Original Study

Epidemiological survey in primary care patients with chronic obstructive pulmonary disease in Greece; The EPIPTOSI study

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SUMMARY. OBJECTIVES: Chronic obstructive pulmonary disease (COPD) is a chronic disease, with significant extrapulmonary effects, associated with high morbidity and mortality. The current study aimed at evaluating the characteristics, health status, management and use of health care resources of primary care patients with COPD in Greece. **METHODS:** EPIPTOSI was an observational, descriptive, cross-sectional study of primary care patients diagnosed with COPD. Data were collected during a single visit via a structured questionnaire. Smoking status, severity, symptoms, treatment, health care resource utilization and the patients' perceptions of health status and treatment were recorded. **RESULTS:** The 930 study patients (Male 66.5%, age 64.9±10.8 years) were classified with mild (22%), moderate (52%) and severe COPD (26%) respectively, based on the Global Initiative for Obstructive Lung Disease (GOLD) criteria, of whom 49.8% were smokers (average pack years 41.2). The average Clinical COPD Questionnaire (CCQ) score was 1.87± 1 (mild: 1.1±0.7, moderate: 1.6±0.8, severe: 2.9±1.5, $p<0.01$). The Geriatric Depression Scale (GDS) mean score for patients ≥65 years was 7.8±0.9, with a close correlation between CCQ score and severity of COPD. Treatment was with inhaled corticosteroids/long-acting β_2-agonists combination (ICS/LABA) for 35.2% of patients and ICS/LABA plus anticholinergics for 27.0%. A total of 48.7% had visited an emergency care unit (ECU) while 26.4% required hospitalization at least once, during the last year. A significant association between COPD severity and hospitalization (OR 7.4 95% CI: 5.3-10.3, $p<0.01$) and ECU visits (OR 7.51 95% CI: 5.16-10.9, $p<0.01$) was found. **CONCLUSIONS:** Most primary care patients with COPD had disease of moderate severity. Although their health status was relatively satisfactory, a considerable number each year visited the ECU of hospitals and were hospitalized for respiratory problems, illustrating the significant burden associated with COPD. ***Pneumon 2012, 25(4):386-394.***

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a complex inflammatory disease involving many different types of cell in the lung parenchyma. It is characterized by slow progressive development of airflow limitation that is reversible to only a limited degree. The Global Initiative on Obstructive Lung Disease (GOLD) has updated the definition of COPD, currently describing it as "*a common preventable and treatable disease, characterized by airflow limitation that is usually progressive and associated with an abnormal inflammatory response in the airways and the lung to noxious particles and gases*"[1]. This definition indicates the inflammatory nature of the disease, while it does not include the terms chronic bronchitis and emphysema and it excludes asthma, which is a form of reversible airflow limitation[2-4].

The prevalence of COPD of any stage in adults rises from 1% in the general population to 9%-10% in people aged ≥ 40 years[5], but the fact that many Stage I patients may be asymptomatic or present with signs that are not perceived as abnormal suggests that global and national estimates could be underestimated[5]. A systematic review and meta-analysis of studies carried out in 29 countries between 1990 and 2004 provided evidence that the prevalence of COPD is much higher in smokers and ex-smokers compared with non-smokers, in people over 40 years of age compared with younger patients, and in men compared with women[6]. In countries where the prevalence of the disease has been closely monitored, the overall prevalence in adults appears to lie between 4% and 10%[6,7]. COPD is a leading but under-recognized cause of morbidity and mortality, and recent global estimates for the interval 2004 -2030 upgraded COPD from fifth to third place among the most common causes of death worldwide[8].

