Predictors of Outcome After Exacerbation of Chronic Obstructive Pulmonary Disease

Angeliki M. Tsimogianni, MD, MRCP, PhD¹, Spyros A. Papiris, MD, FCCP²,
Georgios T. Stathopoulos, MD¹, Effrosyni D. Manali, MD²,
Charis Roussos, MD, MSc, PhD, MRS, FRCP(©)¹, and Anastasia Kotanidou, MD, PhD¹

¹Department of Critical Care and Pulmonary Services, General Hospital "Evangelismos", School of Medicine, National and Kapodistrian University of Athens, Athens, Greece; ²2nd Pulmonary Department, "Attikon" University Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece.

BACKGROUND: The outcome after hospitalization for an exacerbation of chronic obstructive pulmonary disease (COPD) is unfavorable and uncertainty exists about factors predicting short and long-term prognosis.

OBJECTIVE: To identify clinical predictors of length of hospital stay (LOS) and three-year mortality after COPD exacerbations requiring hospitalization.

DESIGN: Retrospective analysis of prospectively collected data.

PARTICIPANTS AND METHODS: All consecutive patients hospitalized with COPD exacerbation were enrolled. Disease severity was estimated by FEV₁, body mass index (BMI), Medical Research Council (MRC) chronic dyspnoea scale, previous hospitalizations, need for long-term oxygen treatment (LTOT), arterial oxygen and carbon dioxide partial pressures (PaO₂ and PaCO₂), pH and respiratory rate. Outcome was assessed by LOS and three-year mortality.

MAIN RESULTS: Out of 81 patients enrolled, three-year mortality data were available for 61. LOS was related to BMI, MRC scale and respiratory rate. Three-year mortality was related to FEV₁, BMI, MRC scale, LTOT, and PaCO₂. Multiple logistic regression analysis demonstrated that MRC scale was the only independent determinant of LOS, [p=0.001, odds ratio (OR) 7.67 (95% CI 2.50–23.41)], whereas MRC scale and BMI predicted three-year mortality, [p=0.001, OR 8.28 (95% CI 2.25–30.47) and p=0.006, OR 6.91 (95% CI 1.74–27.48), respectively]. Cox regression analysis demonstrated identical results. Using receiver-operator-optimized thresholds for these variables (MRC > 2 and BMI < 25 kg/m²), we propose a prediction model that accurately determines three-year mortality risk.

CONCLUSIONS: In this study, MRC scale and BMI predicted outcome after COPD hospitalization. Pending further validation, this predictive model may contribute to identify patients with poor outcome even when spirometric data are unavailable.

KEY WORDS: body mass index; chronic obstructive pulmonary disease; dyspnoea; length of hospital stay; mortality.
J Gen Intern Med 24(9):1043–8
DOI: 10.1007/s11606-009-1061-2
© Society of General Internal Medicine 2009

INTRODUCTION

Exacerbations of chronic obstructive pulmonary disease (COPD) are an important component of the burden of the disease by accelerating lung function decline, precipitating poor health status, increasing healthcare costs, and negatively affecting survival.^{1–3} More precisely, in-hospital mortality for an acute hypercapnic exacerbation approximates 10%, while two-year mortality approximates 50%.³ The economic impact of COPD exacerbations is mainly due to hospital admissions that are often prolonged with a length of hospital stay (LOS) varying between 6 and 13 days according to the severity of exacerbation of the population studied.^{3–5} Despite this fact, few studies^{5,6} have as the primary short-term outcome parameter the length of hospital stay and examine its association with patient characteristics. In the past, shorter length of stay has been associated with low respiratory rate and arterial partial carbon dioxide pressure (PaCO₂) and fewer co-morbid illnesses.⁶

