Factors Associated with Increased Risk of Exacerbation and Hospital Admission in a Cohort of Ambulatory COPD Patients: A Multiple Logistic Regression Analysis

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Abstract

Background and Objective: The aim of this study was to develop and validate two models to estimate the probabilities of frequent exacerbations (more than 1 per year) and admissions for chronic obstructive pulmonary disease (COPD) that can be used in a primary care setting.

Methods: Information was obtained in a cross-sectional observational study on ambulatory COPD patients performed in 201 general practices located throughout Spain. The model for admissions included 713 cases, 499 for the developmental sample and 214 in the validation sample; the model for frequent exacerbations included 896 patients, 627 in the developmental sample and 269 in the validation model. Candidate variables to be included in both models were: age, sex, body mass index (BMI), FEV\textsubscript{1} as percent predicted [FEV\textsubscript{1} (% pred.)], active smoking, chronic mucus hypersecretion (CMH) and significant comorbidity. Results: The admission model contained 2 readily obtainable variables: comorbidity (OR = 1.97; CI 95% = 1.24–3.14) and FEV\textsubscript{1} (% pred.) (OR = 0.72; 0.58–0.88, for every 10 units), and well calibrated in developmental and validation samples (goodness-of-fit tests: p = 0.989 and p = 0.720, respectively). The model for frequent exacerbations included 3 variables: age (OR = 1.21; 1.01–1.44; for every 10 years of increasing age), FEV\textsubscript{1} (% pred.) (OR = 0.82; 0.70–0.96, for every 10 units) and CMH (OR = 1.54; 1.11–2.14) and also well calibrated (p = 0.411 and p = 0.340 in the developmental and validation samples, respectively). Conclusions: Our results suggest that FEV\textsubscript{1} impairment explains part of the risk of frequent exacerbations and hospital admissions. Furthermore, CMH and increasing age are significantly associated with the risk of frequent exacerbations, but severity of exacerbations provoking hospital admissions is associated with the presence of significant comorbidity. These important and easily measurable variables contain valuable information for optimal management of ambulatory patients with COPD.

Key Words
COPD · Exacerbation · Admission · Risk factors · Mucus hypersecretion · Primary care
Introduction

Chronic obstructive pulmonary disease (COPD) is a very prevalent disease in developed countries. It is estimated that approximately 4–6% of adult white males and 1–3% of adult white females suffer from emphysema or chronic airflow obstruction in the United States and some European countries [1–3]. Similarly, recent studies in Spain have shown a 6.4% prevalence of COPD among men between the ages of 35 and 65 [4], and a 9% prevalence among individuals of both sexes between 40 and 70 [5].

Frequent acute exacerbations have been demonstrated to have a negative impact on quality of life of patients with COPD [6]. Furthermore, they are the most frequent cause of hospital admission and death among patients with COPD [7]. Since acute exacerbations are an important feature in the natural history of the disease, it is crucial to identify patients most at risk of suffering from them. The identification of risk factors for acute exacerbations may permit the implementation of measures aimed at avoiding these complications. In a further step, identification of COPD patients with risk factors associated with an increased probability of severe exacerbations that entail hospital admission may alert physicians and induce closer follow-up and the adoption of preventive measures whenever possible.

Most studies on ambulatory COPD patients have focused on identification of factors associated either with relapse after treatment for acute exacerbation [8–11] or with poor evolution of the exacerbated disease [12], and only a few have dealt with factors predicting mortality after admission to hospital for an exacerbation [13–15]. Moreover, recent studies have focused on physiologic measures, such as pulmonary artery pressure, to try to elucidate the increased risk of hospitalization of patients with COPD [16]. However, the possibility of predicting the risk of recurrent exacerbations or hospital admission based on clinical and functional data has only seldom been assessed in small populations [6]). Our modeling goal was to develop and validate two simple systems for estimating the probabilities of frequent exacerbations (two or more exacerbations per year) and hospital admission in ambulatory patients with COPD based on data collected in the clinical records obtained at a control visit to the general physician while in stable phase.

Patients and Method

Sample Selection

This is a cross-sectional observational study on ambulatory COPD patients. The study was conducted between October 1, 1994, and May 30, 1995, in 201 general practices located throughout Spain and selected by a regionally stratified sampling, which included all regions and was weighted according the different populations of each of them. Information was sought of the first 8 unselected consecutive adults seen for whom the general practitioner (GP) considered the diagnosis to be COPD. The methodology of the study has been extensively described previously [17].

