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

Short title: Case-fatality of COPD exacerbations

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Abstract

Objective of the 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 at least 1.5 year survival after a severe COPD exacerbation resulting in hospitalization. Each study’s survival curve 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 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%-confidence interval.

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 hospitalization not only results in higher mortality risks during hospitalization, but also in the time period after discharge and contributes substantially to total COPD mortality.

Word count abstract: 198

Keywords: case-fatality, chronic obstructive pulmonary disease, exacerbation, hospitalization, meta-analysis
**Introduction**

Worldwide, mortality due to COPD is high. According to the WHO, at least 2.7 million deaths are due to COPD every year [1]. The 30-year 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 women - and aging 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 analyzed predictors of mortality in COPD. Among the factors independently associated with mortality in COPD are age, lung function (forced expiratory volume in 1 second, inspiratory capacity divided by total lung capacity), dyspnea, comorbidity, body mass index (BMI), fat-free mass, exercise capacity, PaO₂, C-reactive protein, the BODE-index incorporating BMI, airflow obstruction, dyspnea, and exercise capacity and the number of previous hospitalizations [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 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
hospitalization for a COPD exacerbation to range from 2.5% to 14% [9,10]. Mortality among patients admitted to intensive care 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, the present study aimed to estimate the case-fatality of a severe COPD exacerbation including the time period after hospitalization. This study arose out of our need to capture the impact of exacerbations on mortality within the context of a dynamic, multistate, life-table 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

We performed a comprehensive literature search in MEDLINE and EMBASE for journal articles published after 1990 reporting mortality or survival during and after hospitalization 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 subgroup of hospitalized COPD patients, such as patients requiring mechanical ventilation. Inclusion criteria were: European,
American or Australian study population; a follow-up period that started at hospital entry and lasted at least 1.5 year 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 year 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 (see figure 1). For each study, we extracted the survival curve presented in the paper 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 parameterized using three parameters:

\[
S(t) = (1-g) \exp[-\alpha t - \beta t^2]
\]

with \(t\) time, with \(t=0\) being time of hospital admission

- \(S(t)\) survival probability
- \(\alpha, \beta\) parameters that define the non-linear change in survival over time
- \(g\) case-fatality of the exacerbation
The survival curve was fitted by minimizing the sum of squared differences with the points that were extracted from the curve, or given in the publication. Then we 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. Conditional 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 first selection 60 references were obtained in full (see figure 2). Entire review of these remaining publications resulted in exclusion of another 44 studies for different reasons (figure 2). The main reasons for exclusion were that the association between hospitalization for COPD and mortality was not reported (13 studies) and that the study population consisted of a
selective subgroup of hospitalized 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 ER or pre-hospital setting only, two included hospitalizations for other diagnoses 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 years 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; 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 as presented in the article. Characteristics of the studies included are shown in Table 1.

Case-fatality

Table 2 presents the results of the curve fitting procedure for each of the six studies selected. Details about the parameter values for each study are presented in the online data supplement. 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 about the association between mortality after a hospitalization 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 to die after a hospitalization for an exacerbation increased with 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 ten 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 both these ten studies as well as the six studies that were included in the meta-analysis. Based on all sixteen studies combined, the average in-hospital mortality rate was 6.7%. The average mortality rates at three and six 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 hospitalization. However, we would like to emphasize that the estimated case fatality cannot 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 (Figure 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. This period therefore ranges
from the hospital admission till the point were the estimated survival curve during the stable period approaches the actual observed survival curve (see figure 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 of 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 co-morbidities 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), gender or age. Therefore we searched for information about the association of these variables with mortality within the extracted studies. Within the studies the relation of mortality due to an exacerbation with disease severity or sex was less clear. Mortality after a hospitalization 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 to 71 years, age did no influence the between-study comparison of case-fatalities. The studies included have sampled data spanning a time period of more than 10 years 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 seen within one of the included studies [16]. In contrast, a very 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 hospitalization 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 versus 7 days. The mean in-hospital mortality rate however, did not differ. One study aspect which seemed to have an influence on the results was whether patients included in the study had physician- or spirometry-confirmed COPD or not. Studies including patients with confirmed COPD reported higher mortality rates than studies including patients with a hospitalization for COPD based on 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 hospitalization 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 hospitalization was estimated to be 15.6%, showing the substantial impact of exacerbations on mortality.

