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Including changes in dyspnea after inpatient rehabilitation improves prediction models of exacerbations in COPD

Michael Schuler[a,*], Michael Wittmann[b], Hermann Faller[a], Konrad Schultz[b]

[a] Department of Medical Psychology and Psychotherapy, Medical Sociology and Rehabilitation Science, University of Würzburg, Würzburg, Germany
[b] Klinik Bad Reichenhall, Center of Rehabilitation, Pulmonology and Orthopedics, Bad Reichenhall, Germany

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ABSTRACT

Background: Reducing the probability of future exacerbations is one of the main goals of pulmonary rehabilitation (PR) in COPD. Recent studies identified predictors of future exacerbations. However, PR might alter both predictors and number of exacerbations.

Objectives: This secondary analysis examined which predictors assessed at both the beginning and the end of PR predict the risk of moderate (i.e. use of cortisone and/or antibiotics) and severe (hospitalization) exacerbations in the year after PR.

Methods: A total of n = 383 COPD patients (34.7% female, mean age = 57.8 years (SD = 7.1), mean FEV1% pred = 51.0 (SD = 14.9)) who attended a 3-week inpatient PR were included. Number of moderate and severe exacerbations were assessed one year after PR (T2) via questionnaires. Potential predictors were assessed at the beginning (T0) and the end (T1) of PR. Negative binomial regression models were used.

Results: The mean numbers of severe (M_s)/moderate (M_m) exacerbations in the year after PR ($M_{s,t2} = 0.19$; $M_{m,t2} = 1.07$) was reduced compared to the numbers of exacerbations in the year before PR ($M_{s,t1} = 0.50$, $p < 0.001$; $M_{m,t1} = 1.21$, $p = 0.051$). Previous exacerbations, retirement, change in dyspnea (for severe exacerbations) and dyspnea at T1 (for moderate exacerbations) were identified as significant predictors.

Conclusions: PR might alter associations between predictors and future exacerbations. Dyspnea at the end of PR or change in dyspnea are better predictors than dyspnea at the beginning of PR.

1. Introduction

Acute exacerbations of COPD are one of the major risks for patients with COPD [1]. Exacerbations are the main reasons for hospitalization of COPD patients and are associated with reduced quality of life [2] and worse prognosis [3]. Therefore, exacerbation prevention or at least reducing the risk of exacerbations is a main outcome in the treatment of COPD [1].

Various prediction models for exacerbations were proposed in the literature [4]. They differ widely in statistical methods, setting and predictors, and only a few variables showed predictive value across studies. History of exacerbations appears to be the strongest and most reliable predictor of future exacerbations [5,6]. Furthermore, airflow obstruction (FEV1% pred), sex, age, body mass index (BMI), dyspnea and smoking status are regarded as established predictors of exacerbations [5], though they were not constantly identified as significant predictors, even in high quality studies with many observations [6]. Besides differences in statistical methods used (for example logistic regression, cox regression, negative binomial regression), study designs (prospective or retrospective) or predictors included, two important factors may contribute to the great variety of proposed prediction models.

First, the significance of a predictor may depend on the severity of the exacerbation defined as an outcome. For example, sex tends to be a significant predictor for general exacerbations but not for severe exacerbations [6].

Second, the prediction model identified may depend on the population examined in the study, for example in primary care [5,7], patients hospitalized for acute exacerbations [8,9], patients in pharmacological studies [10] or those in a pulmonary rehabilitation (PR) setting [11]. Hoogendoorn et al. [6] compared prediction models for exacerbations in five different large cohort studies using the same statistical models. Some variables predicted exacerbations in all data sets (for example number of previous exacerbations and FEV1% pred),

* Corresponding author. University of Würzburg, Department of Medical Psychology and Psychotherapy, Medical Sociology and Rehabilitation Science Klinikstr. 3, D-97070, Würzburg, Germany.
E-mail addresses: m.schuler@uni-wuerzburg.de (M. Schuler), michael.wittmann@klinik-bad-reichenhall.de (M. Wittmann), h.faller@uni-wuerzburg.de (H. Faller), konrad.schultz@klinik-bad-reichenhall.de (K. Schultz).

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while other predictors were only identified in a few data sets. For example, age and cardiovascular diseases predicted exacerbations in secondary care patients but not in primary care patients. This observation may have important implications for the practical use of prediction models. One important goal of prediction models is to help health professionals in practice to identify patients with higher risk for exacerbations. Therefore, study samples should match the populations that health professionals deal with in daily practice.

PR is an effective treatment for COPD for both patients with stable COPD [12] and those after exacerbation [13]. Besides improving dyspnea and increasing quality of life, PR reduces hospital readmission, at least in patients with previous exacerbations [13]. To further reduce future exacerbations, health professionals in a rehabilitation setting should be able to identify patients with an increased risk of exacerbations at both the beginning and the end of a PR. However, due to complex selection processes, the population in a PR may differ from the samples in most observational prediction studies. For example, in Germany, a patient has to apply for a PR (mostly a 3-week inpatient PR) at the German Statutory Pension Insurance or the statutory health insurances (loss of earnings during PR is paid by pension insurance or health insurance, respectively). Whether a patient applies for a PR and whether the application is approved depends on many factors that may influence the distributions of the clinical variables in the PR population.

