

Gender differences in predictors of health status in patients with COPD*, **

Preditores do estado de saúde em pacientes com DPOC de acordo com o gênero

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Abstract

Objective: To evaluate the health status (HS) of COPD patients and to identify the main predictors of HS in these patients according to gender. **Methods:** The study included 90 COPD patients (60 males and 30 females; mean age = 64 ± 9 years) with a wide range of airway obstruction disorders (mean $FEV_1 = 56 \pm 19\%$ of predicted). The men were individually matched to the women by % of predicted FEV_1 (ratio: 2:1). The patients were assessed regarding body composition; six-minute walk distance; perception of dyspnea using the Modified Medical Research Council Dyspnea Scale; Saint George's Respiratory Questionnaire (SGRQ); Charlson comorbidity index; and the multidimensional Body mass index, airway Obstruction, Dyspnea, and Exercise capacity (BODE) index. Multiple linear regression analysis was performed to identify the predictors of HS by gender. **Results:** Impairment of HS was greater among the women than among the men for SGRQ total score and for all SGRQ domains (total: $51 \pm 18\%$ vs. $38 \pm 19\%$; $p = 0.002$; symptoms: $61 \pm 22\%$ vs. $42 \pm 21\%$; $p < 0.001$; activity: $62 \pm 18\%$ vs. $49 \pm 21\%$; $p = 0.004$; and impact: $41 \pm 19\%$ vs. $27 \pm 18\%$; $p = 0.001$). The multiple linear regression showed that age and perception of dyspnea correlated with SGRQ total score for both genders (males, $r^2 = 0.42$; females, $r^2 = 0.70$; $p < 0.05$). **Conclusions:** Our results showed an association between gender and HS in COPD patients. Age and dyspnea are determinants of HS in both genders.

Keywords: Pulmonary disease, chronic obstructive; Health status; Dyspnea.

Resumo

Objetivo: Avaliar o estado de saúde (ES) de pacientes com DPOC e identificar os principais preditores do ES nesses pacientes de acordo com o gênero. **Métodos:** Participaram do estudo 90 pacientes com DPOC (60 homens e 30 mulheres); idade média = 64 ± 9 anos) com ampla faixa de distúrbios obstrutivos ($VEF_1 = 56 \pm 19\%$ do predito). Os homens foram pareados individualmente às mulheres em função de VEF_1 , % do predito (razão 2:1). Os pacientes foram avaliados em relação à sua composição corporal, distância percorrida no teste de caminhada de seis minutos; percepção da dispneia através da *Modified Medical Research Council Dyspnea Scale*; *Saint George's Respiratory Questionnaire* (SGRQ); índice de comorbidade de Charlson; e índice *Body mass index, airway Obstruction, Dyspnea, and Exercise capacity* (BODE) multidimensional. A análise de regressão linear múltipla foi feita para identificar os preditores do ES por gênero. **Resultados:** O comprometimento do ES foi maior nas mulheres que nos homens no escore total do SGRQ e em todos os domínios (total: $51 \pm 18\%$ vs. $38 \pm 19\%$; $p = 0,002$; sintomas: $61 \pm 22\%$ vs. $42 \pm 21\%$; $p < 0,001$; atividade: $62 \pm 18\%$ vs. $49 \pm 21\%$; $p = 0,004$; e impacto: $41 \pm 19\%$ vs. $27 \pm 18\%$; $p = 0,001$). A regressão linear múltipla mostrou que a idade e a percepção da dispneia se associaram com o escore total do SGRQ em ambos os gêneros (homens, $r^2 = 0,42$; mulheres, $r^2 = 0,70$; $p < 0,05$). **Conclusões:** Nossos resultados mostraram uma associação entre o gênero e o ES em pacientes com DPOC. A idade e a percepção da dispneia são determinantes do ES em ambos os gêneros.

Descritores: Doença pulmonar obstrutiva crônica; Nível de saúde; Dispneia.