Mortality, the most important outcome parameter, has been previously found to be related to PaO₂/FiO₂ ratio (partial arterial oxygen pressure/fractional inspired oxygen), serum albumin, body-mass index (BMI), age, quality of life, specific co-morbid conditions,^{3,6,7} exacerbation frequency and hospitalization,⁸ use of corticosteroids, PaCO₂,⁴ long-term oxygen treatment (LTOT),⁹ and forced expiratory volume in 1 second (FEV₁)¹⁰. Furthermore, the presence of respiratory acidosis characterizes life-threatening exacerbations.¹¹ The role of the Medical Research Council (MRC) chronic dyspnoea scale in predicting mortality has not been assessed in these studies, and its predictive role has been the primary objective of only one previous study.¹² Moreover, most of previous studies^{3,4,9} assessed six-month and one-year mortality and very few extended follow-up to more than two years.^{7,12,13} However, short- and long-term prognosis of these patients is very important when facing therapeutic decisions and dilemmas of resource allocation.

Received February 19, 2009

Revised June 1, 2009

Accepted June 23, 2009

Published online July 14, 2009

In this study we hypothesized that the above listed indices of systemic COPD effects and of exacerbation severity may predict LOS and three-year mortality after hospitalization for a COPD exacerbation. Moreover, we hypothesized that by combining some of these parameters we will form a model with higher predictive accuracy. To test our hypothesis, we prospectively evaluated patients admitted with an acute exacerbation of COPD for LOS, FEV₁, MRC chronic dyspnoea scale, BMI, previous year hospitalizations, LTOT, PaO₂, PaCO₂, pH, respiratory rate, and three-year mortality.

MATERIALS AND METHODS

Study Protocol

All consecutive patients over the age of 40 years with a diagnosis of COPD and symptoms indicative of an exacerbation who were admitted at a respiratory department of "Sotiria" Chest Diseases Hospital in Athens, Greece, from July 2001 to June 2004, were eligible for this observational study, where data and length of hospital stay were collected prospectively and three-year mortality was assessed retrospectively. Some of the study patients were simultaneously enrolled in a different observational study with completely different endpoints.¹⁴ The physician-investigator (AMT) obtained informed consent from all patients and the ethics committee of the hospital approved the study protocol. Inclusion criteria were: a diagnosis of COPD and presence of an exacerbation according to Global Initiative of Chronic Obstructive Lung Disease definition¹ requiring hospital admission. Briefly, COPD was defined as FEV₁/forced vital capacity (FVC) < 0.70 in a current/ex-smoker over the age of 40 years,¹ and an exacerbation was defined as acute-onset sustained worsening in baseline dyspnoea, cough, and/or sputum beyond normal variation warranting a change in regular medication.^{1,2} Exclusion criteria were: age less than 40 years; asthma; bronchiectasis; pneumonia; cancer; any other active lung disease; presence of an exacerbation requiring endotracheal intubation and intensive care treatment.

Specific demographic (age, gender) and risk epidemiologic (smoking, diabetes, allergies, etc.) information was collected from each eligible patient. Spirometric data were derived from patients charts or personal files from time periods of stability within the calendar year preceding the exacerbation (eg, more than three months apart from an exacerbation). Patients with no available spirometry data ($n=17$) or displaying more than 12% increase in FEV₁ after bronchodilation were excluded ($n=3$)¹⁵. BMI was calculated by dividing the weight in kilograms with the square of height in meters.^{16,17} Subsequently, the patients were asked to describe their level of dyspnoea before the onset of the exacerbation and their MRC score was recorded. The MRC dyspnoea scale^{1,17,18} is a questionnaire that consists of five statements about perceived breathlessness: grade 1, "I get breathless only in strenuous exercise"; grade 2, "I get breathless when hurrying on the level or up a slight hill"; grade 3, "I walk slower than people of the same age on the level, or have to stop for breath when walking at my own pace on the level"; grade 4, "I stop for breath after walking 100 yards or few minutes on the level"; grade 5, "I am too breathless to leave the house." The number of hospitalizations for COPD within the calendar year preceding the exacerbation

was derived from hospital files or patients direct enquiry. Finally, PaO₂, PaCO₂, and pH were measured on an arterial blood sample taken before the institution of oxygen therapy on a blood gas analyzer (Radiometer Copenhagen, Copenhagen, Denmark). The use of LTOT and respiratory rate per minute on admission were also recorded.

