Predictors of 1-Year Mortality at Hospital Admission for Acute Exacerbations of Chronic Obstructive Pulmonary Disease

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For editorial comment see p. 11

Key Words

Chronic obstructive pulmonary disease • Exacerbation • Predictor • Mortality • Gender

Abstract

Background: Acute exacerbations of chronic obstructive pulmonary disease (AE-COPD) are related to high mortality, especially in hospitalized patients. Predictors for severe outcomes are still not sufficiently defined. **Objectives:** To assess the mortality rate and identify potential determinants of mortality in a cohort of patients hospitalized for AE-COPD. **Methods:** A retrospective, observational cohort study including all consecutive patients admitted between January 1, 2009, and April 1, 2010, for AE-COPD. Potential predictors were assessed at initial presentation at the emergency room. The primary outcome was mortality during 1-year follow-up. Univariate and multivariate time-to-event analyses using Cox proportional hazard models were employed for statistical analysis. **Results:** A total of 260 patients were enrolled in this study. Mean age was 70.5 ± 10.8 years, 50.0% were male and 63.4% had severe COPD. The in-hospital mortality rate was 5.8% and the 1-year mortality rate was 27.7%. Independent risk factors for mortality were age [hazard ratio (HR) = 1.04; 95% confidence interval (CI) = 1.01–1.07], male sex

(HR = 2.00; 95% CI = 1.15–3.48), prior hospitalization for AE-COPD in the last 2 years (HR = 2.56; 95% CI = 1.52–4.30), prior recorded congestive heart failure (HR = 1.75; 95% CI = 1.03–2.97), $\text{PaCO}_2 \geq 6.0$ kPa (HR = 2.90; 95% CI = 1.65–5.09) and urea ≥ 8.0 mmol/l (HR = 2.38; 95% CI = 1.42–3.99) at admission.

Conclusions: Age, male sex, prior hospitalization for AE-COPD in the last 2 years, prior recorded congestive heart failure, hypercapnia and elevated levels of urea at hospital admission are independent predictors of mortality within the first year after admission.

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Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death and disability worldwide that still has a rising prevalence and mortality rate [1, 2]. The natural course of COPD is characterized by a progressive decline in pulmonary function and recurrent exacerbations. Exacerbations are major events in the course of the disease, especially when hospitalization is

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required, and represent an important component of the socioeconomic burden related to COPD [3]. An exacerbation of COPD is defined as an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough and/or sputum that is beyond normal day-to-day variations, is acute in onset and may warrant a change in regular medication in a patient with underlying COPD [4]. Mortality related to acute exacerbations of COPD (AE-COPD) is particularly high during hospitalization and the months thereafter [5]. The in-hospital mortality and 1-year mortality vary markedly between studies depending on the mode of recruitment and setting, and range from 2.5 to 30% and 22 to 43%, respectively, in relation to severity of disease [6–9].

Despite being the only major disease showing increasing prevalence and mortality, factors that determine the short- and long-term outcomes of patients with COPD are not yet precisely understood. Several studies have identified predictive factors independently associated with an increased mortality risk due to COPD in general, and acute exacerbations in particular. Predictors thought to be related to mortality include age, BMI, FEV₁, pH, PaCO₂, PaO₂, blood chemistry, previous hospitalizations, specific treatments, cardiac factors and other comorbidities [6, 7, 10–18]. However, independent prognostic factors are quite variable between studies, probably because of differences in patient populations, settings, duration of follow-up, collected variables and statistical methods used. In addition, most of these studies did not take non-invasive ventilation into account.

The present study was designed to assess the mortality rate and potential determinants of mortality in a cohort of patients admitted to Maastricht University Hospital for an AE-COPD. Factors related to increased mortality rate were analyzed in order to identify independent predictors for use in the hospital setting.

Material and Methods

Study Design and Participants

A retrospective, observational cohort study was performed including all consecutive patients who had been admitted to any of the pulmonary wards of Maastricht University Hospital for AE-COPD. This university hospital has an important function as a regional hospital besides its academic function, and the patient population is therefore representative of a general hospital. A stepwise retrospective selection process was used for identification of patients. Patients were initially identified on the basis of ICD-9 codes 496 (COPD) and 786.0–9 (acute respiratory symptoms). Patients already hospitalized before January 1, 2009, were excluded. Discharge letters were screened and patients without a

diagnosis of COPD were excluded. Further screening excluded patients without a final diagnosis of AE-COPD, patients without administration of systemic glucocorticoids or patients initially admitted to another hospital and later referred to our hospital. Then spirometry data were analyzed and patients with an FEV₁/FVC above 70% were excluded (fig. 1).

