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Case fatality of COPD exacerbations: a meta-analysis and statistical modelling approach

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ABSTRACT: The aim of our study was to estimate the case fatality of a severe exacerbation from long-term survival data presented in the literature.

A literature search identified studies reporting ⩾1.5 yr survival after a severe chronic obstructive pulmonary disease (COPD) exacerbation resulting in hospitalisation. The survival curve of each study was divided into a critical and a stable period. Mortality during the stable period was then estimated by extrapolating the survival curve during the stable period back to the time of exacerbation onset. Case fatality was defined as the excess mortality that results from an exacerbation and was calculated as 1 minus the (backwardly) extrapolated survival during the stable period at the time of exacerbation onset. The 95% confidence intervals (CI) of the estimated case fatalities were obtained by bootstrapping. A random effect model was used to combine all estimates into a weighted average with 95% CI.

The meta-analysis based on six studies that fulfilled the inclusion criteria resulted in a weighted average case-fatality rate of 15.6% (95% CI 10.9–20.3), ranging from 11.4% to 19.0% for the individual studies.

A severe COPD exacerbation requiring hospitalisation not only results in higher mortality risks during hospitalisation, but also in the time-period after discharge and contributes substantially to total COPD mortality.

KEYWORDS: Case fatality, chronic obstructive pulmonary disease, exacerbation, hospitalisation, meta-analysis

Worldwide, mortality due to chronic obstructive pulmonary disease (COPD) is high. According to the World Health Organization, at least 2.7 million deaths every year are due to COPD [1]. The 30-yr projections from the Global Burden of Disease Study show a striking increase in COPD as a cause of death to the third place worldwide in 2020 [2]. This increase largely results from a worldwide increase in the prevalence of smoking, especially in the developing countries and among females, and ageing of the population. The excess mortality among patients with COPD is high, not only because of the presence of COPD but also because of the increased prevalence of other smoking-related diseases [3].

Many studies have analysed predictors of mortality in COPD. Among the factors independently associated with mortality in COPD are age, lung function (forced expiratory volume in 1 s and inspiratory capacity divided by total lung capacity), dyspnoea, comorbidity, body mass index (BMI), fat-free mass, exercise capacity, arterial oxygen tension, C-reactive protein, the BODE index (BMI, the degree of airflow obstruction, dyspnoea and exercise capacity), airflow obstruction, dyspnoea and exercise capacity, and the number of previous hospitalisations [4, 5].

Because patients with COPD are often recorded as dying from other causes, it has been suggested that all-cause mortality is probably the best mortality measure to use in COPD [5]. Nevertheless, it is well known that many patients dying do so during a severe COPD exacerbation, when they experience acute respiratory failure [6]. However, there is a relative scarcity of knowledge on mortality rates from COPD exacerbations. Unlike in myocardial infarction and stroke [7], no estimates

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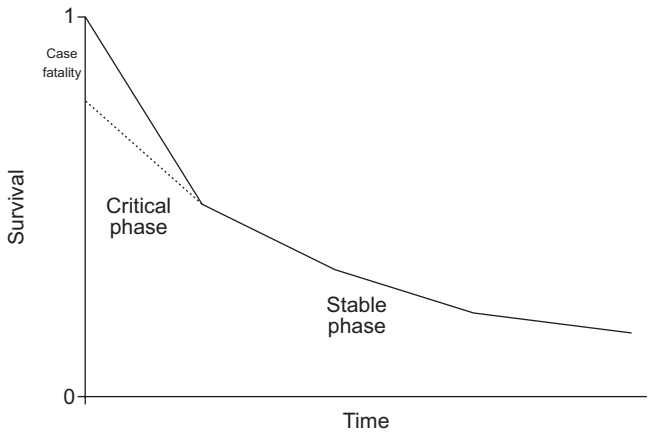

FIGURE 1. Survival curve after hospitalisation for an exacerbation of chronic obstructive pulmonary disease. ·····: the extrapolated curve during the stable phase.

of the case fatality of a COPD exacerbation exist. This may be associated with the absence of consensus on the length of the critical period during which the mortality risk is increased.

