

Predictive Model of Hospital Admission for COPD Exacerbation

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BACKGROUND: The objective of this work was to determine predictive factors of hospital admission for exacerbation during primary care visits in patients with COPD. **METHODS:** A retrospective cohort study was undertaken to assess risk of hospital admission for COPD exacerbation in primary care patients from November 1, 2010 to October 31, 2013. Data sources were primary care electronic medical records and the hospital discharge minimum data set. A total of 2,501 subjects >40 y of age with a spirometry-based COPD diagnosis were included and followed up for 3 y. The dependent variable was hospital admission for exacerbation; independent variables were: clinical parameters, spirometry results, and severity of disease (according to Global Initiative for Chronic Obstructive Lung Disease criteria). The association of these variables with hospital admission was analyzed with the adjusted odds ratio using a logistic regression model. **RESULTS:** Mean age of subjects at the beginning of the study was 68.4 y (SD = 11.6), and 75% were men. Severity was mild in 50.8% of subjects, moderate in 35.3%, severe in 9.4%, and very severe in 4.4%. After 3 y, 32.5% of subjects had been admitted for exacerbation. Predictive values for hospital admission were: age, sex, previous exacerbations, number of visits to the primary care center, comorbidities, smoking, severity (Global Initiative for Chronic Obstructive Lung Disease), and influenza immunization. The area under the receiving operator characteristic curve was 0.72. **CONCLUSIONS:** This model can identify patients at high risk of hospital admission for COPD exacerbation in our setting. Further studies are needed to validate the model in different populations and settings. *Key words:* chronic airways disease; exacerbations; primary care; preventive medicine; electronic medical records; database. [Respir Care 2015;60(9):1288–1294. © 2015 Daedalus Enterprises]

Introduction

Severe COPD exacerbations decrease survival rates and quality of life and increase health costs and use of health resources.¹ Hospital admission accounts for >70% of the

direct health costs generated by COPD.² Understanding the variables related to hospital admission for exacerbation could decrease mortality, increase survival rates, improve quality of life, and reduce health expenditure.

On average, patients with COPD experience 4 episodes of exacerbation/y. Indeed, exacerbation is one of the main causes of hospital admission and mortality in COPD patients.¹ Up to 10% of exacerbation episodes require hospital admission. Moreover, exacerbation episodes accelerate the decline of pulmonary function,³ which results in less physical activity, a decrease in quality of life,⁴ and an increase in mortality.⁵

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Exacerbations in COPD are considered mild when only a change in bronchodilator treatment is required, moderate when antibiotics and/or oral steroids are prescribed, and severe when the patient requires hospital admission.⁶ Screening for factors associated with severe exacerbation is crucial to prevent severe episodes and thus decrease admission rates.

Previous studies have identified risk factors of hospital admission for COPD exacerbation⁷⁻¹²: a decrease in FEV₁; anxiety and depression; duration of disease; nutritional status; sex; age; socioeconomic level; comorbidities; quality of life; and, finally and most significantly, a previous admission for exacerbation.⁷⁻¹⁰ More recently, biomarkers of inflammation have been considered important predictive factors of exacerbation (C-reactive protein, fibrinogen, leukocyte, eosinophil, and lymphocyte count; leukotrienes [B₄, IL-6, IL-8, and TNF- α]; procalcitonin; endothelin; and adrenomedullin).¹¹

Factors such as the characteristics of a population, the prevalence of risk factors, and aspects of the health system can result in geographical variation in the incidence of hospital admissions for exacerbation.¹³ As a consequence, variables associated with hospital admission for exacerbation should be investigated in different settings to produce predictive models that detect patients at risk. A model for patients with COPD in primary care that identifies patients at high risk of hospital admission validated in different populations and settings would contribute to the design of preventive and management strategies aimed at lowering admission rates. The aim of this study was to determine predictive factors of hospital admission for exacerbation in a cohort of primary care patients with COPD.

Methods

A retrospective cohort study with 2,501 subjects diagnosed with COPD from 7 primary care centers of the Lleida Health Region (catchment population 172,950) was undertaken. Only primary care centers assigned to the referral hospitals University Hospital Arnau de Vilanova and Hospital Santa Maria de Lleida were included to guarantee a comprehensive register of patients admitted for exacerbation. Participants were subjects >40 y old with a diagnosis of COPD in 2010 in the primary care electronic medical records. Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria were followed for the diagnosis of COPD: a post-bronchodilator FEV₁/FVC <0.7 in the stable phase of the disease. For a subject to be included in the study, the electronic medical records had to also contain the result of spirometry from the 2 y before the start of the study.

