In-Hospital and 2-Year Survival of Patients Treated With Mechanical Ventilation for Acute Exacerbation of COPD

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OBJECTIVE: To analyze in-hospital and 2-year survival of patients who require mechanical ventilation with intubation after acute respiratory failure due to exacerbation of chronic obstructive pulmonary disease (COPD). The secondary objective was to identify the prognostic factors for in-hospital mortality and mortality at 2 years.

PATIENTS AND METHODS: We retrospectively studied 101 patients with suspected COPD admitted to the intensive care unit between July 1993 and December 1998. Variables potentially related to mortality were analyzed with a univariate model and by logistic regression.

RESULTS: In-hospital survival was 74.3% and 2-year survival was 55.4%. Survival at 2 years was 81% for patients discharged from hospital. The variables associated with in-hospital mortality were age greater than 65 years, electrocardiographic diagnosis of chronic cor pulmonale, and development of multiorgan dysfunction syndrome. No factors predictive of mortality at 2 years were identified.

CONCLUSIONS: The in-hospital survival rate for patients with an acute exacerbation of COPD who require mechanical ventilation is good and the 2-year survival rate is acceptable. Age, electrocardiographic signs of cor pulmonale, and development of multiorgan dysfunction syndrome were associated with greater risk of in-hospital mortality.

Key words: *COPD. Mortality. Mechanical ventilation. Prognosis.*

Supervivencia hospitalaria y a los 2 años de los pacientes con EPOC agudizada y tratados con ventilación mecánica

OBJETIVO: Analizar la supervivencia hospitalaria y a los 2 años de los pacientes con insuficiencia respiratoria aguda, debida a una enfermedad pulmonar obstructiva crónica (EPOC) agudizada, tratados con ventilación mecánica invasiva. Los objetivos secundarios fueron identificar los factores pronósticos de la mortalidad hospitalaria y a los 2 años.

PACIENTES Y MÉTODOS: Se estudió retrospectivamente a 101 pacientes con sospecha de EPOC tratados en la unidad de cuidados intensivos de un hospital universitario entre julio de 1993 y diciembre de 1998. Se realizaron un análisis univariado y otro de regresión logística de las posibles variables relacionadas con la mortalidad.

RESULTADOS: La supervivencia hospitalaria fue del 74,3% y a los 2 años del 55,4%. La supervivencia a los 2 años fue del 81% para los pacientes dados de alta del hospital. Las variables asociadas con la mortalidad hospitalaria fueron la edad superior a los 65 años, el diagnóstico electrocardiográfico de *cor pulmonale* crónico y el desarrollo de un síndrome de disfunción multiorgánica. No se identificaron factores predictores de mortalidad a los 2 años.

CONCLUSIONES: Los pacientes con EPOC agudizada que requieren ventilación mecánica tienen una supervivencia hospitalaria buena y una supervivencia a los 2 años aceptable. La edad, la presencia de signos electrocardiográficos de *cor pulmonale* y el desarrollo de síndrome de disfunción multiorgánica se asociaron a una mayor mortalidad hospitalaria.

Palabras clave: *EPOC. Mortalidad. Ventilación mecánica. Pronóstico.*

Introduction

The prognosis for patients with chronic obstructive pulmonary disease (COPD) who suffer an exacerbation is generally poor, though individual clinical outcomes may vary greatly. Prognosis may be worse if invasive mechanical ventilation (MV) is necessary, but there is no general agreement on the importance of the effect.[1-4] In-hospital mortality is thought to be high in such patients,[5-8] though the results of recent studies are more promising.[9-11] In patients with COPD exacerbation treated with invasive MV, mortality is related to age[9] and course of pulmonary disease as evaluated by exercise tolerance and pulmonary function tests.[6,12] Few studies, however, have analyzed mortality in COPD patients who require MV for exacerbation of unspecified cause and with uncertain outcome.[9,13,14]

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Patients, physicians, and the patients' families would benefit if certain predictive factors could be used to determine the prognosis of COPD patients with exacerbations that require MV, because treatment could be individualized.