Morbidity due to COPD increases with age, is greater in men than women[7,9] and is usually affected by other co-morbid chronic conditions, such as musculoskeletal diseases, diabetes mellitus (DM) and cardiovascular disease[10,11]. The causal relationship of COPD with several comorbidities is not clear, but in conjunction with the disease the patient's health status may be aggravated[12]. Depression has been recognised as one of the major COPD comorbidities. The risk of depression in patients with severe COPD is 2.5 times that of patients with mild or moderate COPD, while the number of patients with COPD presenting with depression increases with increasing disease severity[13]. Depressive symptoms are more frequent in elderly patients, while the prevalence and severity of depression increases as the patient`s functional ability decreases[14,15]. It is of note that patients with COPD have a higher probability of a first episode of depression at any time than patients with other chronic diseases such as DM or healthy individuals[16]. In terms of use of health care resources it was shown that consultations for COPD greatly outnumbered those for asthma, pneumonia, lung and tracheal cancer and tuberculosis[17]. In the EU the total direct costs of respiratory diseases are estimated to account for approximately 6% of the total health care budget, with COPD accounting for more than half of that cost[17].

The reduction of risk factors is considered an important step towards the prevention and management of COPD. Tobacco smoke and occupational exposure to indoor and outdoor pollutants are considered crucial factors in the development and severity of COPD[18]. Cigarette smoking is the most commonly encountered risk factor for COPD[19]. Cigarette smokers have a higher prevalence of respiratory symptoms and lung function abnormalities, greater loss of FEV_1 and higher COPD related mortality than non-smokers. Smoking cessation, on the other hand, is considered to be the single most effective and cost effective way to reduce exposure to COPD promoting factors. It may benefit patients with airway obstruction[20], increase their respiratory function[21] and improve outcome as assessed by questionnaires such as the Clinical COPD Questionnaire (CCQ)[22].

In view of the increasing burden of COPD on both the health status of patients and health care resourses, an epidemiological survey of patients with COPD was conducted to assess their health status, symptoms and perception of their management and treatment in daily life, to examine their level of depression and to estimate their use of health care resources related to COPD.

METHODS

Study design

The EPIPTOSI (i.e., EPIdemiological survey for assessing well-being in PaTients with chronic ObStructive pulmonary dIsease) survey was an epidemiological, descriptive, cross-sectional study with a single visit data collection schedule. The study was conducted according to the Greek national legislation on clinical studies.

Study population

The study population consisted of patients aged 40 years or older with an established diagnosis of COPD, who consulted one of the physicians-investigators participating in the study, in the primary care setting. All study subjects were required to be capable of self-completing the patient questionnaires, as judged by their physicians. The patients were classified into three categories of severity of their disease, mild, moderate and severe, based on the GOLD criteria[23]. Exclusion criteria for the study were age < 40 years, diagnosis of asthma, or demonstrated airflow obstruction reversibility (increased FEV_1 >15% after inhaling a bronchodilator) and poor understanding of the written Greek language. All participating patients gave written informed consent. Each physician-investigator enrolled a series of consecutive patients (maximum 11) who fulfilled the study selection criteria. Data collection for each patient took place at one visit by completion of a data collection form specifically designed for the purpose of the study as described below.

Data recorded by the physician

The physician recorded the following data from the patients' medical files or following direct questioning: demographic details, disease severity, smoking history, respiratory symptoms, current treatment and the patient's perception of it, and use of health care services.

Patient reported outcomes

All participating subjects were required to complete the CCQ and the Geriatric Depression Scale (GDS). The CCQ was developed in order to measure clinical control in patients with COPD. It is a validated 10-item tool yielding an overall score, consisting of 3 domains: symptoms (4 questions), functional state (4 questions) and mental state (2 questions). Scoring is applied from 0 to 6, with 0 representing best control of COPD. The validity, reliability and responsiveness of the CCQ have been tested, with positive outcomes regarding the ability of the questionnaire to detect improvements in COPD control, and with good test-retest variability[24,25]. For the CCQ an average change in score of 0.4 for the total score has been shown to be the minimum clinically significant difference[26]. The weekly version of the questionnaire was used in this study.

