High-risk patients following hospitalisation for an acute exacerbation of COPD

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ABSTRACT The aim of this study was to assess long-term mortality and predictive factors of death after hospital admission for acute exacerbation of chronic obstructive pulmonary disease (COPD).

1824 patients (23.2% female; mean age 70.3±11.3 years) consecutively admitted for acute exacerbation of COPD in the respiratory medicine departments of 68 general hospitals between October 2006 and June 2007 were prospectively enrolled in a follow-up cohort. Their vital status was documented between October 2010 and April 2011.

Vital status was available for 1750 patients (95.9%), among whom 787 (45%) died during follow-up. Multivariate analysis found that age (60–80 years and ⩾80 years *versus* <60 years, relative risk 2.99, 95% CI 2.31–3.89), lower body mass index (25–30 kg·m^{-2} *versus* ⩽20 kg·m^{-2}, relative risk 0.80, 95% CI 0.66–0.97), lung cancer (relative risk 2.08, 95% CI 1.43–3.01), cardiovascular comorbidity (relative risk 1.35, 95% CI 1.16–1.58), previous hospital admissions for acute exacerbation of COPD (four or more *versus* none, relative risk 1.91, 95% CI 1.44–2.53), use of accessory respiratory muscles (relative risk 1.19, 95% CI 1.01–1.40) or lower-limb oedema (relative risk 1.74, 95% CI (1.44–2.12)) at admission and treatment by long-term oxygen therapy at discharge (relative risk 2.09, 95% CI 1.79–2.45) were independent risk factors of death.

Mortality rate during the 4 years following hospital admission for acute exacerbation of COPD was high (45%). Simple clinical information relating to respiratory and general status can help in identifying high-risk patients and targeting more intensive follow-up and care. Interestingly, cardiovascular comorbidities and past hospitalisations for acute exacerbation of COPD, but not forced expiratory volume in 1 s, independently predicted the risk of death.

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Introduction

Worldwide, chronic obstructive pulmonary disease (COPD) is a major cause of mortality with about 3 million deaths every year according to the World Health Organization [1].

Acute exacerbations of COPD are associated with increased morbidity, readmission rates, resource utilisation and mortality. In the literature, many studies reporting survival after acute exacerbation of COPD are short-term studies analysing in-hospital mortality. According to these studies, in-hospital mortality ranges from 2.5% to 30% [2–11]. In a meta-analysis including six European, American and Australian cohort studies with a follow-up period 1.5 years and providing either mortality rates at three time-points after hospital admission or survival curves, 2- and 5-year mortality rates were 43% and 51% [12]. Excess fatality that results from exacerbations after the critical period has been estimated to be 15.6% (95% CI 10.9–20.3) [12].

In France, between October 2006 and June 2007, the College of General Hospital Respiratory Physicians conducted a prospective observational study of all new cases of hospital admission for acute exacerbation of COPD in respiratory medicine departments of general hospitals. The primary objective of this study was to assess long-term ($\geqslant$3 year) mortality and its predictive factors. Its secondary objectives were to collect information on acute exacerbation of COPD leading to hospital admission and to examine predictive factors of in-hospital death and 3-month adverse outcome (*i.e.* death and/or readmission) [13]. Characteristics of patients and exacerbations at inclusion and predictive factors of in-hospital death have already been published [11, 14, 15].

The present article presents the long-term mortality in this French cohort and shows how information collected at hospital admission can provide an opportunity to identify patients at risk of death during follow-up.

Methods

Study design

From October 1, 2006 to June 30, 2007, lung specialists from 68 French general hospitals consecutively included 1849 patients newly admitted into their respiratory medicine department for an acute exacerbation of COPD, regardless of the source of admission (*i.e.* direct or *via* the emergency department, intensive care unit (ICU), outpatient clinic or another department or hospital).

Diagnosis of COPD was established or confirmed by the senior respiratory specialist in charge of the patient during the hospital stay using patient's medical history and data from previous and current clinical examinations and tests.

An acute exacerbation of COPD was defined as an increase in cough, sputum production or dyspnoea in a patient with known COPD or in whom COPD was suspected at entry and confirmed by the senior respiratory specialist during the hospital stay.

