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Risk factors for cardiovascular disease in patients with COPD: mild-to-moderate COPD versus severe-to-very severe COPD

Laura Miranda de Oliveira Caram[1], Renata Ferrari[1], Cristiane Roberta Naves[1], Liana Sousa Coelho[1], Simone Alves do Vale[1], Suzana Erico Tanni[1], Irma Godoy[1]

1. Departamento de Medicina Interna, Área de Pneumologia, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista, Botucatu (SP) Brasil.

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Study carried out in the Departamento de Medicina Interna, Área de Pneumologia, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista, Botucatu (SP) Brasil.

ABSTRACT

Objective: To assess and compare the prevalence of comorbidities and risk factors for cardiovascular disease (CVD) in COPD patients according to disease severity. **Methods:** The study included 25 patients with mild-to-moderate COPD (68% male; mean age, 65 ± 8 years; mean FEV_1, 73 ± 15% of predicted) and 25 with severe-to-very severe COPD (males, 56%; mean age, 69 ± 9 years; mean FEV_1, 40 ± 18% of predicted). Comorbidities were recorded on the basis of data obtained from medical charts and clinical evaluations. Comorbidities were registered on the basis of data obtained from medical charts and clinical evaluations. The Charlson comorbidity index was calculated, and the Hospital Anxiety and Depression Scale (HADS) score was determined. **Results:** Of the 50 patients evaluated, 38 (76%) had been diagnosed with at least one comorbidity, 21 (42%) having been diagnosed with at least one CVD. Twenty-four patients (48%) had more than one CVD. Eighteen (36%) of the patients were current smokers, 10 (20%) had depression, 7 (14%) had dyslipidemia, and 7 (14%) had diabetes mellitus. Current smoking, depression, and dyslipidemia were more prevalent among the patients with mild-to-moderate COPD than among those with severe-to-very severe COPD ($p < 0.001$, $p = 0.008$, and $p = 0.02$, respectively). The prevalence of high blood pressure, diabetes mellitus, alcoholism, ischemic heart disease, and chronic heart failure was comparable between the two groups. The Charlson comorbidity index and HADS scores did not differ between the groups. **Conclusions:** Comorbidities are highly prevalent in COPD, regardless of its severity. Certain risk factors for CVD, themselves classified as diseases (including smoking, dyslipidemia, and depression), appear to be more prevalent in patients with mild-to-moderate COPD.

Keywords: Pulmonary disease, chronic obstructive; Spirometry; Cardiovascular diseases; Risk factors.

INTRODUCTION

COPD is characterized by chronic airflow limitation, a range of pathological changes in the lungs, significant extrapulmonary effects, and major comorbidities that can contribute to increasing the severity of the disease.[1] Common comorbidities in patients with COPD include cardiovascular disease (CVD), anemia, lung cancer, diabetes, osteoporosis, anxiety, and depression.[2] Among COPD patients, CVDs are responsible for approximately 50% of all hospitalizations and 20% of all deaths.[3]

The majority (94%) of all COPD patients have at least one comorbidity and up to 46% have three or more,[4] the most prevalent being high blood pressure (HBP), coronary artery disease (CAD), congestive heart failure (CHF), dyslipidemia, and diabetes mellitus (DM).[2,5] Two previous studies evaluated the prevalence of comorbidities according to COPD severity,[5,6] although neither evaluated all of the risk factors for CVD. Therefore, the aim of the present study was to assess the prevalence of comorbidities and risk factors for CVD in COPD patients, comparing them by COPD severity—mild-to-moderate versus severe-to-very severe.

METHODS

Seventy patients with COPD were recruited from the Pulmonary Outpatient Unit at the Botucatu *Hospital das Clínicas* of the São Paulo State University Botucatu School of Medicine. Patients were included if they met the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria for a diagnosis of COPD[1]: a post-bronchodilator FEV_1/FVC ratio < 0.70 and a < 15% or 200-mL increase in FEV_1 following inhalation of a β_2 agonist; age ≥ 40 years; and a ≥ 10 pack-year smoking history. Patients with a primary diagnosis of another respiratory disease, such as asthma, a restrictive disorder (tuberculosis sequelae or interstitial fibrosis), obstructive sleep apnea-hypopnea syndrome, and lung cancer, were excluded, as were those with a primary diagnosis of unstable angina, CHF (New