The GDS has been extensively tested and used in clinical practice, especially with older populations (≥65 years). The short version of the GDS form, translated into Greek and validated, was employed in this study[27]. This version consists of 15 questions that have shown the highest correlation with depressive symptoms in validation studies. Of those 15 items, 10 are indicative of the presence of depression when answered positively, while the other 5 are indicative of depression when answered negatively. Scores 0-4 are considered normal; 5-8 indicate mild depression; 9-11 indicate moderate depression; and 12-15 indicate severe depression. The short form is more easily used by physically ill and mildly to moderately demented patients who have a short attention span and/or feel easily fatigued and its completion is very quick. The GDS is reported to have 92% sensitivity and 89% specificity when evaluated against diagnostic criteria, while its validity and reliability have been supported through both clinical practice and research[28].

Statistical analysis

Continuous variables were expressed as mean±standard deviation (sd) and median (min-max), and categorical variables as frequencies. The associations between categorical variables (2x2 tables) were tested using Fisher's exact test. The magnitude of association was assessed using the odds ratio (OR) with the respective 95% confidence intervals (CI). The ORs were calculated using logistic regression. Continuous variables were compared using the Kruskal-Wallis test and pairwise Wilcoxon tests with Bonferroni correction. A test was considered statistically significant when p <0.05. The statistical analysis was performed using SAS v.9.

RESULTS

The study was conducted between June and September 2007 by 115 private practice physicians, who were internists (30 %) or pneumonologists (70 %), in both metropolitan areas (Athens, Thessaloniki, Patras, Heraklion, 53%) and regional areas (47%) of Greece. Patient demographics, disease characteristics and treatment datasets from 930 patients enrolled in the study (66.5% males and 33.5% females) were processed and analysed. Demographic data, smoking status and disease characteristics are presented in Table 1.

The most frequent symptom reported by patients was chronic cough (74.6%), followed by expectoration (66.8%), dyspnoea (57.8%) and wheezing (46%). The mean duration of COPD symptoms was 9.32± 6.8 years (Table 2). The majority of patients (84.6%) were receiving daily treatment; 35.2% with a fixed or free combination of long-

TABLE 1. Demographic and disease characteristics of patients in primary health care with chronic obstructive pulmonary disease (COPD)

Sex (n=927)	
Male (n, %)	616, 66.5
Female (n, %)	311, 33.5
Age (mean ± sd) (years)	64.95 ± 10.78 (n=921)
BMI (n=929) (mean ± sd) (kgr/m^2)	27.64 ± 3.92 (n=904)
Smoking (n=912)	
Never smoker, n, **(%)**	154 (16.5)
Mild COPD	47 (30.5)
Moderate COPD	68 (44.2%)
Severe COPD	39 (25.3%)
Current smoker, n, **(%)**	454 (49.8)
Mild COPD	109 (24.0)
Moderate COPD	253 (55.7)
Severe COPD	92 (20.3)
Former smoker, n, **(%)**	304 (32.7)
Mild COPD	45 (14.8)
Moderate COPD	151 (49.7)
Severe COPD	108 (35.5)
Pack-years of cigarettes	41.2
COPD Severity (n=914)	
Mild (n, %)	201, (22.0)
Moderate (n, %)	473, (51.8)
Severe (n, %)	240, (26.2)

TABLE 2. Symptoms of chronic obstructive pulmonary disease (COPD), and duration of symptoms in study population

	N	%
Symptoms		
Chronic cough	694	74.6
Expectoration	622	66.8
Dyspnoea	538	57.8
Wheezing	428	46.0
Other	15	1.6
Duration of symptoms in years (mean ± sd)	9.32 ± 6.8 (n=862)	

acting β_2-agonists (LABA) and inhaled corticosteroids (ICS) (LABA/ICS), while 27% accompanied this regimen with an anticholinergic agent. Most of the patients (64.3%) made use of a short-acting β_2-agonist as rescue therapy, at least 3 times per week (Table 3). Smoking habit was found to be associated with COPD severity; non-smokers had a lower probability of severe COPD than smokers (OR: 0.58