All patients were duly informed of the objectives and requirements of the study and gave their oral consent before inclusion. The study protocol was approved on July 3, 2006 by the advisory committee on information processing in material research in the field of health (Paris, France).

Data collection

At inclusion and discharge, investigators collected data on 1) the patient (*i.e.* anthropometric and sociodemographic characteristics, general medical history and habits); 2) the characteristics of COPD (clinical characteristics and management before the acute exacerbation); 3) the acute exacerbation (aetiology and clinical characteristics); and 4) hospital care (admission modalities, management of acute exacerbation, duration of hospital stay and treatments at discharge).

Statistical analysis

All statistical analyses were conducted by the respiratory epidemiological team of INSERM Unit 700 (Paris, France) using SAS software, version 9.2 (SAS Inc., Cary, NC, USA).

The Kaplan–Meier method was used to build a survival curve. Follow-up ranged from 0 to 54 months. A description of the population on all questionnaire variables was performed according to the vital status of patients at the end of the follow-up. Prognostic factors of death were identified using univariate analyses followed by multivariate analysis. For statistical analysis, ischaemic heart disease and congestive heart failure have been grouped under the term ''cardiovascular comorbidity''.

For the multivariate analysis, a backward stepwise procedure with a Cox's proportional hazard model was applied. It included, for selection, the variables that were significant at $p<0.10$ in the univariate analyses.

Variables were eliminated one at a time from the model on the basis of likelihood ratio tests. For variables with more than two categories (*e.g.* hospital admission for acute exacerbation was split into five categories), dummy variables were used, which were forced into the model when at least one category was significant. Variables were eligible for inclusion in the final multivariate model if they were significantly associated with death at a two-tailed p-value of <0.05.

Results

Among the 1849 patients enrolled, 25 were not included in the study cohort as their diagnosis of COPD was uncertain. Among the 1824 patients of the study cohort, 74 were excluded from the study population: 45 died during the hospital stay and 29 were lost to follow-up or were followed <9 months after inclusion. The study population therefore included 1750 patients (fig. 1). Their main characteristics are presented in table 1.

Long-term survival

During the follow-up period, 787 (45%) patients died. Median follow-up duration for these patients was 18 months. The median follow-up duration was 45 months for patients who did not die during the follow-up period. Survival rates at 1, 2, 3 and 4 years were 83.2%, 70.6%, 61.4% and 55.1%, respectively (fig. 2).

Factors associated with death: univariate analysis

Table S1 shows patients characteristics associated with death in univariate analysis, *i.e.* sex, age (fig. 3), body mass index (BMI), a history of asthma, gastro-oesophageal reflux disease (GORD), secondary pulmonary hypertension, chronic right ventricular failure, lung cancer, presence of comorbid cardiovascular disease (*i.e.* ischaemic heart disease or congestive heart failure) (fig. 4) and previous diagnosis of COPD. Smoking status at admission was not associated with an increased risk of death during follow-up.

Many COPD characteristics were also associated with death (table S2): Medical Research Council dyspnoea score, forced expiratory volume in 1 s (FEV_1), FEV_1/forced (expiratory) vital capacity, arterial carbon dioxide pressure (P_{aCO_2}), arterial oxygen pressure (P_{aO_2}), Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage of airflow obstruction, ongoing long-term oxygen therapy, noninvasive ventilation, long-term oral corticosteroids and acute exacerbation and hospitalisation for an acute exacerbation within the previous year (fig. 5).

As shown in table S3, characteristics of the exacerbation associated with long-term risk of death were a suspected or documented infectious aetiology, left heart failure, intense dyspnoea at hospital admission, total number of clinical signs of severity within the first 24 h, and among these signs dyspnoea at rest, cyanosis, arterial oxygen saturation measured by pulse oximetry, use of accessory respiratory muscles, paradoxical abdominal movement, respiratory rate >25 breaths·min^{-1}, tachycardia (>110 beats·min^{-1}), blotches and lower limb oedema. Increased cough and sputum change were not statistically significantly associated with death.