The dependent variable was hospital admission for severe exacerbation of COPD obtained from the hospital

QUICK LOOK

Current knowledge

Severe COPD exacerbations decrease survival rates and quality of life and increase health costs and use of health resources. Hospital admission accounts for >70% of the direct health costs generated by COPD. On average, patients with COPD experience 4 exacerbations/y. Up to 10% of exacerbation episodes require hospital admission. Understanding the variables related to hospital admission for exacerbation could decrease mortality, increase survival rates, improve quality of life, and reduce health expenditure.

What this paper contributes to our knowledge

In this 3-y retrospective cohort study of the risk of hospital admission in COPD subjects, a model predicted which subjects would require hospitalization. Predictive values for hospital admission were: age, sex, previous exacerbations, number of visits to the primary care center, comorbidities, smoking, severity (GOLD stage), and influenza immunization. Preventive measures and modification of treatment in these patients could be targeted in an attempt to lower admission rates and health costs and improve survival and quality of life.

discharge minimum data set of any of the referral hospitals. Exacerbation of COPD was defined as an increase in dyspnea and/or in the amount and purulence of sputum.¹⁴ In accordance with American Thoracic Society guidelines, patients were admitted when no sufficient response to primary care treatment was obtained. The number of exacerbations that required hospital admission between November 2010 and October 2013 was computed for each subject.

The study included the following data: age, sex, spirometry results (FEV₁/FVC, FVC, and FEV₁), comorbidities (heart failure, ischemic heart disease, diabetes, chronic kidney failure, atrial fibrillation, and anemia), history of smoking, 23-valent pneumococcal and influenza immunizations for the 2009/2010 season, years since COPD was diagnosed, number of visits to the health center and number of exacerbations during 2009, and COPD severity according to the GOLD guidelines. Data sources were the primary care electronic medical records and the hospital discharge minimum data set. This study was approved by the Clinical Research Ethics Committee of the Primary Care Research Institute (IDIAP) Jordi Gol of Barcelona (P14/025).

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Table 1. Characteristics of the Cohort at the Beginning of the Study (2010) and Hospital Admissions During the 3-y Follow-up

| | All | Hospital Admission | | <i>P</i> |
|--|--------------|------------------------|-----------------------|----------|
| | | No (<i>n</i> = 1,689) | Yes (<i>n</i> = 812) | |
| Age, y (SD) | 68.4 (11.6) | 66.6 (11.9) | 72.0 (10.2) | .001 |
| COPD history, y (SD) | 3.6 (4.3) | 3.3 (4.0) | 4.1 (4.7) | .001 |
| Visits to primary care (2009), <i>n</i> (SD) | 24.6 (18.3) | 21.97 (16.3) | 30.1 (20.7) | .001 |
| Females, <i>n</i> (%) | 626 (25.0) | 462 (27.4) | 164 (20.2) | .001 |
| 23-valent pneumococcal immunization, <i>n</i> (%) | 1,762 (70.5) | 1,110 (65.7) | 652 (80.3) | .001 |
| Influenza immunization (2009/2010 season), <i>n</i> (%) | 1786 (71.4) | 1,128 (66.8) | 658 (81.0) | .001 |
| COPD exacerbation in year before start of study (2009), <i>n</i> (%) | 506 (20.2) | 262 (15.6) | 244 (30.1) | .001 |
| Comorbidities*, <i>n</i> (SD) | 0.43 (0.70) | 0.35 (0.60) | 0.6 (0.80) | .001 |
| Smoking, <i>n</i> (%) | 844 (33.8) | 594 (35.2) | 250 (30.8) | .01 |
| COPD severity (GOLD), <i>n</i> (%) | | | | .001 |
| Mild | 1,271 (50.8) | 941 (55.7) | 330 (40.6) | |
| Moderate | 883 (35.3) | 578 (34.2) | 305 (37.6) | |
| Severe | 236 (9.4) | 118 (7) | 118 (14.5) | |
| Very severe | 111 (4.4) | 52 (3.1) | 59 (7.3) | |

*Comorbidities include: ischemic heart disease, heart failure, diabetes, anemia, atrial fibrillation, and chronic kidney failure.

