

# Logistic regression model to predict chronic obstructive pulmonary disease exacerbation

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## Abstract

**Introduction:** Acute exacerbations of disease symptoms in patients with chronic obstructive pulmonary disease (COPD) often lead to hospitalization and impose a great financial burden on the health care system. Nonetheless, there is a paucity of data regarding the predictors of disease exacerbation in these patients. This study aimed to determine factors which can predict rehospitalization in COPD patients.

**Material and methods:** A total of 157 COPD patients were selected via systematic sampling from all the patients admitted to the Chest Clinic of Baqiyatallah Hospital during the year 2006. Subjects were followed for 12 months for the occurrence of any disease exacerbation that led to hospitalization. Demographic data [gender, age, marital status, monthly income (less than 200 \$, and equal to or higher than 200 \$), level of education (below diploma and diploma or higher)], spirometric findings [percent predicted vital capacity (VC % predicted), percent predicted FVC (FVC % predicted), and percent predicted FEV<sub>1</sub> (FEV<sub>1</sub> % predicted)], physical comorbidity (assessed by Ifudu index), presence of anxiety or depression (evaluated with the Hospital Anxiety Depression Scale), and body mass index (BMI) were recorded for each patient. Multivariate regression was applied to find out the predicting factors of disease exacerbation.

**Results:** Over the 12-month period, 87 (55%) experienced disease exacerbation. Significant associations were found between COPD exacerbation and monthly income ( $p=0.001$ ), comorbidity score ( $p=0.05$ ), anxiety ( $p=0.013$ ) and depression ( $p=0.025$ ). VC % predicted, FVC % predicted and FEV<sub>1</sub> % predicted had no significant association with disease exacerbation ( $p>0.05$ ). Predictors of COPD exacerbation were found to be monthly income lower than 200 \$ ( $p=0.002$ ), higher comorbidity score ( $p=0.05$ ) and depression ( $p=0.05$ ). A prediction equation was designed to help clinicians predict disease exacerbation.

**Conclusions:** Physical comorbidity, severity of depression and low income can be used to predict COPD exacerbation. We recommend that more attention be given to these predictors.

**Key words:** chronic obstructive pulmonary disease, hospitalization, exacerbation, predicting factors.

## Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death worldwide, and the fourth most common cause of death in the United States [1-3]. It has been estimated that COPD will become the third leading cause of mortality in the world by the year 2020 [4]. The prevalence of this condition has been reported at about 3% in India [5],

7% in the US [6], 8% in Sweden [7], 9% in Spain [8], and 23% in England [9].

COPD is usually accompanied by frequent bouts of disease exacerbation, characterized by deterioration of respiratory symptoms such as dyspnoea, cough and sputum production [2, 3, 10]. Such acute exacerbations in COPD patients often lead to repeated rehospitalization, which makes up an important part of the health service for these subjects. Disease exacerbations damage health status [11], increase mortality [12], and impose a financial burden on the health care system [13]. More than 200,000 annual hospitalizations have been reported from the United Kingdom, with each patient occupying a hospital bed for an average duration of 10 days [14]. The financial burden of such annual hospitalizations has been reported at about 846,000 £ [15]. Based on the National Medical Expenditure Survey in the US, over 70% of the money spent on COPD patients is related to their hospitalizations and care in an emergency setting [16].

Previous studies have shown the role of some factors in rehospitalization in COPD patients, among which are poor lung function [17-19], old age [19], low quality of life [11, 20], low physical activity [17, 20], previous disease exacerbations [11], previous hospitalizations [17, 18], being under prescription of long-term oxygen therapy [18], systemic and pulmonary hypertension [21], use of inhaled corticosteroids [22], and mental disorders such as anxiety and depression [10]. However, some studies have reported quite opposite results, reporting no role for pulmonary function [20, 21, 23] in terms of forced expiratory volume in one second (FEV<sub>1</sub>), old age [21], use of placebo or even medications [24] and mental disorders [25] in the risk of rehospitalization. On the other hand, few studies are available that have investigated more than one risk factor for disease exacerbation in COPD [18, 21]. Thus, there is still a paucity of information on the topic of predicting factors and determinants of disease exacerbation in COPD. This study aimed to explore the predictors for disease exacerbation in COPD patients.

## Material and methods

In a prospective setting, a total of 157 COPD patients were selected through systematic sampling from the patients admitted to the Chest Clinic of Baqiyatallah Hospital during the first half of the year 2006. Inclusion criteria were COPD, established in accordance with the clinical definition of the disease, age higher than 40 years, and the state of being current/ex-smokers. Exclusion criteria were set as having a history of asthma, being under oxygen therapy, recent history of myocardial infarction, heart failure, or cardiac arrhythmia. Subjects were followed for 12 months for the occurrence of any acute exacerbation in their condition. An acute exacerbation

was defined as worsening in respiratory symptoms that required hospital admission.

