Mortality predictors following acute exacerbation of COPD


Predictors of 1-year mortality in patients discharged from hospital following acute exacerbation of chronic obstructive pulmonary disease

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Abstract

Introduction: acute exacerbation of COPD (AECOPD) is a major cause of hospital admission, and predicts subsequent medium-term mortality. We aimed to examine mortality predictors in patients discharged from hospital after AECOPD.

Methods: we obtained baseline demographic and clinical data from 100 patients (mean age (range) = 73 (60–98) years; 48 males) admitted with AECOPD. All completed the following validated questionnaires: a quality of life questionnaire (Breathing Problems Questionnaire; BPQ); a screening questionnaire for depression (Brief Assessment Schedule Depression Cards; BASDEC); a disability questionnaire (Manchester Respiratory Activities of Daily Living questionnaire; MRADL). Following discharge all were prospectively followed and survival/mortality at 12 months confirmed from hospital notes and by contacting general practitioners.

Results: the prevalence of depression at recruitment was 56%. One-year mortality in the whole group was 36%. Odds ratios (95% confidence intervals) for mortality predictors (univariate logistic regression analysis) were: use of long-term oxygen therapy = 2.72 (1.06–6.97); subsequent readmission = 2.57 (1.08–6.12); MRADL score = 0.87 (0.80–0.94) (disability predicting death); BASDEC score = 1.13 (1.02–1.26) (depression predicting death); BPQ score = 1.08 (1.04–1.12) (low quality of life predicting death); length of original hospital stay = 1.03 (1.00–1.07). On multivariate logistic regression analysis the only mortality predictor was BPQ with an odds ratio (95% confidence limits) of 1.13 (1.04–1.22). In terms of mortality prediction for

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individuals, a threshold MRADL score of <12 gave a sensitivity of 86%, specificity of 55%, positive predictive value of 88% and negative predictive value of 52%, with similar predictive values using BPQ as an independent variable.

Conclusions: 1-year mortality after AECOPD admission is high. The presence of depressive illness (which is extremely common), and levels of both disability and impairment of quality of life are univariate predictors of 1-year mortality in this patient group. This model may be useful in predicting prognosis for individuals and thus in guiding treatment decisions.

Keywords: chronic obstructive pulmonary disease, elderly, mortality, disability, depression

Introduction
The NICE Chronic Obstructive Pulmonary Disease (COPD) guidelines estimate that 900,000 people (1.5% of the population) are diagnosed with COPD in the UK [1]. Acute exacerbation (AECOPD) is a major cause of hospital admission and is associated with impaired quality of life, reduced survival and higher healthcare expenditure [2]. In other chronic diseases, untreated, unrecognised depression is associated with increased disability, increased health-care usage, non-compliance with medical treatment and excess mortality [3, 4].

We have previously reported in an elderly outpatient COPD population that disability was a predictor of mortality at 30 months [5]. The first aim of the present study was to assess prospectively the mortality rate in older patients discharged following AECOPD admission and to examine predictors of mortality.

Despite evidence of high mortality following hospital discharge after AECOPD, there are little data to guide clinicians on identification of individuals at risk of death in the short–medium term. Such information might help target intervention to reduce mortality or to identify patients who would benefit from palliative care referral. We thus also aimed to assess the sensitivity, specificity, and positive and negative predictive values of any factors predicting 1-year mortality in individuals.

Methods
Subjects
Male and female subjects aged ≥60 years were recruited from those consecutively admitted to an inner-city university teaching hospital between November 2001 and June 2002 with AECOPD (defined by national guidelines [6] as the presence of ≥2 of: increased sputum purulence; increased sputum volume; increased dyspnoea; increased wheeze; increased chest tightness; new/increased fluid retention). Our trust operates an integrated medical admissions policy, all adults being admitted via a single medical admissions unit. Patients were recruited from this unit on a daily basis (weekend admissions being recruited on Mondays). During the study we did not operate an AECOPD ‘hospital at home’ or early discharge scheme. Subjects have not been studied previously. Following discharge, all were followed prospectively for 12 months. Hospital readmission was monitored and survival/mortality confirmed from general practitioners and hospital notes. The study was approved by the local research ethics committee, and witnessed, written, informed consent was obtained.

