for diagnosis (Rennard et al 2002). Similarly, in a large survey conducted in Spain in 6,758 adults, the prevalence of chronic respiratory

symptoms was 36%, but only 56% of the individuals with symptoms consulted a physician and of these, only 42% underwent spirometry (Miravittles et al 2006). The Perceive Study, conducted in 5 European countries and the US demonstrated the burden associated with the exacerbations of COPD and the impact of the exacerbations on daily life activities (Miravittles et al 2007a). In contrast with the current study, no confirmation of the diagnosis or severity of COPD was possible because of the lack of spirometry in the aforementioned surveys. Moreover, they collected information only on patients from Europe and North America and no data from Asia-Pacific or Latin America were available. In our study only patients with confirmed COPD by spirometry were included and most of the patients had post-bronchodilator values. However, a few patients had only one value registered for spirometry. Most were severe patients who needed to take their bronchodilators to relieve their severe dyspnea before attending the clinics and perform spirometry; therefore, their values can be considered post-bronchodilator values. Additionally, although we recognize the importance of COPD in never smokers, we recruited only patients who were either smokers or ex-smokers to avoid misclassification of patients with other respiratory diseases such as asthma.

Recent well-conducted epidemiological studies have provided information on the burden of the disease in those areas. The PLATINO project observed a prevalence of COPD (GOLD II to IV) in Latin America ranging from 2.9% in Mexico City to 7.1% in Montevideo, again highlighting the importance of geographical variation (Menezes et al 2005). Using the same protocol, the BOLD initiative, performed in 12 sites around the world, demonstrated a significant variation in the prevalence of COPD (GOLD II to IV), ranging from 8.5% in males in Reykjavik to 22.2% in Cape Town and from 3.7% in women in Hanover to 16.7% in Cape Town. Interestingly, significant heterogeneity was observed between sites, especially in women (Buist et al 2007). These differences can be observed among different areas of the same country, as was demonstrated in a Spanish study in 7 different cities, in which the prevalence of COPD ranged from 4.9% to 18% (Sobradillo et al 2000). Not only prevalence but also severity of impairment in functional status and perceived health may vary in different racial groups within the same country, as demonstrated in different population groups in the US (Adams et al 2006). At least part of these differences can be caused by exposure to other risk factors, such as biomass smoke exposure (Ramirez-Venegas et al 2006) or environmental exposure (Montn  mery et al 2001). A significant exposure to biomass fuel was declared by 42%

of the COPD patients in Hong Kong and in 32% in Ecuador, compared with only 8% in Spain or 15% in Argentina. Other possibilities are the different perception of symptoms, which have demonstrated to be related to cultural factors in some racial groups (Han et al 2005).

We observed significant differences in the characteristics and management of the disease according to the socioeconomic status of the patients. It is important to point out the existing limitations for adequate classification of socioeconomic status among different countries. However, the results obtained are consistent with other published national series (Montn  mery et al 2001; Ellison-Loschmann et al 2007; Hegwald and Crapo et al 2007). The current results demonstrate a higher exposure to biomass fuel in patients with lower socioeconomic status and better lung function in upper classes. Treatment also showed some differences, with a higher use of old, cheaper, SABAs and theophyllines and a lower use of tiotropium and combination therapy with LABA + ICS in patients of lower class and education. This variation in the use of drugs may largely be due to the economic level of the patients since national health coverage was poor in the countries showing the highest differences. These results concur with other epidemiological surveys which demonstrated a significant negative correlation between lung function and socioeconomic status (Hegwald and Crapo 2007). However, there is a lack of evidence of the long-term impact of inadequate or insufficient treatment of COPD in patients of lower socioeconomic status, as observed in our study.

Exacerbations are a frequent event in the natural history of COPD. Our patient population had had a mean of 1.6 episodes the previous year and the frequency of exacerbations was significantly associated with an older age and a more severe baseline dyspnea. There was a weak but significant correlation between a more impaired FEV₁(%) and more frequent exacerbations ($r = -0.256$; $p < 0.0001$). The relationship between impaired lung function and more frequent exacerbations has been observed in clinical trials (Burge and Wedzicha 2003) and observational studies (Miravittles et al 1999), but it has also been demonstrated in this study in heterogeneous populations from different countries, which together reinforces the relationship between the natural history of the disease and the frequency of exacerbations.