LOS was used as a parameter of short-term outcome. In agreement with most studies^{3,5} showing LOS of 8 to 9 days we found a median LOS of 8 days and we categorized LOS in two groups: LOS ≤ 8, (usual stay) and LOS > 8, (prolonged stay). Patients intubated and transferred to the intensive care unit were excluded from the study ($n=5$). Three years after discharge, the patients or their relatives were contacted by telephone and their survival status was recorded. Twenty patients were not traced and were excluded from survival analyses. Three-year mortality was used as a parameter of long-term outcome.

Statistical Analysis

Non continuous data are reported as frequencies. Continuous variables normally distributed are reported as mean ± standard deviation (SD). Not normally distributed data are reported as median (interquartile range, IQR), or with the entire distribution for variables with limited number of categories. Comparisons between groups were done by chi-square, Student's t-test, or Mann-Whitney U-test for nominal, continuous normally distributed and continuous not normally distributed variables, respectively. Multiple stepwise logistic regression analysis with backward elimination method and Cox regression analysis with backward elimination method were performed to examine the independent effect of the variables with $p<0.1$ on univariate analysis, on length of hospital stay and three-year mortality. Subsequently, the independent determinants associated with mortality were included in two models: a standard one and a simplified one. Finally, receiver-operator characteristic (ROC) curve analysis was done for independent determinants associated with LOS and three-year mortality, as well as the standard and simplified model. The best cutoff points for each variable was selected using the Youden index. Analyses were done using the Statistical Package for the Social Sciences version 13.0.0 (SPSS, Chicago, IL). Probability values less than 0.05 were considered significant.

RESULTS

Of 106 patients prospectively enrolled in the study, 5 were intubated and transferred to intensive care unit, 17 were not able to yield consistent spirometry data, and 3 had marked response to bronchodilation; all the above were excluded from the study. The characteristics of the remaining 81 patients are shown in Table 1.

In-hospital mortality was 4.9% (4/81 patients) and all deaths occurred after prolonged hospital stay (> 8 days). Twenty-seven patients had prolonged LOS. Patients with usual LOS had lower MRC score (distributed as 10/30/12/2/0 versus 3/5/12/7/0) and respiratory rate/minute (25±5 versus 27±5) than patients with prolonged LOS and higher BMI (kg/m²) (28.8±6.8 versus 25.7±5.4), all p -values < 0.05. On the contrary, the other parameters were not different between groups (data not shown).

Table 1. Baseline Characteristics of 81 Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease

Age [years; mean $\pm$ SD (range)]	68 $\pm$ 9 (44–87)
Sex (male/female; n)	57/24
Smoking (never/ex/current; n)	0/37/44
FEV₁ [% predicted; mean $\pm$ SD (range)]	47 $\pm$ 17 (15–87)
GOLD Stage (I/II/III/IV; n)	2/33/32/14
BMI [*] [kg/m ² ; mean $\pm$ SD (range)]	28 $\pm$ 7 (17–54)
MRC score [§] (1/2/3/4/5; n)	13/35/24/9/0
Previous year hospitalizations (0/1/2/3/4/5; n)	43/21/6/9/1/1
LTOT [†] (yes/no; n)	41/40
PaO₂ [kPa; mean $\pm$ SD (range)]	7.4 $\pm$ 1.6 (4.0–11.2)
PaCO₂ [kPa; mean $\pm$ SD (range)]	5.9 $\pm$ 1.5 (3.2–10.6)
Respiratory rate [mean $\pm$ SD (range)]	26 $\pm$ 5 (16–36)
pH [mean $\pm$ SD (range)]	7.42 $\pm$ 0.05 (7.29–7.55)
LOS [‡] [days; median(IQR)]	8 (6–11.5)
3-yr survival (yes/no/unknown; n)	36/25/20

*Body-mass index; [§]Medical Research Council; [†]Long-term oxygen treatment; [‡]Length of hospital stay.

