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Website: https://eurasianjpulmonol.org DOI: 10.14744/ejp.2022.7002

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> Received: 08-07-2022 Revised: 15-08-2022 Accepted: 17-08-2022 Published: 13-10-2022

Disease history of patients with COPD

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Abstract:

BACKGROUND AND AIM: This study aimed to obtain real-life data of patients diagnosed with chronic obstructive pulmonary disease (COPD) at least one year ago, including smoking history, inhaler device training, and the number of exacerbations.

METHODS: This study was planned as a nationwide, prospective, observational, multicenter, and noninterventional study, and web-based electronic case forms were used to register the patients.

RESULTS: A total of 460 patients from 11 centers were included, of whom 88.3% were males. Of the total patients, 137 (29.8%) were current smokers, and 292 (63.5%) were ex-smokers. One hundred twenty-four (29.6%) patients did not receive inhaler device training. Repeated inhaler device training in the follow-up visits was not performed in 255 (60.8%) patients. Of the total participants, 187 (41.0%) reported no exacerbations in the previous year. The mean number of exacerbations per person over the previous year was 1.19. The annual rates of influenza and pneumococcal vaccines were 34.8% and 4.2%, respectively.

CONCLUSIONS: Patients should be trained more efficiently in the risks of COPD, use of inhaler devices, exacerbations, and improving quality of life.

Keywords:

COPD, exacerbation, inhaler device, smoking

Introduction

Chronic obstructive pulmonary disease (COPD) is a common global health problem that represents a significant healthcare burden, and its high prevalence makes it one of the leading causes of morbidity and mortality worldwide.^[1] COPD, which occurs due to tobacco smoking and household air pollution, is an important cause of mortality, especially in low- and middle-income countries.^[2] Although COPD is preventable and treatable, it is the third most common cause of mortality following cardiovascular ischemic cardiac disease and cerebrovascular disease.^[3] Nevertheless,

How to cite this article: Süerdem M, Sarıoğlu N, Ogan N, Arslan S, Yıldırım G, Erçen Diken Ö, et al. Disease history of patients with COPD. Eurasian J Pulmonol 2022;24:206-11.

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COPD receives little attention compared with other diseases causing global morbidity and mortality.

Although its prevalence is expected to be around 10% in the 40-year-plus population, not many patients are not diagnosed for the presence of COPD.^[4,5] The inadequate education level of the public and patients and noncompliance with treatment are important global problems. Turkey is among the countries with the highest prevalence of COPD, and patients are diagnosed only at advanced stages.^[6,7] In the present study, we aimed to evaluate the real-life data of COPD patients and identify problems that can be corrected in patient follow-ups.

Materials and Methods

This nationwide, prospective, observational, multicenter, and noninterventional questionnaire study used a web-based electronic case form. The study approval was obtained from the Non-Interventional Clinical Research Ethics Board of Selçuk University (2016/89). The study was conducted according to the principles of the Declaration of Helsinki.

The study was carried out between November 2015 and June 2016 in 11 centers from the West, Inner, and southeast Anatolian regions of Turkey. Patients who were diagnosed with COPD at least one year earlier and who were started on treatment were included. Patients diagnosed with asthma before the age of 40 years and those who were considered to have problems answering the survey questions due to mental problems were excluded from the study. For the definitive diagnosis of COPD, the ratio of post-bronchodilator forced expiratory volume in 1 s to forced vital capacity (FEV₁/FVC) (also known as the Tiffeneau index) was required to be ≤ 0.70 .^[8,9]

A written and signed informed consent was obtained from each patient before conducting the survey. In this study, a web-based online survey form prepared by an independent informatics company (BTM Research and Development Communication Informatics Technologies, Konya, Turkey) was used. The survey form facilitated the garnering of demographic information in addition to the risk factors, exacerbations, and the training of inhaler devices. The data were recorded in an online system simultaneously when the survey was completely answered. A standard spirometric examination and bronchodilation test were performed by certified special technicians using the American Thoracic Society/European Respiratory Society criteria at all centers.^[10] Spirometry was performed 12 h and 24 h after the use of long-acting bronchodilators. The patients inhaled a 400 μ g β 2-agonist (salbutamol) by aerosol (metered-dose inhaler) with a spacer, and the test was repeated after 20 min to evaluate post-bronchodilator FEV₁/FVC. Exacerbation was defined as increased symptom severity causing a change in daily treatment and/or presentation to the emergency room and admission to the hospital.^[8]

Statistical analysis

All statistical analyses were performed using R version 3.6.0 (The R Foundation for Statistical Computing, Vienna, Austria; https://r-project.org). Descriptive statistics of the findings were expressed as mean±standard deviation and described as counts (n) and percentages (%).