The most frequently reported outcome of death due to COPD exacerbations is short-term, in-hospital mortality [8]. Previous studies have estimated in-hospital mortality after hospitalisation for a COPD exacerbation to range from 2.5% to 14% [9, 10]. Mortality among patients admitted to intensive care units (ICUs) is much higher, *i.e.* up to 30% [11]. In-hospital mortality is insufficient to assess case fatality for at least two reasons. There is a selection bias towards patients with longer hospital stays and it does not incorporate the mortality that occurs after hospital discharge but is still attributable to the index exacerbation. Therefore, our study aimed to estimate the case fatality of a severe COPD exacerbation including the time-period after hospitalisation. This study arose out of our need to capture the impact of exacerbations on mortality within the context of a dynamic, COPD progression model [12, 13] used to evaluate the impact of different COPD interventions. To fully simulate the potential long-term impact of interventions which successfully prevent or treat exacerbations, the impact of severe exacerbations on mortality needed to be estimated. As the COPD population in the model is specified by age, which is a significant predictor of mortality in COPD [5], we also investigated the association between age and mortality after a severe exacerbation.

METHODS AND MATERIALS

We performed a comprehensive literature search in MEDLINE and EMBASE for journal articles published after 1990 reporting mortality or survival during and after hospitalisation for an exacerbation of COPD using the MESH (sub)headings ''chronic obstructive pulmonary disease or COPD or chronic bronchitis'' in combination with ''mortality or dead or death* or life expectancy or survival or prognosis'' and ''hospital* or admission* or admitt* or exacerbation* or disease episodes''. We also searched references listed from articles retrieved. Studies were excluded if the patient population was a

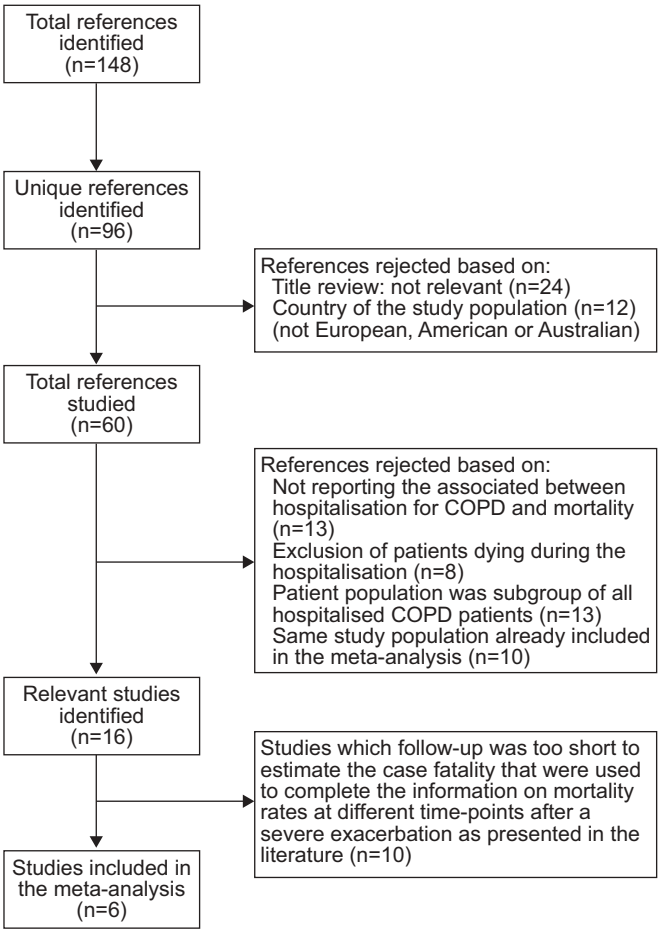

FIGURE 2. Results of the systemic literature search. COPD: chronic obstructive pulmonary disease.

subgroup of hospitalised COPD patients, such as patients requiring mechanical ventilation. Inclusion criteria were: a European, American or Australian study population; a follow-up period that started at hospital entry and lasted $\geqslant$1.5 yr; and presenting mortality rates at three or more time-points after hospital admission, or presenting a survival curve. Studies that fulfilled all inclusion criteria except for a follow-up of 1.5 yr or the presence of three data points were used to complete the information on the average mortality rates at different time-points after a severe exacerbation as presented in the literature. In addition to information on the average mortality rates at different time-points, data on the association between mortality and age was extracted from the studies.