Twenty patients were not traced three-years post-discharge and were not included in the survival analysis; their characteristics did not differ significantly from patients available for the survival analysis. Only BMI expressed as absolute number (kg/m²) (27 $\pm$ 6 for patients traced versus 30 $\pm$ 8 for patients lost; $p=0.023$) but not as categorical variable (33% of patients traced versus 25% of patients lost had BMI<25 kg/m²; $p>0.05$), and long-term oxygen use (56% of patients traced versus 30% of patients lost received LTOT; $p<0.05$) differed between patients traced or not at three-years.

Three-year mortality was 41% (25/61 patients). Survivors had higher FEV₁ (% predicted) (52 $\pm$ 17 versus 39 $\pm$ 13) and BMI (kg/m²) (28.1 $\pm$ 4.8 vs 25.0 $\pm$ 6.3), lower MRC score (distributed as 7/22/4/3/0 vs 1/6/13/5/0) and PaCO₂ (kPa) (5.5 $\pm$ 1.5 vs 6.5 $\pm$ 1.5) and less frequently LTOT (39% vs 80%) than deceased patients, all p -values<0.05. On the contrary, age, hospitalizations, PaO₂, respiratory rate, and pH were not different between groups (data not shown).

Subsequently, we performed ROC analysis for variables significantly ($p<0.10$) associated with LOS (BMI, MRC score, LTOT, respiratory rate and pH) and for variables significantly ($p<0.10$) associated with three-year mortality (FEV₁, BMI, MRC score, LTOT and PaCO₂) in order to identify the optimal cutoff points useful to predict LOS and three-year mortality, these data are available upon request. Using these cutoff points to categorize patients, we performed multiple logistic regression and Cox regression analyses to identify the independent effect of the variables studied on LOS and three-year mortality. In multiple logistic as well as in Cox regression analyses, MRC score was the only independent determinant of prolonged LOS [$p=0.001$, odds ratio = 7.67 (95% CI=2.50–23.41) and $p=0.013$ hazard ratio = 1.77 (95% CI 1.07–2.80), respectively]. The visual inspection of the log minus log function plots for the final Cox model including MRC showed adequate proportionality.

For both analyses, only MRC score and BMI were independently associated with three-year mortality (Table 2). Again, the visual inspection of the log minus log function plots for the final Cox model including MRC and BMI showed adequate proportionality.

Using these two variables, (MRC > 2 and BMI < 25 kg/m²) we generated a simplified weighted model to predict three-year mortality. By adding to the model FEV₁ we generated a more

Table 2. Impact of Recorded Variables in Categories (from ROC * Analysis) on Three-year Mortality Using Multiple Logistic Regression Analysis and Cox Regression Analysis

Variables	Multiple logistic analysis		Cox regression analysis	
	OR (95% CI)	P	HR (95% CI)	P
FEV ₁ <40% predicted	2.80 (0.70–11.12)	0.14	1.70 (0.66–4.37)	0.26
BMI [§] <25 kg/m ²	6.91 (1.74–27.48)	0.006	2.84 (1.22–6.65)	0.016
MRC score [†] > 2	8.28 (2.2–30.47)	0.001	3.60 (1.42–9.10)	0.007
LTOT [‡] yes	1.41 (0.26–7.41)	0.68	1.39 (0.34–5.70)	0.65
PaCO ₂ $\geq$ 5.8 kPa	1.15 (0.23–5.68)	0.86	1.24 (0.45–3.42)	0.67

*Receiver Operating Characteristic curve; [§] Body mass index; [†] Medical Research Council; [‡]Long-term oxygen therapy.

standard model for three-year mortality prediction, these data are also available upon request. On ROC analysis of the simplified and standard model and their constituents, both models had high predictive accuracy (Fig. 1 and Table 3). Specifically, on the simplified model, when none of the risk factors were present (score = 0), 86% of patients were alive after three years; when both risk factors were present (score = 3.5) 92% of the patients died within three years. This predictive accuracy is equivalent to a more standard model including FEV₁ (Table 3).