Results

Web-based records of 460 patients from 11 centers were obtained. After examining the patients' web-based electronic case records, only 460 patients were evaluated due to deficiencies and inconsistencies in the records. The male and female distribution of the patients was 406 (88.3%) and 54 (11.7%), respectively. In addition to the gender distribution of patients, smoking habits, postbronchodilator spirometry parameters, and body mass index (BMI) are shown in Table 1.

Of the patient sample, 5.4% were 50 years or younger, and 72.6% were 60 years or older (Table 2). The mean BMI was 26.20 ± 5.80 kg/m² (25.53 ± 4.97 and 31.22 ± 8.58 in males and females, respectively). It was determined that 187 (41.0%) patients did not have an exacerbation in the past year. The proportions of patients who had one, two, and more than two exacerbations in the past year were 96 (21.0%), 71 (15.6%), and 102 (22.4%), respectively. The mean number of exacerbations per person over the previous year was 1.19.

The number of patients with a history of smoking was 429 (93.3%). At the time of the survey, 137 (29.8%) patients were actively smoking cigarettes, and 292 (63.5%) were former smokers. The mean cigarette pack per year value was 45.24±23.41. Among those patients, only 25.7% were referred to smoking cessation outpatient clinics. The percent-

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Table 1: Demographic and clinical characteristics of patients

	n	%	Mean±SD
Sex			
Male	406	88.26	
Female	54	11.74	
Smoking			
Current smoker	137	29.7	
Ex-smoker	292	63.4	
Nonsmoker	31	6.7	
Post-broncohodilator spirometry			
FVC (L) (% predicted)			2.36±0.88
			(72.4±14.5)
FEV_1 (L) (% predicted)			1.36±0.57
			(53.2±11.2)
FEV ₁ /FVC (%)			0.57±0.09
Body mass index (kg/m ²)			
Male			25.53±4.97
Female			31.22±8.58
Total			26.20±5.80

Table 2: Distribution of patients by age groups

Age (years)	Male		Female		All patients	
	n	%	n	%	n	%
<40	4	1.0	0	0	4	0.9
40–49	18	4.4	3	5.6	21	4.6
50–59	92	22.7	9	16.7	101	22.0
60–69	151	37.2	16	29.6	167	36.3
≥70	141	34.7	26	48.2	167	36.3

a noninterventional longitudinal prospective study of 2164 COPD patients in 12 high-income countries, the rate of females was 35.0%,^[13] while 11.7% of the patients in the present study were females. In a study on the epidemiology of COPD in Malatya province, 80.0% of the patients were males and 20.0% were females.^[14] The main reason for the higher prevalence of COPD in males can be attributed to the higher rate of cigarette smoking addiction among men in Turkey.

Data are presented as mean±SD or n (%). FVC: Forced vital capacity, FEV,: Forced expiratory volume in 1 s

age of patients who quit was 44.6% after being diagnosed with COPD. Of those who had quit smoking, 13.0% did so with the support provided by smoking cessation outpatient clinics, while 87.0% of the patients quit smoking spontaneously. There was no smoking history in 31 (6.7%) patients. All of these patients were women and had a history of exposure to biofuels. Occupational exposure that may be a risk factor for COPD was present in 152 (33.0%) patients.

Among the patients, 70.2% reported that they heard for the first time the term COPD at the time of diagnosis. The percentage of patients who received no information about the disease at the time of diagnosis was 47.8%. At the time of the first prescription, 124 (29.7%) patients were not trained in the use of inhaler devices. At the followup visits, the technique of using inhaler devices was not questioned in 255 (60.9%) patients, and repeated training was not given. The rate of patients whose inhaler device was changed was 38.6%. The patients who received annual influenza and pneumococcal vaccines constituted 34.8% and 4.2%, respectively. The percentage of patients who did not attend regular control visits was 41.0%.