Our general approach was as follows (fig. 1). For each study we extracted the survival curve presented in the article or estimated the curve from the presented data ourselves. We roughly distinguished between the critical and the stable period after hospital admission with the survival curve during the stable period being flatter than the one during the critical period. Several data points from the curve during the stable period were extracted to estimate survival during this period. Only data points well after the critical period were included. For each study the survival function during the stable period was then parameterised using three parameters.

TABLE 1 Characteristics of studies included in the meta-analysis that aimed to calculate the case fatality of a chronic obstructive pulmonary disease (COPD) exacerbation

First author [ref.]	Patients n	Males %	Mean age yrs	Mean FEV_1 % pred	Patient selection	Definition exacerbation	Mean hospital length of stay days	Country
Connors [15]	1016	51	70	0.80 L, ~30% pred	Patients (aged >18 yr) with clinical diagnosis of COPD recorded by a physician	Hospitalisation in combination with breathlessness, respiratory failure or change in mental status due to COPD as main reason for admission and $P_{a,CO_2} \geqslant 50$ mmHg	9	USA
Vestbo [16]	487	55	67	60	Patients (aged >20 yr) admitted for COPD (Copenhagen City Heart Study)	Hospitalisation (>24 h) with primary diagnosis ICD-8: 491–492	Not reported	Denmark
Groenewegen [17]	171	61	70	35	Patients with COPD (ATS criteria), with a FEV_1 <70% and reversibility <11% who were admitted	Increase of two out of three symptoms: dyspnoea, cough, sputum severe enough to warrant hospitalisation	11.7	Netherlands
Gunen [18]	205	88	65	38	Patients with COPD (ATS criteria) who were admitted	Hospitalisation for severe increase of symptoms (cough, purulent sputum and dyspnoea), cyanosis and oedema, confusion, lethargy, coma, use of accessory muscles for ventilation, treatment failure, acidosis, hypoxaemia and/or hypercapnia or new arrhythmias	11.6	Turkey
McGhan [19]	54269	97	69	Not reported	Patients admitted for COPD	Hospitalisation with primary diagnosis ICD-9: 490–492 or 496 or diagnosis related group code of COPD with a primary or secondary discharge diagnosis of COPD	6.5	USA
Brekke [20]	996	49	71	47	Patients (aged >40 yr) admitted for COPD	Hospitalisation with primary discharge diagnosis ICD-10: J44.0, J44.1, J44.x with J13-J18.9	Not reported	Norway

FEV_1: forced expiratory volume in 1 s; % pred: % predicted; ATS: American Thoracic Society; P_{a,CO_2}: arterial carbon dioxide tension; ICD: International Classification of Diseases.

$$S(t) = (1-g)\,\mathrm{Exp}[-\alpha t - \beta t^2]$$

With t being the time, t=0 being time of hospital admission, S(t) the survival probability, α and β the parameters that define the nonlinear change in survival over time, and g the case fatality of the exacerbation.

The survival curve was fitted by minimising the sum of squared differences with the points that were extracted from the curve, or given in the publication. We then extrapolated the survival curve during the stable period back to the time of hospital admission and calculated where the curve intersected the vertical axis (*i.e.* the start of hospital admission). The case fatality was defined as the excess mortality that results from an exacerbation and equals: g=1-S(0). Uncertainty intervals for each parameter were obtained from bootstrapping. Based on the given initial sample size and the calculated survival probabilities for each interval during the follow-up period, we randomly draw new survival numbers assuming binomial distributions. In this way we generated new survival curves, resulting in newly calculated values for the model parameters. The 2.5% and 97.5% percentile values correspond with the 95% uncertainty interval. Finally, estimates from all studies were combined to calculate the weighted average for g, using random effect meta-analysis [14]. The weights were based on a combination of the sampling error (variance of case fatality within each study) and the random-effect variance (variance of case fatality between all studies).