DISCUSSION

In the present study, we set forth the hypothesis that clinical surrogates of COPD severity and systemic effects could predict short- and long-term outcome after hospitalization for an exacerbation of COPD. To test this hypothesis, we prospectively evaluated patients admitted at a tertiary hospital with an

Figure 1. Receiver-operator curves of body mass index (BMI) < 25 kg/m², Medical Research Council (MRC) chronic dyspnoea score > 2, and simplified score in predicting three-year mortality of patients with exacerbation of COPD.

Table 3. Results of *ROC Analysis of Simplified Score, [§]BOD Score and their Constituents for Prediction of Three-year Survival of Patients After a Severe Exacerbation of COPD

Characteristic	AUC [†] (95% CI)	P	Sensitivity	Specificity	PPV [#]	NPV [#]
MRC score >2	0.76(0.64-0.89)	0.001	72%	81%	72%	81%
BMI [‡] < 25 kg/m ²	0.73(0.59-0.86)	0.002	60%	76%	75%	86%
Simplified score	0.83(0.72-0.94)	0.001	84%	70%	66%	86%
FEV ₁ < 40% predicted	0.70(0.56-0.83)	0.010	64%	75%	64%	75%
BOD score ^{**}	0.86(0.76-0.96)	0.001	76%	81%	73%	83%
Survival status N (%)						
Simplified score	Alive		Deceased		Total	
0	25 (86%)		4 (14%)		29	
1.5	4 (57%)		3 (43%)		7	
2	6 (50%)		6 (50%)		12	
3.5	1 (8%)		12 (92%)		13	
BOD score						
0	19 (91%)		2 (9%)		21	
1-1.5	10 (71%)		4 (29%)		14	
2-3.5	6 (40%)		9 (60%)		15	
4.5	1 (9%)		10 (91%)		11	

Receiver Operating Characteristic curve; [§]BMI-Obstruction-Dyspnoea; [†]Area under curve; ^{||} Medical Research Council; [‡]Body-mass-index; [#]PPV-NPV, positive and negative predictive values; ^{}Best cut-off point = 0.75; ^{**} Best cut-off point = 1.75.

acute exacerbation of COPD. Using simple analyses, we showed that MRC score and BMI predicted length of hospital stay and three-year mortality. Moreover, we combined these characteristics into a regression coefficient-weighted prediction model, which can provide accurate identification of patients likely or not likely to die within the coming three years, even when spirometric data are not readily available.

In the published literature, in-hospital mortality, LOS, six-month mortality, and one-year mortality have been the most commonly used outcome parameters in patients with COPD exacerbation.^{3,4,19} However, few previous studies^{5,6} had as their main outcome measure the length of hospital stay. Moreover, in our study, we preferred to assess three-year mortality instead of one-year mortality in order to have a complete estimation of COPD patients' outcome, in the short- and long-term, knowledge that could influence management. Three-year mortality was the primary endpoint of the TORCH trial¹³ and was found to be less than 16%, but the population included in that study was different from our study. Patients included in the TORCH trial were mainly outpatients, able to attend their scheduled 12-weekly visits and not patients hospitalized for a severe exacerbation associated with unfavorable prognosis.^{3,8} Furthermore, patients excluded from the TORCH trial, such as those over the age of 80 years or those who withdrew during the run-in period ($n=2370$), could be the ones with more troublesome disease and worse prognosis. Studies assessing

mortality after emergency department visit or hospital admission found results comparable to our findings.^{7,19}

Previous studies have identified associations between various clinical factors in patients with COPD and outcome.^{3-4,6-10} Factors associated with LOS was the primary objective of only one previous study.⁶ The MRC score has not been assessed in those studies and was only examined in one previous study¹² which only compared dyspnoea score with FEV₁. Herein, we used a systematic approach to stratify patients with COPD exacerbation according to their three-year mortality risk and according to their probability of prolonged length of stay.