Discussion

COPD is common among men in high- and low-income countries.^[6,11] The increase in tobacco smoking among women in high-income countries may lead to a similar prevalence for both sexes.^[12] In the ECLIPSE study,

No exacerbations in the previous year were reported by 41.0% of the patients, while one, two, and more than two exacerbations in the previous year were reported by 21.0%, 15.6%, and 22.4%, respectively. The number of exacerbations per patient per year was 1.19. The mean number of exacerbations per year was 0.8 in the ECLIPSE study.^[13] Compared to this study, which included highincome countries, it was not surprising to find a greater number of annual exacerbations in our country. However, about half of COPD exacerbations are not reported by patients.^[15] Therefore, the actual number of exacerbations may be twice as high as those determined.

The mean BMI of the patients in the present study was 25.53±4.97 in males and 31.22±8.58 in females, corresponding to overweight and in the range of obesity, respectively. The overall mean 26.20±5.80 BMI in this present study was found to be similar to the mean BMI level of 25.5 in Turkey, reported by the Turkish Statistics Institution. Similar to this study, the mean BMI was 27.0 in the ECLIPSE study.^[13] The adverse effects of a high BMI on diseases in patients with chronic conditions, such as cardiovascular disease, diabetes, and asthma, are well defined. Although a high BMI is not accepted as a risk factor for COPD, its effects on the clinical presentation of the disease have been increasingly recognized with increasing symptoms. The degree of static lung hyperinflation is lower in overweight and obese patients with COPD when compared with normal-weight or lowweight patients, and inspiratory capacity increases in

parallel to the weight of an individual.^[16] Misdiagnoses of COPD in overweight and obese individuals have been reported as a significant problem.^[17]

We found that 5.4% of patients are younger than 50 years, which is a very important finding that reflects the inadequacy of COPD awareness among family physicians and society in Turkey. Progressive airway obstruction, a characteristic finding of COPD, may be overlooked for years unless a spirometry measurement is performed. The optimum method of diagnosis of COPD is the demonstration of limited airflow by post-bronchodilator spirometry.^[8] The DIDASCO study showed that 42.0% of patients were not diagnosed when spirometry was not performed in primary care.^[18]

Delays in the diagnosis of COPD are a global problem, with 60.0%–85.0% of patients with mild-to-moderate COPD remaining undiagnosed.^[19-21] Primary care physicians should be aware of the disease, should discuss the risk factors with patients, and should carry out spirometry tests in patients to the defined standards in health-care centers to prevent delays in the diagnosis of particularly early-stage COPD. The American Thoracic Society and British Thoracic Society strongly recommend that primary care physicians apply spirometry routinely for the early diagnosis of COPD. ^[22,23] According to the National Lung Health Education Program (NLHEP), spirometry should be performed in all conditions, for example, blood pressure measurement, to gain a better understanding of lung health.^[24]

Among our patients, 29.8% were active smokers at the time of diagnosis. This rate was 36.0% in the ECLIPSE study^[13] and 30.6% in the international multicenter Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) study.^[25] Quitting smoking is the most effective way of preventing COPD and improving its clinical course in all stages of the disease.^[8] The decrease in FEV₁ was demonstrated to be significantly slowed in patients with COPD who quit smoking in the Lung Health Study.^[26] As a rule, COPD patients who smoke should be referred to smoking cessation clinics. For a more effective smoking cessation program and treatment, the rule that the treatment costs of COPD patients who have quit smoking can be paid by the social security institution.

No education on the use of inhalers was provided to one-third (29.7%) of the patients at the time of diagnosis and 60.9% in the follow-up visits. Education on the use of the inhaler devices prescribed to patients with asthma and COPD in Turkey is at a low level. The most important reason for this situation is the excessive workload of physicians and therefore do not have enough time for training. The use of inhaler devices was found to be technically correct in 26.4% and 34.2% in two different studies involving patients who were left to learn how to use the devices themselves.^[27,28] In a multicenter trial, Turkish Respiratory Society (TRS) Inhalation Therapy Group study (INTEDA-1), 44.0% of physicians reported that the education provided on the use of the devices to their patients was insufficient, and 45.0% stated that they provided no intensive education.^[29]

Technical errors in the use of inhaler devices are a significant global problem for patients with asthma and COPD. Exacerbations resulting from uncontrolled disease facilitate disease progression and can result in significant economic loss, in addition to increased mortality risk. In a study exploring the risk factors for exacerbations of COPD in four hospitals in Barcelona, 43.0% of the patients were found to be using their inhaler devices incorrectly.^[30] Strategies should be developed to address this crucial issue. The INTEDA-1 has strongly recommended providing respiratory education training to nurses to improve inhaler device use among patients.^[29]