Most patients received treatment for COPD and this treatment differed widely among countries, suggesting that implementation of international guidelines is not uniform around the world. SABAs are widely used, but more new and expensive drugs such as tiotropium and combination

therapy with LABA + ICS are more frequently prescribed in countries with a higher economic level and in patients of higher socioeconomic classes. In fact, country was the only variable significantly associated with prescription of the three drugs analyzed in multivariate models. The lack of adherence to treatment guidelines for COPD has been extensively demonstrated in previous studies (Jackevicius et al 1997; Miravittles et al 1999; Roche et al 2001; Rennard et al 2002; De Miguel et al 2003; Esteban et al 2006; Miravittles et al 2007b). Our results highlight this problem and identify some of the aspects related to the prescription of different drugs. Another interesting observation is the analysis of prescription of theophyllines and ICS. Evolutionary studies have demonstrated that theophyllines have been replaced by the use of ICS in patients with COPD over time (Van Andel et al 1999). However, the use of theophyllines is still very frequent in countries such as Hong Kong and Ecuador, probably for economic reasons. According to the guidelines at the time of data collection, there was a lack of adjustment in the use of these two drugs. According to the guidelines, 41.9% of the prescriptions of ICS were not prescribed correctly and, conversely, in 27.8% of the cases in which they were indicated, the ICS were not prescribed. Similarly, a large survey on 11,973 patients with COPD in Spain showed that 69% of patients with mild COPD were receiving ICS regularly (Viejo-Bañuelos et al 2006). A recent study has shown that some patients with COPD receiving ICS had clinical characteristics similar to asthma (Miravittles et al 2007b) which could justify its use even if FEV₁ is above 50% predicted (Siva et al 2007). Most patients with an indication of theophyllines were not receiving them, perhaps because of the risk of side effects, whereas 26.6% of patients treated with theophyllines should have received other more appropriate drugs.

The EPOCA study was an attempt to characterize COPD patients and patterns of management in different countries by using the same protocol and with a simple and fast data collection through a web-enabled database on the internet. This is one of the few observational studies performed in COPD patients using this new technology (Miravittles et al 2002). Despite its relatively small sample size, it has allowed the identification of significant differences in the clinical characteristics and management of COPD across countries. The results do not aim to be fully representative of the populations of COPD patients in each of the countries participating. The selection of investigators was not random or weighted according to the population of the countries. To perform such a full-scale representative survey would be a tremendous task, clearly beyond the scope and the possibilities of our

study. However, keeping this limitation in mind, our results demonstrate, at an international level, the large variability of characteristics of COPD patients and their management. The results obtained have shown that the characteristics of patients with COPD vary in different countries and patterns of management differ according to socioeconomic factors. A significant number of patients were not receiving treatment according to guidelines, which may result in suboptimal effects of therapy. More efforts are required to disseminate and implement international guidelines and attempt to adapt these guidelines to the socioeconomic reality of each setting. The national scientific societies may play an important role in disseminating the guidelines through national key opinion leaders, local publications translated into their own languages and local scientific meetings.

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Author contribution

Marc Miravittles, study design, analysis and interpretation of data, and writing of the manuscript. Antonio Anzueto, study design, analysis and interpretation of data, and critical review of the manuscript. Cristina Murio, analysis and interpretation of data, monitoring of the study, and critical review of the manuscript. Gema Tirado-Conde, Gur Levy, Alejandra Ramirez-Venegas, Fanny Ko, Byron Canelos-Estrella, Eduardo Giugno, Miguel Bergna, and Ivan Chérrez, data collection, critical review of the manuscript. Hana Muellerova securing funding for the study, study design, and critical review of the manuscript. Joan B. Soriano, study design, analysis and interpretation of data and critical review of the manuscript.

Disclosures

HM is an employee of GlaxoSmithKline, the company sponsoring this study. The other authors have no conflicts of interest to declare in relation to this manuscript.

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Appendix I

Organization of the EPOCA study

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