The main objective of this retrospective study was to investigate in-hospital survival and 2-year survival of patients treated with MV for suspected exacerbation of COPD. An additional objective was to identify possible prognostic factors related to in-hospital mortality and 2-year mortality.

Material and Methods

Study Population

We consulted the database of the intensive care unit (ICU) of our hospital in order to analyze all patients admitted for COPD exacerbation who required MV between July 1993 and December 1998. COPD was diagnosed clinically from the patient's clinical history and smoking habit, in accordance with the guidelines of the American Thoracic Society. Exacerbation was defined as an increase in normal dyspnea with no apparent cause that was severe enough to warrant admission to hospital.[9,15] Thus, COPD patients with respiratory failure due to a specific cause, such as pneumonia, bronchial asthma, restrictive pulmonary disease due to obesity or kyphoscoliosis, left heart failure, or pulmonary embolism, were excluded.

Only the information on the first admission to the ICU requiring treatment with MV was analyzed. MV was indicated if one or more of the following conditions was met[16]: severe dyspnea with use of accessory muscles, paradoxical respiration, respiratory arrest, respiratory frequency above 35 breaths/min, impaired mental status, respiratory acidosis (pH<7.26), hypoxemia (PaO_2<60 mm Hg) or desaturation (oxygen saturation <90%) resistant to oxygen supplied through a mask, and hemodynamic instability. Noninvasive MV was not often used during the study period. All patients received standard treatment with broad-spectrum antibiotics, inhaled or aerosol bronchodilators, and systemic corticosteroids, before being connected to MV. All patients were treated with Evita ventilators (Dräger, Lübeck, Germany) and disconnected as early as possible with pressure support.

Data Collection

The following data were collected retrospectively:

— Clinical history: smoking habit (active or ex-smoker), cor pulmonale diagnosed from electrocardiographic signs of overload or hypertrophy of right chambers, high blood pressure, and diabetes. The severity of dyspnea and physical activity were assessed with a modified version of the scale used by Menzies et al[6] (mild when physical activity is tolerated, moderate when physical activity is limited, and severe when the patient is housebound). Prior treatment (corticosteroids, bronchodilators, and home oxygen) and the spirometry results prior to admission or 6 months after discharge from hospital were also reviewed when available.

— Admission to hospital: pH and $PaCO_2$ before intubation, disease severity at the time of admission measured with the Simplified Acute Physiology Score (SAPS) II, complications such as cardiorespiratory arrest prior to MV, atrial and ventricular arrhythmias requiring treatment while the patient was on MV, pneumonia associated with MV, pneumothorax, and multiorgan dysfunction syndrome (MODS).

— Time on MV, time in ICU and in hospital, and in-hospital mortality.

Patients were followed up 2 years after discharge from hospital by review of their clinical history and by telephone calls. If patients or a family member could not be contacted, the corresponding registrar's office was checked for a record of death.

MODS was diagnosed when 2 or more organs failed according to the following criteria[17]: *a)* respiratory: MV required; *b)* cardiovascular: septic shock requiring inotropic support; *c)* renal: hemodialysis required or serum creatinine greater than 3.5 mg/dL; *d)* gastrointestinal: intestinal perforation, hemorrhagic necrotizing pancreatitis or gastrointestinal bleeding requiring 2 or more transfusions of packed red blood cells; *e)* neurological: score without sedation on Glasgow Coma Scale less than 8; *f)* hepatic: total bilirubin greater than 3 mg/dL and transaminases more than twice the upper limit of normal; *g)* hematological: less than 3000 leukocytes/μL or platelet count less than 50 000 platelets/μL.

Statistical Analysis

Quantitative variables are presented as mean values, 95% confidence intervals, and medians. The Student *t* test for unpaired continuous data and the χ^2 test for discontinuous data were used in a univariate analysis to identify factors related to primary mortality. Significant variables from the univariate analysis were entered in a multivariate analysis with a stepwise multiple logistic regression. The statistical program SPSS was used for the statistical analysis. A *P* value less than or equal to .05 was considered significant.