The diagnosis of COPD was based on the GP’s judgement, but had to be confirmed by a spirometric test which displayed at least an FEV₁ <80% of predicted values and an FEV₁/VC ratio <70%, as suggested by the British Thoracic Society guidelines [18]. The predicted values used were those of Roca et al. [19]. The examination had to be performed in a stable phase, at least 1 month after recovery from an exacerbation, and not more than 6 months from the date of inclusion in the study. Exacerbations were defined in terms of symptoms according to Anthonisen et al. [20]. Briefly, a patient was considered to be in a phase of exacerbation when he/she presented with increased dyspnea, increased sputum volume and/or sputum purulence. Exclusion criteria included diagnosed cystic fibrosis, asthma or severe bronchiectasis.

Data were collected through a questionnaire which covered demographic data, pulmonary risk factors, concomitant illnesses, COPD characteristics which included pulmonary function tests (forced spirometry), drug usage in stable phase and during exacerbations and the number and characteristics of exacerbations of COPD.

The questionnaires were completed by the GPs at the time of the patient’s medical visit. All questionnaires and spirometry data submitted were reviewed and rated for quality by two experienced pneumologists (MM and CM) who filtered inconsistencies. Questionnaires which did not have precise information or which had missing values on items of number of previous exacerbations or hospital admissions were excluded from the analysis.

A regression model was constructed to identify the variables associated with frequent exacerbations and admissions. The model was constructed using a randomly selected subsample of 70% of the subjects included (developmental model). The model obtained was tested with data derived from the remaining 30% of the total population (validation sample), as described by Hosmer and Lemeshow [21]. Developmental and validation samples were created by assigning each patient a random number between 0 and 1. Patients with a random number of 0.70 or less formed the developmental sample, and the remaining patients formed the validation sample. This process was performed separately for both models: frequent exacerbations and admissions.

We wanted our models to accurately reflect the exacerbation and admission experience of the patient sample while containing the minimum number of variables necessary to calibrate and discriminate well in the developmental and validation samples. Only clearly definable and reliably obtained terms were included; the use of laboratory values, radiological examinations and measurements that cannot be performed as part of routine patient care was avoided. Candidate variables to be included in both models were: age, sex, body mass index (BMI) calculated as kg·m⁻², FEV₁ as percent predicted, smoking habits (active smoker vs non- or ex-smoker), presence or absence of chronic mucus hypersecretion (CMH) defined as emission...
of more than 30 ml of sputum daily (more than a cup) which has lasted at least 3 months a year, for more than 1 year [22], and comorbidty, coded as ‘0 = no; 1 = yes’ for any of the following: ischemic heart disease, chronic heart failure or diabetes mellitus.

**Statistical Analysis**

In the model for hospital admissions, the association of categorical independent variables with admissions was assessed by the $\chi^2$ test, and the significance of continuous variables was assessed with Student’s $t$ test and Wilcoxon’s Rank Sum test. Variables were eligible for entry into a multiple logistic regression model if they were significantly associated with admissions at a $p < 0.25$ and at least 2% of the population exhibited that factor [20]. The $k$ statistic was used to assess interrater reliability of variables. Estimated coefficients and their standard errors (SEs) were calculated using the method of maximum likelihood. Variables were eliminated from the model one at a time based on likelihood ratio tests.

When all statistically nonsignificant ($p > 0.05$) variables had been eliminated from the multivariate model, calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test [21]. This test evaluates the degree of correspondence between a model’s estimated probability of admission and the actual admission experience of patients over groups spanning the entire range of probabilities.

Discrimination was assessed using the area under the receiver operating characteristic (ROC) curve [23] to evaluate how well the model distinguished patients who were admitted the previous year from patients who were not. The statistic represents, for all possible pairs of patients, the proportion in which the patient who was admitted had a higher probability of admission than the patient who was not.

Modeling for frequent exacerbations, i.e. more than one per year, followed the same process as the modeling for admissions.

All the data were analysed using the SAS 6.04 statistical package (SAS Institute, Cary, N.C., USA).