Demographic data [gender, age, marital status, monthly income (less than 200 \$ US, and equal to or higher than 200 \$ US), education (below diploma and diploma or higher)], weight, height, spirometric findings [predicted vital capacity (VC predicted), FEV<sub>1</sub> predicted, predicted forced vital capacity (FVC predicted)], the presence of physical comorbidity (assessed by Ifudu index), and the presence of anxiety or depression [evaluated by the Hospital Anxiety Depression Scale (HADS)] were recorded for all of the patients. Body mass index (BMI) was calculated for each subject by dividing weight in kilograms by height in metres squared.

Ifudu comorbidity index – initially designed for patients under haemodialysis – is a numerical scale which measures comorbidity in patients and has 14 components for the evaluation of patients' health care history. The systems evaluated in this scale are as follows:

- 1) stable angina or myocardial infarction (ischaemic heart diseases),
- 2) other cardiovascular problems (hypertension, congestive heart failure, cardiomyopathy, and other non-ischaemic diseases),
- 3) chronic respiratory diseases including asthma or chronic obstructive pulmonary disease (COPD),
- 4) autonomic neuropathy (gastroparesis, diarrhoea, cystopathy, obstipation, orthostatic hypotension),
- 5) other neurological problems (including cerebrovascular accident or brain attacks),
- 6) neuromuscular disorders (as well as musculo-skeletal diseases),
- 7) infections including AIDS,
- 8) pancreas and biliary diseases (hepatitis, hepatic disorder, pancreatic enzyme defect),
- 9) haematological disorders (excluding anaemia),
- 10) low back pain, spine or joint disorders,
- 11) visual disorders (decreased visual acuity up to complete blindness),
- 12) limb amputation (from fingers to lower extremities),
- 13) mental or emotional illness, and
- 14) genitourinary diseases.

Each component takes a score ranging from 0 (absence of comorbidity) to 3 (presence of severe comorbidity). Total comorbidity score would be the sum of the scores gained from each of the above components, where higher scores represent greater comorbidity [26]. Given that our patients had COPD and that we were assessing the presence of physical comorbidity, the 3<sup>rd</sup> and 13<sup>th</sup> component of the Ifudu questionnaire were not considered for the evaluation of comorbidities in our subjects.

HADS is a questionnaire used to assess symptoms of anxiety and depression. HADS consists of two subscales, anxiety and depression, and it contains

14 items. Each item is scaled on a four-point scale from 0 to 3 (0 for absence of symptoms and 3 for the presence of severe symptoms), giving maximum scores of 21 for anxiety and depression. Scores below 11 are considered normal, while scores equal to or higher than 11 in any subscale signify abnormal symptoms [27]. HADS was validated for application in the Iranian population by Montazeri and coworkers in 2003 [28]. The HADS questionnaire has been routinely applied for the evaluation of anxiety and depression in different nations, and judged by the published articles, its use by researchers has quadrupled over the period between 1996 and 2002 [29].

### Statistical analysis

Statistical analyses were performed using SPSS version 13 for Windows. Quantitative variables with normal distribution were defined by mean ( $\pm$  SD), and those with skewed distribution by median and 25 or 75 interquartiles. Qualitative variables were described using tables of frequency. Scores of anxiety, depression and comorbidity in patients who experienced exacerbation and those who did not were compared using Mann Whitney. Categorical variables were compared using chi-square test, and forward multivariate logistic regression was applied to determine the predictors of disease exacerbation. Statistical significance was set as  $p < 0.05$ .

## Results

### Subjects

Men comprised 63% of the study group ( $n=98$ ). Mean age of patients was  $58.3 \pm 11.0$  years (range,

30-79 years). A total of 139 (88%) subjects were married and 18 (12%) single. With regard to education, 125 (80%) patients were below high school diploma and 32 (20%) had diploma or higher degrees. Sixty-one (39%) subjects had a monthly income of less than 200 \$, and 96 (61%) equal to or higher than 200 \$. Mean BMI of subjects was  $26.1 \pm 3.8$  (range, 14.9-36.3  $\text{kg/m}^2$ ). Median (25 and 75% inter-quartile range) comorbidity score was 3 (0-6) (range, 0-15). Mean values (range) of VC % predicted, FEV<sub>1</sub> % predicted, and FVC % predicted were  $83 \pm 12$  (41-109),  $77 \pm 15$  (34-105), and  $82 \pm 13$  (43-109), respectively.

### Exacerbation

During the 12-month follow-up, 87 (55%) patients were hospitalized due to exacerbation of their COPD.