GOLD = Global Initiative for Chronic Obstructive Lung Disease.

Statistical Analysis

A descriptive analysis of the data was carried out. Continuous variables were described using the mean and SD, and categorical variables were described with the absolute and relative frequencies.

Hypothesis testing to evaluate the association of independent variables with the event of interest (hospital admission for COPD exacerbation) was performed using the chi-square test for categorical variables and Student *t* test or Mann-Whitney *U* test for continuous variables. The crude odds ratio (OR) was calculated for each independent variable included in the model.

The score included all variables associated with the outcome with *P* < .2. The risk score was adjusted for the 3-y period with a logistic regression analysis using automatic (forward and backward) variable selection algorithms. Selected variables were included in the model if the *P* value of the effect was < .1. The characteristics of the calibration were evaluated by the Hosmer-Lemeshow test, and the discriminatory power was evaluated using the C statistic of the area under the curve.

Statistical interaction and quadratic effects were tested for all quantitative variables. Statistical significance was considered to be *P* < .05. All analyses were performed using the statistical package SPSS 15.0.

Results

A total of 2,501 subjects with COPD were included in the study. Mean age at the start of the study was 68.4 y

(SD = 11.6), and 3 of 4 subjects were men. Severity of disease (GOLD) was mild in 50.8% of subjects, moderate in 35.3%, severe in 9.4%, and very severe in 4.4%. The year before the start of the study, 1 of 5 subjects had been admitted at least once for exacerbation, and the average number of visits to the physician or nurse in primary care was 25. With regard to immunizations, 70.5% had received the 23-valent pneumococcal vaccine, and 71.4% had received the influenza vaccine during the 2009/2010 season (season before the start of the study).

Table 1 shows the descriptive variables of the cohort at the start of the study. A high percentage of subjects had attended the primary care center during the year before the start of the study, and a high prevalence of comorbidities was recorded (heart failure, ischemic heart disease, diabetes, chronic kidney failure, atrial fibrillation, and anemia). During the 3-y follow-up, 32.5% of the cohort subjects required admission. Subjects with a higher grade of severity (GOLD) had higher rates of admission. With regard to the 23-valent pneumococcal and influenza immunizations (2009 season), subjects with a more severe grade of disease (GOLD) had higher rates of immunization (*P* = .001) (Table 2). A correlation between immunization and severity was found. Subjects with more severe disease had a higher risk of admission, and more of them had been immunized. Smoking also increased the risk of admission (Table 3).

The multivariate analysis (Table 3) found a significant association between the following factors and risk of hospital admission for COPD exacerbation: age 51–60 y (adjusted OR = 1.67, 95% CI: 1.01–2.75), 61–70 y (adjusted OR = 1.70,

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Table 2. Hospital Admission in Relation to Immunization and COPD Severity (Global Initiative for Chronic Obstructive Lung Disease)

| | Mild (<i>n</i> = 1,271) | Moderate (<i>n</i> = 883) | Severe (<i>n</i> = 236) | Very Severe (<i>n</i> = 111) | Total (<i>N</i> = 2,501) | <i>P</i> |
|--|-----------------------------|-------------------------------|-----------------------------|----------------------------------|------------------------------|----------|
| 23-valent pneumococcal immunization, <i>n</i> (%) | 866 (68.1) | 628 (71.1) | 185 (78.4) | 83 (74.8) | 1,762 (70.5) | .002 |
| Influenza immunization (2009/2010 season), <i>n</i> (%) | 880 (69.2) | 636 (72.0) | 183 (77.5) | 87 (78.4) | 1,786 (71.4) | .002 |
| Hospital admission for COPD exacerbation (2010–2013), <i>n</i> (%) | 330 (26) | 305 (34.5) | 118 (50.0) | 59 (53.2) | 812 (32.5) | .001 |