Finally, some features of hospital stay were associated with death (table S4): first admission *via* an ICU, ICU stay, in-hospital treatment with oxygen therapy, increased duration of hospital stay, discharge treatment with oxygen therapy, noninvasive ventilation, systemic corticosteroids, antibiotics or physiotherapy.

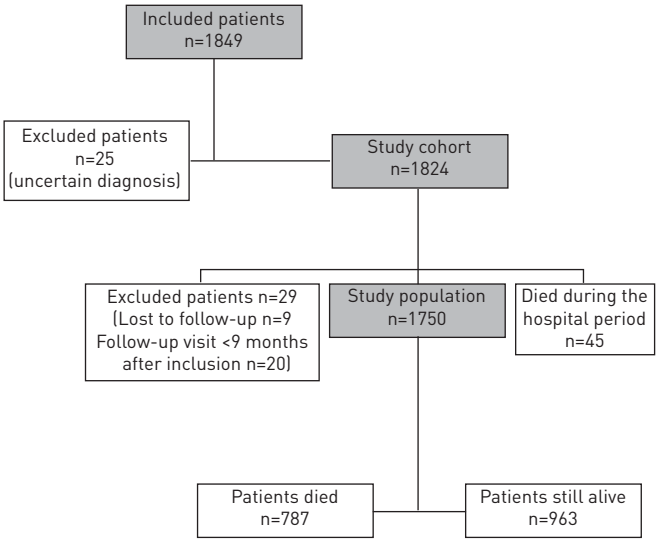

FIGURE 1 Study follow-up.

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TABLE 1 Main baseline characteristics of patients studied

Subjects	1750
Age years	70.1±11.2
<60	353 (20.2)
60–80	1005 (57.4)
⩾80	392 (22.4)
Female	406 (23.2)
BMI[#] kg·m^{-2}	
⩽20	339 (20.0)
20–25	582 (34.4)
25–30	456 (27.0)
⩾30	315 (18.6)
Smoking status	
Nonsmoker	116 (6.6)
Ex-smoker	1060 (60.6)
Current smoker	574 (32.8)
Cumulative smoking[¶] pack-years	43.3±25.2
⩾1 cardiovascular comorbidity[+,§]	525 (30.0)
GORD	80 (4.6)
Lung cancer	47 (2.7)
COPD at inclusion	279 (15.9)
FEV1 % predicted	45.6±17.7
FEV1 by GOLD stage[f,##]	
⩾80%	71 (4.6)
50–80%	511 (33.0)
30–50%	671 (43.3)
⩽30%	296 (19.1)
FEV1/FVC ratio[¶¶] %	52.7±14.4
Acute exacerbations within the previous year[++]	
0	634 (36.8)
1	358 (20.8)
2	344 (19.9)
3	170 (9.9)
⩾4	219 (12.7)
Severity signs at admission[§] n	2.78±2.10
Duration of hospital stay[§§] days	12.0±9.3

Data are presented as n, mean±SD or n (%). BMI: body mass index; GORD: gastro-oesophageal reflux disease; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 s; GOLD: Global Initiative for Chronic Obstructive Lung Disease; FVC: forced vital capacity. [#]: n=1692; [¶]: n=1585; [+]: ischaemic heart disease or congestive heart failure; [§]: n=1749; [f]: according to the last respiratory function tests performed before inclusion in the study; [##]: n=1549; [¶¶]: n=1521; [++]: n=1725; [§§]: n=1735.

Predictive factors of death: multivariate analysis

Multivariate analysis (table 2) found that age (60–80 years and ⩾80 years *versus* <60 years), male sex, presence of lung cancer and cardiovascular comorbidity, hospital admission for acute exacerbations within the previous year (1, 2, 3 or ⩾4 *versus* 0), use of accessory respiratory muscles or lower-limb oedema at admission and treatment by oxygen therapy at discharge were independent predictors of death during follow-up. Conversely, high BMI (25–30 kg·m^{-2} and ⩾30 kg·m^{-2} *versus* 20–25 kg·m^{-2}) and history of GORD were independent predictors of long-term survival.