Patients were enrolled between January 1, 2009, and April 1, 2010, according to the following inclusion criteria: (1) established diagnosis of COPD as identified from the patient's pulmonary function test results (FEV₁/FVC <70% and FEV₁ reversibility <11%) or, if unavailable, based on the patient's clinical history with compatible physical examination findings in accordance with the GOLD guidelines [19]; (2) symptoms indicating a severe AE-COPD requiring hospital admission, and (3) treatment with systemic glucocorticoids. An exacerbation was defined by the presence of a sustained increase in at least two of three symptoms (dyspnea, cough and sputum purulence), requiring modification of regular treatment and necessitating admission to the hospital [20]. The clinical setting consists of a regular pulmonary ward with integrated intermediate care available to all acute patients. Intensive care units are located on the same floor of the building. Noninvasive and also invasive ventilation was accessible immediately to all patients if needed.

Each patient was included only once in the study and received medical treatment at the discretion of the attending physician. Exclusion criteria included follow-up at a hospital other than Maastricht University Hospital, other primary diagnoses than AE-COPD at hospital discharge or objection against the use of patient data for research goals. The study protocol was reviewed and approved by the Hospital Research and Medical Ethics Committee.

Data Collection

Data were collected retrospectively from discharge letters, medical files and electronic patient records. If any data regarding pulmonary function testing or survival status were missing, we contacted the general practitioner or municipal personal records database. Details of epidemiological and clinical data collection can be found in the online suppl. tables (for all online suppl. material, see www.karger.com/doi/10.1159/000342036).

Measurements

The following measurements were assessed during the hospital stay: arterial blood gas levels, blood chemistry, need for intubation or noninvasive ventilation and active comorbidity. The decision to start and stop ventilation and the orders of supplementary arterial blood gas or blood chemistry reports were made on clinical grounds.

Outcomes and Study End Points

In-hospital mortality and length of hospital stay were determined for each patient. Patients were followed up for 1 year after hospital admission by review of clinical notes and electronic in-patient and out-patient records. Information on the following parameters were collected: survival status, survival time, cause of death, need of hospital readmission, number of hospital readmissions, need of hospital readmission for AE-COPD and time to (first) readmission for AE-COPD. The primary outcome was 1-year all-cause mortality, determined in the following ways. In case of an in-hospital death, the date was recorded and verified by hospital records. The date of death of patients who died after hospital discharge was verified from hospital records, general

Fig. 1. Flowchart of cohort selection. ICD-9 code 496: chronic airway obstruction, not elsewhere classified (chronic: nonspecific lung disease, obstructive lung disease, obstructive pulmonary disease not otherwise specified). ICD-9 code 786.0–9: symptoms involving respiratory system and other chest symptoms (respiratory: distress, insufficiency).

practitioners records or the death records of the patients' residence. The survival status and cause of death of all patients was confirmed in this way. Unfortunately, mortality registration in the Netherlands does not allow access to actual records to determine the cause of death, which is why the cause of death could not be clarified in 23 of the deceased patients (31.9%).

Statistical Analysis

All analyses were performed using SPSS for Windows (version 18). Univariate analyses were performed using independent t tests, χ^2 tests or Fisher's exact tests, as appropriate. Continuous variables that were not normally distributed were categorized and divided into clinically relevant groups prior to the analysis. A multiple Cox model for proportional hazards was used for our primary analysis of the independent effects of each variable on time to death. Potentially relevant clinical predictors, according to the univariate analyses ($p < 0.05$), were introduced into the starting model and then eliminated manually backwards step-by-step, dependent on the largest p value. Patients with missing covariate data of any of the introduced predictors were excluded at the starting point and remained so during the following process. All items showing statistical significance at $p \leq 0.05$ were retained in the final prediction model.

Results

Patient Characteristics

Between January 1, 2009, and April 1, 2010, 260 patients were admitted to any of the pulmonary wards of Maastricht University Hospital with a primary diagnosis of AE-COPD and treated with systemic glucocorticoids. Patient selection and 1-year outcome are displayed in figure 1 and the most important demographic characteristics are listed in table 1. Mean age was 70.5 ± 10.8 years, and 130 patients (50.0%) were male. The majority of patients were retired (96.4%), lived at home (84.5%) with a partner or kin (52.2%) and had severe COPD defined as GOLD stage III–IV (63.4%). One hundred and thirty patients (50.0%) had been previously admitted for a COPD exacerbation, 86 (33.1%) had been hospitalized for this cause within the last 2 years and 23 (8.8%) had received treatment with noninvasive positive pressure ventilation during this period. Of the study population, 242 (93.4%)

Table 1. Demographic and prior health-care utilization characteristics of patients hospitalized for AE-COPD, stratified by 1-year outcome