Table 3. Predictive Factors of Hospital Admission for COPD Exacerbation After a 3-y Follow-up

| | Hospital admission | | <i>P</i> |
|---|--------------------|------------------|----------|
| | Crude OR (CI) | Adjusted OR (CI) | |
| Age (reference: ≤50 y) | | | .002 |
| 51–60 y | 2.40 (1.49–3.86) | 1.67 (1.01–2.75) | .046 |
| 61–70 y | 3.26 (2.09–5.11) | 1.70 (1.01–2.88) | .046 |
| 71–80 y | 5.06 (3.25–7.88) | 2.17 (1.24–3.79) | .006 |
| >80 y | 6.71 (4.26–10.57) | 2.78 (1.56–4.95) | .001 |
| Sex (female) | 0.67 (0.55–0.82) | 0.71 (0.57–0.88) | .002 |
| COPD in year before study (2009) | 2.34 (1.92–2.86) | 1.94 (1.56–2.41) | .001 |
| Smoking | 0.82 (0.69–0.98) | 1.30 (1.04–1.61) | .02 |
| COPD severity (GOLD) (reference: mild) | | | .001 |
| Moderate | 1.50 (1.25–1.81) | 1.39 (1.14–1.70) | .001 |
| Severe | 2.85 (2.15–3.79) | 4.00 (2.32–6.89) | .001 |
| Very severe | 3.24 (2.18–4.79) | 4.56 (2.47–8.42) | .001 |
| Influenza immunization (2009/2010 season) | 2.12 (1.74–2.60) | | |
| INT: influenza immunization (2009/2010 season) + COPD severity (GOLD) (severe and very severe) | NA | 0.54 (0.30–0.96) | .036 |
| INT: Smoking + age (mean y) | NA | 1.03 (1.01–1.05) | .008 |
| | 1.61 (1.44–1.81) | 1.26 (1.11–1.43) | .001 |
| No. of visits (2009) (reference: ≤25) | | | .12 |
| 25–50 | 2.19 (1.82–2.64) | 1.78 (1.44–2.19) | .001 |
| >50 | 3.43 (2.51–4.68) | 2.21 (1.56–3.13) | .001 |
| Hosmer-Lemeshow test | | 10.54 | .23 |
| ROC curve | | 0.72 (0.70–0.74) | .001 |

OR = odds ratio

GOLD = Global Initiative for Chronic Obstructive Lung Disease

INT = interaction

NA = not applicable

ROC = receiving operator characteristic

95% CI: 1.01–2.88), 71–80 y (adjusted OR = 2.17, 95% CI: 1.24–3.79), or >80 y (adjusted OR = 2.78, 95% CI: 1.56–4.95) in relation to the reference category (ie, age ≤50 y); sex (female: adjusted OR = 0.71, 95% CI: 0.57–0.88); previous exacerbations (adjusted OR = 1.94, 95% CI: 1.56–2.41); smoking (adjusted OR = 1.30, 95% CI: 1.04–1.61); severity (GOLD) moderate (adjusted OR = 1.39, 95% CI: 1.14–1.70), severe (adjusted OR = 4.00, 95% CI: 2.32–6.89), or very severe (adjusted OR = 4.56, 95% CI: 2.47–8.42) in relation to the reference category (ie, mild severity grade); comorbidities (adjusted OR = 1.26, 95% CI: 1.11–1.43); number of visits to the primary care center of 25–50 (adjusted OR = 1.78, 95% CI: 1.44–2.19) or >50 visits (adjusted OR = 2.21, 95% CI: 1.56–3.13) in relation to the reference

category (≤25 visits); and influenza immunization for severe and very severe COPD (adjusted OR = 0.54, 95% CI: 0.30–0.96). All of these variables had a statistically significant association with hospital admission for COPD exacerbation with a discriminatory power of 0.72. Figure 1 shows the discriminatory power and calibration of the model.

Table 4 shows the predictive model of the risk of hospital admission for COPD exacerbation, which includes 8 items with a score between 0 and 6. Female sex and influenza immunization (season 2009/2010) in very severe COPD subjects are protective factors. The scores for each item are as follows: age (51–60 y = 2 points; 61–70 y = 2 points; 71–80 y = 3 points; >80 y = 4 points); sex (female) = –2 points; history of COPD exacerbation = 3 points; smok-

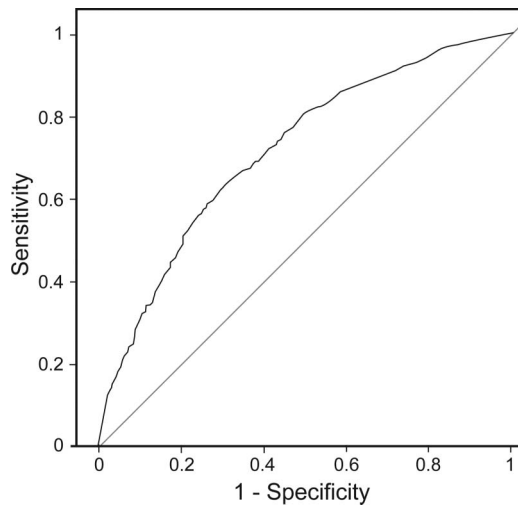


Fig. 1. Hospital admission receiver operating characteristic curve for exacerbations in COPD subjects.