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Introduction

It is well known that COPD is a preventable and treatable disease, characterized by airflow limitation that is not fully reversible. In addition, it is well established that COPD is associated with systemic consequences that adversely interfere with the disease prognoses, including fat-free mass (FFM) depletion,⁽¹⁾ exercise intolerance,⁽²⁾ and impairment of health status (HS).⁽³⁾ Although recent surveillance studies on COPD have shown that the prevalence of COPD and hospitalizations due to the disease has increased in women,⁽⁴⁾ there have been few reports comparing its impact and its systemic manifestations between genders.⁽⁵⁻¹⁰⁾ Results from these studies have suggested that, among COPD patients, the perception of dyspnea, exercise intolerance and HS impairment are greater in females than in males.⁽⁵⁻¹⁰⁾

The assessment of HS quantifies the overall impact of the disease and is an important outcome measure in patients with COPD.⁽¹¹⁾ The perception of dyspnea, nutritional depletion, a decrease in exercise tolerance, as well as the onset of symptoms of anxiety and depression, have been identified as predictors of HS scores in COPD patients of both genders pooled together.⁽¹²⁻¹⁴⁾ However, we only identified two studies evaluating the relative contribution of different factors to HS scores in COPD patients according to the gender.^(6,8) Although the perception of dyspnea was selected as a predictor of HS for men in both studies,^(6,8) the characteristics associated with HS in women differed between the two studies.^(6,8) Our hypotheses are that women have greater impairment of HS than do men and that the predictors of HS differ between the genders. Therefore, the objective of the present study was to further evaluate the HS of patients with COPD separated by gender using the Saint George's Respiratory Questionnaire (SGRQ) scores and to identify the main predictors of HS in these patients, who had a wide range of airway obstruction disorders.

Methods

The sampling frame for this study was consecutive COPD patients treated at the outpatient clinic of a single institution. We recruited 30 women and 85 men with COPD presenting with a wide range of disease severity. Sixty men

were matched to the women taking into consideration the value of FEV₁% after bronchodilator administration (\pm 8% of predicted), according to what had been described in previous studies,^(6,8) resulting in a male/female ratio of 2:1. Therefore, the final sample comprised 30 women and 60 men. The matching process was done randomly and after the confirmation of the diagnosis of COPD.

The patients were included if they met the criteria for the diagnosis of COPD according to guidelines established by the Global Initiative for Chronic Obstructive Lung Disease⁽¹⁵⁾: FEV₁/FVC ratio, after bronchodilator administration, < 0.70; and a < 15% or 200 mL increase in FEV₁ after the inhalation of a β_2 agonist. Patients who were not considered clinically stable (i.e., with changes in the dose or in the frequency of medications, exacerbation of the disease, or hospital admissions in the preceding six weeks) were excluded. The following exclusion criteria were also applied: inability to perform lung function tests or the six-minute walk test (6MWT); inability to understand or to complete the quality of life questionnaires; and myocardial infarction (within the preceding four months), unstable angina or congestive heart failure (New York Heart Association class II or IV).

All patients gave written informed consent. All procedures were approved by the Research Ethics Committee of the São Paulo State University School of Medicine, located in the city of Botucatu, Brazil.

Spirometry was performed prior to and 15 min after the inhalation of 400 μ g of albuterol using a Koko spirometer (Ferraris Respiratory, Louisville, CO, USA), according to the American Thoracic Society (ATS) criteria.⁽¹⁶⁾ The FEV₁ values were expressed in liters, % FVC, and % of reference values.⁽¹⁷⁾ We evaluated SpO₂ using a portable oximeter (Onyx 9500; Nonin Medical Inc., Plymouth, MN, USA).

Body weight and height were measured, and BMI (weight/height²) was calculated. The body composition was also evaluated using a bioelectrical impedance analyzer (BIA 101A; RJL systems, Detroit, MI, USA) in accordance with the European Society of Parenteral and Enteral Nutrition guidelines.⁽¹⁸⁾ Using a group-specific regression equation developed by Kyle et al.,⁽¹⁹⁾ FFM (kg) was estimated, and the FFM index (FFMI, expressed as FFM/height²) was calcu-

lated. Fat mass was defined as the total body weight minus FFM. Lean body mass depletion was defined as an FFMI $< 15 \text{ kg/m}^2$ for women and $< 16 \text{ kg/m}^2$ for men.⁽¹⁾

A translated version of the SGRQ, validated for use in Brazil,⁽²⁰⁾ was used in order to evaluate the HS of the patients. A translated version of the baseline dyspnea index⁽²¹⁾ was used in order to evaluate the perception of dyspnea.