Exclusion criteria were: previous history of diagnosed depression and/or use of anti-depressant medication; use of oral corticosteroids in the past 6 weeks (excluding current admission); other severe/life-threatening or acute unstable medical illness (e.g. acute coronary event, haemodynamically unstable gastrointestinal bleed); dementia (assessed historically and by stable score of <7 on Hodkinson Abbreviated Mental Test [7]); refusal of consent. During the study, non-invasive ventilation for AECOPD was not routinely available in our trust. Patients were included provided that they did not need invasive ventilation. Prior to discharge, socio-demographic characteristics were obtained using a semi-structured questionnaire. Body mass index was measured at discharge, as was spirometry (best of three measurements within 5% of each other performed by trained personnel if not already recorded (same criteria) during the previous 3 months). Co-morbid conditions and duration of hospital stay were recorded. During initial hospitalisation all subjects completed outcome measures detailed below.

Outcome measures
Depression
The Brief Assessment Schedule Depression Cards (BAS-DEC) comprises a 19-item deck of cards, self-administered with responses of ‘true’, ‘false’ and ‘don’t know’. Two items are weighted to 2 points, other affirmative responses 1 point and ‘don’t know’ responses 0.5 points (maximum score 21). A score of ≥7 suggests ‘a case’ of depression [8]. In our hands BASDEC performs well against the Geriatric Mental State Schedule in differentiating depressed from non-depressed elderly COPD patients, with a sensitivity of 100%, specificity of 93%, positive predictive value of 91% and negative predictive value of 100% [9].

Physical disability
The Manchester Respiratory Activities of Daily Living questionnaire (MRADL) consists of 21 self-report, disease-specific activities of daily living questions, in four sub-domains [10]. It is validated in older COPD patients [5, 10]. Low scores signify difficulties in daily activities.

Quality of life (QoL)
The Breathing Problems Questionnaire (BPQ) is a self-administered, disease-specific QoL questionnaire [11],
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highly discriminative between elderly, healthy, sex-matched controls and elderly COPD patients [12]. The range of composite scores is from 0 to 104, with high scores signifying impaired QoL. Although it is not formally validated for inpatients, our own (unpublished) data have shown only minor improvements in QoL and depression scores several weeks post-discharge for AECOPD.

Data analysis

Statistical analyses were performed using SPSS for Windows, version 11.0. Where appropriate, descriptive analysis was performed. Logistic regression analysis was performed with ‘death’ as the dependent variable to examine mortality predictors, with assessment of co-linearity to examine confounding inter-relationships between variables. We computed the odds ratio (OR) and its 95% confidence interval (CI). We considered a variable to predict outcome (death) if CI excluded the value ‘1’. Significance was at the 5% level.

We also assessed whether any factors or combination of factors predictive of mortality could be employed to calculate mortality risks for individuals in terms of: sensitivity (percentage of subjects dead at 12 months identified by this predictor(s)); specificity (percentage of subjects alive at 12 months whose survival was identified by this predictor(s)); positive predictive value (PPV; percentage of subjects who this factor(s) predicted would be dead at 12 months and who indeed had died by this time); negative predictive value (NPV; percentage of subjects who this factor(s) predicted would be alive at 12 months and who in fact survived).

Results

We approached 133 hospitalised AECOPD patients. Twenty-one were excluded (three demented, five on antidepressants, six with unstable ischaemic heart disease, two with cancer, five with recent oral corticosteroid use). Of the remainder, eight declined to participate. Forty died in hospital. Thus, 100 subjects (mean (range) age = 73 (60–98) years; 48 males) were included in analyses. All completed the questionnaires and spirometry as per recruitment criteria. Twenty-one were receiving long-term oxygen therapy (LTOT) at recruitment and subsequently.

Fifty-five patients had one or more readmissions during 12 months follow-up. Of these, 29 had one readmission, 17 had two, seven had three and two had four readmissions.

In the whole sample, mean (SD) 1 second forced expiratory volume (FEV1) was 0.81 (0.3) l. Only 12 patients had no co-morbidities. Co-morbidities comprised ischaemic heart disease (% = 38), hypertension (% = 15), diabetes mellitus (% = 12), hearing and/or visual impairment (% = 10), osteoporosis (% = 9), osteoarthritis (% = 7), deep vein thrombosis (% = 5), peripheral vascular disease (% = 4) and hepatic disease (% = 3). Nine patients were acidic (pH < 7.35) on admission.

The prevalence of depression at baseline (BASDEC ≥ 7) was 56%. Baseline characteristics of both groups (died and survived) are given in Table 1.