Discussion

This large long-term prospective study found a high all-cause mortality rate following hospital admission for acute exacerbation of COPD, with 45% of patients dying within 48 months. Clinical predictors of an increased risk of long-term mortality included: increasing age, low BMI, presence of some comorbidities (*i.e.* lung cancer or heart disease), history of hospital admissions for acute exacerbation of COPD during the previous year, clinical severity of the acute episode and need for oxygen therapy at discharge. Conversely, the severity of airflow obstruction was not associated with survival.

Relationship between the degree of airflow obstruction, dyspnoea and mortality

The lack of association between FEV1 and survival in multivariate analysis is in apparent contradiction with the findings of many studies, including that of CELLI *et al.* [16], in which the authors developed the BMI,

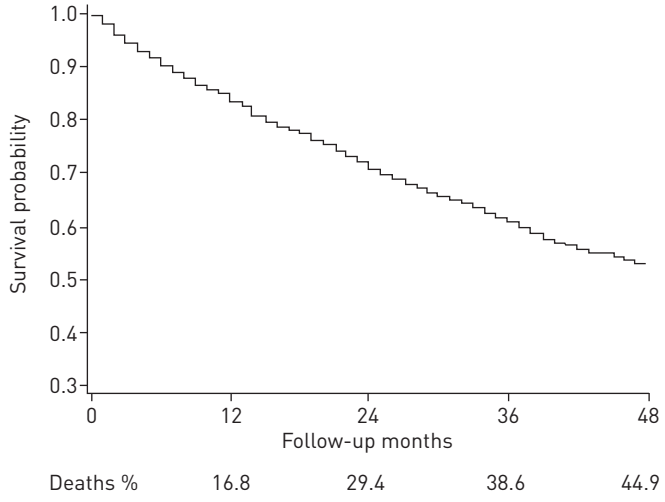

FIGURE 2 Kaplan–Meier survival curve.

obstruction, dyspnoea and exercise capacity (BODE) index. In their study, FEV1 was independently associated with the risk of death during the 52 months of follow-up, and was therefore a component of the BODE prognostic index, together with dyspnoea, BMI and exercise tolerance. While the patients the study by CELLI *et al.* [16] were stable, all patients in the present study were, by definition, in a sufficiently severe situation to justify hospitalisation, which might explain why FEV1 was not an independent predictor of long-term mortality, despite being strongly associated with this outcome in univariate analysis. In line with this hypothesis, most patients had severe to very severe airflow obstruction (62.9%) and it is well known that patients with more severe airflow obstruction tend to be hospitalised more frequently when an exacerbation occurs [17]. Indeed, in our study, FEV1 and previous hospitalisations exhibited marked co-linearity, and when previous hospitalisations were not entered into the multivariate model, FEV1 remained independently associated with survival (data not shown). In addition, the prognostic value of FEV1 could be overwhelmed by that of clinical signs of severity at admission, since the risk of increased severity of the acute episode obviously increases with the baseline disease severity. In the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study, the risk of severe exacerbations increased with the severity of airflow obstruction [17]. In that study, the best predictor of the occurrence of subsequent exacerbations was the history of exacerbations, which was indeed a significant prognostic factor in our population, at least when considering severe exacerbations (see below). Interestingly, and in accordance with other cohort studies [18], our results show that, in patients hospitalised for an acute exacerbation of COPD, the severity of this acute episode predicts long-term survival.

Similarly, in our cohort the severity of dyspnoea at steady state before hospital admission was strongly associated with mortality in univariate analysis but did not independently predict this outcome in multivariate analysis. Again, this could relate to the relative homogeneity of the population in terms of

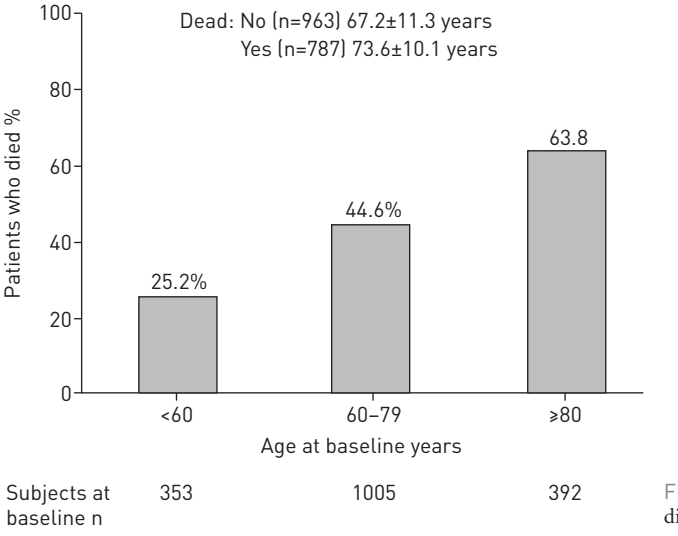

FIGURE 3 Percentage of patients who died, according to baseline age. $p<0.0001$.

