CHEST

Defining the "Frequent Exacerbator" Phenotype in COPD

A Hypothesis-Free Approach

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BACKGROUND: The COPD "frequent exacerbator" phenotype is usually defined by at least two treated exacerbations per year and is associated with a huge impact on patient health. However, existence of this phenotype and corresponding thresholds still need to be formally confirmed by statistical methods analyzing exacerbation profiles with no specific a priori hypothesis. The aim of this study was to confirm the existence of the frequent exacerbator phenotype with an innovative unbiased statistical analysis of prospectively recorded exacerbations.

METHODS: Data from patients with COPD from the French cohort in Exacerbations of COPD Patients (EXACO) were analyzed using the KmL method designed to cluster longitudinal data and receiver operating characteristic (ROC) curve analysis to determine the best threshold to allocate patients to identified clusters. Univariate and multivariate analyses were performed to study characteristics associated with different clusters.

RESULTS: Two clusters of patients were identified based on exacerbation frequency over time, with 2.89 exacerbations per year on average in the first cluster (n = 348) and 0.71 on average in the second cluster (n = 116). The best threshold to distinguish these clusters was two moderate to severe exacerbations per year. Frequent exacerbators had more airflow limitation, symptoms, and health-related quality of life impairment. A simple clinical score was derived to help identify patients at risk of exacerbations.

CONCLUSIONS: These analyses confirmed the existence and clinical relevance of a frequent exacerbator subgroup of patients with COPD and the currently used threshold to define this phenotype.

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FOR EDITORIAL COMMENT, SEE PAGE 1087

ABBREVIATIONS: AUC = area under the curve; GOLD = Global Initiative for Chronic Obstructive Lung Disease; mMRC = modified Medical Research Council; ROC = receiver operating characteristic

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COPD is a chronic inflammatory disease of the airways characterized by an airflow limitation that is not fully reversible.[1] The course of the disease is punctuated by acute exacerbations associated with high morbidity, mortality, and costs.[2,3] Exacerbations become more frequent and more severe as COPD progresses,[4] and their recurrence is associated with a decline in lung function and health status of patients.[5,6] Exacerbations can occur across all stages of airflow limitation measured by FEV_1, which emphasizes the need to identify other predictors of high exacerbation risk.[4]

During past years, authors have attempted to characterize a specific phenotype of patients with COPD with frequent exacerbations, as identified using various thresholds mostly derived from the median exacerbation frequency in various cohorts, with subsequent confirmation of their association with health status and prognosis.[7] In the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study, about 60% of patients with two or more moderate to severe exacerbations during 1 year also had at least two exacerbations during the following year.[4] In these patients, exacerbation frequency was considered relatively stable over the 3-year study period. Consequently, most authors have been using this cutoff to describe the frequent exacerbator phenotype.[4,8] This definition is now part of the Global Initiative for Chronic Obstructive Lung Disease guidelines (GOLD).[1] However, intrasubject variability of annual exacerbation frequency limits the ability of this criteria to predict the future risk of exacerbations at an individual level.[4,9]

The first objective of this study was to determine, using a hypothesis-free analysis, whether patients cluster together based on prospectively recorded frequencies of moderate to severe exacerbations over 4 years of follow-up. The subsequent main objective was to define the best thresholds to allocate patients to these clusters. Secondary objectives were to describe clinical characteristics associated with these clusters and to determine whether a simple score can be derived to identify patients at risk of frequent exacerbations.

Methods

Study Design and Patients

The Exacerbations of COPD Patients (EXACO) study is a prospective cohort study conducted in France and approved by the Institutional Review Board of the French-language Society of Respiratory Medicine (CEPRO 2012-026). One hundred thirty-two respiratory physicians, covering office-based and hospital settings from the private and public sectors, enrolled 835 consecutive patients with COPD from October 2005 to January 2007 and followed them over 4 years. Inclusion criteria were a $\geq$ 2 GOLD stage of airflow limitation (postbronchodilator $FEV_1/FVC < 70\%$ and $FEV_1 \leq 80\%$ of predicted), age $\geq$ 40 years, a current or past smoking history $\geq$ 15 pack-years, and no exacerbation in the month preceding enrollment. Patients with other respiratory diseases, those diagnosed with cancer in the preceding 3 years, or those unable to complete the follow-up requirements were excluded. Selection and characteristics of physicians and data collected are detailed in e-Appendix 1.

Exacerbations

Exacerbation was identified as $\geq$ 2 consecutive days with sustained worsening of patient's symptoms beyond day to day variations leading to a change in treatment (details in e-Appendix 1).[10] The severity of exacerbations has been classified according to health care use: mild in case of self-management, moderate if the patient was not hospitalized but received a prescription of systemic corticosteroids or antibiotics, or both, and severe if the patient was hospitalized. Only moderate to severe exacerbations were taken into account and pooled for analysis.

Different collecting tools were organized to avoid underreporting. First, patients were asked to complete a monthly questionnaire regarding their respiratory symptoms and respiratory status. In the event of deterioration, patients were asked to immediately complete an additional questionnaire. Second, patients were contacted by telephone every 3 months to ensure that all events were collected. Finally, at each follow-up visit, the respiratory physicians asked the patient to report the number of COPD exacerbations requiring a change in treatment or hospitalization since the last consultation, and the information was recorded. Dates of symptoms were used to avoid double counting a single exacerbation.

Data Analysis

Two sets of analyses were performed. The main analysis used data from all patients with complete information on annual exacerbations during each of the 4 years of follow-up to ensure maximal longitudinal robustness (Fig 1). The second, called the extended analysis, was a confirmatory analysis using data from all patients with at least 2 years of follow-up. We used KmL analysis, which is an implementation of a nonparametric algorithm designed to work specifically on longitudinal data (details in e-Appendix 1).[11] It provides scope for dealing with missing values and runs the algorithm several times, varying the starting conditions or the number of clusters sought, or both; thereby it identifies clusters of patients with similar evolution of exacerbation frequency over the 4 years. To ensure maximal robustness of findings, three different indexes were used to choose the optimal number of clusters (Fig 2A): the Calinski and Harabatz index, the Ray and Turi index, and the Davies and Bouldin index.[11] Higher indexes correspond to larger between-cluster variances and smaller within-cluster variances. Receiver operating characteristic (ROC) curve analysis was performed to identify the best threshold to separate clusters.

Data are reported as means $\pm$ SD or percentages as appropriate. Comparisons of quantitative data between groups were carried out using a Student t test after an F test for quantitative data, and a Fisher exact test was performed for qualitative data. Factors associated with the frequent exacerbator cluster were assessed by an iteratively reweighted least squares method for univariate analysis, and variables with $P < .1$ were included in a bidirectional stepwise