Results

Of 194 patients with COPD treated with MV over 5.5 years, 93 were excluded due to a specific cause of acute respiratory failure. The causes were pneumonia in 63 patients, heart failure in 19, pulmonary thromboembolism in 2, asthma in 5, and restrictive lung disease in 4.

Thus, 101 patients were analyzed with a mean (SD) age of 70 (8) years. Ninety percent were men, 41% were active smokers, and 16% required home oxygen. Tables 1 and 2 show the clinical characteristics of the survivors (n=75) and those who died in hospital (n=26). Pulmonary function tests were available for 70 patients (Table 1).

Of the 26 patients who died in hospital (corresponding to a mortality rate of 25.7%), 16 (61%) died while on MV and 10 (39%) after extubation. Seventeen patients died in the ICU—11 due to MODS, 4 due to brain death after cardiac arrest, 1 due to barotrauma, and 1 due to ventricular arrhythmias. Nine patients died in the hospital ward after discharge from the ICU, but the cause of death was not recorded. Of the 75 patients discharged from hospital, 11 had died after 2 years and 18 were lost to follow up. Thus, in the

TABLE 1
Clinical Characteristics of Patients With Exacerbation of Chronic Obstructive Pulmonary Disease on Admission to Hospital*

	S (n=75)	NS (n=26)	RR	95% CI	*P*
Age >65 years, %	62.7	92.3	5.1	1.3-20.1	.004†
Women, %	9.3	11.5	0.8	0.3-2.3	.74
Smoking habit, %					.25
Active smokers	45.3	30.8			
Ex-smokers	54.7	69.2			
Comorbidity, %					
Cor pulmonale	41.3	69.2	2.4	1.1-5.0	.014†
Congestive heart failure	12.0	23.1	1.7	0.8-3.6	.17
Ischemic heart disease	16.0	15.4	1.0	0.4-2.4	.94
Arterial hypertension	14.7	15.4	1.0	0.4-2.6	.93
Diabetes mellitus	13.3	15.4	1.1	0.5-2.8	.79
Severity of dyspnea, %					.41
Mild	17.3	7.7			
Moderate	66.7	69.2			
Severe	16.0	23.1			
Treatment, %					
Corticoids	48.0	30.8	0.6	0.3-1.2	.13
Bronchodilators	70.7	69.2	1.0	0.5-1.9	.89
Home oxygen	16.0	15.4	1.0	0.4-2.4	.94
Previous hospitalizations	58.7	69.2	1.4	0.7-2.9	.34
Spirometry	60	10			
FEV_1, L	1.0 (0.51)	1.0 (0.75)			.98
FEV_1, %	35 (13)	31 (12)			.43
FEV_1/FVC, %	49 (13)	45 (13)			.40

*FEV_1 indicates forced expiratory volume in 1 second; FVC, forced vital capacity; CI, confidence interval; NS, not survivors; RR, relative risk; S, survivors.
†Significant.

TABLE 2
Clinical Characteristics of Patients With Exacerbation of Chronic Obstructive Pulmonary Disease During Hospital Stay*

	S (n=75)	NS (n=26)	RR	95% CI	*P*
Severity					
SAPS (II) (points)	38 (10)	41 (4)			.13
Complications (%)					
Cardiac arrest prior to MV	0	15.4	4.4	3.0-6.4	.0005†
Ventricular arrhythmias with MV	0	15.4	4.4	3.0-6.4	.0005†
Atrial arrhythmias with MV	8.0	23.1	2.2	1.1-4.4	.0406†
Pneumonia associated with MV	14.7	15.4	1.3	0.6-3.1	.47
Pneumothorax	2.7	11.5	2.5	1.1-5.6	.072
MODS	6.7	42.3	3.9	2.2-6.8	<.0001†
Treatment, %					
Tracheostomy	8.0	26.9	2.5	1.3-4.7	.0130†
CVVH/dialysis	1.3	7.7	2.7	1.1-6.5	.0998

*CVVH indicates continuous venovenous hemofiltration; CI, confidence interval; NS, not survivors; RR, relative risk; S, survivors; MODS, multiorgan dysfunction syndrome; MV, mechanical ventilation.
†Significant.

group of 57 evaluable patients, mortality was 19.3%. The overall mortality after 2 years was 44.6% excluding patients lost to follow up (Figure 1).