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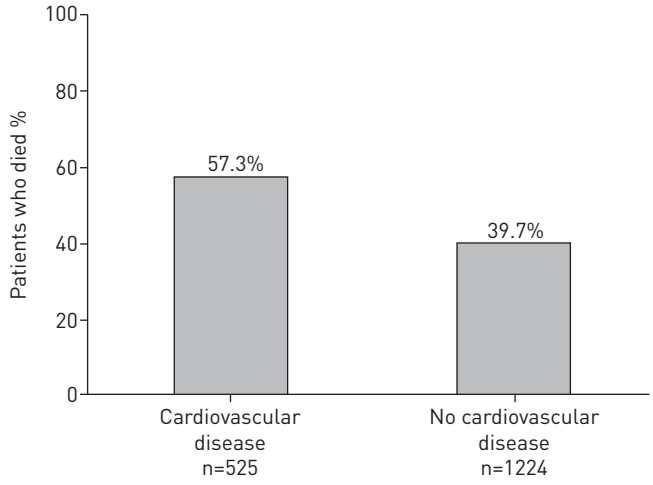

FIGURE 4 Percentage of patients who died (n=787), according to presence of cardiovascular disease at baseline. p<0.0001.

severity. In addition, confounders likely play a significant role. Indeed, the severity of dyspnoea relates to factors other than disease severity, such as the level of usual physical activity, BMI and some associated comorbidities, in particular congestive heart failure [19], which were identified as independent prognostic factors in our population. In some patients, the role of these factors as determinants of the level of dyspnoea might even be more important than that of airflow obstruction [20].

Clinical signs of severity on admission

Most clinical signs of severity recorded on admission did not individually predict long-term mortality in an independent manner, with the exception of lower limb oedema and the use of accessory inspiratory muscles.

Other studies also reported an association between lower limb oedema and in-hospital and post-discharge mortality [9, 21–23]. Indeed, in many patients the occurrence of lower limb oedema probably reflects the presence of some degree of chronic right ventricular failure, and is thus a marker of very severe underlying disease. In a study of patients visiting emergency departments for acute exacerbation of COPD, the use of accessory inspiratory muscles was also a predictor of in-hospital mortality [2]. In that study, patients were not followed after discharge. One difficulty with such physical signs is that their assessment is not standardised and may depend on the physician's experience. Indeed, we have no way to be sure that what was reported as "use of accessory inspiratory muscles" did not correspond to inspiratory depression of supraclavicular areas, a marker of the severity of hyperinflation and inspiratory load.

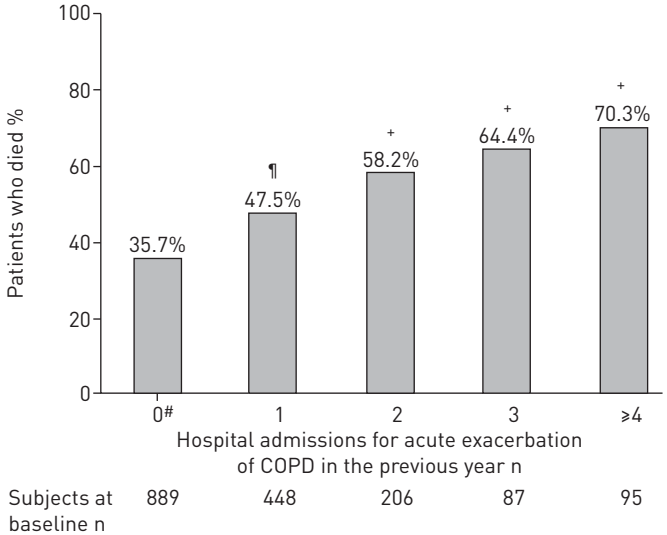

FIGURE 5 Percentage of dead patients according to the number of hospital admissions for acute exacerbation of chronic obstructive pulmonary disease (COPD) within the previous year. n=773. #: no hospitalisations for acute exacerbation of COPD or COPD unknown at inclusion; ¶: p=0.0001; +: p<0.0001.