Characteristics	All (n = 260)	Deceased (n = 72)	Alive (n = 188)	p value
Sex				
Male	130 (50.0)	45 (62.5)	85 (45.2)	<0.05 [#]
Female	130 (50.0)	27 (37.5)	103 (54.8)	
Age, years	70.5 ± 10.8	73.7 ± 10.6	69.3 ± 10.7	<0.05 [#]
Social status				
Retired (n = 251/68/183)	242 (96.4)	67 (98.5)	175 (95.6)	NS
Living at own home (n = 252/68/184)	213 (84.5)	54 (79.4)	159 (86.4)	NS
Living alone (n = 251/68/183)	120 (47.8)	32 (47.1)	88 (48.1)	NS
GOLD stage (n = 246/65/181)				
I	15 (6.1)	2 (3.1)	13 (7.2)	<0.10
II	75 (30.5)	15 (23.1)	60 (33.1)	
III	77 (31.3)	19 (29.2)	58 (32.1)	
IV	79 (32.1)	29 (44.6)	50 (27.6)	
FEV ₁ (n = 245/64/181), liters	1.05 ± 0.42	0.92 ± 0.34	1.09 ± 0.44	<0.05
FEV ₁ (n = 246/65/181), % predicted	45.0 ± 18.0	39.5 ± 17.4	47.0 ± 17.8	<0.05 [#]
FVC (n = 246/65/181), % predicted	84.5 ± 22.7	77.4 ± 23.0	87.1 ± 22.2	<0.05
FEV ₁ /FVC (n = 246/65/181), %	41.0 ± 0.8	39.2 ± 11.6	41.7 ± 12.0	NS
PEF (n = 245/64/181), % predicted	52.9 ± 19.2	47.0 ± 17.3	55.0 ± 19.5	<0.05
RV/TLC (n = 226/59/167), %	60.0 ± 11.0	63.8 ± 10.7	58.7 ± 10.7	<0.05
TLCO (n = 213/55/158), % predicted	47.4 ± 19.3	42.9 ± 20.6	49.0 ± 18.6	<0.05
TLCO/VA (n = 212/55/157), % predicted	58.8 ± 23.8	54.0 ± 3.8	60.4 ± 23.7	<0.10
No. of hospital admissions for COPD exacerbation in the last 2 years				<0.05
0	174 (66.9)	39 (54.2)	135 (71.8)	
1	45 (17.4)	14 (19.4)	31 (16.5)	
2–3	30 (11.5)	12 (16.7)	18 (9.6)	
≥4	11 (4.2)	7 (9.7)	4 (2.1)	
Hospital admission for COPD exacerbation in the last 2 years	86 (33.1)	33 (45.8)	53 (28.2)	<0.05 [#]
Treated with antibiotics	72 (27.7)	29 (40.3)	43 (22.9)	<0.05
Treated with NPPV	23 (8.8)	11 (15.3)	12 (6.4)	<0.05
Treated with MV	2 (0.8)	0	2 (1.1)	NS
Home treatment (n = 258/70/188)	241 (93.4)	173 (92.0)	68 (97.1)	NS
Long-acting β ₂ -agonists	209 (81.0)	61 (87.1)	148 (78.7)	NS
Short-acting β ₂ -agonists	133 (51.6)	30 (42.9)	103 (54.8)	<0.10
Short-acting anticholinergics	83 (32.2)	30 (42.9)	53 (28.2)	<0.05
Long-acting anticholinergics	156 (60.5)	43 (61.4)	113 (60.1)	NS
Inhaled glucocorticoids	201 (77.9)	55 (78.6)	146 (77.7)	NS
Long-term oral glucocorticoids	38 (14.7)	15 (21.4)	23 (12.2)	<0.10
Theophylline	23 (8.9)	7 (10.0)	16 (8.5)	NS
LTOT	69 (26.7)	27 (38.6)	42 (22.3)	<0.05 [#]
NPPV	9 (3.5)	5 (7.1)	4 (2.1)	<0.10
CPAP	3 (1.2)	1 (1.4)	2 (1.1)	NS
Antibiotics ¹	96 (37.2)	24 (34.3)	72 (38.3)	NS

Data are presented as n (%) or mean ± SD. NPPV = Noninvasive positive pressure ventilation; MV = mechanical ventilation; LTOT = long-term oxygen therapy; CPAP = continuous positive airway pressure; NS = not significant.

[#] Included in multivariate analysis. ¹ Pre-existing antibiotic treatment for the acute event.

patients already had home treatment for AE-COPD, mostly intensified inhalation medication, and 69 (26.7%) were on long-term oxygen therapy.

Clinically relevant comorbidity was present in more than half of all patients prior to hospital admission. Mainly cardiac and respiratory diseases were highly prevalent, in 65 and 60% of the patients, respectively. Also, 26.2% of patients had cancer and 30% peripheral vascular disease. Furthermore, psychiatric comorbidity had been recorded frequently, mainly composed of conditions like depression, anxiety and addiction (see also online suppl. table 1e).