Table 4. Predictive Model of Hospital Admission by COPD Exacerbation

| | Score |
|--|-------|
| Age (reference: ≤ 50 y) | |
| 51–60 y | 2 |
| 61–70 y | 2 |
| 71–80 y | 3 |
| >80 y | 4 |
| Sex (female) | –2 |
| History of COPD exacerbation | 3 |
| Smoking | 1 |
| COPD severity (GOLD) (reference: mild) | |
| Moderate | 1 |
| Severe | 6 |
| Very severe | 7 |
| Severe or very severe (GOLD) + influenza immunization (2009/2010 season) | –3 |
| Smoking + function age* | 1 |
| Comorbidities† | 1 |
| No. of visits year prior to the study (reference: ≤ 25) | |
| 26–50 | 3 |
| >50 | 3 |

PROB = $\exp[-2.35 + (\text{score} + 1) \cdot \theta] / [1 + \exp[-2.35 + (\text{score} + 1) \cdot \theta]]$.

*Function age: $(\text{age [y]} - 68) / 10$.

†Comorbidities include ischemic heart disease, heart failure, diabetes, anemia, atrial fibrillation, and chronic kidney failure.

ing = 1 point; COPD severity (GOLD) (moderate = 1 point; severe = 6 points; very severe = 7 points); severe or very severe (GOLD) + influenza immunization = –3; smoking + function age = 1 point; comorbidities = 1 point; and number of visits during the previous year (26–50 visits = 3 points; >50 visits = 3 points). For instance, for a 78-y-old male subject with severe COPD (GOLD index) who visited 30 times during the previous year, the total score is 14 points:

age = 3 points; sex = 0 points; history of COPD exacerbation = 0 points; smoking = 1 point; COPD severity = 6 points; COPD severity + vaccine = 0 points; smoking + function age = 1 point; comorbidities = 0 points; number of visits = 3 points. In this case, the probability predicted by the model and that predicted using the score are closely correlated (Pearson correlation = 0.99). In our tool, a score of <5 indicates a predicted probability of <20%, a score between 5 and 15 indicates a predicted probability of 20–80%, and finally, a score of >15 indicates a predicted probability of >80%.

Discussion

In this study, we produced a model to predict the risk of hospital admission due to exacerbation in subjects with COPD to be used specifically during primary care visits. Subjects admitted to a hospital for COPD exacerbation were more frequently male and older, their grade of disease severity was higher (GOLD), they had experienced more exacerbation episodes during the year before the start of the study, and they had more frequently visited the primary care center, probably as a consequence of the higher prevalence of comorbidities in this group. The rate of admission in older subjects was higher due to the decline of pulmonary function with time and the cumulative effect of risk factors such as smoking. Indeed, older subjects with a history of smoking had higher admission rates than non-smokers. This study confirms the protective effect of influenza immunization to prevent hospital admission for COPD exacerbations. This predictive model can be easily implemented during primary care and specialist visits to screen patients at high risk of hospital admission.

Age and sex of participants were similar to those in other studies.^{15,16} The study population was old and mainly male, probably because smoking started late in women in our setting.¹⁶ The predictive factors of hospital admission in our study, such as old age,¹⁶ history of smoking,^{17,18} comorbidities,^{18,19} severity of disease (GOLD),⁷ and previous admissions for exacerbation,²⁰ have already been described.

Comorbidities are an important predictive factor of hospital admission. Different studies have found an average number of 1.5–4.4 comorbidities in subjects with COPD.^{18,19} Cardiovascular disease is the most common and also the most frequent cause of hospital admission and mortality in COPD patients.^{21,22} The predictive model of Miravittles et al²³ included comorbidities together with severity as risk factors of hospital admission for exacerbation. In this study, we quantified comorbidities indirectly through the number of visits to the primary care center during the year before the start of the study. The number of visits was found to be an independent risk factor for hospital admission, as described previously.²²

Severity of COPD is considered an independent predictive factor for hospital admission.²⁴ Hospital admissions are caused by a significant decline in pulmonary function, usually a combination of a decrease in FEV₁ and infections by more aggressive bacteria.²⁵

As reported previously,^{5,26} a history of prior exacerbation(s) doubles the risk of admission. It is possible that patients admitted have a more severe form of disease even when pulmonary function as measured by the FEV₁ is similar to that of patients who do not experience exacerbations.