Correspondence to:
Laura Miranda de Oliveira Caram. Departamento de Medicina Interna, Área de Pneumologia, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista, Distrito de Rubião Junior, s/n, CEP 18618-970, Botucatu, SP, Brasil.
Tel.: 55 14 3880-1171. Fax: 55 14 3882-2238. E-mail: laucaram@hotmail.com
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York Heart Association functional class III or IV), or any other chronic disease, such as uncontrolled DM, kidney failure, liver failure, and cancer. We took into consideration the post-bronchodilator values of FEV_1 (% of the predicted value) and arterial blood gas parameters. We categorized the severity of COPD according to the GOLD stages,[1] as mild-to-moderate (GOLD stage I or II) or severe-to-very severe (GOLD stage III or IV).

The study was approved by the Research Ethics Committee of the Botucatu *Hospital das Clínicas*. All participating patients gave written informed consent.

Laboratory tests, pulmonary function tests, and pulse oximetry

Laboratory tests included complete blood counts, as well as determination of the following: lipid profile; total and fractional protein levels; fasting glucose level; hepatic function; and renal function. The biochemical tests were performed according to the methods applied by the Clinical Analysis Laboratory of the institution.

Pre- and post-bronchodilator spirometry were performed with a portable spirometer (Koko; Ferraris Respiratory, Louisville, CO, USA), in accordance with the American Thoracic Society criteria.[7] Values of FEV_1 were expressed in liters, as percentages of the FVC, and as percentages of the reference values.[8] The SpO_2 was assessed with an oximeter (Onyx 9500; Nonin Medical Inc., Plymouth, MN, USA) while the patients were breathing room air.

Comorbidities

Comorbidities were identified in medical records and confirmed at clinical evaluation. Current smoking was considered a comorbidity, in accordance with the International Statistical Classification of Diseases, 10th Revision, in which nicotine dependence is coded as F17. The smoking status was confirmed by measuring carbon monoxide (CO) in exhaled air with a CO analyzer (Micro CO Meter, Cardinal Health, Chatham, UK). An exhaled CO level > 6.0 ppm was considered indicative of current smoking.[9]

For each patient, we calculated the Charlson comorbidity index.[10] The Hospital Anxiety and Depression Scale (HADS), which has been translated to Portuguese and validated for use in Brazil,[11] was used in order to evaluate symptoms related to anxiety and depression.

Nutritional assessment

We determined body weight and height using a calibrated platform scale with a stadiometer (Filizola, São Paulo, Brazil). The body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Body composition was evaluated by bioelectrical impedance (BIA 101A; RJL Systems Inc., Clinton Township, MI, USA), in accordance with the guidelines established by the European Society for Parenteral and Enteral Nutrition.[12] Fat-free mass (FFM, in kg) was calculated through the use of a group-specific regression equation developed by Kyle et al.[13] We also calculated the FFM index (FFMI), using the following equation:

$$FFMI = FFM/height^2$$

Statistical analyses

Descriptive statistics were calculated for the features of all participants. Data are expressed as mean ± standard deviation or as median and interquartile range (25-75%), depending on their distribution. Categorical variables are expressed as absolute and relative frequency. The chi-square test and Fisher's exact test were used in order to compare categorical variables. For comparisons between the two groups, an unpaired t-test was used for continuous variables and the Mann-Whitney test was used for ordinal variables. The level of significance was set at 5%. All analyses were performed with the SigmaStat program, version 3.2 (Systat Software Inc., San Jose, CA, USA).

RESULTS

Twenty patients were excluded from the final analysis, 15 because their primary diagnosis was not COPD and 5 because they did not complete the protocol. Therefore, 50 patients were included in the final analysis: 25 with mild-to-moderate COPD and 25 with severe-to-very severe COPD. Age, gender, smoking history (pack-years), BMI, and FFMI were not statistically different between the groups (Table 1). Of the 50 patients evaluated, 9 (18%) were obese (BMI ≥ 30 kg/m^2), 3 in the mild-to-moderate COPD group and 6 in the severe-to-very severe COPD group ($p = 0.39$).[14] Five patients had very severe COPD and were on long-term oxygen therapy. Figure 1 shows the maintenance medications used by the patients.