Clinical Data

Forty-three patients (16.7%) had a BMI below 20, 111 (43.7%) were current smokers, 99 (39.1%) had a pulse oxygen saturation value below 90% and 117 (46.4%) had oxygen demand defined as the need for constant oxygen administration (table 2). Signs of peripheral edema and neurological impairment were present in 83 (31.9%) and 26 (10.0%) patients, respectively. Blood gas measurements showed acidosis, hypercapnia and moderate hypoxemia in 84 (32.7%), 138 (53.7%) and 121 (47.1%) patients, respectively. Mean hemoglobin was 8.6 ± 1.1 mmol/l, 77 (30.1%) patients had a urea ≥ 8.0 mmol/l and 54 (20.9%) had increased creatinine levels. X-ray reports revealed signs of pneumonia and tumor in 71 (27.3%) and 7 (2.7%) cases, respectively. Patients with pneumonia were explicitly not excluded as the intention of this study was to give a real-life picture of COPD management, and up to now there is no consensus on how to deal with patients clinically presenting with AE-COPD and concurrent pulmonary infiltrates. Moreover, the presence of pulmonary infiltrates could present a risk factor for mortality.

Mortality and Readmissions during 1-Year Follow-Up

The median hospital stay was 8 (5–14) days, and the majority of patients (62.7%) were discharged within 10 days. The in-hospital mortality rate was 5.8% and the 1-year mortality rate was 27.7% because of 15 and 72 deaths, respectively (see also online suppl. table 3e). Of the 15 in-hospital deaths, 13 (86.7%) were caused by respiratory failure. Of the 245 discharged patients, 135 (55.1%) were readmitted within 1 year, 91 (37.1%) due to acute exacerbations. The distribution between GOLD stage unknown and I–IV of the 91 readmitted patients was 3.3, 3.3, 27.5, 28.6 and 37.4%. These 91 patients had a total of 168 AE-COPD readmissions in the first year of follow-up leading to an average readmission rate of 1.85

per readmitted patient, ranging from 1 to 6, and a median time to readmission of 47 (21–156) days, ranging from 1 to 336 days. The majority of these patients received antibiotics (74.7%) and 32 (35.2%) were treated with NPPV during at least one admission.

Predictors of Mortality

Univariate analyses were performed on all available data to identify variables associated with increased 1-year mortality. These variables included male sex, increasing age, decreasing FEV₁, LTOT, hospitalizations for AE-COPD in the last 2 years and certain comorbidities (cardiac arrhythmia, congestive heart failure, pneumonia) recorded prior to the current admission (table 1 and online suppl. table 1e). Further risk factors at hospital admission associated with lower survival rates included a BMI below 20, abnormalities in arterial blood gas (pH, PaCO₂, base excess) and blood values [hemoglobin, urea, C-reactive protein (CRP); table 2].

Of the original 260 patients, 24 were excluded because of missing covariate data, leaving 236 patients for the primary analysis. Table 3 shows the independent predictors of 1-year mortality at hospital admission for AE-COPD that remained in the final model: age [hazard ratio (HR) = 1.04; 95% confidence interval (CI) = 1.01–1.07], male sex (HR = 2.00; 95% CI = 1.15–3.48), prior hospitalization for AE-COPD in the last 2 years (HR = 2.56; 95% CI = 1.52–4.30), prior recorded congestive heart failure (HR = 1.75; 95% CI = 1.03–2.97), PaCO₂ ≥ 6.0 kPa (HR = 2.90; 95% CI = 1.65–5.09) and urea ≥ 8.0 mmol/l (HR = 2.38; 95% CI = 1.42–3.99) at admission.

Characteristics of Patients Stratified by Gender

Male patients had significantly lower spirometric values (FEV₁, FVC, FEV₁/FVC), more comorbidities (cardiac and respiratory) and higher serum CRP and creatinine levels (table 4). None of these variables, however, appeared to be independently associated with an increased risk of death.

Survival of Patients Stratified by Gender

Figure 2 shows the cumulative survival of patients stratified by gender. Male patients with confirmed COPD by spirometry showed a significantly decreased rate of survival compared to female patients ($p = 0.004$).

Sensitivity Analysis

To assess the potential influence of patients who did not have a (recent) lung function test to confirm the diagnosis or stage of COPD, we created Cox proportional

Table 2. Characteristics at emergency room presentation, stratified by 1-year outcome