TABLE 3. Treatment of chronic obstructive pulmonary disease (COPD) in study population (n=930)

	N	%
Daily treatment		
Yes	787	84.6
No	140	15.0
Missing	3	0.4
Treatment category		
Fixed combination ICS/LABA	256	27.5
Fixed combination ICS/LABA plus anticholinergic	218	23.4
Free combination ICS/LABA	72	7.7
Free combination ICS/LABA plus anticholinergic	64	3.6
SABA	41	4.4
ICS/SABA	27	2.9
Anticholinergic	19	2.6
SABA plus anticholinergic	17	1.8
ICS	12	1.3
Other	27	2.9
Reliever Therapy		
Every day	357	39.4
2-3 times per week	225	24.9
3-4 times per month	133	14.7
Rarely	190	21.0

ICS = Inhaled corticosteroids; LABA = long acting β_2 agonists; SABA = short acting β_2 agonists

95% CI: 0.44-0.78, p<0.01).

CCQ and GDS

The average total CCQ score was 1.87 ± 1.1 with significant differences between groups related to increasing disease severity. Patients suffering from mild COPD reported a CCQ score of 1.11 ± 0.74, compared to 1.65 ± 0.80 and 2.91 ± 1.55 of patients with moderate and severe COPD, respectively (p <0.01) (Figure 1). The mean GDS score for patients >65 years was 7.8±0.9, which indicates mild depression.

Patients' perceptions of treatment

Almost 69% of the patients perceived their therapy as providing full coverage against their disease symptoms, compared with 31.5% who reported inadequate control. Improvement of the disease condition had led to dose reduction in 42.6% of cases, while 34.9% continued the treatment in the same dosage and 22.5% had discontin-

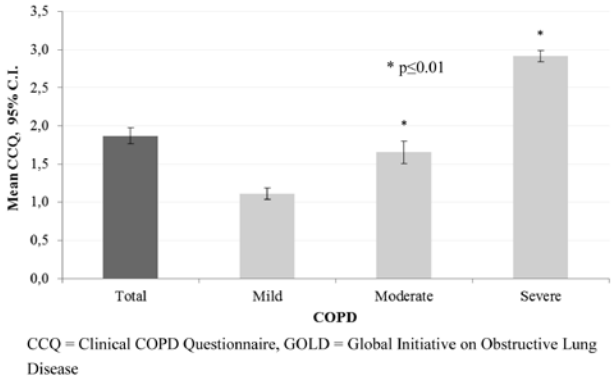

FIGURE 1. CCQ score in patients with chronic obstructive pulmonary disease (COPD) according to severity of the disease (mild, moderate, severe, by the GOLD criteria)
CCQ = Clinical COPD Questionnaire, GOLD = Global Initiative on Obstructive Lung Disease, *p≤0.01

ued treatment. In the case of condition improvement, treatment changes had been initiated on medical advice (48.4%), personal decision (39.7%) or according to a plan pre-agreed with the physician (11.9%). In case of worsening of the condition, 53.8% of patients had increased the dosage, while 22.5% complemented treatment with an additional agent. Increase of dosage and addition of a new drug was reported by 14.9%, followed by a complete change in the treatment regimen in 7.3% of patients (Table 4).

Health care resources

Approximately 49% of patients reported at least 1 visit to a hospital emergency care unit (ECU) within the past year. Hospitalization due to COPD exacerbations was reported by 26.4% of patients (1-2 and ≥3 times over the past year) and intensive care unit (ICU) admission by 5.1% of patients (Table 5). The patients hospitalized ≥ 3 times in the past year had a significantly higher CCQ score (3.2±1.4) than either those who were hospitalized 1-2 times (2.67±1.05) or those who were not hospitalized at all (1.57±0.9) (p≤0.01 for both comparisons). In terms of ECU visits, the CCQ scores were 3.01±1.22 and 2.22±1.04 for those attending an ECU ≥3 and 1-2 times respectively, compared with 1.38±0.85 for patients who had not visited an ECU (p≤0.01) (Figure 2). Finally, patients with severe COPD had an almost 7-fold higher probability of hospitalization than those with non-severe COPD (OR: 7.44 95% CI: 5.35-10.3, p<0.01), and a similar pattern was shown for ECU visits (OR 7.51 95% CI: 5.16-10.9, p<0.01).