Thirty-eight patients (76%) presented with at least one comorbidity, 21 (42%) presenting with at least one cardiovascular comorbidity: HBP, in 40% of the sample; CAD, in 10%; or New York Heart Association functional class I CHF, in 6%. Twenty-four patients (48%) presented more than one CVD. Of the 50 patients evaluated, 18 (36%) were classified as active smokers, 10 (20%) were diagnosed with depression, 7 (14%) were diagnosed with dyslipidemia, 7 (14%) were diagnosed with DM, and 4 (8%) were diagnosed with alcoholism.

Of the 25 patients in the mild-to-moderate COPD group, 14 (56%) were classified as current smokers, 5 (20%) had been diagnosed with dyslipidemia, and 7 (28%) had been diagnosed with depression. Of the 25 patients in the severe-to-very severe COPD group, only 4 (16%) were classified as current smokers, only 2 (8%) had been diagnosed with dyslipidemia, and only 3 (12%) had been diagnosed with depression.

Current smoking and dyslipidemia were more prevalent in the mild-to-moderate COPD group than in the severe-to-very severe COPD group ($p < 0.001$ and $p = 0.02$, respectively), whereas the prevalence of HBP, DM, alcoholism, CAD, and CHF was comparable between the two groups (Table 2). Although the

Table 1. Demographic and clinical characteristics of the sample as a whole, of the patients with mild-to-moderate COPD, and of the patients with severe-to-very severe COPD.[a]

Variable	Patients with COPD		p*
	Total (n = 50)	GOLD stage I or II (n = 25)	GOLD stage III or IV (n = 25)	
Male/female gender, n	31/19	17/8	14/11	0.24
Age, years	67 ± 9	65 ± 8	69 ± 9	0.08
FVC, L	2.5 ± 0.9	3.2 ± 0.8	1.9 ± 0.5	< 0.001
FVC, % of predicted	81.3 ± 24.6	98.4 ± 19.4	64.3 ± 16.2	< 0.001
FEV_1, L	1.3 (0.8-1.7)	1.7 (1.4-2.2)	0.8 (0.6-1.0)	< 0.001
FEV_1, % of predicted	56.8 ± 23.6	73.2 ± 15.6	40.4 ± 18.4	< 0.001
BMI, kg/m^2	25.0 ± 4.9	24.4 ± 4.6	25.7 ± 5.3	0.39
FFM, kg	16.5 ± 2.9	16.7 ± 2.6	16.2 ± 3.1	0.59
Smoking history, pack-years	49.9 (24.0-80.0)	50.0 (22.3-80.0)	44.0 (24.3-92.5)	0.71
Carbon monoxide, ppm	0.0 (0.0-5.0)	4.0 (0.0-8.0)	0.0 (0.0-5.0)	0.003
SpO_2, %	93.0 ± 4.2	94.8 ± 2.4	91.3 ± 4.9	0.003

GOLD: Global Initiative for Chronic Obstructive Lung Disease; GOLD stage I or II: mild-to-moderate COPD; GOLD stage III or IV: severe-to-very severe COPD; BMI: body mass index; and FFM: fat-free mass. [a]Except where otherwise indicated, data are reported as mean ± SD or as median (25-75% interquartile range). *GOLD stage I or II versus GOLD stage III or IV (unpaired t-test, Mann-Whitney test, or chi-square test).