Acknowledgements
The authors acknowledge dr. Brekke and dr. McGhan for the additional information and data they provided. The authors also thank Maiwenn Al for her help with the statistical analyses.
References


Figure legends

Figure 1: Survival curve after hospitalization for an exacerbation of COPD. The dotted line represents the extrapolated curve during the stable phase

Figure 2: Results of the systemic literature search
Table 1: Characteristics of studies included in the meta-analysis that aimed to calculate the case-fatality of a COPD exacerbation

<table>
<thead>
<tr>
<th>1st author of the study, year of publication</th>
<th>N</th>
<th>% Males</th>
<th>Mean age</th>
<th>Mean FEV1% predicted</th>
<th>Patient selection</th>
<th>Definition exacerbation</th>
<th>Mean hospital length of stay (days)</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connors, 1996 [15]</td>
<td>1016</td>
<td>51</td>
<td>70</td>
<td>0.80L about 30% pred</td>
<td>Patients (age&gt;18yr) with clinical diagnosis of COPD recorded by a physician</td>
<td>Hospitalization in combination with breathlessness, respiratory failure, or change in mental status due to COPD as main reason for admission and PaCO2&gt;=50mmHg</td>
<td>9</td>
<td>USA</td>
</tr>
<tr>
<td>Vestbo, 1998 [16]</td>
<td>487</td>
<td>55</td>
<td>67</td>
<td>60</td>
<td>Patients (age&gt;20yr) admitted for COPD (Copenhagen City Heart Study)</td>
<td>Hospitalization (&gt;24 hours) with primary diagnosis ICD-8:491-492</td>
<td>Not reported</td>
<td>Denmark</td>
</tr>
<tr>
<td>Groenewegen, 2003 [17]</td>
<td>171</td>
<td>61</td>
<td>70</td>
<td>35</td>
<td>Patients with COPD (ATS criteria), with a FEV1&lt;70% and reversibility&lt;11% who were admitted</td>
<td>Increase of two of three symptoms: dyspnea, cough, sputum severe enough to warrant hospitalization</td>
<td>11.7</td>
<td>Netherlands</td>
</tr>
<tr>
<td>Gunen, 2005 [18]</td>
<td>205</td>
<td>88</td>
<td>65</td>
<td>38</td>
<td>Patients with COPD (ATS criteria) who were admitted</td>
<td>Hospitalization for severe increase of symptoms (cough, purulent sputum and dyspnea), cyanosis and oedema, confusion, lethargy, coma, use of accessory muscles for ventilation, treatment failure, acidosis, hypoxemia and/or hypercapnia or new arrhythmias</td>
<td>11.6</td>
<td>Turkey</td>
</tr>
<tr>
<td>McGhan, 2007 [19]</td>
<td>54269</td>
<td>97</td>
<td>69</td>
<td>Not reported</td>
<td>Patients admitted for COPD</td>
<td>Hospitalization 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</td>
<td>6.5</td>
<td>USA</td>
</tr>
<tr>
<td>Brekke, 2008 [20]</td>
<td>996</td>
<td>49</td>
<td>71</td>
<td>47</td>
<td>Patients (age&gt;40 yr) admitted for COPD</td>
<td>Hospitalization with primary discharge diagnosis ICD-10:J44.0, J44.1, J44.x with J13-J18.9</td>
<td>Not reported</td>
<td>Norway</td>
</tr>
</tbody>
</table>
Table 2: Estimated case-fatality of a COPD exacerbation

<table>
<thead>
<tr>
<th>1st author of the study, year of publication</th>
<th>N</th>
<th>Estimated mean case-fatality (95% confidence limits)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connors, 1996</td>
<td>1016</td>
<td>17.2% (11.5-23.1%)</td>
</tr>
<tr>
<td>Vestbo, 1998</td>
<td>487</td>
<td>12.3% (5.8-18.4%)</td>
</tr>
<tr>
<td>Groenewegen, 2003</td>
<td>171</td>
<td>17.7% (10.2-25.8%)</td>
</tr>
<tr>
<td>Gunen, 2005</td>
<td>205</td>
<td>16.7% (7.9-25.4%)</td>
</tr>
<tr>
<td>McGhan, 2007</td>
<td>54,269</td>
<td>11.4% (10.6-12.2%)</td>
</tr>
<tr>
<td>Brekke, 2008</td>
<td>996</td>
<td>19.0% (18.7-19.3%)#</td>
</tr>
<tr>
<td>Overall estimate*</td>
<td></td>
<td>15.6% (10.9-20.3%)</td>
</tr>
</tbody>
</table>