Characteristics	All (n = 260)	Deceased (n = 72)	Alive (n = 188)	p value
BMI (n = 258/70/188)				<0.05 [#]
<20	43 (16.7)	19 (27.1)	24 (12.8)	
20–25	122 (47.3)	34 (48.6)	88 (46.8)	
>25	93 (36.0)	17 (24.3)	76 (40.4)	
Smoking (n = 254/69/185)				NS
Current smoker	111 (43.7)	31 (44.9)	80 (43.2)	
Ex-smoker	140 (55.1)	36 (52.2)	102 (56.3)	
Nonsmoker	3 (1.2)	2 (2.9)	1 (0.5)	
Pack years (n = 129/20/109)	43.8 ± 16.1	54.9 ± 19.0	41.8 ± 14.7	<0.05
Oxygen saturation <90% (n = 253/69/184)	99 (39.1)	25 (36.2)	74 (40.2)	NS
Additional oxygen (n = 252/68/184)	117 (46.4)	44 (64.7)	73 (39.7)	<0.05
Impaired consciousness	26 (10.0)	12 (16.7)	14 (7.4)	<0.05 [#]
Use of accessory respiratory muscles	52 (20.0)	14 (19.4)	38 (20.2)	NS
Elevated CVP	26 (10.0)	10 (13.9)	16 (8.5)	NS
Peripheral edema	83 (31.9)	29 (40.3)	54 (28.7)	<0.10
Wheezing	196 (75.4)	51 (70.8)	145 (77.1)	NS
Crepitations	79 (30.4)	23 (31.9)	56 (29.8)	NS
Arterial blood gas (n = 257/72/185)				
pH ≤7.25	21 (8.2)	11 (15.3)	10 (5.4)	<0.05 [#]
pH 7.25–7.35	63 (24.5)	23 (31.9)	40 (21.6)	
pH ≥7.35	173 (67.3)	38 (52.8)	135 (73.0)	
PaCO ₂ , kPa ≥6.0	138 (53.7)	50 (69.4)	88 (47.6)	<0.05 [#]
PaO ₂ , kPa <7.5	121 (47.1)	32 (44.4)	89 (48.1)	NS
BE, mmol/l ≥2.5	105 (40.9)	37 (51.4)	68 (36.8)	<0.05 [#]
HCO ₃ ⁻ , mmol/l ≥27.0	85 (33.1)	32 (44.4)	53 (28.6)	<0.05
SaO ₂ <90%	131 (51.0)	38 (52.8)	93 (50.3)	NS
Hemoglobin (n = 258/72/186), mmol/l	8.6 ± 1.1	8.3 ± 1.4	8.8 ± 0.9	<0.05 [#]
WBC (n = 259/72/187), 10 ⁹ /l >15.0	69 (26.6)	24 (33.3)	45 (24.1)	NS
Glucose (n = 246/69/177), mmol/l >11.0	36 (14.6)	13 (18.8)	23 (13.0)	NS
Sodium (n = 257/72/185), mmol/l <135	50 (19.5)	14 (19.4)	36 (19.5)	NS
Urea (n = 256/70/186), mmol/l ≥8.0	77 (30.1)	32 (45.7)	45 (24.2)	<0.05 [#]
Creatinine (n = 258/72/186), μmol/l >115	54 (20.9)	23 (31.9)	31 (16.7)	<0.05
CRP (n = 257/72/185), mg/l				
<50	141 (54.9)	36 (50.0)	105 (56.8)	<0.05 [#]
50–200	80 (31.1)	31 (43.1)	49 (26.5)	
>200	36 (14.0)	5 (6.9)	31 (16.7)	
Chest X-ray findings				
Pulmonary edema	26 (10.0)	12 (16.7)	14 (7.4)	<0.10
Pneumonia	71 (27.3)	23 (31.9)	48 (25.5)	NS
Tumor	7 (2.7)	4 (5.6)	3 (1.6)	<0.10
Heart failure	34 (13.1)	10 (13.9)	24 (12.8)	NS

Data are presented as n (%) or mean ± SD. 1 pack year = 20 cigarettes per day for 1 year. NS = Not significant; CVP = central venous pressure; WBC = white blood cells.

[#] Included in multivariate analysis.

Fig. 2. Cumulative survival of patients with confirmed COPD by spirometry stratified by gender (n = 246, p = 0.004).

Table 3. Predictors of 1-year mortality measured at hospital admission for AE-COPD – multivariate analysis (Cox proportional hazards)

Characteristics	HR	95% CI	p value
Sex, male	2.00	1.15–3.48	0.014
Age, years	1.04	1.01–1.07	0.016
Hospital admission for COPD exacerbation in the last 2 years prior to current admission	2.56	1.52–4.30	<0.001
Congestive heart failure, documented prior to current admission	1.75	1.03–2.97	0.038
PaCO ₂ , kPa ≥6.0	2.90	1.65–5.09	<0.001
Urea, mmol/l ≥8.0	2.38	1.42–3.99	0.001
Total patients 236 (dead: 61, alive: 175).			

hazards models without FEV₁ as a potential predictor, thereby including patients with missing values for pulmonary function tests. These models were not substantially different from the primary models that included FEV₁ for any of the significant variables.