TABLE 4. Perception of treatmen and changes in medications of patients with chronic obstructive pulmonary disease (COPD) (n=930).

	N	%
Perception that medication provides full protection (n=912)		
Yes	625	68.5
No	287	31.5
Actions when condition improves (n=920)		
Discontinue treatment	207	22.5
Reduce dosage	392	42.6
Continue same treatment	321	34.9
In the case of improvement, treatment changes are initiated by: (n=876)		
Medical advice	424	48.4
Personal decision	348	39.7
Plans pre-agreed with physician	104	11.9
Actions when condition deteriorates (n=907)		
Increase dosage	488	53.8
Add drug to treatment	204	22.5
Change treatment	66	7.3
Increase dosage and add new drug	135	14.9
Other	14	1.5
In the case of deterioration, treatment changes are initiated by: (n=917)		
Medical advice	571	62.3
Personal decision	219	23.9
Plan pre-agreed with physician	100	10.9
Missing	27	2.9

TABLE 5. Use of health care resources by patients with chronic obstructive pulmonary disease (COPD) (n=930)

		0	1-2	≥ 3	Total
ECU Visits	N	406	267	19	792
	%	51.3	33.7	15	
Hospitalizations	N	665	203	35	903
	%	73.6	22.5	3.9	
ICU admissions	N	857	46		903
	%	94.9	5.1		

ECU: Emergency care unit. ICU: Intensive care unit.

DISCUSSION

The objectives of this study were to assess the health status in a population of patients with COPD during their routine disease monitoring in the primary health care

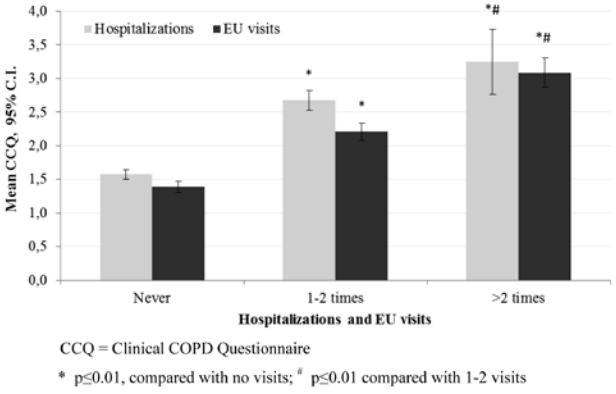

FIGURE 2. Association between CCQ score and hospitalizations and emergency care unit (ECU) visits in patients with chronic obstructive pulmonary disease (COPD) N= 930
CCQ = Clinical COPD Questionnaire
* P≤0.01, compared with no visits/hospitalization; # p≤0.01 compared with 1-2 visits/hospitalization.

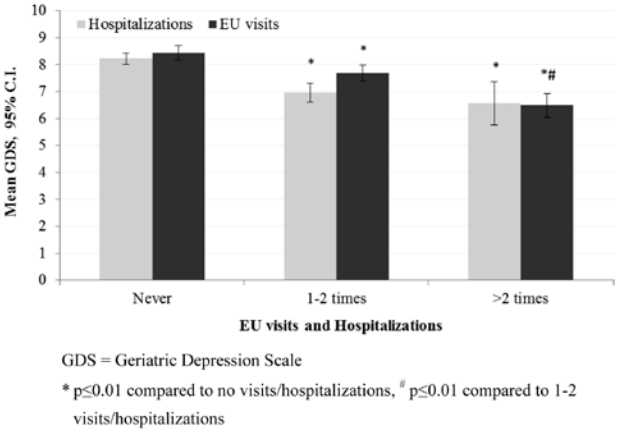

FIGURE 3. Association between GDS in patients aged ≥65 years with chronic obstructive pulmonary disease (COPD) and hospitalizations and emergency care unit (ECU) visits.
GDS = Geriatric Depression Scale
* P≤0.01 compared to no visits/hospitalizations, # p≤0.01 compared to 1-2 visits/hospitalizations