In-hospital mortality (Tables 1 and 2) was associated with age greater than 65 years (33.8% vs 6.7%), with presence of chronic cor pulmonale, and with the following complications: heart failure before MV, ventricular arrhythmias (tachycardia and fibrillation) and atrial arrhythmias (fibrillation and flutter) during MV, and MODS. As predictors of mortality, logistic regression analysis identified age greater than 65 years (mortality of 33.8% vs 6.7% for age was less than 65 years), diagnosis of cor pulmonale (36.7% vs 15.4% in patients not diagnosed with this condition), and development of MODS (68.8% vs 17.6% in patients who did not have MODS) (Table 3). The incidence of MODS was the similar in patients diagnosed with cor pulmonale (18%) and those without cor pulmonale (19%). At 2 years, no factor predictive of mortality was identified in patients discharged from hospital.

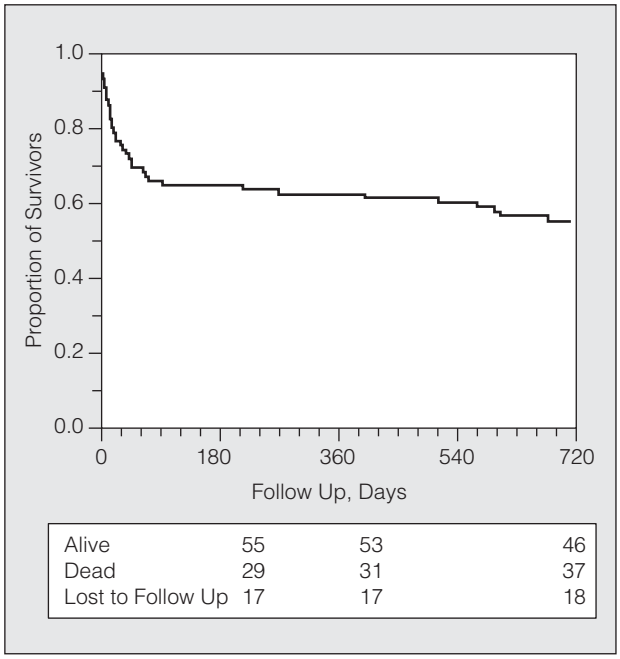

Figure 1. Two-year Kaplan-Meier survival curve for patients with chronic obstructive pulmonary disease who needed mechanical ventilation due to an exacerbation.

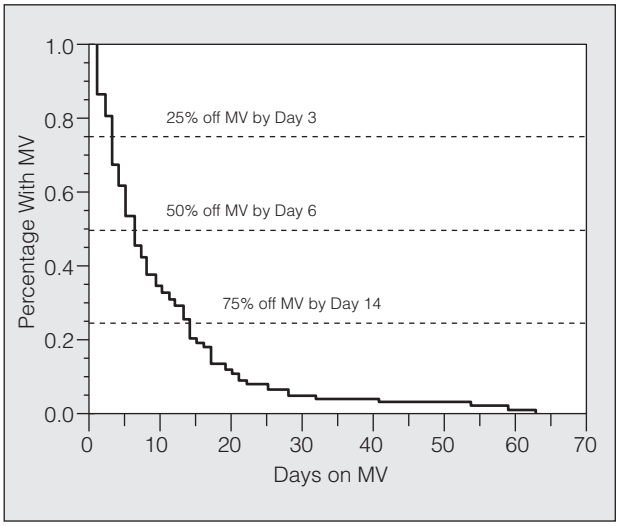

Figure 2. Kaplan-Meier curve for time until discontinuation of mechanical ventilation (MV) for patients with exacerbation of chronic obstructive pulmonary disease.