The 6MWT was performed in accordance with the ATS guidelines.⁽²²⁾ Patients were instructed to walk for 6 min, attempting to cover as much ground as possible within the time allotted. A research assistant timed the test, and standardized verbal encouragement was given. The SpO₂ of the patients was monitored throughout the test. Hypoxic patients at baseline and patients whose SpO₂ decreased to $< 85\%$ during the test were given oxygen by a physical therapist who wheeled an oxygen tank on a handcart alongside the patient. Prior to and after the test, SpO₂, HR, RR, sensation of dyspnea (Borg scale), and blood pressure were determined. The distance covered was measured in meters and is also expressed as % of predicted values.⁽²³⁾

For the calculation of the Body mass index, airway Obstruction, Dyspnea, and Exercise capacity (BODE) index, we used the model devised by Celli et al.⁽²⁾ For each threshold value of FEV₁, six-minute walk distance (6MWD), and Modified Medical Research Council Dyspnea Scale (MMRC) score, the patients received points ranging from 0 (lowest value) to 3 (maximal value). For BMI, the values were 1 (BMI $\leq 21 \text{ kg/m}^2$) or 0 (BMI $> 21 \text{ kg/m}^2$). The scores of each variable were added, so the BODE index ranged from 0 to 10 points. The Charlson comorbidity index was used in order to determine the degree of comorbidity.⁽²⁴⁾

Statistical analysis was performed using the software SigmaStat, version 2.03 (SPSS Inc., Chicago, IL, USA) and R, version 2.6.1 (R Foundation for Statistical Computing, Vienna, Austria). The results are presented as mean \pm SD or median (25-75% interquartile range), depending on the distribution. Either Student's t-test or Mann-Whitney U-rank sum test was used in order to compare the general characteristics by gender. Multiple linear regression analysis was used in order to identify the predictors of HS for each gender, including the studied

variables. Values of $p < 0.05$ were considered statistically significant.

Results

The characteristics of the patients are presented in Table 1. We evaluated 90 patients with COPD: 60 men (66%) and 30 women (34%). In comparison with the men, the women were significantly younger, smoked less and presented with fewer comorbidities. The FFM values and 6MWD values (in % of predicted) were lower for the women than for the men. The FEV₁/FVC ratio was significantly lower in the men. However, there were no significant differences between the genders in terms of the expected FEV₁ values (% of predicted), the proportion of patients with mild/moderate COPD (62% vs. 57%), or the proportion of patients with severe/very severe disease (38% vs. 43%). The MMRC scores and the BODE index values were similar between the genders.

As can be seen in Figure 1, the women showed greater impairment of HS than did the men for the SGRQ total score and for all

Table 1 – Baseline characteristics of the patients with COPD, by gender.^a

Variable	Men (n = 60)	Women (n = 30)	p
Age, years	67 \pm 8	58 \pm 8	< 0.001
Smoking history, pack-years	56 (40-84)	40 (30-50)	0.003
SpO ₂ , %	94 \pm 2	93 \pm 3	0.445
BMI, kg/m ²	25 \pm 5	27 \pm 7	0.220
FFM, kg	45 \pm 5	35 \pm 7	< 0.001
FFMI, kg/m ²	16 (15-17)	15 (13-17)	0.004
FEV ₁ , % of predicted	55 \pm 20	58 \pm 17	0.545
FEV ₁ /FVC	48 \pm 11	57 \pm 9	< 0.001
MMRC	1 (1-2)	2 (1-3)	0.050
6MWD, m	440 \pm 79	413 \pm 87	0.140
6MWD, % of predicted	91 \pm 15	81 \pm 13	0.002
BODE index	2 (1-4)	2.5 (1-5)	0.584
Charlson comorbidity index	4 (3-5)	3 (2-4)	0.015

FFM: fat-free mass; FFMI: fat-free mass index; MMRC: Modified Medical Research Council; 6MWD: six-minute walk distance; and BODE: Body mass index, airway Obstruction, Dyspnea, and Exercise capacity. ^aValues are presented as mean \pm SD or as median (25-75% interquartile range).