Patients who received annual influenza and pneumonia vaccines constituted 34.8% and 4.2%, respectively. Despite the recommendation of the guidelines, the vaccine rates in our patients were very low. Vaccination is considered a very important preventive measure for COPD patients, as it prevents exacerbations and reduces the risk of hospitalization.^[31,32] For an effective vaccination program for COPD patients, primary care physicians should inform patients to accept vaccinations.

Although COPD is a common disease and an important public health problem in our society, its awareness is not very high. The fact that 70.2% of our patients were not informed about COPD when they were first diagnosed is one of the important indicators of this subject. To increase the rate of early diagnosis of COPD and reduce its morbidity, it is important to raise awareness and educate society. To increase awareness of the disease in society, all educational tools and written and visual media should be effectively used.

The most important limitation of this study is that the number of cases is not very high. The other limitations are that current treatments are not questioned, and the GOLD grouping system is not used.

Conclusion

Sustainable and effective educational activities about COPD and its risk factors should be conducted. Patients should be trained more efficiently in the risks of COPD, use of inhaler devices, exacerbations, and improving quality of life. COPD patients who are current smokers should be referred to smoking cessation units. The use of spirometry should be generalized in primary health-care facilities.

Conflicts of interest

There are no conflicts of interest.

Ethics Committee Approval

The study was approved by the Selçuk University Non-Interventional Clinical Research Ethics Committee (No: 2016/89, Date: 15/03/2016).

Financial support and sponsorship Nil.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept – M.S.; Design – M.S.; Supervision – M.S.; Funding – M.S., N.S., N.O., S.A., G.Y., Ö.E.D., F.B., G.G., N.Y.D., A.Ş., H.T., E.K.; Materials – M.S., N.S., N.O., S.A., G.Y., Ö.E.D., F.B., G.G., N.Y.D., A.Ş., H.T., E.K.; Data collection &/or processing – M.S., N.S., N.O., S.A., G.Y., Ö.E.D., F.B., G.G., N.Y.D., A.Ş., H.T., E.K.; Analysis and/ or interpretation – M.S.; Literature search – M.S.; Writing – M.S.; Critical review – M.S., A.Ş.

References

- López-Campos JL, Tan W, Soriano JB. Global burden of COPD. Respirology 2016;21:14–23. [CrossRef]
- 2. Quaderi SA, Hurst JR. The unmet global burden of COPD. Glob Health Epidemiol Genom 2018;3:e4. [CrossRef]
- 3. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388:1459–544. [CrossRef]
- Ehteshami-Afshar S, FitzGerald JM, Doyle-Waters MM, Sadatsafavi M. The global economic burden of asthma and chronic obstructive pulmonary disease. Int J Tuberc Lung Dis 2016;20:11–23. [CrossRef]
- Mannino DM, Gagnon RC, Petty TL, Lydick E. Obstructive lung disease and low lung function in adults in the United States: data from the National Health and Nutrition Examination Survey, 1988-1994. Arch Intern Med 2000;160:1683–9. [CrossRef]
- Buist AS, Vollmer WM, McBurnie MA. Worldwide burden of COPD in high- and low-income countries. Part I. The burden of

obstructive lung disease (BOLD) initiative. Int J Tuberc Lung Dis 2008;12:703–8.