Discussion

The purpose of the present study was to determine predictors of mortality in patients hospitalized for AE-COPD. We identified 6 simple, immediately accessible and strong predictors of 1-year mortality at hospital admission for AE-COPD: age, male sex, prior hospitalization for AE-COPD in the last 2 years, prior recorded congestive heart failure, hypercapnia and elevated urea at hospital admission.

We observed an in-hospital mortality rate of 5.8% and a 1-year mortality rate of 27.7% which is similar to findings of other studies, demonstrating a high mortality in cohorts of unselected patients after hospitalization for AE-COPD, both in-hospital and during 1-year follow-up [6, 7, 21]. It is important to acknowledge that mortality continues to rise, even after hospital discharge, which is only in part attributable to the natural course of the disease. The main cause of in-hospital death in our population was respiratory failure. A recent postmortem analysis of major causes of early death in patients hospitalized with COPD exacerbation found that cardiac failure was the most frequent primary cause of death followed by pneumonia and pulmonary thromboembolism. Respiratory failure only ranked fourth as the primary cause of death in this study [22]. However, all patients died within 24 h of admission to the hospital in this study whereas in our study almost all patients died much later after admission (142 ± 125 days). Therefore, these patients may represent a different group of high-risk patients compared to our patients.

Another important aspect is that during follow-up the number of hospital readmissions was high, with 55.1% of patients having one or more hospital readmissions, and 37.1% of the population having been readmitted because of an acute exacerbation. This is similar to other reports and highlights the importance of AE-COPD requiring hospital admission for the course of the disease [21].

Significant findings in this study include the fact that increasing age, male sex, prior hospitalization for AE-COPD, prior recorded congestive heart failure, PaCO₂ ≥6.0 kPa and urea ≥8.0 mmol/l at hospital admission seem to be independent predictors associated with in-

Table 4. Selected characteristics of patients hospitalized for AE-COPD stratified by gender

Characteristics	All (n = 260)	Female (n = 130)	Male (n = 130)	p value
Age, years	70.5 ± 10.8	69.8 ± 11.2	71.2 ± 10.5	NS
Social status				
Retired (n = 251/127/124)	242 (96.4)	124 (97.6)	118 (95.2)	NS
Living at own home (n = 252/127/125)	213 (84.5)	108 (85.0)	105 (84.0)	NS
Living alone (n = 251/127/124)	120 (47.8)	74 (58.3)	46 (37.1)	<0.05
GOLD stage (n = 246/120/126)				<0.05
I	15 (6.1)	13 (10.8)	2 (1.6)	
II	75 (30.5)	43 (35.8)	32 (25.4)	
III	77 (31.3)	31 (25.8)	46 (36.5)	
IV	79 (32.1)	33 (27.5)	46 (36.5)	
FEV ₁ (n = 245/120/125), liters	1.05 ± 0.42	0.94 ± 0.36	1.15 ± 0.45	<0.05
FEV ₁ (n = 246/120/126), % predicted	45.0 ± 18.0	49.6 ± 19.4	40.6 ± 15.3	<0.05
FVC (n = 246/120/126), % predicted	84.5 ± 22.7	90.1 ± 23.9	79.2 ± 20.3	<0.05
Tiffeneau (n = 246/120/126), %	41.0 ± 0.8	43.6 ± 11.7	38.6 ± 11.6	<0.05
No. of hospital admissions for COPD exacerbation in the last 2 years				<0.05
0	174 (66.9)	91 (70.0)	83 (63.8)	
1	45 (17.4)	26 (20.0)	19 (14.6)	
2–3	30 (11.5)	11 (8.5)	19 (14.6)	
≥4	11 (4.2)	2 (1.5)	9 (6.9)	
Hospital admission for COPD exacerbation in the last 2 years	86 (33.1)	39 (30.0)	47 (36.2)	NS
Treated with antibiotics	72 (27.7)	30 (23.1)	42 (32.2)	<0.10
Treated with NPPV	23 (8.8)	14 (10.8)	9 (6.9)	NS
Treated with MV	2 (0.8)	1 (0.8)	1 (0.8)	NS
Comorbidity ¹				
Cardiac comorbidities	169 (65.0)	87 (66.9)	82 (63.1)	NS
Congestive heart failure	58 (22.3)	23 (17.7)	35 (26.9)	<0.10
Respiratory comorbidities	156 (60.0)	69 (53.1)	87 (66.9)	<0.05
Pneumonia ²	82 (31.5)	31 (23.8)	51 (39.2)	<0.05
Pneumothorax	15 (5.8)	2 (1.5)	13 (10.0)	<0.05
Psychiatric comorbidities	47 (18.1)	23 (17.7)	24 (18.5)	NS
Depression/anxiety	27 (10.4)	18 (13.8)	9 (6.9)	<0.10
Addiction	21 (8.1)	4 (3.1)	17 (13.1)	<0.05
Gastrointestinal disease	39 (15.0)	21 (16.2)	18 (13.8)	NS
Gastrointestinal bleeding	11 (4.2)	10 (7.7)	1 (0.8)	<0.05
Further characteristics				
Peripheral edema	83 (31.9)	34 (26.2)	49 (37.7)	<0.05
Creatinine (n = 258/129/129), μmol/l >115	54 (20.9)	18 (14.0)	36 (27.9)	<0.05
CRP (n = 257/129/128), mg/l				
<50	141 (54.9)	79 (61.2)	62 (48.4)	<0.10
50–200	80 (31.1)	37 (28.7)	43 (33.6)	
>200	36 (14.0)	13 (10.1)	23 (18.0)	
Chest X-ray findings				
Pneumonia	71 (27.3)	26 (20.0)	45 (34.6)	<0.05