### Exacerbation associated factors

There was a significant association between the frequency of disease exacerbation and monthly income, with low income subjects suffering from more exacerbations ( $p=0.001$ ). Subjects who had been hospitalized for COPD exacerbation had marginally greater scores of comorbidity [3 (0-6) vs. 3 (0-6),  $p=0.075$ ], and significantly higher scores of anxiety [14 (12-17) vs. 12 (10-15),  $p=0.008$ ] and depression [12 (10-15) vs. 11 (9-13),  $p=0.039$ ] compared with subjects who had not. No significant link was found between disease exacerbation and gender, age, marital status, educational level or BMI ( $p > 0.05$ ). No significant difference was noted between patients with exacerbation and patients without exacerbation with regard to the values of VC, FEV<sub>1</sub> and FVC predicted ( $p > 0.05$ ) (Table I).

**Table I.** Demographic characteristics of studied patients and mean ( $\pm$  SD) values of quantitative variables in studied subjects

Variable	Subgroup	Hospitalized (n=87)	Not hospitalized (n=70)	P-value*
Gender	male	52 (60%)	46 (66%)	0.412*
	female	35 (40%)	24 (34%)	
Marital status	married	78 (90%)	61 (87%)	0.690*
	single	9 (10%)	9 (13%)	
Monthly income	<200 \$ USD	46 (53%)	15 (21%)	0.001*
	$\geq$ 200 \$ USD	41 (47%)	55 (79%)	
Educational level	below diploma	68 (78%)	57 (81%)	0.671*
	diploma or higher	19 (22%)	13 (19%)	
Age (years)		$58.4 \pm 11.9$	$58.2 \pm 10$	0.907**
BMI		$25.4 \pm 4.5$	$26.6 \pm 4.3$	0.123**
VC predicted		$83 \pm 12$	$82 \pm 14$	0.712**
FVC predicted		$83 \pm 12$	$82 \pm 13$	0.653**
FEV <sub>1</sub> predicted		$78 \pm 15$	$76 \pm 16$	0.321**

\*Chi-squared test

\*\*Independent sample t-test

**Table II.** Association between different coexisting diseases and exacerbation

Comorbidity	Hospitalized (n=87)	Not hospitalized (n=70)	P-value
1) Stable angina or myocardial infarction (ischaemic heart diseases)	7 (8%)	1 (1.4%)	0.061**
2) Other cardiovascular problems (hypertension, congestive heart failure, cardiomyopathy, and other non-ischaemic diseases)	31 (35.6%)	12 (17.1%)	0.010*
3) Chronic respiratory diseases including asthma or chronic obstructive pulmonary disease (COPD)	N/A	N/A	N/A
4) Autonomic neuropathy (gastroparesis, diarrhoea, cystopathy, obstipation, orthostatic hypotension)	0 (0%)	0 (0%)	—**
5) Other neurological problems (including cerebrovascular accident or brain attacks)	1 (1.1%)	1 (1.4%)	0.446**
6) Neuromuscular disorders (as well as musculoskeletal diseases)	7 (8%)	4 (5.7%)	0.404**
7) Infections including AIDS	8 (9.2%)	2 (2.9%)	0.106**
8) Pancreas and biliary diseases (hepatitis, hepatic disorder, pancreatic enzyme defect)	0 (0%)	1 (1.4%)	0.446**
9) Haematological disorders (excluding anaemia)	6 (6.9%)	11 (15.7%)	0.077*
10) Low back pain, spine or joint disorders	35 (40.2%)	25 (35.7%)	0.563*
11) Visual disorders (decreased visual acuity up to complete blindness)	0 (0%)	0 (0%)	—**
12) Limb amputation (from fingers to lower extremities)	6 (6.9%)	5 (7.1%)	0.952*
13) Mental or emotional illness	N/A	N/A	N/A
14) Genitourinary diseases	26 (29.9%)	14 (20%)	0.158*

\* $\chi^2$ ; \*\*Fisher exact

Of all the different comorbidities, non-ischaemic cardiovascular problems (such as hypertension, congestive heart failure and cardiomyopathy) were correlated with exacerbation. Ischaemic heart diseases (such as stable angina or myocardial infarction) and haematological disorders, however, were marginally correlated with COPD exacerbation. None of the other somatic comorbidities was correlated with COPD exacerbation (Table II).

#### Predictors for COPD exacerbation

Monthly income, comorbidity score and depression were independent predictors for re-admission in the multivariable analysis (Table III). To predict the exacerbation in COPD patients, the following model can be used:

Logit (exacerbation) = (1.28 × monthly income) + (0.1 × comorbidity score) + (0.11 × HADS depression score) – 1.79.

Logit (readmission) =  $\ln\{P(\text{readmission})/[1 - P(\text{readmission})]\}$ .

The probability of rehospitalization divided by the probability of lack of rehospitalization is in fact the risk ratio for readmission. The above formula predicts the Neperian logarithm (ln) of the risk of readmission. The constant figures in this formula are positive, which means the chance of readmission increases with increasing values of the three variables, i.e. income, comorbidity and depression.