TABLE 2 Independent risk factors of death 48 months after hospital admission for acute exacerbation of chronic obstructive pulmonary disease (COPD) (multivariate analysis)

	Relative risk (95% CI)	p-value
Patient characteristics		
Age (*versus* <60 years)		
60–80 years	1.73 (1.35–2.20)	<0.0001
⩾80 years	2.99 (2.31–3.89)	<0.0001
BMI (*versus* 20–25 kg·m^{-2})		
⩽20 kg·m^{-2}	1.21 (0.99–1.47)	0.06
25–30 kg·m^{-2}	0.80 (0.66–0.97)	0.02
⩾30 kg·m^{-2}	0.75 (0.60–0.94)	0.01
Comorbidity (*versus* none)		
GORD	0.62 (0.40–0.94)	0.03
Cardiovascular diseases[#]	1.35 (1.16–1.58)	0.0001
Lung cancer	2.08 (1.43–3.01)	0.0001
COPD characteristics		
Hospital admission for acute exacerbation(s) within the previous year (*versus* 0)		
0	1	
1	1.28 (1.07–1.53)	0.007
2	1.45 (1.15–1.81)	0.001
3	1.76 (1.31–2.35)	0.0002
⩾4	1.91 (1.44–2.53)	<0.0001
Acute exacerbation characteristics		
Severity signs within the first 24 h (*versus* none)		
Use of secondary respiratory muscles	1.19 (1.01–1.40)	0.03
Lower-limb oedema	1.74 (1.44–2.12)	<0.0001
Hospitalisation characteristics		
Oxygen therapy at discharge (*versus* none)	2.09 (1.79–2.45)	<0.0001

BMI: body mass index; GORD: gastro-oesophageal reflux disease. [#]: ischaemic heart disease or congestive heart failure.

Relationship between previous hospitalisations and survival

Our data confirm that all-cause mortality increases with the number of hospitalisations during the previous year (OR 1.28, 1.45, 1.76 and 1.91 for 1, 2, 3 or 4 hospitalisations for exacerbation during the previous year, respectively). Some authors did not find similar results. Among the 171 patients studied by GROENEWEGEN *et al.* [7], 1-year mortality following hospitalisation was not influenced by the number of hospital readmissions in multivariate analysis, which might relate to the relatively short duration of follow-up. Conversely, in a cohort study of 304 COPD patients, SOLER-CATALUÑA *et al.* [18] demonstrated that the risk of death during follow-up was influenced by the frequency of severe acute exacerbation of COPD, and especially those requiring hospitalisation. GUDMUNSSON *et al.* [23] and ALMAGRO *et al.* [24] performed multivariate analyses in hospitalised COPD patients and showed that patients admitted to hospital in the previous year, regardless of the cause, have a higher risk of death following discharge. Other factors associated with mortality differed between these two studies: they included health status, marital status, depression and Charlson index in the study by ALMAGRO *et al.* [24], and older age, lower lung function, diabetes and poor health status in that by GUDMUNSSON *et al.* [23]. These discrepancies are likely to be due to relatively small sample sizes (n=135 and 416, respectively) and limited follow-up duration (2 years). Finally, several other authors reported a relationship between the frequency of hospitalisations and the risk of death and readmission [25].

Characteristics of high-risk patients

Our data show that patients at high risk of death during follow-up have lower BMI, more frequent cardiovascular comorbidities and previous hospitalisations for exacerbations.