Furthermore, PR itself may alter both the risk for exacerbations and the respective prediction variables [12,13]. For example, if PR reduces dyspnea [12], it is unclear, whether dyspnea assessed at the beginning of the PR, at the end of the PR or the change in dyspnea during PR (or none of these) predict the risk of future exacerbations.

In this study, we examined whether predictors assessed at the beginning of an inpatient PR predict the number of exacerbations in the year after the inpatient rehabilitation. Furthermore, we tested whether the prediction model may be improved by adding outcome parameters assessed at the end of inpatient PR.

2. Material and methods

2.1. Sample

This is a secondary analysis of the RIMTCORE study, a randomized controlled trial that examined the effects of inspiration muscle training as add-on to inpatient PR [14]. The RIMTCORE study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. It was approved by the local ethics committee (Bayerische Landesärztekammer, No. 12107) and was registered on the German Clinical Trials Register (DRKS00004609). All patients provided written informed consent.

COPD patients who underwent a 3-week inpatient PR in the Bad Reichenhall Clinic were recruited from 02/2013-07/2014. In the Bad Reichenhall Clinic, most rehabilitation patients are assigned by the German pension insurance, i.e. most patients are still in working age (< 66 years in Germany). All admitted COPD-Patients with GOLD-Stage II-IV were asked to participate, regardless of prior exacerbations or comorbidities. Further details of the primary study are published elsewhere [14]. Questionnaire data were assessed at the beginning, the end and 3/6/9/12 months after PR. Lung function parameters and exercise capacity were assessed at the beginning and the end of rehabilitation. For this sub-study, data from the beginning (T0), the end (T1) and after 12 months (T2) were used.

A total of N = 561 patients completed inpatient rehabilitation. All patients received an intensive inpatient PR, including physical training, patient education and respiratory physiotherapy as obligatory components. For more details and differences between intervention and control group, see Ref. [14]. All patients were approached by letter to complete questionnaires at T2 (i.e. no patient attended the clinic personally at T2). The analyses of this sub-study are based on a subsample of n = 383 patients who returned questionnaires at T2.

3. Assessment

3.1. Exacerbations

Number of exacerbations in the year (12 months) before PR was assessed via questionnaire at T0. Number of exacerbations in the year after PR was assessed via questionnaire at T2. Exacerbations were classified as either (1) general exacerbations (significant worsening of COPD symptoms as dyspnea, cough and sputum), (2) moderate exacerbations (necessity to take oral corticosteroids and/or antibiotics to handle this exacerbation) or (3) severe exacerbations (hospitalization due to this exacerbation). All three kinds of exacerbations before PR were used as predictors in this study, but only moderate and severe exacerbation after PR were used as outcomes. A translated English version of the questions is presented in the online supplement.

3.2. Patient reported outcomes

Dyspnea was assessed using the modified MRC breathlessness scale [15]. Health-related quality of life was assessed using the St. Georg Respiratory Questionnaire (SGRQ) [16]. Cough/phlegm was assessed by taking the mean of the items 5 and 6 of the Clinical COPD Questionnaire (CCQ) [17,18]. Depression was assessed using the Patient Health Questionnaire-9 (PHQ-9) [19] and anxiety was measured using the Generalized Anxiety Disorder scale-7 (GAD-7) [20].

3.2.1. Exercise capacity

Exercise capacity was assessed at both T0 and T1 using 6-min walk distance (6MWD) on a track length of 30 m according to the 2002 ATS statement [21]. At T0 and T1, respectively, each patient performed 2 tests with an interval of 1 h. The best of each test results was used in this study.

3.3. Lung function measurement

Forced expiratory volume in 1 s (FEV1), residual volume (RV) and total lung capacity (TLC) were determined before and after bronchodilation by spirometry and body plethysmography (MasterLab, CareFusion, Hoechberg, Germany). The latter values were used in this study. The maximum static inspiratory pressure a subject can generate at the mouth (PImax) was measured using a commercially available mouth occlusion pressure device (CareFusion, Hoechberg, Germany).

4. Statistical analyses

Numbers of moderate and severe exacerbation before and after rehabilitation were computed and compared with each other using time as predictor in generalized equation estimators with a negative binomial regression model. Negative binomial regression models [22] were used to test prediction models for both outcomes, i.e. moderate and severe exacerbations in the year after PR. Results are presented as incidence rate ratios (IRR). The following procedure was used to select predictors: In a first step, it was tested whether each outcome was best predicted by the number of general, moderate or severe exacerbation in the year before PR, respectively, or a combination of them (Model 1). In a second step, the following predictors (assessed at T0) were included at once: intervention/control group (1 = intervention group), sex (1 = female), age (in years), FEV1% pred, BMI < 20 (1 = yes), comorbid cardiovascular disease (1 = yes), 6MWD (in meters), smoking status (1 = smoker) and dyspnea (Model 2). These variables were shown to predict exacerbations in a variety of previous studies [5,6,10]. Comorbid cardiovascular disease included heart failure, valvular heart disease, arrhythmia or coronary heart disease. In a third step, the following predictors presented in some studies [5,6] as well as some potential predictors assessed in the RIMTCORE study were tested separately in addition to Model 2 (all predictors were assessed at T0):