# Based on patient-level data

*Overall weighted average case-fatality based on random effects analysis.
Table 3: Characteristics of studies with a follow-up less than 1.5 years, 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

<table>
<thead>
<tr>
<th>1st author of the study, year of publication</th>
<th>N</th>
<th>% Males</th>
<th>Mean age</th>
<th>Mean FEV₁,% predicted</th>
<th>Patient selection</th>
<th>Definition exacerbation</th>
<th>Mean hospital length of stay (days)</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fusso, 1995 [10]</td>
<td>590</td>
<td>79</td>
<td>68</td>
<td>Not reported</td>
<td>Patients with COPD (ATS criteria) who were admitted</td>
<td>Increased dyspnea, reduced usual performance with or without change in sputum, blood temperature and body weight less than 5 days prior to hospitalization</td>
<td>Not reported</td>
<td>Italy</td>
</tr>
<tr>
<td>Cydulka, 1997 [21]</td>
<td>131974</td>
<td>49</td>
<td>75</td>
<td>Not reported</td>
<td>Patients (age&gt;65yr) admitted for COPD</td>
<td>Hospitalization with first diagnosis ICD-9: 490-492, 496</td>
<td>6</td>
<td>USA</td>
</tr>
<tr>
<td>Eriksen, 2003 [22]</td>
<td>300</td>
<td>40</td>
<td>71</td>
<td>35</td>
<td>Patients with COPD confirmed by physician or spirometry that were admitted</td>
<td>Hospitalization for COPD exacerbation: J44.0, 44.1, 44.8, 44.9</td>
<td>9.9</td>
<td>Denmark</td>
</tr>
<tr>
<td>Patil, 2003 [9]</td>
<td>71130</td>
<td>44</td>
<td>70</td>
<td>Not reported</td>
<td>Patients (age&gt;40 yr) admitted for COPD</td>
<td>Hospitalization with discharge code ICD-9: 491.21</td>
<td>5</td>
<td>USA</td>
</tr>
<tr>
<td>Yohannes, 2005 [23]</td>
<td>104</td>
<td>48</td>
<td>73</td>
<td>40</td>
<td>Patients (age &gt;60yr) admitted for COPD</td>
<td>Hospitalization for exacerbation defined as: presence of ≥2 symptoms: increased sputum purulence or volume, dyspnea, wheeze, chest tightness, or fluid retention</td>
<td>15</td>
<td>UK</td>
</tr>
<tr>
<td>Wang, 2005 [24]</td>
<td>282</td>
<td>41</td>
<td>71</td>
<td>36</td>
<td>Patients (&gt;40yr), smoker/ex-smoker, FEV₁&lt;80%, FEV₁/FVC&lt;70%, no other lung disease who were admitted</td>
<td>Hospital admission for an acute exacerbation of COPD</td>
<td>10</td>
<td>Canada</td>
</tr>
<tr>
<td>Price, 2006 [25]</td>
<td>7529</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Patients with physician-diagnosed COPD who were admitted</td>
<td>Acute hospital admission for COPD</td>
<td>8.3</td>
<td>UK</td>
</tr>
<tr>
<td>Authors</td>
<td>Year</td>
<td>Patients</td>
<td>Age</td>
<td>COPD</td>
<td>Hospitalization</td>
<td>Country</td>
<td>Notes</td>
<td></td>
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<tr>
<td>--------------------</td>
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<td>------</td>
<td>-----------------</td>
<td>---------</td>
<td>-----------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Bustamante</td>
<td>2007</td>
<td>763</td>
<td>81</td>
<td>76</td>
<td>47</td>
<td>Spain</td>
<td>Patients (age&gt;45yr) with COPD according to GOLD who were admitted</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hospitalization with diagnosis: ICD-9: 491.21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kinnunen</td>
<td>2007</td>
<td>72896#</td>
<td>74</td>
<td>72</td>
<td>Not reported</td>
<td>Finland</td>
<td>Patients (age&gt;44yr) admitted for COPD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hospital admission with primary diagnosis ICD-8,9: 491, 942, 496 ICD-10: J41, 42, 43, 44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dransfield</td>
<td>2008</td>
<td>825</td>
<td>50</td>
<td>66</td>
<td>Not reported</td>
<td>USA</td>
<td>Patients admitted for COPD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hospitalization with primary discharge code ICD-9: 491.21 or primary diagnosis of respiratory failure 518.81 with second, diagnosis COPD exacerbation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\# Number of admissions instead of number of patients
Table 4: Mortality rates after hospitalization for a COPD exacerbation at different time points for the six studies included and the ten studies excluded from the meta-analysis fulfilling all inclusion criteria except for a follow-up more than 1.5 years.