Similarly to previous reports, this 8-variable model highlights the role of old age, smoking, severity of disease (GOLD), higher use of health services, and history of COPD exacerbation.^{16,18-20} The model also takes into account the protective effect of influenza immunization in subjects with more severe forms of disease and the lower admission rates in women.

Some authors from the United States, such as Rowe et al²⁷ and Tsai et al,²⁸ reported higher admission rates (49.3 and 62%, respectively) than we did. The differences observed are most likely attributable to our cohort originating from primary care, where the average severity of the disease is lower.

This study has some limitations: The data have been obtained from the primary care electronic clinical records and from hospital discharge records, where variables such as smoking and immunizations can be underreported. The study included subjects with a spirometry result from the 2 y before the start of the study to ensure that all subjects were correctly diagnosed. Patients with COPD that did not have a spirometry result were excluded. However, these patients probably had mild COPD. Also, subjects were considered immunized against influenza or pneumococcal disease only when the immunization was registered in the primary care electronic medical records. When patients are immunized in private clinics, this might not be adequately recorded. In consequence, the effects of smoking and the protective effect of the influenza and 23-valent pneumococcal immunization might be underestimated. In addition, only admissions to the 2 referral hospitals (University Hospital Arnau de Vilanova and Hospital Santa Maria de Lleida) were computed. Although most patients would be admitted to these public hospitals, we cannot rule out admission to private clinics. The decisions by physicians to determine whether the patient should be admitted or treated in the community were assumed to be adequate. The effect of influenza immunization might be underestimated, since we only considered immunization in the 2009/2010 season. However, once they have received the influenza vaccine, patients tend to be immunized every year,²⁹ and thus those immunized during the 2009/2010 season were probably also immunized during the following seasons.

This study contributes information on variables associated with hospital admission for exacerbation in a cohort of primary care subjects diagnosed with COPD. It is important to underscore that primary care is the first port of call for most of these patients when their condition worsens, and therefore a model aimed at primary care might greatly impact admission rates. The model includes variables that are easy to collect (age, sex, exacerbations during the previous year, influenza immunization, comorbidities, and smoking), and thus it can be used in primary care visits to screen those subjects with COPD at higher risk of admission with the aim of reducing exacerbation rates and associated health costs.

Conclusions

The study was able to create a model to predict COPD exacerbation and admission rates in a specific cohort of subjects from primary care. The model includes factors that have been described in the past as being important for prediction of COPD exacerbations. The use of this model in everyday clinical practice could detect patients with COPD at high risk of hospital admission. Further prospective studies in different cohorts of subjects with COPD are needed for external validation of this predictive model.

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REFERENCES

1. Soler-Cataluña JJ, Martínez-García MÁ, Serra PC. Multidimensional impact of COPD exacerbations. *Arch Bronconeumol* 2010;46(Suppl 11):12-19.
2. Mannino DM, Higuichi K, Yu TC, Zhou H, Li Y, Tian H, Suh K. Economic burden of chronic obstructive pulmonary disease by presence of comorbidities. *Chest* 2015;148(1):138-150.
3. Donaldson GC, Seemungal TR, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002;57(10):847-852.
4. Steer J, Gibson GJ, Bourke SC. Longitudinal change in quality of life following hospitalisation for acute exacerbations of COPD. *BMJ Open Respir Res* 2015;2(1):e000069.
5. Soler-Cataluña JJ, Martínez-García MA, Román Sánchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax* 2005; 60(11):925-931.
6. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2013;187(4):347-365.
7. García-Aymerich J, Farrero E, Féliz MA, Izquierdo J, Marrades RM, Antó JM. Risk factors of readmission to hospital for a COPD exacerbation: a prospective study. *Thorax* 2003;58(2):100-105.