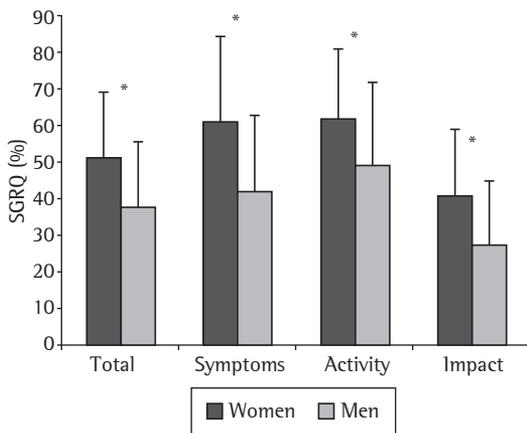


Figure 1 - Mean Saint George's Respiratory Questionnaire (SGRQ) scores (total and domains) by gender (* $p < 0.05$).

SGRQ domains: total ($51 \pm 18\%$ vs. $38 \pm 19\%$; $p = 0.002$); symptoms ($61 \pm 22\%$ vs. $42 \pm 21\%$; $p < 0.001$); activity ($62 \pm 18\%$ vs. $49 \pm 21\%$; $p = 0.004$); and impact ($41 \pm 19\%$ vs. $27 \pm 18\%$; $p = 0.001$). The results of the multiple linear regression analysis by gender are presented in Table 2. Age and sensation of dyspnea were associated with the SGRQ total scores for both genders ($p < 0.05$).

Discussion

The results of this study showed that, for a similar degree of airflow obstruction, the women with COPD presented greater impairment of HS than did the men in all SGRQ domains. The mean differences between the genders were all

higher than the four points considered as the minimal values of clinically significant difference for SGRQ.⁽²⁵⁾ In the multiple linear regression analysis, age and perception of dyspnea were statistically associated with HS in both genders. However, for the women, those two variables explained 70% of the variation in the SGRQ score, compared with only 42% for the men.

Our findings are in agreement with the results of previous studies, suggesting that, among COPD patients, the impairment of HS is greater in women than in men.^(6-8,10,26,27) In a study designed to investigate the association between HS and hospital readmissions in COPD patients, women presented higher scores in the activity and impact domains at baseline.⁽²⁶⁾ In addition, the women showed greater impairment at baseline and less improvement in HS, evaluated using the Medical Outcomes Study 36-item Short-form Health Survey (SF-36), after lung transplantation, despite presenting greater spirometric gains than did the men.⁽²⁷⁾ In another study,⁽⁷⁾ the authors evaluated 202 COPD patients (155 men, 47 women), using the SGRQ, and found that the women had worse symptom-related quality of life and higher levels of depression and anxiety than did the men. In a more recent study, a total of 10,711 COPD patients (75.6% males) were evaluated, and female smokers had poorer HS, as evidenced by their scores on the mental component of the 12-item Short-form Health Survey, than did male smokers.⁽¹⁰⁾ Other studies using the SGRQ or SF-36 to evaluate COPD patients have also shown HS impairment to be greater in the women than in the men.^(6,8)

Table 2 - Results of multiple linear regression analysis by gender using the Saint George's Respiratory Questionnaire total scores as a dependent variable.

Patient	Independent variable	Coefficient (95% CI)	p
Men ($r^2 = 0.42$)	Age, years	-0.72 (-1.24 - -0.20)	0.01
	FEV ₁ , % of predicted	-0.05 (-0.27-0.15)	0.57
	6MWD, m	-0.002 (-0.06-0.06)	0.93
	FFM, kg	-0.56 (-1.4-0.23)	0.17
	SpO ₂ , %	0.17 (-0.77-0.96)	0.83
	MMRC	12.24 (7.16-17.5)	< 0.001
Women ($r^2 = 0.70$)	Age, years	-1.14 (-1.77 - -0.50)	0.001
	FEV ₁ , % of predicted	-0.19 (-0.52-0.14)	0.24
	6MWD, m	-0.05 (-0.12-0.02)	0.17
	FFM, kg	-0.57 (-1.27-0.13)	0.11
	SpO ₂ , %	-0.53 (-2.08-1.02)	0.49
	MMRC	7.20 (1.79-12.6)	0.01

6MWD: six-minute walk distance; FFM: fat-free mass; and MMRC: Modified Medical Research Council.