The mean duration of MV was 10 days (median, 6 days; interquartile range, 3 to 14 days) (Figure 2). The patients who died spent longer on MV and stayed longer in the ICU (Table 4), but there were no statistically significant differences regarding in-hospital stay (Table 4). Thirty-three patients (33%) required MV for less than 72 hours. Mortality was lower in this patient subgroup than in patients on MV for 72 hours or more (18% vs 29%), though this difference was not statistically significant (*P*=.23). However, mortality was significantly higher for the 9 patients who needed MV for more than 21 days compared to the remaining patients (56% vs 24%, *P*=.032).

TABLE 3
Logistic Regression of Variables Predictive of Mortality in Patients With Exacerbation of Chronic Obstructive Pulmonary Disease Treated With Mechanical Ventilation*

	β Coefficient	OR (95% CI)	*P*
MODS	2.71	15.0 (3.6-62.8)	.0002
Age >65 years	2.42	11.2 (1.9-66.2)	.0076
Cor pulmonale	1.74	5.7 (1.7-18.9)	.0047

*CI indicates confidence interval; OR, odds ratio; MODS, multiorgan dysfunction syndrome.

Discussion

In-hospital survival in this study of patients with COPD exacerbation who were admitted to the ICU and required MV was 74.3%. For patients discharged from hospital, survival after 2 years was 81%. The logistic regression analysis showed that age greater than 65 years, presence of cor pulmonale diagnosed electrocardiographically, and development of MODS were independently associated with mortality.

In-hospital mortality in our patients is similar to that of other series[7,9,18] and less than 46%, the rate reported by Hudson.[5] In a very recent retrospective study of patients with COPD undergoing their first severe exacerbation of unknown cause, hospital mortality was

TABLE 4
Days on Mechanical Ventilation and Days in Intensive Care Unit (ICU) and in Hospital of Patients With Exacerbation of Chronic Obstructive Pulmonary Disease*

	Total (n=101)	S (n=75)	NS (n=26)	*P*
Days on mechanical ventilation				
Mean, SD	10.0 (11.5)	8.0 (9.1)	15.5 (16.0)	.028†
Median, range	6 (1-63)	5 (1-63)	11.5 (1-59)	
Days in ICU				
Mean, SD	12.3 (14.7)	10.4 (13.0)	17.6 (18.4)	.068
Median, range	7 (1-99)	7 (1-99)	11.5 (1-64)	
Days in hospital				
Mean, SD	25.0 (20.2)	25.9 (19.1)	22.6 (23.2)	.48
FollowMedian, range	19 (1-128)	20 (3-128)	13.5 (1-97)	

*NS indicates survivors; S, survivors. †Significant.

20%.[14] Mortality at 2 years was 58% in contrast to the mortality at 2 years of 44.6% in our study. The different mortality rates may be explained by differences such as age,[15,19] disease severity, origin of COPD exacerbation,[6,9] whether or not only the first severe exacerbation was considered, and use of different treatments such as noninvasive MV.[6] An indication of the severity of the exacerbations in patients admitted to our ICU is given by the fact that, to be admitted, conventional medical treatment had failed in the emergency service and the hospital ward.

Advanced age was a prognostic factor for in-hospital mortality in our study, in agreement with other studies in patients with COPD[9,15,19,20] and other diseases.[13,21] Senneff et al[9] found that mortality among COPD patients treated with or without MV was 10% for patients aged less than 65 years and 33% for those aged over 65 years. These differences are similar to those in our study, though age is not always an independent prognostic factor for mortality in patients with COPD who require MV.[11]

In our study, the presence of chronic cor pulmonale diagnosed by electrocardiography[22] was also an important prognostic factor for in-hospital mortality. This is in line with the study of Incalzi et al,[15] in which 2 electrocardiographic signs of cor pulmonale (an S1, S2, S3 pattern and a P-wave axis >+90º indicating right atrial overload) were predictors of mortality in patients admitted for COPD exacerbation.