At 12 months, 36 patients (61–97 (mean 75) years; 36% of the total; 18 men) had died (Table 1). Causes of death were: respiratory failure, n = 11; cardiovascular, n = 7; pneumonia, n = 3; ischaemic heart disease, n = 3; and stroke, n = 2. In 10, cause of death was unknown. Thirteen of those who died (54%) were receiving LTOT.

Using logistic regression analysis with ‘death’ as dependent variable and BASDEC ≥ 7 as independent categorical variable revealed an OR (CI) of 2.94 (1.22–7.09) (P < 0.01).

When BASDEC was employed as a continuous variable in univariate logistic regression, the OR (CI) of BASDEC as a mortality predictor was 1.13 (1.02–1.26) (P < 0.02). (i.e. for every one point increase in BASDEC score, the mortality ratio increased by 13%). Table 2 shows results of univariate logistic regression analysis detailing variables with significant predictive effect on mortality. Age, gender, smoking status, social class, FEV1, body mass index, co-morbidity, arterial blood gas levels and pack-years smoked were not predictors. Analysis of co-linearity showed significant inter-relationship between BPQ and MRADL. On multivariate logistic regression analysis incorporating all the predictors from Table 2, the only mortality predictor was BPQ score

Table 1. Baseline characteristic of COPD patients who died versus those alive (mean (SD))

<table>
<thead>
<tr>
<th>Variable</th>
<th>Died (n = 36)</th>
<th>Alive (n = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>74.8 (7)</td>
<td>72.3 (7)</td>
</tr>
<tr>
<td>BMI</td>
<td>22.3 (3)</td>
<td>23.6 (5)</td>
</tr>
<tr>
<td>MRADL</td>
<td>7.5 (5)</td>
<td>12.2 (6)</td>
</tr>
<tr>
<td>BPQ</td>
<td>56.9 (11)</td>
<td>43 (13)</td>
</tr>
<tr>
<td>FEV1 (Lit)</td>
<td>0.88 (0.3)</td>
<td>0.77 (0.3)</td>
</tr>
<tr>
<td>Percentage of FEV1</td>
<td>39 (14)</td>
<td>40 (15)</td>
</tr>
<tr>
<td>Pack-years</td>
<td>41 (26)</td>
<td>36 (22)</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>21 (17)</td>
<td>12 (4)</td>
</tr>
<tr>
<td>PaCO2 (mmHg)</td>
<td>43.5 (2)</td>
<td>45.7 (2)</td>
</tr>
<tr>
<td>PaO2 (mmHg)</td>
<td>66.7 (3)</td>
<td>74.2 (5)</td>
</tr>
<tr>
<td>pH value</td>
<td>7.41 (0.07)</td>
<td>7.38 (0.06)</td>
</tr>
<tr>
<td>SaO2 (%)</td>
<td>90.2 (7)</td>
<td>90.3 (7)</td>
</tr>
</tbody>
</table>

MRADL = Manchester Respiratory Activities of Daily Living scale; BPQ = Breathing Problems Questionnaire; FEV1 = forced expiratory volume in 1 second; BMI = body mass index; SaO2 = oxygen saturation.

Table 2. Individual predictors of mortality in older patients with acute exacerbation of COPD (univariate logistic regression analysis)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta</th>
<th>SE</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASDEC</td>
<td>0.125</td>
<td>0.05</td>
<td>1.13</td>
<td>1.02–1.26</td>
<td>0.02</td>
</tr>
<tr>
<td>MRADL</td>
<td>–0.144</td>
<td>0.04</td>
<td>0.87</td>
<td>0.80–0.94</td>
<td>0.0001</td>
</tr>
<tr>
<td>BPQ</td>
<td>0.082</td>
<td>0.02</td>
<td>1.08</td>
<td>1.04–1.12</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hospital readmission</td>
<td>0.946</td>
<td>0.44</td>
<td>2.57</td>
<td>1.08–6.12</td>
<td>0.03</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>0.033</td>
<td>0.01</td>
<td>1.03</td>
<td>1.00–1.07</td>
<td>0.03</td>
</tr>
<tr>
<td>LTOT</td>
<td>1.002</td>
<td>0.48</td>
<td>2.72</td>
<td>1.06–6.97</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*For a unit increase of the relevant categories (BASDEC is a score from 0 to 21 (high score ≥ 7 suggesting case of depression), MRADL is a score from 0 to 21 (low score implying worse physical function), BPQ is a score from 0 to 105 (high score corresponding to impaired QoL), length of stay (duration of hospital stay because of exacerbation), readmission (hospital readmission because of acute exacerbation versus not readmitted) and LTOT (the effect of LTOT compared to receiving no LTOT). BASDEC = Brief Assessment Schedule Depression Cards; MRADL = Manchester Respiratory Activities of Daily Living scale; BPQ = Breathing Problems Questionnaire; LTOT = long-term oxygen therapy.
with an OR of 1.13 (CI=1.04–1.22; P<0.002). Removal of MRADL from the model (in view of the co-linearity analysis) did not affect the results.