One important finding of this study is that the age and the perception of dyspnea were the main determinants of the variation in the SGRQ total score in both genders. Most studies exploring factors associated with HS have evaluated COPD patients of both genders.⁽¹²⁻¹⁴⁾ We identified two studies that evaluated predictors of HS according to the gender.^(6,8) In agreement with our findings, one of those studies⁽⁶⁾ showed that the perception of dyspnea impairs HS in both genders. However, the authors showed differences between genders in terms of which variables other than the perception of dyspnea impair HS (exercise tolerance, degree of hyperinflation and presence of comorbidities for men; arterial oxygenation for women). Another group of authors⁽⁸⁾ showed that the perception of dyspnea (assessed with the oxygen cost diagram) was the variable that was most strongly associated with SGRQ scores in males, whereas the score on the well-being scale (Morale Scale), and not the perception of dyspnea, was the main determinant of HS in females.

The possible mechanisms by which the perception of dyspnea influences the HS of men and women were not evaluated in this study. A recent study showed that the central respiratory drive was the best single predictor of functional dyspnea scores in women with COPD (this variable explained 30% of the variation in the perception of dyspnea determined by MMRC), whereas, in men with COPD, the predictors of MMRC scores were the central respiratory drive, the nutritional status, PaO₂ and DLCO. These variables explained 80% of the variations of MMRC scores in men. This suggests that respiratory factors explained most of these variations in men, but other factors should be systematically explored in the evaluation of the perception of dyspnea in women with COPD.⁽²⁸⁾

In our study, age was associated with HS in both genders. However, the women were significantly younger than were the men, even though the women presented greater impairment of HS and less exercise tolerance (in relation to the predicted values), showing a tendency towards a greater perception of dyspnea and lower FFM. In addition, the women smoked less and had fewer comorbidities than did the men. However, the BODE index was similar in both genders. These results are in accordance with those of previous studies,^(6,9) which suggested that women are

more susceptible to the effects of tobacco smoke and that COPD becomes more clinically evident at an earlier age in women than in men. This might explain why age was associated with HS in both genders.

In the present study, the 6MWD was not significantly shorter in the women than in the men. However, the women covered less distance than would be expected, based on regression equations for women compared with men.⁽²³⁾ This supports the finding of a previous study that showed lower 6MWD values, expressed as % of predicted, in women.⁽⁵⁾ However, the 6MWD was not associated with HS in either gender. This might be attributable to an association between dyspnea and walk distance or to the sample size (the number of women). This is in contrast with a previous study that showed the influence of exercise tolerance on men.⁽⁶⁾

The present study has some limitations. We did not assess symptoms of depression and anxiety. In fact, psychological factors have been shown to have a major impact on the HS of COPD patients.⁽¹⁴⁾ In addition, among COPD patients, the prevalence of psychiatric disorders is higher in women^(7,29) and has been associated with greater psychological distress, worse perceived symptom control and greater functional impairment.⁽³⁰⁾ The lack of these evaluations in our study might have influenced the results and, therefore, psychological or sociocultural aspects should also be investigated in further studies designed to assess gender differences in the HS of COPD patients. In addition, the patients were selected from the outpatient clinic of a university hospital and therefore might not represent the COPD population at large. Furthermore, we evaluated more men than women. However, this is in agreement with the higher proportion of men with COPD in the general population, as reported in international studies.⁽¹⁵⁾ Finally, this was a cross-sectional study; therefore, prospective studies with adequate sampling and sample size should be conducted to verify the hypothesis of association between gender and HS in COPD patients.

In summary, in a sample of COPD patients with similar degrees of airway obstruction, our results show an association between the gender and HS. Age and the perception of dyspnea were found to be major determinants of HS in both genders. Future studies evaluating addi-

tional variables, as well as interventions to improve dyspnea and other gender-related characteristics, are needed in order to improve the understanding of gender differences in the HS of COPD patients.

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