To estimate the association between age and mortality after a severe exacerbation, the relative risks of age on mortality within a study, if reported, were extracted from the retrieved references. The association with age within each separate study was investigated because there was little difference in the mean age between the different studies. The weighted average relative risk was calculated using the variance in the individual studies as a weight.

RESULTS

After the first selection, 60 references were obtained in full (fig. 2). An entire review of these remaining publications resulted in the exclusion of another 44 studies for different reasons (fig. 2). The main reasons for exclusion were that the association between hospitalisation for COPD and mortality was not reported (13 studies) and that the study population consisted of a selective subgroup of hospitalised patients (13 studies). Of the latter 13 studies, six studies included patients admitted to ICU or requiring (non)mechanical ventilation only, three included patients treated in the emergency room or pre-hospital setting only, two included hospitalisations for diagnoses other than COPD, while two studies included patients with a first admission or a very mild exacerbation only.

Of the remaining 16 studies, 10 studies met all inclusion criteria except for the 1.5 yrs of follow-up. Hence, a total of six studies were finally included in the meta-analysis to calculate the case fatality rate [15–20]. None of these studies evaluated the effect of an intervention as they were all cohort studies. For one of these six studies, the study of BREKKE *et al.* [20], we had access to the patient level data. For the other five studies results were based on the data presented in the article. Characteristics of the included studies are shown in table 1.

Case fatality

Table 2 presents the results of the curve fitting procedure for each of the selected six studies. Details about the parameter values for each study are presented in the supplementary data. The estimated average case-fatality rate for the individual studies varied between 11.4% and 19.0%. The overall weighted mean value of the case fatality of an exacerbation was 15.6% (95% CI 10.9–20.3%).

Association between mortality and age

All of the six studies included in the meta-analysis reported on the association between mortality after a hospitalisation for an exacerbation and age. Age was a significant predictor of mortality in univariate analyses (five studies) and remained an independent predictor after correction for other explanatory variables in multivariate analyses (4 studies). On average the probability of dying after hospitalisation for an exacerbation increased by 4.1% per year increase in age (RR 1.041, 95% CI 1.037–1.045) (six studies).

Average mortality rates at different time-points presented in the literature

Characteristics of the 10 studies with an insufficient length of follow-up are shown in table 3 [9, 10, 21–28]. Table 4 shows the average mortality probabilities at different time-points for these 10 studies as well as the six studies that were included in the meta-analysis. Based on all 16 studies combined, the average in-hospital mortality rate was 6.7%. The average mortality rates at 3 and 6 months were 18% and 26%, respectively.

DISCUSSION

In this study the case fatality of an exacerbation was calculated by extrapolating the survival curve during the stable period to the time of exacerbation onset. The weighted average case-fatality rate was estimated to be 15.6%, with the individual studies varying from 11.4% to 19.0%. The average in-hospital mortality rate was 6.7%, which strongly supports the notion that the critical period indeed exceeds the duration of the hospitalisation.

TABLE 2 Estimated case fatality of a chronic obstructive pulmonary disease exacerbation

First author [ref.]	Patients n	Estimated mean case fatality % (95% CI)
CONNORS [15]	1016	17.2 (11.5–23.1)
VESTBO [16]	487	12.3 (5.8–18.4)
GROENEWEGEN [17]	171	17.7 (10.2–25.8)
GUNEN [18]	205	16.7 (7.9–25.4)
MCGHAN [19]	54269	11.4 (10.6–12.2)
BREKKE [20]	996	19.0 (18.7–19.3)¶
Overall estimate#		15.6 (10.9–20.3)

#: Overall weighted average case fatality based on random effects analysis; ¶: based on patient level data.