In the present study, we confirmed the association of FEV₁, LTOT and PaCO₂ with mortality. Despite the fact that FEV₁ was previously regarded as the most significant correlate of survival in COPD,¹⁰ newer data have questioned its independent prognostic role,^{16,20} in agreement with our findings. The association of LTOT with prognosis is easily understood as LTOT reflects more severe stage IV disease, possibly with *cor pulmonale*, which is a well known adverse prognostic factor.^{3,9} Similarly, the association of PaCO₂ with survival could be attributed to the fact that the emergence of hypercapnia in COPD patients characterizes more severe disease and occurs in patients who easily decompensate and develop respiratory failure, an uncontested poor prognostic factor.²¹ Surprisingly, exacerbations were not associated with mortality in contrast to previous studies,⁸ probably because we recorded only the number of

severe exacerbations requiring hospitalization and not the total number of exacerbations; the numbers are small. Arterial blood gas pH was also not related to mortality, as patients with significant respiratory acidosis were transferred to the intensive care unit and subsequently excluded from our study.

The most important finding of the present study is that two easily obtained clinical parameters, BMI and MRC score, have the best predictive value and could assist the clinician in determining COPD patients likely to have prolonged hospitalization or die in upcoming years. Importantly, our results are not a product of statistical analysis, as two different statistical analyses, multiple logistic and Cox regression, identified the same parameters as independent determinants of LOS and mortality. According to the two different analyses, only the risk associated with these parameters differed.

The association of BMI with LOS and three-year survival is not surprising, as low BMI reflects higher degree of systemic inflammation, a mechanism possibly involved in disease progression.²² Previous studies found a strong association between BMI and survival that is not linear but has an inflection point, below which mortality increases.^{15,20,23} This value of BMI varied between 21–25 kg/m² in previous studies and in our hands it was 25 kg/m² (or even higher for LOS), which could be attributed to the high percentage of overweight patients²⁴ in our Greek population. On the other hand, the prognostic role of the MRC dyspnoea scale in COPD is a relatively new finding. The study of Bestall and co-workers¹⁸ showed that this scale is a simple and valid method of assessing the disability of COPD patients and could be used in the classification of COPD severity. In the study of Nishimura and co-workers,¹² the level of dyspnoea has been shown to be a better predictor of five-year mortality than the spirometric classification of disease itself. Furthermore, dyspnoea level determines health-related quality of life,²⁵ and physical activity of COPD patients that have an impact on readmission risk and long-term prognosis,^{9,26–29} and these factors are amenable to improvement with pulmonary rehabilitation. The importance of dyspnoea and BMI in predicting survival has recently been further recognized by Celli and co-workers,¹⁷ who included MRC dyspnoea scale and BMI together with FEV₁ and distance walked in 6 minutes in the BODE index, nowadays recognized as the best predictor of mortality from respiratory or other causes in patients with COPD.

The results of our work can be regarded an additional tool to BODE and BOD (without 6-min walk test) indices in situations like the emergency department or the first hours on the ward when the 6-minute walk test can not be performed and it is even impossible to obtain spirometric information. In these situations, our simplified model can assist clinicians in identifying, at first glance, COPD patients at increased risk for prolonged hospital stay and higher mortality risk and try to optimize their hospital management, intensity of follow up, as well as targeting them for rehabilitation programs immediately post-discharge, to improve their nutritional status, dyspnoea level, physical activity and ultimately their outcome. As COPD presents an epidemic on the rise and a great healthcare burden, measures to guide resource allocation for these patients become more important. The knowledge of prognosis of these patients would also assist patients and their relatives making important decisions for their life and give end-of-life directives.