setting, and to ascertain whether they present depressive characteristics. In addition, it sought to assess the burden of disease in terms of utilization of health care resources as indicated by ECU visits, hospitalizations, and ICU admissions.

COPD is a complex chronic disease with increasing prevalence and significant associated morbidity that is expected to intensify as a public health problem in the future[29]. In parallel with the aging of the population of developed countries, it is expected to rise to the third place of all-cause mortality by the year 2030,[8].

The prevalence of COPD is an issue that has only recently been addressed in Greece. A nationwide study conducted by the COPD group of the Hellenic Thoracic Society provided valid data on the prevalence and severity of COPD in Greece in adult smokers aged ≥35 years with tobacco smoke exposure that equalled at least 100 cigarettes[30]. The overall prevalence of COPD estimated in that study was 8.4%, with a variation between urban, suburban and rural areas ranging from 6% to 10%, with urban areas showing the higher COPD prevalence. Smoking intensity and age were significantly associated with higher COPD prevalence. That study reported a different disease severity distribution in the observed population (i.e., 57.4% mild, 25.3% moderate and 16.0% severe) from that in the present study of patients with a variety of smoking habits aged > 40 years with COPD treated in the primary health care setting. The disease severity distribution in patients with a diagnosis of COPD found in the present study is in accordance with recent international documentation of diagnosed COPD, which shows a higher prevalence of moderate disease[31-33], regardless of the tool employed to assess disease severity. The patients in the present study presented symptoms of chronic cough, expectoration, dyspnoea and wheezing at high to very high rates. Chronic cough and exertional dyspnoea in particular have been reported in several studies to be frequent symptoms of COPD[34].

The self assessed health status of the patients with COPD in this study revealed by the CCQ questionnaire was relatively satisfactory regardless of disease severity. Their CCQ scores were associated with COPD severity, and the patients with severe and moderate COPD recorded significantly higher CCQ values. CCQ has been correlated with COPD severity and tested against other, longer validated tools that assess the health status of patients with respiratory diseases. The St George's Respiratory Questionnaire (SGRQ) for example, is a standardized self-administered airways disease-specific questionnaire consisting of three categories: symptoms, activity and impact, numbering up to 50 items. CCQ presents strong correlation with SGRQ for patients with clinical and spirometrically verified COPD, regardless of COPD severity[24]. Hence CCQ is considered a valid and convenient, patient friendly questionnaire for assessing COPD health status. In spite of their relatively satisfactory health status as assessed by CCQ, almost 1 in 2 study subjects had visited a hospital ECU and 1 in 4 had been hospitalized in the year prior to study entry,

showing that COPD poses a significant burden to both the patients and society. This high number of patients being hospitalised or attending ECUs is in contradiction with the satisfactory levels on CCQ recorded in the study. This observation cannot be fully explained with the available data, but the high mean age of the study patients (more than 50% were aged ≥65 years) could possibly account for this paradox. As was to be expected, disease severity and health status as measured by CCQ were strong determinants of both ECU visits and hospitalization.