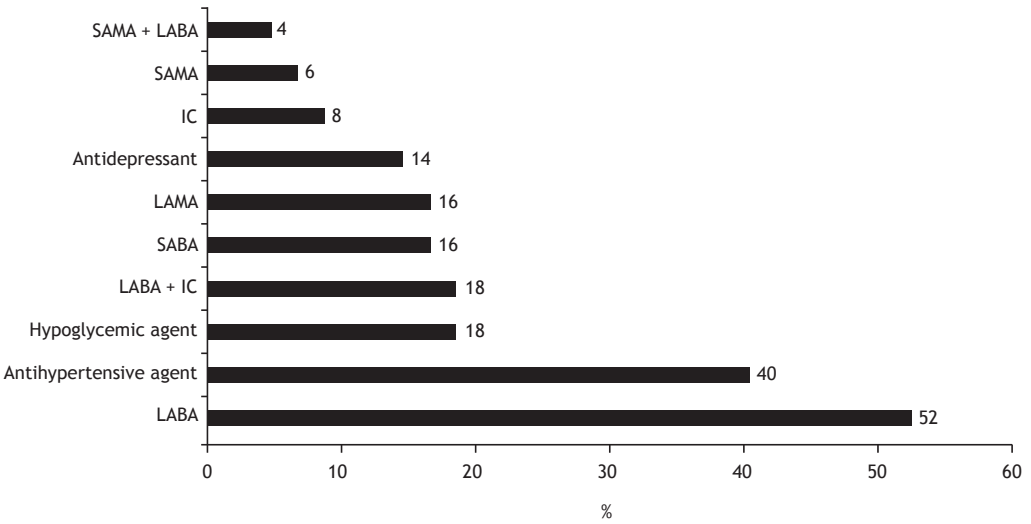

Figure 1. Medications used by the COPD patients in the study sample (n = 50). SAMA: short-acting muscarinic antagonist; LABA: long-acting β_2 agonist; IC: inhaled corticosteroid; LAMA: long-acting muscarinic antagonist; and SABA: short-acting β_2 agonist.

prevalence of depression was significantly higher in the mild-to-moderate COPD group (p=0.008), the HADS scores were not significantly different between the groups (p = 0.93 and p = 0.89 for anxiety and depression, respectively). All 7 of the patients who had previously been diagnosed with depression were receiving pharmacological treatment.

In the majority of the patients diagnosed with dyslipidemia, the concentrations of lipids (total cholesterol, HDL, LDL, and triglycerides) were within normal values, and the lipid profile, according to the Brazilian Society of Cardiology IV Brazilian Guidelines on Dyslipidemia and Prevention of Atherosclerosis,[15] was similar between the two groups. All 7 of the patients who had previously been diagnosed with dyslipidemia were receiving pharmacological treatment.

The Charlson comorbidity index did not differ between the mild-to-moderate COPD and severe-to-very severe COPD groups. For the sample as a whole, the mean Charlson comorbidity index was 3.5 ± 1.3.

DISCUSSION

The main finding of the present study is that risk factors for CVD, including smoking and dyslipidemia, were more prevalent among patients with mild-to-moderate COPD than among those with severe-to-very severe COPD. The prevalence of depression was also higher in the former group.

The prevalence of current smoking in our sample was 36%. Shahab et al.[16] evaluated 1,093 COPD patients and found a similar (34.9%) prevalence of

Table 2. Comorbidities in the sample as a whole, among the patients with mild-to-moderate COPD, and among the patients with severe-to-very severe COPD.[a]

Variable	Total (n = 50)	Patients with COPD		p*
		GOLD stage I or II (n = 25)	GOLD stage III or IV (n = 25)	
Smoking	18 (36)	14 (56)	4 (16)	< 0.001
High blood pressure	20 (40)	9 (36)	11 (44)	0.31
Depression	10 (20)	7 (28)	3 (12)	0.008
Dyslipidemia	7 (14)	5 (20)	2 (8)	0.02
Diabetes mellitus	7 (14)	3 (12)	4 (16)	0.54
Coronary artery disease	5 (10)	2 (8)	3 (12)	0.48
Alcoholism	4 (8)	3 (12)	1 (4)	0.06
Congestive heart failure	3 (6)	1 (4)	2 (8)	0.37
Charlson comorbidity index	3.5 ± 1.3	3.2 ± 1.1	3.9 ± 1.3	0.06

GOLD: Global Initiative for Chronic Obstructive Lung Disease; GOLD stage I or II: mild-to-moderate COPD; and GOLD stage III or IV: severe-to-very severe COPD. [a]Data are reported as n (%) or as mean ± SD. *GOLD stage I or II versus GOLD stage III or IV (unpaired t-test, chi-square test, or Fisher's exact test).