**Results**

**Admission Model**

Data were collected on 1,078 patients, of whom 1,001 met the inclusion criteria. When patients with missing data or those for whom information on previous admissions could not be ascertained were excluded, 713 cases were available for the development and validation of the model: 499 in the developmental sample and 214 in the validation sample. The overall rate of patients being admitted the previous year was 22.2%; 21.8% in the developmental sample and 23.8% in the validation sample. The results of bivariate analysis of independent variables recorded in stable phase are shown in table 1. Mean age was 69.5 years among patients who were admitted at least once the last year and 67.8 years among patients who had not been admitted the year before. Of admitted patients, 35.7% had at least one co-morbid condition in contrast to 22.8% among those not admitted. Mean FEV$_1$ was 49.7% of predicted in the admitted population and 53.3% in the nonadmitted group. Each of these variables was selected as showing a significant difference of at least 0.25.

Multiple logistic regression modeling in the developmental data set resulted in a model containing 2 variables. Table 2 presents the estimated logistic regression coefficients, estimated SEs, adjusted odds ratios (ORs), and 95% confidence intervals (CIs) for the adjusted ORs for the final model for admissions. The presence of any of the following: cardiac insufficiency, ischemic heart disease or diabetes mellitus had an odds ratio of 1.97, meaning that a patient having one of these conditions would be 1.97 times as likely to be admitted as another patient not having these conditions. The OR for FEV$_1$% provides an estimate of the increased risk of admission associated with an increase of 10 units, controlling for all other variables in the model. The negative value denotes an inverse relation: as FEV$_1$% increases the risk for admission decreases.

The Hosmer-Lemeshow goodness-of-fit test indicated that the model was also well calibrated ($p = 0.989$); the

| Table 1. Variables in the model of hospital admissions recorded at stable phase |
|------------------|------------------|------------------|
| Variable         | No admissions    | At least one admission | p value |
| Sex, % men       | 86.9             | 88.9              | 0.566  |
| Age, years       | 67.8 (9.2)       | 69.5 (9.6)        | 0.097  |
| BMI, kg/m$^2$    | 27.0 (4.0)       | 26.8 (4.1)        | 0.681  |
| Active smokers, %| 21.2             | 25.6              | 0.328  |
| Comorbidity, %   | 48.9             | 46.7              | 0.687  |
| Comorbidity, %   | 22.8             | 35.7              | 0.006  |
| FEV$_1$, % pred. | 53.3 (10.3)      | 49.7 (10.8)       | 0.001  |

Figures in parentheses are standard deviations.

| Table 2. Variables in the models for admissions with their estimated coefficients, SEs (in parentheses), adjusted ORs, and 95% CIs for the adjusted ORs |
|------------------|------------------|------------------|
| Variable         | $\beta$         | Estimated adjusted OR | 95% CI |
| Constant         | 0.2317          | 1.24–3.14         |
| Comorbidity      | 0.6792 (0.5333) | 1.97             | 0.58–0.88 |
| FEV$_1$ (% pred.)| −0.033 (0.0103) | 0.72             |

ORs correspond to 10 units.
Table 3. Variables in the model of frequent exacerbations recorded at stable phase

<table>
<thead>
<tr>
<th>Variable</th>
<th>Less than 2 exacerbations</th>
<th>2 or more exacerbations</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, % men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active smokers, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMH, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbidity, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁, % pred.</td>
<td>53.6 (9.7)</td>
<td>51.7 (10.6)</td>
<td>0.023</td>
</tr>
</tbody>
</table>

Figures in parentheses are standard deviations.

Table 4. Variables in the models for frequent exacerbations with their estimated coefficients, SEs (in parentheses), adjusted ORs, and 95% CIs for the adjusted OR

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>Estimated adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>−0.3028</td>
<td>0.4358 (0.1670)</td>
<td>1.54 (1.11–2.14)</td>
</tr>
<tr>
<td>CMH</td>
<td>0.0193 (0.0082)</td>
<td>0.82 (0.70–0.96)</td>
<td></td>
</tr>
<tr>
<td>FEV₁ (% pred.)</td>
<td>0.0188 (0.009)</td>
<td>1.21 (1.01–1.44)</td>
<td></td>
</tr>
</tbody>
</table>

1 ORs correspond to 10 units.

Discussion

Acute exacerbations are an important feature in the natural history of COPD. Patients with COPD experience exacerbations with a frequency of 0.1 per patient per month of observation [24]. Our findings show that patients having suffered 2 or more acute exacerbations in the last year was 54.9%, 54.2% in the developmental sample and 55.8% in the validation sample.