TABLE 3 Characteristics of studies with a follow-up <1.5 yrs excluded from the meta-analysis used to obtain information on mortality rates at different time-points after a severe exacerbation as presented in the literature

First author [ref.]	Patients n	Males %	Mean age yrs	Mean FEV_1 % pred	Patient selection	Definition exacerbation	Mean hospital length of stay days	Country
Fuso [10]	590	79	68	Not reported	Patients with COPD (ATS criteria) who were admitted	Increased dyspnoea, reduced usual performance with or without change in sputum, blood temperature and body weight <5 days prior to hospitalisation	Not reported	Italy
Cydulka [21]	131974	49	75	Not reported	Patients (aged >65 yrs) admitted for COPD	Hospitalisation with first diagnosis ICD-9: 490–492, 496	6	USA
Eriksen [22]	300	40	71	35	Patients with COPD, confirmed by physician or spirometry, who were admitted	Hospitalisation for COPD exacerbation: J44.0, 44.1, 44.8, 44.9	9.9	Denmark
Patil [9]	71130	44	70	Not reported	Patients (aged >40 yrs) admitted for COPD	Hospitalisation with discharge code ICD-9: 491.21	5	USA
Yohannes [23]	104	48	73	40	Patients (aged >60 yrs) admitted for COPD	Hospitalisation for exacerbation defined as: presence of at least two symptoms: increased sputum purulence or volume, dyspnoea, wheeze, chest tightness or fluid retention	15	UK
Wang [24]	282	41	71	36	Patients (>40 yrs), smoker/ex-smoker, FEV_1 <80%, FEV_1/FVC<70% and no other lung disease who were admitted	Hospital admission for an acute exacerbation of COPD	10	Canada
Price [25]	7529	Not reported	Not reported	Not reported	Patients with physician-diagnosed COPD who were admitted	Acute hospital admission for COPD	8.3	UK
Bustamente [26]	763	81	76	47	Patients (aged >45 yrs) with COPD according to GOLD who were admitted	Hospitalisation with diagnosis ICD-9: 491.21	10.6	Spain
Kinnunen [27]	72896#	74	72	Not reported	Patients (aged >44 yrs) admitted for COPD	Hospital admission with primary diagnosis ICD-8,9: 491, 942, 496 ICD-10: J41, 42, 43, 44	8.1	Finland
Dransfield [28]	825	50	66	Not reported	Patients admitted for COPD	Hospitalisation with primary discharge code ICD-9: 491.21 or primary diagnosis of respiratory failure 518.81 with second diagnosis COPD exacerbation	5.7	USA

FEV1: forced expiratory volume in 1 s; % pred: % predicted; COPD: chronic obstructive pulmonary disease; ATS: American Thoracic Society; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ICD: International Classification of Diseases. #: number of admissions instead of number of patients.

TABLE 4 Mortality rates after hospitalisation for a chronic obstructive pulmonary disease exacerbation at different time-points for the six studies included and the 10 studies excluded from the meta-analysis fulfilling all inclusion criteria except follow-up >1.5 yrs

	Patients n	Mortality rate %					
		In-hospital	3 months	6 months	1 yr	2 yrs	5 yrs
Studies included in the meta-analysis							
Connors [15]	1016	11	NR	33	43	49	NR
Vestbo [16]	487	NR	NR	NR	NR	NR	44
Groenewegen [17]	171	8	16	18	23	NR	NR
Gunen [18]	205	8.3	NR	24	33	39	NR
McGhan [19]	54269	3.6	NR	NR	24	NR	57
Brekke [20]	996	9.9	22	27	32	41	NR
Studies excluded from the meta-analysis#							
Fuso [10]	590	14	NR	NR	NR	NR	NR
Cydulka [21]¶	131974	6	NR	NR	NR	NR	NR
Eriksen [22]	300	8.6	19	NR	36	NR	NR
Patil [9]	71130	2.5	NR	NR	NR	NR	NR
Yohannes [23]	104	3.8	NR	NR	38	NR	NR
Wang [24]	282	9.9	NR	NR	NR	NR	NR
Price [25]	7529	7.4	15	NR	NR	NR	NR
Bustamente [26]	763	6.4	NR	NR	NR	NR	NR
Kinnunen [27]	72896§	3.2	NR	NR	NR	NR	NR
Dransfield [28]	825	5.2	NR	NR	NR	NR	NR
Overall estimate based on all 16 studies % (95% CI)+		6.7 (5.7–7.7)	18 (14–22)	26 (20–32)	33 (25–40)	43 (37–50)	51 (38–63)

NR: not reported. #: follow-up <1.5 yrs; ¶: results year 1991; +: overall weighted average mortality rates based on random effects analysis; §: number of admissions instead of number of patients.