<table>
<thead>
<tr>
<th>Studies included in the meta-analysis</th>
<th>N</th>
<th>In-hospital</th>
<th>3 months</th>
<th>6 months</th>
<th>1 year</th>
<th>2 year</th>
<th>5 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connors, 1996</td>
<td>1016</td>
<td>11%</td>
<td>-</td>
<td>33%</td>
<td>43%</td>
<td>49%</td>
<td>-</td>
</tr>
<tr>
<td>Vestbo, 1998</td>
<td>487</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>44%</td>
</tr>
<tr>
<td>Groenewegen, 2003</td>
<td>171</td>
<td>8%</td>
<td>16%</td>
<td>18%</td>
<td>23%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gunen, 2005</td>
<td>205</td>
<td>8.3%</td>
<td>-</td>
<td>24%</td>
<td>33%</td>
<td>39%</td>
<td>-</td>
</tr>
<tr>
<td>McGhan, 2007</td>
<td>54269</td>
<td>3.6%</td>
<td>-</td>
<td>-</td>
<td>24%</td>
<td>-</td>
<td>57%</td>
</tr>
<tr>
<td>Brekke, 2008</td>
<td>996</td>
<td>9.9%</td>
<td>22%</td>
<td>27%</td>
<td>32%</td>
<td>41%</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Studies (follow-up&lt;1.5 years) excluded from the meta-analysis</th>
<th>N</th>
<th>In-hospital</th>
<th>3 months</th>
<th>6 months</th>
<th>1 year</th>
<th>2 year</th>
<th>5 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fusco, 1995</td>
<td>590</td>
<td>14%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cydulka*, 1997</td>
<td>131974</td>
<td>6%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Eriksen, 2003</td>
<td>300</td>
<td>8.6%</td>
<td>19%</td>
<td>-</td>
<td>36%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Patil, 2003</td>
<td>71130</td>
<td>2.5%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Yohannes, 2005</td>
<td>104</td>
<td>3.8%</td>
<td>-</td>
<td>-</td>
<td>38%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Wang, 2005</td>
<td>282</td>
<td>9.9%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Price, 2006</td>
<td>7529</td>
<td>7.4%</td>
<td>15%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bustamente, 2007</td>
<td>763</td>
<td>6.4%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kinnunen, 2007</td>
<td>72896*</td>
<td>3.2%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dransfield, 2008</td>
<td>825</td>
<td>5.2%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Overall estimate based on all 16 studies (95% confidence limits): 6.7% (5.7-7.7%), 18% (14-22%), 26% (20-32%), 33% (25-40%), 43% (37-50%), 51% (38-63%)

* Results year 1991
# Number of admissions instead of number of patients
- Not reported
$Overall weighted average mortality rates based on random effects analysis.
Figure 1: Survival curve after hospitalization for an exacerbation of COPD. The dotted line represents the extrapolated curve during the stable phase.
Figure 2: Results of the systematic literature search

Total references identified
n=148

Unique references identified n=96

References rejected based on:
- Title review: not relevant (n=24)
- Country of the study population (n=12)
  (not European, American or Australian)

Total references studied n=60

References rejected based on:
- Not reporting the association between hospitalization for COPD and mortality (n=13)
- Exclusion of patients dying during the hospitalization (n=8)
- Patient population was subgroup of all hospitalized COPD patients (n=13)
- Same study population already included in the meta-analysis (n=10)

Relevant studies identified n=16

Studies which follow-up was too short to estimate the case-fatality that were used to complete the information on mortality rates at different time points after a severe exacerbation as presented in the literature (n=10)

Studies included in the meta-analysis n=6