Independent variables included in the model were also those showing a probability of less than 0.25 in bivariate analysis, and at least 2% of the population exhibited that factor. The results of bivariate analysis of independent variables recorded in stable phase related to the risk of frequent exacerbations of COPD are shown in table 3.

Men were more likely to have suffered from recurrent exacerbations, 90.6 versus 87.1%. Similarly to the risk of admission, a lower FEV₁ (% pred.) was associated with increasing risk of exacerbations, although differences were not as high as in the admissions model. Finally, CMH was significantly associated with frequent exacerbations: 52.6% of patients with this symptom presented 2 or more exacerbations in the last year compared with 40% of those who did not.

Multiple logistic regression modeling in the developmental data set resulted in a model containing 3 variables. The area under the ROC curve was 0.633. In this test, a large p value indicates that the model is performing well, which means that there is no large discrepancy between observed and expected rates of admissions.

When the model was applied to the validation data, the area under the ROC curve was 0.582 and the p value for the goodness-of-fit was 0.720, indicating that the model validated well, especially by demonstrating good calibration, and acceptable discrimination.

Exacerbation Model

The same process was followed to construct a model for the identification of factors independently associated with an increased risk of frequent exacerbations, i.e. more than 1 exacerbation per year. Complete information on the number of acute exacerbations the previous year was obtained from 896 patients: data from 627 patients were included in the developmental model and from 269 patients in the validation model. The percentage of patients having suffered 2 or more acute exacerbations in the last year was 54.9%, 54.2% in the developmental sample and 55.8% in the validation sample.

The area under the ROC curve was 0.601. When the model was applied to the validation data, the area under the ROC curve was 0.655 and the p value for the goodness-of-fit 0.3408. These results demonstrated that there were no significant differences between events observed and predicted from the model, and the discrimination of the model, as shown by the ROC curve, is acceptable.

Acute exacerbations are an important feature in the natural history of COPD. Patients with COPD experience exacerbations with a frequency of 0.1 per patient per month of observation [24]. Our findings show that in-
Increasing age, severity of FEV\(_1\) impairment and the presence of CMH are factors independently associated with increased risk of suffering 2 or more acute exacerbations of COPD per year. Similarly, FEV\(_1\) impairment is associated with increasing risk of hospital admission during the same period. However, in the latter case, CMH is not significantly associated with the risk of admission, while the presence of significant comorbidity, such as diabetes mellitus, cardiac insufficiency or ischemic heart disease, is. From these results it can be speculated that age and CMH are facilitating factors for exacerbations, but the severity and prognosis of exacerbation is best predicted by the presence or absence of significant comorbid conditions.

We found no association between current smoking or BMI and risk of exacerbations or admission.

The extrapolation of our results must be made with caution since the collection of data was retrospective and thus subject to different types of bias. The first is recall bias, due to failure to remember incidents that occurred during the previous year. This is more likely to have occurred in the model for previous exacerbations since some mild episodes might have been omitted, while admissions are highly unlikely to have been forgotten. However, this bias is very difficult to control even in prospective studies. Seemungal et al. [6], in a prospective study on the effect of acute exacerbations on quality of life of COPD patients, found that almost one half of the exacerbations recorded on daily diary cards were not reported to their physicians. Considering this possible lack of information, the model developed here might have predictive value for recurrent exacerbations severe enough to be mentioned by the patient in a further medical visit, while milder exacerbations with lower impact on patient perceptions may remain unreported. The second possible bias comes from the extrapolation of our results to the prediction of future exacerbations or admissions; for this to be made with guarantee, results should be tested first in a prospective cohort. Unfortunately, since the collection of data was retrospective, the compliance with bronchodilator or anti-inflammatory medication and its possible influence on the outcomes of the study could not be reliably assessed.

We observed that the presence of coexisting diabetes or significant cardiac disease was not associated with an increased probability of frequent exacerbations, but with an increased risk of admission. These results concur in part with the above-mentioned prospective study, which in a cohort of 70 COPD patients with a mean FEV\(_1\) of 40% of predicted found that coexisting cardiac and pulmonary disease were not associated with frequent exacerbations. However, Ball et al. [12] found that coexistent cardiopulmonary disease was a risk factor for being referred to hospital after being treated for an acute exacerbation, and Antonelli Incalzi et al. [15] found age and cardiac comorbidity to be among the best predictors of mortality in a cohort of COPD patients discharged after an acute exacerbation. These results, together with ours, suggest that comorbidity does not appear to be a risk factor for frequent exacerbations, but a risk factor for severe life-threatening exacerbations that can provoke admission and even be a cause of death, particularly in older patients [13]. Concurring with our results, other authors have also shown that diabetes appears to be a risk factor for severe exacerbations, requiring longer periods of hospitalization associated with the isolation of more aggressive bacteria in sputum culture [10]. All these results, together with the finding that comorbidity may significantly affect quality of life even in mild COPD [25], require that special attention be paid to the diagnosis of other coexisting diseases, particularly cardiac dysfunction and diabetes, and that COPD patients with these associated conditions be more closely followed.