- Suerdem M, Gunen H, Akyildiz L, Cilli A, Ozlu T, Uzaslan E, et al. Demographic, clinical and management characteristics of newly diagnosed COPD patients in Turkey: a real-life study. Int J Chron Obstruct Pulmon Dis 2020;15:261–7. [CrossRef]
- NICE guideline. Chronic obstructive pulmonary disease in over 16s: diagnosis and management. Available at: www.nice.org.uk/ guidance/ng115. Accessed Aug 25, 2022.
- Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of COPD. Available at: http://www.gold copd.org/. Accessed Aug 25, 2022.
- Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al; ATS/ERS Task Force. Standardisation of spirometry. Eur Respir J 2005;26:319–38. [CrossRef]
- 11. Adeloye D, Chua S, Lee C, Basquill C, Papana A, Theodoratou E, et al; Global Health Epidemiology Reference Group (GHERG). Global and regional estimates of COPD prevalence: Systematic review and meta-analysis. J Glob Health 2015;5:020415. [CrossRef]
- World Health Organization. Chronic respiratory diseases. Burden of COPD. Available at: http://www.who.int/respiratory/copd/ burden/en/. Accessed Jun 25, 2020.
- Vestbo J, Agusti A, Wouters EF, Bakke P, Calverley PM, Celli B, et al; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints Study Investigators. Should we view chronic obstructive pulmonary disease differently after ECLIPSE? A clinical perspective from the study team. Am J Respir Crit Care Med 2014;189:1022–30. [CrossRef]
- Gunen H, Hacievliyagil SS, Yetkin O, Gulbas G, Mutlu LC, Pehlivan E. Prevalence of COPD: first epidemiological study of a large region in Turkey. Eur J Intern Med 2008;19:499–504. [CrossRef]
- Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;157:1418–22. [CrossRef]
- O'Donnell DE, Deesomchok A, Lam YM, Guenette JA, Amornputtisathaporn N, Forkert L, et al. Effects of BMI on static lung volumes in patients with airway obstruction. Chest 2011;140:461–8. [CrossRef]
- Collins BF, Ramenofsky D, Au DH, Ma J, Uman JE, Feemster LC. The association of weight with the detection of airflow obstruction and inhaled treatment among patients with a clinical diagnosis of COPD. Chest 2014;146:1513–20. [CrossRef]
- Buffels J, Degryse J, Heyrman J, Decramer M; DIDASCO Study. Office spirometry significantly improves early detection of COPD in general practice: the DIDASCO Study. Ches. 2004;125:1394–9.
- Miravitlles M, Soriano JB, García-Río F, Muñoz L, Duran-Tauleria E, Sanchez G, et al. Prevalence of COPD in Spain: impact of undiagnosed COPD on quality of life and daily life activities. Thorax 2009;64:863–8. [CrossRef]
- Soriano JB, Maier WC, Egger P, Visick G, Thakrar B, Sykes J, et al. Recent trends in physician diagnosed COPD in women and men in the UK. Thorax 2000;55:789–94. [CrossRef]
- Hvidsten SC, Storesund L, Wentzel-Larsen T, Gulsvik A, Lehmann S. Prevalence and predictors of undiagnosed chronic obstructive pulmonary disease in a Norwegian adult general population. Clin Respir J 2010;4:13–21. [CrossRef]
- Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. American Thoracic Society. Am J Respir Crit Care Med 1995;152:S77–121.

- BTS guidelines for the management of chronic obstructive pulmonary disease. The COPD Guidelines Group of the Standards of Care Committee of the BTS. Thorax 1997;52 Suppl 5:S1–28. [CrossRef]
- 24. Strategies in preserving lung health and preventing COPD and associated diseases. The National Lung Health Education Program (NLHEP). Chest 1998;113:1235–635. [CrossRef]
- Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, et al; UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med 2008;359:1543–54. [CrossRef]
- Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. JAMA 1994;272:1497–505. [CrossRef]
- 27. Aydemir Y. Assessment of the factors affecting the failure to use inhaler devices before and after training. Respir Med 2015;109:451–8.

- 28. Aydemir Y. Misuse of inhalation devices-effective parameters and the role of education. Solunum 2013;15:32–8. [CrossRef]
- Calışkaner AZ, Oztürk C, Ceylan E, Pekcan S, Yılmaz O, Oztürk S, et al. The knowledge and considerations of the physicians regarding the inhaler devices in asthma and COPD: the INTEDA-1 study. Tuberk Toraks 2013;61:183–92. [CrossRef]
- Garcia-Aymerich J, Barreiro E, Farrero E, Marrades RM, Morera J, Antó JM. Patients hospitalized for COPD have a high prevalence of modifiable risk factors for exacerbation (EFRAM study). Eur Respir J 2000;16:1037–42. [CrossRef]
- Poole PJ, Chacko E, Wood-Baker RW, Cates CJ. Influenza vaccine for patients with chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2006:CD002733. [CrossRef]
- 32. Walters JA, Smith S, Poole P, Granger RH, Wood-Baker R. Injectable vaccines for preventing pneumococcal infection in patients with chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2010:CD001390. [CrossRef]