The GDS scale has been extensively and successfully utilised to evaluate the level of depression in patients aged ≥65 years. The mean GDS score for this study population aged ≥65 years was low, which indicates mild depression. The importance of psychological factors in general, has been recognised in patients who are adjusting to COPD. Coping strategies, high levels of self-efficacy and social support have been recognised as important parameters contributing to the satisfactory mental health and psycho-emotional stability of patients with COPD whose disease is accompanied by depression, anxiety and impaired quality of life[35,36]. Another cross-sectional survey conducted on patients with COPD in the primary health care setting showed that moderate to high levels of depressive symptoms were present in 6 in 10, and identified 3 independent predictors of depressive symptoms with considerable impact, which were being a former smoker, having a high level of self-efficacy and care prior to deterioration in symptoms, and higher perceived illness severity[37]. It is of note that patients with COPD who have depressive symptoms present a significantly higher risk of exacerbations, which implies that for patients with moderate to severe COPD, depression is associated with disease progression[38], increased visits to the physicianand the ECU, and overall increased health care utilization[37].

The main goal of pharmacotherapy in the management of COPD is prevention and control of symptoms, reduction of the frequency and severity of exacerbations and improvement of exercise tolerance and overall health status[1]. In this study almost 60% of patients were receiving combination treatment. Specifically, fixed or free combinations of ICS/LABA were used by 35% of patients and a combination of ICS/LABA plus an anticholinergic agent by 27%, which means that the percentage of patients receiving combination treatment with ICS/LABA, with or without the addition of anticholinergics, was high. It would be anticipated that such extensive use of ICS/LABA should lead to better control of exacerbations and hence fewer hospitalizations and emergency care unit visits[39-41]. However, more than half of the enrolled patients in the present study were aged over 65 years, while the percentage of patients with severe COPD was also high. These two characteristics of the study population, together with the fact that the Greek health care system lacks an integrated, standardized primary care service to provide the first point of contact for patients in an exacerbation prior to admission to a hospital may explain the high percentages of hospital ECU visits and admissions recorded in the present study.

One interesting finding of our study was that almost one in two patients with COPD was an active smoker. Other studies have also reported the problem of smoking in patients with COPD. Martin and co-workers in 2008 conducted a study in 9,405 patients with COPD of whom 22.6% were current smokers, while another study in Spain, of 11,973 patients with COPD patients reported that 35% continued smoking[33], while it was estimated that only 4% of these received smoking cessation treatment. The mean pack years (41.2) recorded in the present study for patients with COPD is similar to estimates from other studies[33,42]. These findings regarding the high prevalence of smoking indicate the need for effective intervention strategies directed towards reduction smoking in this particularly vulnerable population. Such intervention strategies would remove one very important COPD risk factor for which association with disease severity has been proved and there is also documentation of improvement of respiratory function following smoking cessation.

In conclusion, most patients with COPD visiting a primary care physician in Greece have disease of moderate severity. Although their health status was relatively satisfactory, a considerable number of patients had visited the ECU of hospitals and were hospitalized due to respiratory problems, showing the significant health burden associated with COPD. Finally, despite the fact that smoking status is associated with COPD severity, still an alarmingly large number of patients with diagnosed COPD continue to be active smokers, making educational intervention and support mechanisms directed towards life style modification and smoking cessation important aids to optimal patient rehabilitation.

Study limitations

The present study was hindered by specific limitations that should be considered when interpreting the results. Some weaknesses were inherent to the study design and arose from the selection of participating physicians and patients. For example, during the selection of physicians

and patients to be enrolled in the study, no record was kept of those who denied participation. The sample used for study consisted of patients with mild to severe COPD, who were visiting their primary care physicians for a regular treatment consultation. This selection procedure, however, despite the fact that it potentially reduces the external validity of the data, simulates as closely as possible the standard clinical practice in a life-like environment, and hence may present a more realistic view of management and treatment of COPD in primary care.

AUTHORS' CONFLICT OF INTERESTS:

Dr Christos P. Carvounis has received honoraria from Mount Sinai Medical Center and has received research grants as National Coordinator of four Phase IV local studies. He has received grants and acted as a consultant for AstraZeneca. Mr. Nikos Nikas and Dr. Elena Panitti are AstraZeneca employees.

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