CMH was another factor identified as associated with recurrent exacerbations. The influence of CMH on the risk of frequent exacerbations was assessed in a previous prospective study [7] where the authors found no significant association of daily sputum production with frequent exacerbations; however, they found that exacerbation frequency was related to 'bronchitic symptoms' with an OR = 1.56 in multivariate analysis. Differences may be quantitative, since patients with 'bronchitic symptoms' are usually defined as presenting persistent cough with sputum production. It is possible that patients reporting 'bronchitic symptoms' have severer symptoms than those reporting only sputum production. In this respect we considered CMH to be the daily emission of 30 ml of expectorated matter or more. Unfortunately, there is no information in the former paper regarding the quantitation of expectoration.

In a previous population-based study, CMH was found to be a significant predictor of COPD-related death with pulmonary infection implicated [22]. However, to our knowledge, no previous studies have investigated the relationship between CMH and the probability of admission due to COPD exacerbation. Our results suggest that CMH renders the patient more prone to suffering recurrent exacerbations, but does not determine the severity of the exacerbations as it appeared not to be a factor associated with admissions. As the present study was performed retrospectively on stable ambulatory patients, these results

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do not rule out the fact that in patients with severely exacerbated, CMH may also be a risk factor for death, as suggested in former studies [22, 26]. The consistent and important association of decreasing FEV1 with both the risk of frequent exacerbations and admissions is not surprising and needs no further discussion, since low FEV1 is a preeminent risk factor for mortality from COPD in most epidemiological studies [4, 5, 13, 16, 27]. This effect may be determined by the association of more severely impaired FEV1 and the isolation of more aggressive bacteria causing the exacerbations [28].

The model developed here for the prediction of admissions indicates that a COPD patient with a FEV1 of 22% of predicted and with diabetes and/or cardiac comorbidity has an increased probability (+0.54%) of being admitted in 1 year (see Appendix). This level of risk is extremely high if confirmed in prospective studies. Furthermore, considering that survival of COPD patients is progressively increasing, together with the growing prevalence of the disease, the number of COPD patients with these clinical characteristics is expected to increase in the future, which will imply the need for closer follow-up and precise therapeutic and preventive measures to try to avoid the risk of hospital admission.

In conclusion, retrospective information collected in a cohort of ambulatory COPD patients suggests that FEV1 impairment is an important factor that explains part of the risk of frequent exacerbations and hospital admissions. Moreover, CMH and increasing age are significantly associated with the risk of frequent exacerbations, and the presence of significant comorbidity is associated with the risk of severe exacerbations which entail admissions. The clinical assessment of COPD patients in general practice should include these important and easily measurable variables.

Appendix

The calculation of probability of frequent exacerbation or hospital admission requires the following steps:

(1) Compute the logit g(x) defined as 
\[ g(x) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_k x_k \]
where \( \beta_0 \) is the constant and \( \beta_k \) is the estimated coefficient for the ith variable times the value of the ith variable, with \( i \) taking on the values from 1 to \( k \), and \( k \) being the number of variables in the model. Age and FEV1 (% pred.) are entered as years and percentages, respectively, while CMH and comorbidity take the values of 0 or 1, signifying the absence or presence, respectively.

(2) Transform the logit into a probability through the following calculation: 
\[ P(\text{admission}) = \frac{e^{g(x)}}{1 + e^{g(x)}} \]
For example, a patient with comorbidity and a FEV1 (% pred.) of 22% would have a probability of being admitted in 1 year of: \( \logit = 0.2317 + 0.6792 - 0.033 - 0.22 = 0.1909; e^{0.1909}/1 + e^{0.1909} = 0.54 \). The probability of admission is 54%. This probability is an estimate, or expectation, based on the admission rate of a large group of similar patients and represents the proportion of patients expected to exhibit the outcome.

References

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