The strongest prognostic factor in this study was the development of MODS during MV—11 of the 16 patients (68.8%) with MODS died. Mortality in the group of 85 patients who did not develop MODS was 5.9% during MV and 11.8% after interruption of MV, although these findings alone do not unequivocally suggest that MODS is a reliable prognostic factor due to the low number of patients in our study.

Forced expiratory volume in 1 second, long considered an important prognostic factor,[12,15,19] was not predictive of mortality in our study, though this parameter was not determined in all patients, particularly those who died. The limited number of test results could partly be explained because we only analyzed the first period of treatment with MV and because some patients might not have undergone appropriate pulmonary function testing. Initial diagnosis of COPD by spirometry was, however, not confirmed in 31% of our patients, a percentage similar to that of other studies.[6,10,11]

Time on MV was not an independent prognostic factor for mortality, even though some of our patients required prolonged MV (for more than 21 days), in contrast to the pattern seen in a similar study.[11] The extent of physiological abnormalities, measured by SAPS II, was also not correlated with mortality, consistent with the findings of Portier et al.[23] Results on the influence of physiological abnormalities (assessed by SAPS or Acute Physiological and Chronic Health Evaluation [APACHE] II score) on prognosis are contradictory. Seneff et al[9] showed that mortality is not related to baseline functional capacity, comorbidities, arterial blood pH, or use of MV, whereas other authors found that respiratory acidosis (pH<7.26),[24,25] APACHE II score, and $PaCO_2$ at the time of admission were predictive of mortality.[11,14,26]

Predictive models able to identify patients with a high probability of dying (≥90%) in hospital due to COPD exacerbation are not available. One of the 2 best powered studies, SUPPORT,[26] managed to identify up to 10 factors predictive of mortality at 6 months, whereas the study of Seneff et al[9] identified 3 factors, as in our study. These models cannot, however, successfully predict a patient's probability of survival. Of the 3 predictive factors identified in our study, the only treatable one that is not targeted by standard treatment is cor pulmonale. We lowered hypoxemia as far as possible in patients with COPD exacerbation to reduce subsequent pulmonary hypertension.

Our study has several limitations related to its retrospective and single-center design. The number of patients is low. We do not have precise information on nutritional status or quality of life prior to admission. The percentage of patients who used home oxygen was low, probably because its use was underestimated or because patients had not given up smoking. Management of respiratory insufficiency did not follow a prospective protocol and bias related to the individual preferences of the treating physician may have affected outcome, although, during the study period, our center applied the guidelines for clinical practice common in many ICUs. Normal treatment of our patients at the time did not usually include noninvasive MV, though we currently prefer this type of treatment in patients who meet established criteria.[16]

In-hospital mortality in our study is similar or lower than that seen in other diseases (for example cardiogenic pulmonary edema or severe pneumonia) treated with MV.[11,13] Given that patients who are still alive after 6 months can show improvement in cognitive disorders and other health disorders detected on discharge from hospital,[27] we think they should be offered the possibility of MV. Scientific evidence that supports admission of the patient with COPD to an ICU has been reviewed recently in an article written jointly by intensivists and pulmonologists.[28] The authors affirm that patients with COPD should receive all the support necessary when faced with severe respiratory insufficiency. However, further studies are needed to establish the prognostic factors for patients with COPD who require MV. This would help physicians provide better advice for patients and their families regarding the different treatments and outcomes, particularly since prognosis is currently difficult.

In conclusion, in-hospital survival and survival at 2 years for patients discharged from hospital after treatment of COPD exacerbation with MV because conventional treatment had failed was good in this retrospective study. Overall survival at 2 years was only slightly better than

50%. The prognostic factors of in-hospital mortality were age, presence of electrocardiographic signs of chronic cor pulmonale, and, in particular, development of MODS. We did not find factors that predicted mortality in patients discharged from hospital.

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