However, we would like to emphasise that the estimated case fatality can not be compared with the mortality rates at different time-points as these represent different concepts. The case fatality was calculated as one minus the survival that would have been expected if the patient would have been stable (fig. 1), while mortality at a certain time-points was calculated as one minus the survival at that specific point in time. This also implies that the exact distinction between the critical and stable period after exacerbation onset, however, could not be determined by comparing the case-fatality rate with mortality rates at different points in time. The critical period was defined as the period in which mortality is increased compared to the stable situation. Therefore, this period ranges from the hospital admission until the point were the estimated survival curve during the stable period approaches the actual observed survival curve (fig. 1). Estimating the point where the two survival curves approach each other is only possible if patient-level data are available or when we make additional assumptions on how the case fatality changes over time within the critical period. We had patient-level data from one study, the study of Brekke *et al.* [20]. For this study the critical period was estimated to last 4.4 months. The length of the critical period is likely to vary according to the population studied; in patients with several comorbidities the exacerbation may have both more severe [9, 19] and longer lasting impact and similarly the critical period could last longer in the elderly.

Due to limited data and the homogeneity of the different studies we were not able to specify the case fatality by subgroups, such as COPD severity (defined by lung function), sex or age. Therefore, we searched for information about the association of these variables with mortality within the extracted studies. Within the studies the relationship of mortality due to an exacerbation with disease severity or sex was less clear. Mortality after hospitalisation for an exacerbation was, however, highly dependent on age (RR 1.041 per increase in year of age).

As the study populations of the six studies selected for the meta-analysis were almost the same with respect to the mean age, 65–71 yrs, age did not influence the between-study comparison of case fatalities. The studies included have sampled data spanning a time-period of >10 yrs but no obvious pattern of change over time in case fatality can be seen. This could be the result of the variation in treatment and management between the different countries but was actually also observed in one of the included studies [16]. In contrast, a recent study found indications of a slight improvement of exacerbation-related mortality over time [29].

Despite the homogeneity between the studies with respect to age, the study populations may have differed on other aspects. Although we selected studies from Western countries, the criteria used for hospitalisation, for example, are not similar across countries. This is related to local treatment patterns, which in turn may be driven by local guidelines, medical traditions,

cultural aspects, financing and reimbursement schemes, *etc*. In our selected studies the mean length of stay was significantly longer in the European studies compared to studies from the USA, 11 days *versus* 7 days. However, the mean in-hospital mortality rate did not differ. One study aspect which seemed to have an influence on the results was whether or not patients included in the study had physician- or spirometry-confirmed COPD. Studies including patients with confirmed COPD reported higher mortality rates than studies including patients with hospitalisation for COPD based on International Classification of Disease (ICD) coding. The mean in-hospital mortality rate for both groups were 9.2% (95% CI 7.4–10.9%) and 4.8% (95% CI 3.5–6.1%), respectively. Two of the studies used in the meta-analysis included patients with a hospitalisation for COPD based on ICD coding. If the largest of these two studies, the study of McGHAN [19], was excluded from the meta-analysis, the average case-fatality rate would have been higher, *i.e.* 17.9% (95% CI 15.8–20%). Studies using ICD coding only to define COPD may report lower mortality rates because they also included mild patients or patients with, for example, asthma that were wrongly coded.

In conclusion, mortality in COPD is common and severe exacerbations of COPD are one of the major causes of death in COPD. In this study the case-fatality rate of a severe exacerbation resulting in hospitalisation was estimated to be 15.6%, showing the substantial impact of exacerbations on mortality.

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STATEMENT OF INTEREST

Statements of interest for J. Vestbo and T.L. Feenstra can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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