#### Discussion

This research is one of the few studies [18, 21] that have explored the influence of demographic, spirometric and psychological factors, and concomitant comorbidities on disease exacerbation in COPD patients, in a developing country, with its own recourse limitations. We showed that out of

**Table III.** Predictors of disease exacerbation in studied COPD patients

Variable	Relative risk (RR)	$\beta$	p-value	95% CI for RR
Monthly income	2.20	1.28	0.002	1.84-7.03
Ifudu comorbidity score	0.93	0.10	0.050	1.01-1.21
Depression	0.31	0.11	0.050	1.02-1.22
Constant	29.00	1.79	0.012	–

gender, age, marital status, monthly income, education, BMI, spirometric indices, comorbidity score, anxiety and depression, only income, comorbidity and depression could predict the risk of exacerbation of COPD patients.

To date, results from different studies have been quite variable. Former reports have pointed to the effect of pulmonary function [17-19], quality of life [11, 20], physical activity [17, 20], history of previous exacerbations [11], prior account of hospitalization [17, 18], being under long-term oxygen therapy [18], systemic and pulmonary hypertension [21] on disease exacerbation in COPD. In agreement with this study, several authors have shown that gender and age have no predictive role in this regard [11, 18, 20, 21]. The study by Miravittles et al., however, showed that older age is an important predictor for disease exacerbation [19]. One explanation for such different results on the effect of age is probably that sample sizes are different, and so are demographic characteristics of them, say, average age. Another reason could be different definitions that authors have used for disease exacerbation in their studies, as Madison and Irwin previously suggested [30]. In the current study, the definition we applied for disease exacerbation was in line with several previous reports [20, 21, 23].

Similar to some previous studies [20, 21, 23], we could not find any association between pulmonary function – assessed by FEV<sub>1</sub> – and the risk of hospitalization due to disease exacerbation. Nonetheless, there are reports that FEV<sub>1</sub> can predict the risk of COPD exacerbation and hence hospitalization [17-19]. Such diversity in this finding may be the result of the limited number of patients in some studies [21, 23], or the result of treating FEV<sub>1</sub> as a categorical variable rather than continuous [21, 31]. Contrary to this study, some researchers have shown that low BMI can predict a higher risk of disease exacerbation and hospitalization [18, 21] and can affect the prognosis of COPD patients [32].

In our study, only the severity of depression, and not anxiety, predicted the possibility of COPD exacerbation. Dahlen and Janson, studying 43 asthmatic and COPD patients, found that anxiety and depression were related to the outcome of emergency treatment [33]. The study by Stehr and colleagues on 33 male COPD patients showed that some psychological factors, such as negative attitude about disease prognosis, were more common in patients who suffered from relapse in their disease [34-41]. Lack of motivation and helplessness, which are linked to depression, may affect adherence to psychiatric, medical and rehabilitation recommendations [41]. Worse symptoms and activities (even after controlling for chronicity and severity of COPD, comorbidities, and behavioural, psychosocial and socioeconomic

variables) in depressed COPD patients [39] may explain this difference. The presence of psychological problems in COPD patients is known to be linked with advanced age [35] and cigarette smoking; hence, we may be able to conclude that mental disorders are indirectly related to COPD exacerbations [38]. A cohort of COPD patients reported that poor baseline psychological distress of the patient is associated with greater reduction in FEV<sub>1</sub>, and more severe development of chronic bronchitis, bronchial infection and symptoms of breathlessness [40].

Unfortunately, the proper diagnosis and treatment of a concurrent psychiatric complication of COPD may be missed when COPD patients are treated in medical clinics. So far, only a few intervention studies have been conducted. Nonetheless, results suggest that the treatment of concurrent psychiatric disorders leads to an improvement in the physical as well as psychological state of the patient [42, 43].

Regarding the association between low income and exacerbation in our study, a literature review highlights poverty and poor socioeconomic level not only as risk factors for COPD [44, 45] but also as main contributors to the exacerbation [46] and mortality [47] of COPD patients. The mechanism may be more than just the patients' compliance [48]; it seems to be related to poorer health behaviours [49]. Therefore, governmental strategies for poor COPD patients to minimize their out-of-pocket prescription expenses through drug cost-sharing policies may be effective. This co-payment can significantly reduce the burden on low-income patients [50, 51].

We acknowledge some limitations of this study. We did not assess some other potential risk factors for disease exacerbation, such as number of previous hospitalizations. The limited number of patients is probably another weakness to this study.

In conclusions, the study shows that monthly income, concomitant physical comorbidity and depression are the predictors of disease exacerbation in COPD in Iran. These predicting factors for disease exacerbation are what health policy makers in our country with limitations in resources should seriously consider.

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