8. Almagro P, Barreiro B, Ochoa de Echaguen A, Quintana S, Rodríguez Carballeira M, Heredia JL, Garau J. Risk factors for hospital readmission in patients with chronic obstructive pulmonary disease. *Respiration* 2006;73(3):311-317.
9. Müllerová H, Shukla A, Hawkins A, Quint J. Risk factors for acute exacerbations of COPD in a primary care population: a retrospective observational cohort study. *BMJ Open* 2014;4(12):e006171.
10. Donaldson GC, Wedzicha JA. COPD exacerbations. 1: epidemiology. *Thorax* 2006;61(2):164-168.
11. Sapey E, Stockley RA. COPD exacerbations. 2: aetiology. *Thorax* 2006;61(3):250-258.
12. Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010;363(12):1128-1138.
13. Otero González I, Blanco Aparicio M, Montero Martínez C, Valiño López P, Vereá Hernando H. The epidemiology of COPD and asthma exacerbations in a general hospital. *Arch Bronconeumol* 2002;38(6):256-262.
14. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987;106(2):196-204.
15. Groenewegen KH, Schols AM, Wouters EF. Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. *Chest* 2003;124(2):459-467.
16. de Melo MN, Ernst P, Suissa S. Inhaled corticosteroids and the risk of a first exacerbation in COPD patients. *Eur Respir J* 2004;23(5):692-697.
17. Abu Hassan H, Abd Aziz N, Hassan Y, Hassan HF. Does the duration of smoking cessation have an impact on hospital admission and health-related quality of life amongst COPD patients? *Int J Chron Obs Pulmon Dis* 2014;9:493-498. doi: 10.2147/COPD.S56637.
18. García-Sanz MT, Pol-Balado C, Abellás C, Cánive-Gómez JC, Antón-Sanmartín D, González-Barcala FJ. Factors associated with hospital admission in patients reaching the emergency department with COPD exacerbation. *Multidiscip Respir Med* 2012;7(1):6.
19. Stoller JK. Clinical practice. Acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 2002;346(13):988-994.
20. Chu CM, Chan VL, Lin AW, Wong IW, Leung WS, Lai CK. Re-admission rates and life threatening events in COPD survivors treated with non-invasive ventilation for acute hypercapnic respiratory failure. *Thorax* 2004;59(12):1020-1025.
21. Feary JR, Rodrigues LC, Smith CJ, Hubbard RB, Gibson JE. Prevalence of major comorbidities in subjects with COPD and incidence of myocardial infarction and stroke: a comprehensive analysis using data from primary care. *Thorax* 2010;65(11):956-962.
22. Niewoehner DE, Lokhnygina Y, Rice K, Kuschner WG, Sharafkhaneh A, Sarosi GA, et al. Risk indexes for exacerbations and hospitalizations due to COPD. *Chest* 2007;131(1):20-28.
23. Miravittles M, Guerrero T, Mayordomo C, Sánchez-Agudo L, Nicolau F, Segú JL. Factors associated with increased risk of exacerbation and hospital admission in a cohort of ambulatory COPD patients: a multiple logistic regression analysis: the EOLO study group. *Respiration* 2000;67(5):495-501.
24. Man SF, Connett JE, Anthonisen NR, Wise RA, Tashkin DP, Sin DD. C-reactive protein and mortality in mild to moderate chronic obstructive pulmonary disease. *Thorax* 2006;61(10):849-853.
25. García-Aymerich J, Serra Pons I, Mannino DM, Maas AK, Miller DP, Davis KJ. Lung function impairment, COPD hospitalisations and subsequent mortality. *Thorax* 2011;66(7):585-590.
26. Almagro P, Calbo E, Ochoa de Echaguen A, Barreiro B, Quintana S, Heredia JL, Garau J. Mortality after hospitalization for COPD. *Chest* 2002;121(5):1441-1448.
27. Rowe BH, Villa-Roel C, Guttman A, Ross S, Mackey D, Sivilotti ML, et al. Predictors of hospital admission for chronic obstructive pulmonary disease exacerbations in canadian emergency departments. *Acad Emerg Med* 2009;16(4):316-324.
28. Tsai CL, Clark S, Cydulka RK, Rowe BH, Camargo CA. Factors associated with hospital admission among emergency department patients with chronic obstructive pulmonary disease exacerbation. *Acad Emerg Med* 2007;14(1):6-14.
29. Montserrat-Capdevila J, Godoy P, Marsal JR, Cruz I, Solanes M. [Effectiveness of influenza vaccination in preventing hospital admission due to exacerbations of chronic obstructive pulmonary disease]. *Enferm Infecc Microbiol Clin* 2014;32(2):70-75.