Data are presented as n (%) or mean ± SD. NPPV = Noninvasive positive pressure ventilation; MV = mechanical ventilation; NS = not significant.

¹ Comorbid conditions do not have to be active. ² Recorded by pulmonary physician.

creased mortality. Aside from male sex, most of these factors have been well established in previous studies, and some have also been applied in prediction models [7, 17, 21, 23].

Male sex is an independent predictor of death in our study. The effect of gender on mortality in patients with COPD remains controversial. To our knowledge, only a few studies have previously shown an increased risk of death in men with COPD, and only found a small influence [8, 21, 24]. A possible explanation as to why most reports did not find a gender effect could be the fact that the majority of these studies included only a few or no female patients at all, therefore reducing the possibility of detecting an actual difference. Due to the gender distribution in our patient population, this study appears to be ideal to address this issue and we are therefore the first to report such a prominent association of male sex with an increased risk of death. In comparison with female patients, men had significantly lower spirometric values (FEV₁, FVC, FEV₁/FVC), more comorbidity (cardiac and respiratory), higher serum CRP and creatinine levels. However, none of these variables appeared to be independently associated with an increased risk of death. Nevertheless, these findings do indicate a poorer health status of male COPD patients admitted to hospital with an AE-COPD.

Our findings and those of other studies suggest that a history of hospitalization for AE-COPD identifies a subgroup of COPD patients with a poor prognosis [6, 14, 15, 17, 25]. We observed a higher rate of mortality among patients who had been admitted in the 2 years prior to the study period. Furthermore, the frequency of admissions and treatment with antibiotics or NPPV during these admissions are also associated with increased mortality. Our findings support previous reports about the influence of hospital admission on mortality in AE-COPD [26].

The presence of congestive heart failure was an independent predictor of 1-year mortality in our study. The effect of comorbidity on mortality in general is complex. Instead of compressing all comorbidity into an index such as the Charlson index, we explored the impact of specific comorbid conditions separately [27]. Selected diseases like heart failure, cardiac ischemia and pneumonia have been previously shown to influence the prognosis in severe COPD patients [13, 15, 28–30]. Congestive heart failure as well as COPD has to be considered as advanced chronic organ failure. Clinically, these entities are difficult to differentiate as symptoms are very similar. Moreover, both diseases often coexist and patients suffer

from multiple symptoms, which are often undertreated [31, 32]. Acute left heart dysfunction has been shown to be present in 25–30% of patients with AE-COPD [33, 34]. Furthermore, other studies have also shown that congestive heart failure is an independent risk factor for survival in patients with COPD who had acute exacerbations requiring hospitalization [15].

We found an increased PaCO₂ to be a significant risk factor for mortality in our population, similar to findings of other studies [7, 14, 35, 36]. Hypercapnia is a result of alveolar hypoventilation. In COPD it results mainly from severe airflow limitation and hyperinflation, which increase during acute exacerbations. The respiratory muscle load, which is already high during stable state, may increase and a respiratory muscle fatigue may develop. Hypercapnia and respiratory acidosis can further decrease respiratory muscle function due to the deleterious effects of acidosis on mitochondrial metabolism and decreased energy production. A vicious cycle may develop leading to increased morbidity and mortality.

An interesting finding of this study is that increased urea levels were predictive of mortality. This is in analogy to the situation in community-acquired pneumonia [37]. In COPD, clinically stable patients with hypercapnia show impaired secretion of sodium and water and correlations have been found between the degree of hypercapnia and the impairment in sodium excretion [38]. Hypoxemia decreases urinary sodium output probably related to a decline in glomerular filtration rate. Correction of hypoxemia has been shown to result in increased natriuresis [39]. Moreover, renal blood flow is severely decreased during AE-COPD, extensive edema may develop and hypercapnia even further diminishes renal blood flow [40]. All these mechanisms may help to explain why elevated urea is predictive of mortality in AE-COPD and highlights the complex interactions of different pathophysiological factors. Interestingly, most of the relevant pathophysiological factors also play an important role as predictors of mortality. Furthermore, it has been shown that sufficient metabolic compensation of respiratory acidosis and adequate renal function significantly decrease mortality [41].