Certain limitations of our study are not to be overlooked. The comorbidities of our patients have not been included in the analyses but patients with known lung cancer, one of the most common comorbidities in COPD patients,³⁰ were excluded from the study. Three-year survival was assessed retrospectively with telephone inquiry and 20 of the patients were not traced, but their characteristics did not differ significantly from the rest of the patients. In addition, death certificates were not checked and cause of death is not provided, as all information regarding survival comes from patients' relatives. Finally, our study was developed in a single centre and we did not validate our findings in a new cohort of patients from a different centre, something that remains to be done.

Despite these shortcomings, we show herein that the MRC chronic dyspnoea score and BMI can be used to predict length of hospital stay and three-year mortality with an accuracy comparable to BOD score. Pending further prospective validation, this finding can be useful in patient management especially when spirometric data are not available.

Acknowledgements: The authors wish to thank the following Chest Physicians for helping with the evaluation of patients: Dr. Spyros Tzannes, Dr. Alexandra Klitsa, Dr. Ioanna Kostara, Dr. Dimitra Haimala, and the Nursing Staff of Emergency and Pulmonary Department of "Sotiria", Chest Diseases Hospital. The statistician Christina Sotiropoulou had a major contribution in the statistical analysis and revision of the paper.

This work was supported by the Thorax Foundation, Athens, Greece.

Conflict of Interest: None disclosed.

Corresponding Author: Angeliki M. Tsimogianni, MD, MRCP, PhD; Department of Critical Care and Pulmonary Services, General Hospital "Evangelismos", School of Medicine, National and Kapodistrian University of Athens, 3 Ploutarhou Str, 10675 Athens, Greece (e-mail: agret@tee.gr).

REFERENCES

1. Global strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease. Global Initiative for Chronic Lung Disease (GOLD) report updated November 2008. Available at: <http://www.goldcopd.com/>. Accessed 11th June 2009.
2. Celli BR, Barnes PJ. Exacerbations of chronic obstructive pulmonary disease. *Eur Respir J*. 2007;29:1224–38.
3. Connors AFJ, Dawson NV, Thomas C, Harrell FE, Desbiens N, Fulkerson WJ, Kussin P, Bellamy P, Goldman L, Knaus W. Outcomes following acute exacerbation of severe chronic obstructive airways disease. *Am J Respir Crit Care Med*. 1996;154:959–67.
4. Groenewegen K, Schols A, Wouters E. Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. *Chest*. 2003;124:459–67.
5. Mushlin AI, Black ER, Connolly CA, Buonaccorso KM, Eberly SW. The necessary length of hospital stay for chronic pulmonary disease. *JAMA*. 1991;266(1):80–3.
6. Villalta J, Sequeira E, Cereijo AC, Sisó A, de la Sierra A. Factors predicting a short length of stay for acute exacerbations of chronic obstructive pulmonary disease. *Med Clin (Barc)*. 2005;124(17):648–50.
7. Gunen H, Hacıevliyagil SS, Kosar F, Mutlu LC, Gulbas G, Pehlivan E, Sahin I, Kizkin O. Factors affecting survival of hospitalised patients with COPD. *Eur Respir J*. 2005;26(2):234–41.
8. Soler-Cataluna JJ, Martinez-Garcia MA, Roman Sanchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax*. 2005;60:925–31.