These results suggest the existence of a ''high-risk profile''. Several recent studies underlined the importance of characterising patients thoroughly beyond the degree of airflow obstruction. Using principal component and cluster analyses in 322 patients, BURGEL *et al.* [26] identified four phenotypes of COPD patients. The authors followed the cohort for a median duration of 3.35 years. Mortality rate during this period was 19.8%, and differed between phenotypes: the lowest mortality was observed in so-called ''phenotype 2'' (*i.e.* patients with less airflow obstruction, few comorbidities and exacerbations), which tends to corroborate our

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findings [27]. In a cohort of 342 patients hospitalised for the first time for an acute exacerbation of COPD and followed over 4 years, GARCIA-AYMERICH *et al.* [28] identified three distinct phenotypes: ''severe respiratory'', ''moderate'' and ''systemic'' COPD. As in our population, patients who were hospitalised more frequently were at higher risk of dying during follow-up, as well as patients with cardiovascular comorbid illnesses. However, note that in the present study no objective measurements were specifically performed at inclusion to confirm the presence of cardiovascular disease. Cardiovascular diseases are indeed frequent causes of death in COPD [29], and represent a risk factor of increased mortality in several studies with long-term follow-up after an acute exacerbation of COPD [30, 31]. Conversely, high BMI is protective, as in the BODE index study [16], while poor nutritional status predicts shorter survival [32]. P_{aO_2}, P_{aCO_2} and pH were all associated with mortality during follow-up in univariate analyses, but did not remain independently associated with survival in the multivariate model.

Lung cancer, another known cause of mortality among COPD patients [33], was the only other comorbidity associated with an increased risk of death in the present cohort. Although many studies, including ours, have found that age is a risk factor of mortality, disease duration could be a more prominent prognostic factor [34].

Surprisingly, we found that a diagnosis of GORD exerted a protective role in terms of all-cause mortality. This result is in apparent contradiction with data from the ECLIPSE study [17], where GORD was a risk factor for exacerbations. Interestingly, in idiopathic pulmonary fibrosis, treatment of GORD is associated with better outcomes [35]. Since, in our study, the diagnosis of GORD was probably accompanied by the corresponding treatment, such a protective role of antireflux therapy might be hypothesised, mortality being higher in patients with asymptomatic, and therefore untreated, GORD. However, we have no way to test this hypothesis.

Strengths and limitations of the study

On the one hand, prognostic factors identified here are purely clinical and very easy to collect at entry in the ward. Therefore, they might be helpful to guide the intensity of follow-up and treatment including pharmacological agents aimed at reducing the risk of exacerbation or rehabilitation, which has been shown to decrease mortality following hospitalisations for acute exacerbation of COPD [36]. Since these prognostic factors were identified in a high number of patients who were prospectively followed over a long period of time (48 months) with very few patients lost to follow-up (29 (1.59%) out of 1824) and very few missing data (see tables), the results can be considered as robust, at least in the considered population.

On the other hand, some specific characteristics of this population have to be considered when interpreting the results. First, patients were included following admission to a respiratory medicine department, which by definition excluded patients cared for on a purely ambulatory basis, and patients with acute exacerbation of COPD who died before admission, *e.g.* in the emergency department or in the ICU. In addition, we report here predictors of survival following discharge. Thus, patients who died during their stay in the medical ward were also excluded from the analysis. They were few (n=45, 2.5%) and their characteristics have been reported previously [11]. Therefore, prognostic factors identified here cannot be generalised to all COPD patients who present to the hospital with an acute exacerbation of COPD. Besides, some potentially important prognostic factors such as exercise tolerance (which plays an important role as part of the BODE index) were not recorded, which actually corresponds to what usually happens in real life. Finally, exact causes of death were not determined, which prevents us from linking them to specific risk factors. However, this was not a purpose of the study.

In conclusion, the present study shows that, in patients admitted for acute exacerbation of COPD to respiratory medicine wards of French general hospitals, the long-term risk of death is high and correlates with markers of both respiratory and nonrespiratory status, *i.e.* age, lower BMI, presence of lung cancer, cardiovascular comorbidity, previous hospital admission(s) for acute exacerbation of COPD, some clinical signs of severity on admission and need for long-term oxygen therapy at discharge. Conversely, FEV_1 was not an independent predictor of death during follow-up. Hospital admission should provide an opportunity for clinicians to identify at-risk patients and provide them with closer follow-up and the best available preventive pharmacological and nonpharmacological treatments.

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