current smoking. In the *Projeto Latino-Americano de Investigação em Obstrução Pulmonar* (PLATINO, Latin American Project for the Investigation of Obstructive Lung Disease) study,[17] the observed prevalence of smoking among patients with COPD categorized as GOLD stage II-IV was 26.2%, which, albeit high, is lower than that identified in our sample. That can be explained, at least in part, by the fact that the PLATINO study sample included subjects who lived in the greater metropolitan area of the city of São Paulo, whereas our sample was composed of subjects living in small towns or rural areas of the state.[17] Black-Shinn et al.[18] also showed that the prevalence of current smoking was higher among patients in the early stages of COPD than among those with severe COPD, which is in line with the findings of another study, which reported a positive association between being a former smoker and having severe airflow limitation.[19] Similarly, in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study, patients with GOLD stage II, III, and IV COPD were compared, and the proportion of current smokers decreased in parallel with increased disease severity.[5] However, there are some data showing that the rates of current smoking actually increase as COPD becomes more severe.[16]

Dyslipidemia was present in 14% of the patients in our sample. This is considerably lower than the 40% prevalence of dyslipidemia (38% among males and 42% among females) reported for the general population of Brazil[15] and the 39% reported in an international study.[20] Two previous studies reported the prevalence of dyslipidemia among COPD patients to be 26.5% and 28.0%, respectively.[21,22] In our study, a diagnosis of dyslipidemia was more prevalent among the patients with mild-to-moderate COPD than among those with severe-to-very severe COPD. That finding could be attributable to the fact that the number of current smokers is usually higher among the patients with mild-to-moderate COPD.[23] To our knowledge, there have been no previous studies comparing the prevalence of dyslipidemia among the stages of COPD severity. Our findings regarding dyslipidemia merit attention, especially in view of the fact that one cross-sectional study of COPD patients showed that the rate of first cardiovascular event (myocardial infarction and stroke), which is usually associated with dyslipidemia, was higher among younger subjects than among those of more advanced age.[24] The authors of that study suggested that the risk of cardiovascular mortality is higher in patients with mild-to-moderate COPD than in those with severe-to-very severe COPD. It has also been demonstrated that lung cancer and cardiovascular comorbidities constitute the leading cause of death in patients with mild-to-moderate COPD, accounting for up to two thirds of all deaths among such patients, whereas respiratory failure is the predominant cause of death in patients with advanced COPD.[4]

Depression was diagnosed in 20% of our patients. That is in agreement with the findings of two previous studies, in which the reported prevalence of depression among COPD patients was 23.1% and 35.0%, respectively.[25,26] In the ECLIPSE study, the overall prevalence of depression in COPD patients was 17%, and there was a statistically significant difference between GOLD stages among females.[5] In another study of COPD patients, Echave-Sustaeta et al.[27] reported that the prevalence of depression was 11.1% and found no association between depression and COPD severity. The higher number of current smokers among patients with mild-to-moderate COPD is a possible explanation for the higher prevalence of depression in such patients. In fact, it has previously been shown that anxiety and depression scores are associated with current smoking.[28,29]

In the present study, the mean Charlson comorbidity index did not differ between the mild-to-moderate COPD and severe-to-very severe COPD groups. For the sample as a whole, the mean Charlson comorbidity index was 3.5, similar to the 3.9 reported by Díez-Manglano et al.,[22] although higher than the 2.5 reported by Echave-Sustaeta et al.[27] and the 2.7 reported by Almagro et al.[2] Although COPD, myocardial infarction, CHF, and DM are included in the Charlson comorbidity index, other highly

prevalent diseases observed in our study, including current smoking, HBP, dyslipidemia, alcoholism, and depression, are not. Therefore, the exclusive use of the Charlson comorbidity index could result in an underestimation of the prevalence of comorbidities and of their influence on the prognosis of COPD patients. After age and chronic symptoms, comorbidities are the most important predictive factors of the future health care costs and direct costs of COPD.[4] In addition, our findings underscore the need for a new comorbidity index to be applied in patients with COPD, given that some highly prevalent comorbidities are not included in the index currently available.

Our study has certain limitations. Although the comorbidities observed in our study are similar to those identified in the current literature, the prospective design and characteristics of the patient sample could explain some of our findings. In addition, the small size of our sample might impose some limitations on the interpretation of our data.

In conclusion, the prevalence of comorbidities is high among patients with COPD, regardless of disease severity. In addition, smoking and dyslipidemia appear to be more prevalent in mild-to-moderate COPD. Therefore, controlling these comorbidities might be a key measure in the early phases of the disease, in order to decrease mortality due to cardiovascular events. Our findings show the importance of therapeutic measures to promote smoking cessation and of early diagnosis to prevent the progression of airflow obstruction.

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