Symptoms irregularity and increased risk of COPD acute exacerbations

Chronic Obstructive Pulmonary Disease (COPD) is a complex and heterogeneous disease. Acute exacerbations are trajectory-changing events in the natural history of the disease and are also an important cause of morbidity and the main cause of mortality, during and after hospitalization.[1] Some demographic, clinical or functional characteristics displayed by some individuals may allow the identification of groups of patients with different risk of acute exacerbation. This may be crucial for the busy clinician, facilitating the choice of the best therapeutic approach from the beginning. We present the preliminary results of a cross-sectional study aimed at evaluating whether some patients' characteristics can predict an increased risk of acute exacerbations of COPD (ECOPD), and thus influence therapeutic options.[2] The variables under study were age, gender, education level, income, smoking status, airflow limitation, symptoms and symptoms irregularity.

COPD out-patients over 40 years old, diagnosed according to GOLD criteria,[3] were recruited consecutively between March 2016 and May 2017, and all gave their written informed consent. Exclusion criteria were refusal to participate and inability to understand simple questionnaires. The study was approved by the hospital de Guimarães Ethics Committee, the Research Ethics Committee of Minho' University and by the Portuguese data Protection Agency. A survey of demographic and clinical data was applied, and the assessment of symptoms was done using the COPD Assessment Test (CAT) and the Medical Research Council Dyspnea Questionnaire (mMRC). ECOPD were defined as a worsening of one or more major respiratory symptoms, requiring an unplanned medical visit that led to any extra treatment or to a treatment change. Symptom irregularities were defined as a worsening of one or more respiratory symptoms in winter and/or with changes in weather that led to the use of rescue medication but did not require an unplanned medical visit. A statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

We studied 310 COPD patients, all Caucasian, 79.4% males (mean age = 67.66 years), 84.4% retired and 79% urban inhabitants. Low education level (≤6 years at school) was declared by 87.8%, very-low education level (≤3 years) by 29.7%, and low income (<530 €) by 65.2% of subjects. The majority of patients (59.8%) declared low socioeconomic status (Graffar social classification score 4 and occasionally 5). Tobacco smoking was the most common exposure identified in 74.8% of patients. 5.2% were modest smokers, defined, according to previous literature, as <10 pack-years,[4] and 17.7% were current smokers. The mean tobacco amount was 48.7 ± 32.6 pack-year. Self-reported occupational exposure to dust, gas or fumes relevant to COPD, and sustained indoor exposure to household air pollution from coal and biomass fuel combustion was stated by 55.5% of patients and by 62.5% of women, respectively. Eighty-three patients (27.1%) had a history of childhood asthma or a previous diagnosis of asthma before age 40 years. A history of frequent (≥2) treated exacerbations was recorded by 38.4% of patients in the previous year. The mean FEV_1 was 1.37 L or 53.4% of the predicted values (GLI 2012 Spirometry reference Equations [5–7]). An mMRC grade ≥2 was observed in 62.6% and a CAT score >10 by 72.8% of the responders. The distribution of patients according to GOLD 2017 stage and classification were 10%, 41.9%, 35.2% and 12.9% stage 1 to 4, and 22.9%, 39.4%, 2.3% and 35.5% GOLD A to D.

We found a significant association between the risk of exacerbations and both education level ($p = .020$) and income ($p = .007$). Binary logistic regression indicates an odds ratio of 1.9 times more risk of ECOPD for very-low education level (≤3 years of school) and 2 times more risk of exacerbations for lower income, when controlling for age and gender.

Age was also not related to an increased risk of exacerbation ($p = .153$) nor with GOLD 2017 stage or classification ($p = .637$ and $p = .528$, respectively). We found no association between age and clinical worsening of the disease (CAT < 10, mean age = 67.9 years; CAT ≥ 10, mean age = 64.9 years; mMRC < 2, mean age = 67.9 years; mMRC ≥ 2, mean age = 67.5 years). There was no association between age and airflow limitation ($p = .545$, being the correlation coefficient between age and $FEV_1\% = .034$).

We found no significant differences between genders related to age (mean age of men and women were 67.5 years and 68.1 years, respectively) and to airflow limitation (mean $FEV_1\%$ was 53.1 in man and 54.3 in women). CAT score and mMRC grade was higher in women ($p = .004$ and $p = .026$, respectively). Female gender was also related to an increased risk of exacerbation ($p = .003$).

Patients with a smoking history are mainly male. Current smokers have a significantly lower mean age than ex-smokers or never-smokers (61.2, 67.4 and 72.8 years, respectively, $p = .000$). Current smokers, ex-smokers and the never-smokers reporting significant occupational or in-door exposure relevant to COPD, present comparable airflow limitation ($p = .511$) and risk of exacerbation ($p = .150$). Never-smokers have significantly higher CAT score ($p = .013$) and mMRC grade ($p = .025$). We found also no association between pack-years smoking history and GOLD stage (GOLD 1–4: 43.7; 43.8; 55.6 and 47.6 average number of pack-year, $p = .103$).

Patients with mMRC grade ≥2 ($p = .000$) or CAT score ≥10 ($p = .000$) were at increased risk of acute exacerbation. Patients with higher airflow limitation, according to GOLD stage, were also at increased risk of acute exacerbation ($p = .000$). We found a strong association between airflow limitation, according to GOLD classification, and mMRC grade ($p = .000$) or CAT total score ($p = .000$). Many patients (62.3%) report irregularity of symptoms. We found a significant association between symptom variability and a history of frequent (≥2) treated exacerbations ($p = .004$), when controlling for gender, previous history of asthma and $FEV_1\%$ (Table 1). This was expected, since acute exacerbations are major forms of symptoms' irregularity.

Different COPD previous exposure factors often overlap in the same patient. In never-smoking patients, and in the absence of measurable exposure data, the risk of COPD may be overestimated. However, many epidemiological studies have relied on self-reported exposure,[8] and this is how, in clinical practice, the risk of developing COPD is assessed. In contrast to other studies, never-smoking COPD patients are more symptomatic than patients with a smoking history,[9]

and we found no association between the degree of airflow limitation and different COPD risk factors or smoking history.[10] Smoking history was also not related to risk of ECOPD. Probably because patients are being treated, aging was not related to airflow limitation, symptoms or acute exacerbations. These findings are in contrast with some observational studies.[11] Women are more at risk of ECOPD. As in other populations studied, very-low education level and low income were also related with an increased risk of acute exacerbation.[12] Patients with higher airflow limitation are more symptomatic. They are at increased risk of ECOPD. Patients recording irregularity of symptoms also seem to be more prone to acute exacerbations of COPD. Because of the greater tendency to exacerbate, more attention needs to be paid to these patients. A ''hit hard'' approach and a closer follow-up would be a good therapeutic option.[13] A trial of inhaled corticosteroids association in symptomatic patients despite optimized bronchodilation is also recommended.[14]

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