Although all our patients presented with the clinical picture of AE-COPD and clearly fulfilled the proposed and generally accepted criteria for AE-COPD, 71 of them showed infiltrates on chest X-ray and retrospectively were also diagnosed with pneumonia. This represents a common clinical situation and up to now there is no consensus on how to categorize these patients. Almost all of them (93%) were treated with antibiotics and thus re-

ceived efficient therapy. If we excluded these 71 patients from the multivariate analysis, the variables of age, gender, prior hospitalization for AE-COPD and hypercapnia remained significantly related to mortality. Urea was the last variable to be excluded from the analysis ($p = 0.075$) just preceded by prior recorded congestive heart failure. This finding allows 2 different conclusions. First, the identification of elevated urea as a predictor of mortality was driven by AE-COPD patients with pulmonary infiltrates. This would imply that detection of elevated urea in AE-COPD patients identifies a subgroup of patients with probable pneumonia at increased risk of death. Second, it seems also plausible that elevation in urea is a marker of specific pathophysiological changes (see above) associated with increased mortality permitting progression of airways infection to parenchymal infection. Similar reasoning may explain the influence of prior recorded congestive heart failure on mortality, but further research is clearly warranted to clarify these important aspects.

Changes in lung function play an important role in the pathophysiology of COPD, and almost all spirometric measurements were predictive of mortality in univariate analysis but not in multivariate analysis. In particular, no predictive value was suggested when FEV₁ was assessed in multivariate analysis, despite being the most widely used parameter of lung function impairment and its role in classification of the disease into GOLD stages [19]. On the one hand, this might be explained by the low variability of FEV₁ values in our patients, making differentiating between survivors and nonsurvivors difficult. Although almost all patients (94.6%) in our study have had a lung function measurement to confirm the diagnosis of COPD, a considerable proportion did not have a pulmonary function test within 3 years of index hospitalization. The accuracy and validity of these measurements are therefore at least questionable, especially for application in a prediction model to be used at hospital admission. However, this represents a frequently encountered situation of daily clinical practice, as many COPD patients do not present with recent lung function measurements. On the other hand, this result is not surprising as FEV₁ as well as other lung function parameters have been shown to be poor predictors of mortality in stable disease [42]. Moreover, FEV₁ measured at exacerbation might well be an important predictor but cannot be measured during acute exacerbation in most patients.

Similar to other studies, we found an influence of BMI on survival, showing that low body weight is a predictor of long-term mortality in hospitalized patients with AE-

COPD [15, 35, 43, 44]. Our results support the concept that wasting represents an important component of systemic manifestations of COPD related to morbidity and mortality.

Although current smoking status did not have any influence on mortality, the amount of pack years smoked did clearly have predictive value. Unfortunately, this parameter was not recorded systematically and we could not use this variable for the multivariate analysis. However, these results support the notion that smoking has a negative effect on different features of COPD and therefore should be regarded as an important risk factor for death.

Our study has some limitations. First, it is a retrospective, single-center cohort study and data might not be representative for other centers. Because we used administrative data, we were limited by the accuracy with which diagnoses were routinely coded, meaning we might have missed some patients. The sample size of 260 patients allows for reliable analyses but might have been too low to detect other potentially important predictors. Furthermore, the sample size might be too small to extrapolate our findings to other settings because it was too low for cross-validating the prediction model. Further research is needed to externally validate the model in a different patient population. Second, assessments of variables were not standardized due to the retrospective design of the study. Results of spirometry were not obtained in a systematic way making the accuracy and validity of these values at least questionable. Nevertheless, we are convinced that data presented here are accurate because of the meticulous criteria used and validation of the data as outlined above. Finally, the high prevalence of (active) comorbidity has to be taken into account when interpreting the results, although it reflects what happens in daily practice.

We believe, however, that these limitations did not significantly influence the main findings of the present study. Moreover, the data obtained represent clinical reality and may therefore be very relevant to clinical practice. Our work identified several variables that may be useful predictors of mortality at hospital admission for AE-COPD. Strengths of our study include the ideal gender distribution, the amount of collected data and the fact that the diagnosis of COPD in this study relied on original doctor's records and was confirmed by lung function in almost all patients. All patients finally included into the study definitively had a diagnosis of AE-COPD.

Conclusion

The present study provides clear prognostic factors for use in patients with an AE-COPD requiring hospitalization presenting to the emergency room. Age, male sex, prior hospitalization for AE-COPD in the last 2 years,

prior recorded congestive heart failure, $\text{PaCO}_2 \geq 6.0$ kPa and urea ≥ 8.0 mmol/l at hospital admission represent powerful predictors of the risk of death within the first year after admission. These predictors are easily registered at the emergency room, rendering an application in a general clinical setting possible.

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