9. **Yohannes AM, Baldwin RC, Connolly MJ.** Predictors of 1-year mortality in patients discharged from hospital following acute exacerbation of chronic obstructive pulmonary disease. *Age Ageing*. 2005;34(5):491-6.
10. **Menzies R, Gibbons W, Goldberg P.** Determinants of weaning and survival among patients with COPD who require mechanical ventilation for acute respiratory failure. *Chest*. 1995;398-405.
11. **Burge S, Wedzicha JA.** COPD exacerbations: definitions and classifications. *Eur Respir J*. 2003;21(Suppl 41):46s-53s.
12. **Nishimura K, Izumi T, Tsukino M, Oga T.** Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. *Chest*. 2002;121:1434-40.
13. **Calverley P, Anderson J, Celli B, Ferguson GT, Jenkins Ch, Jones PW, Yates JC, Vestbo J.** Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med*. 2007;356:775-89.
14. **Tsimogianni AM, Papiris SA, Kanavaki S, Stathopoulos GT, Sotir-opoulou C, Manali ED, Michalopoulou P, Roussos C, Kotanidou A.** Predictors of positive sputum cultures in exacerbations of chronic obstructive pulmonary disease. *Respirology*, in press
15. American Thoracic Society. Standardization of spirometry: 1994 update. *Am J Respir Crit Care Med*. 1995;152:1107-36.
16. **Agustí AG, Noguera A, Sauleda J, Sala E, Pons J, Busquets X.** Systemic effects of chronic obstructive pulmonary disease. *Eur Respir J*. 2003;21:347-60.
17. **Celli B, Cote C, Mario J, Casanova C, Montes de Oca M, Mendez RA, Plata VP, Cabral HJ.** The body-mass index, airflow obstruction, dyspnea and exercise capacity index in Chronic Obstructive Pulmonary Disease. *N Engl J Med*. 2004;350:1005-12.
18. **Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA.** Usefulness of the Medical Research Council (MRC) dyspnea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax*. 1999;54:581-6.
19. **Kim S, Clark S, Camargo CA Jr.** Mortality after an emergency department visit for exacerbation of chronic obstructive pulmonary disease. *COPD*. 2006;3(2):75-81.
20. **Budweiser S, Jörres RA, Riedl T, Heinemann F, Hitzl AP, Windisch W, Pfeifer M.** Predictors of survival in COPD patients with chronic hypercapnic respiratory failure receiving noninvasive home ventilation. *Chest*. 2007;131(6):1650-8.
21. **Ai-Ping C, Lee KH, Lim TK.** In-hospital mortality and 5-year mortality of patients treated in the ICU for acute exacerbation of COPD. A retrospective study. *Chest*. 2005;128:518-24.
22. **Sethi S, Muscarella K, Evans N, Klingman KL, Grant BJ, Murphy TF.** Airway inflammation and etiology of acute exacerbation of chronic bronchitis. *Chest*. 2000;118(6):1557-65.
23. **Van der Valk P, Monninkhof E, Van der Palen J, Zielhuis G, van Herwaarden C, Hendrix R.** Clinical predictors of bacterial involvement in exacerbations of chronic obstructive pulmonary disease. *Clin Infect Dis*. 2004;39(7):980-6.
24. **Panagiotakos DB, Pitsavos C, Chrysoshoou C, Risvas G, Kontogianni MD, Zampelas A, Stefanadis C.** Epidemiology of overweight and obesity in Greek adult population: the ATTICA Study. *Obes Res*. 2004;12(12):1914-20.
25. **Hajiro T, Nishimura K, Tsukino M, Ikeda A, Oga T, Izumi T.** A comparison of the level of dyspnea vs disease severity in indicating the health-related quality of life of patients with COPD. *Chest*. 1999;116:1632-7.
26. **Donaldson GC, Seemungal TAR, Blowmik A, Wedzicha JA.** Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax*. 2002;57:847-52.
27. **Almagro P, Calbo E, Ochoa de Echaguen A, Barreiro B, Quintana S, Heredia JL, Garau J.** Mortality after hospitalisation for COPD. *Chest*. 2002;121:1441-8.
28. **Garcia-Aymeric J, Farrero E, Felez MA, Izquierdo J, Marrades RM, Anto JM.** Risk factors for readmission to hospital for a COPD exacerbation: a prospective study. *Thorax*. 2003;58:100-5.
29. **Pitta F, Troosters Th, Probst V, Spruit MA, Decramer M, Gosselink R.** Physical activity and Hospitalization for Exacerbation of COPD. *Chest*. 2006;129:536-44.
30. **Sin DD, Anthonisen NR, Soriano JB, Agustí AG.** Mortality in COPD: role of comorbidities. *Eur Respir J*. 2006;28:1245-57.