In the prediction of mortality for individual patients, MRADL and BPQ in isolation improved the superior tools. With a threshold MRADL <10, predictive values for 1-year mortality were: sensitivity 75%; specificity 63%; PPV 82%; NPV 53%. With a threshold MRADL <12, predictive values were as follows: sensitivity 86%; specificity 55%; PPV 88%; NPV 52%. Increasing or reducing the threshold MRADL further gave inferior values. With a PBQ threshold ≥48 (the mean score for the whole group), predictive values were: sensitivity 83%; specificity 69%; PPV 88%; NPV 52%. Combining MRADL and BPQ at any combination of thresholds did not improve predictive values. Length of hospital stay (any threshold), BASDEC score (any threshold) did not affect the results.

**Discussion**

The present study confirms the high 1-year mortality in older patients hospitalised for AECOPD. One-year mortality is predicted by impairment of QoL, by severity of physical disability related to COPD, by use of LTOT, by hospital readmission and by depressive illness, but multivariate logistic regression analysis suggests that of these the only significant predictor is (poor) QoL.

However, perhaps the most important clinical finding relates to identification of 1-year mortality in individuals, where MRADL and BPQ estimation both produce very good predictive values for sensitivity and PPV, but relatively low specificity and NPV (i.e. are good at identifying mortality but less good at predicting survival). As the important outcome in terms of targeting preventative intervention or palliative care is mortality, we believe that this is an important finding. A 1-year mortality of 36% is typical of the literature evidence and worse than that for many cancers, yet provision of palliative care to patients with advanced COPD is patchy. Further refinement of these tools, with particular emphasis on NPV and specificity, and confirmation of their validity in larger studies, may allow screening of AECOPD patients and appropriate referral to palliative care teams. Even at this stage we would suggest that BPQ or MRADL might be useful in this regard.

Several previous studies have examined mortality following AECOPD admission. Seneff’s group [13] studying AECOPD intensive care admissions found a 59% 1-year mortality (including in-hospital deaths). Vilkmrank’s group [14] showed a 2-year mortality of over 20% in a young elderly group (65–69 years). Connors et al. [15] found 1- and 2-year mortality of 43 and 49%, respectively, in a large study of AECOPD patients (mean age 70). Sin and Tu [16] showed a 1-year mortality rate of approximately 56% in very elderly COPD patients, though Saryal and colleagues [17], in a smaller study of much younger patients, showed lower mortality rates. The recently published British Thoracic Society AECOPD Audit found 14% mortality at 3 months [18]. Others, however, have shown mortality rates of approximately 20–25% at 1 year [19–21]. Our 1-year mortality rate of 36% is consistent with these data. It confirms the high medium-term risk of mortality despite a low in-hospital mortality rate (4 out of 104 patients in our study).

Although we were unable to determine accurately why patients had been placed on LTOT, the findings that LTOT use at recruitment and subsequent readmission are strong predictors of 1-year mortality is not surprising [15, 19, 20]. Both of these features are likely to be surrogates for disease severity, as is length of initial hospital stay, which we also found to be a mortality predictor, in agreement with Incalzi et al. [19]. We did not find arterial blood gas parameters at presentation to be mortality predictors. This agrees with some but not all previous data [13, 19, 21, 22]. It is not surprising that in Seneff’s study [13], severity of respiratory failure in patients admitted to the intensive care unit was a mortality predictor, as half of this mortality was in in-patients. Connors [15] found pO₂ but not pCO₂ to be a predictor, but Almagro [20] found the converse. In the latter case, however, only pCO₂ at discharge was significant, a finding not confirmed by others [17]. The Connors study [15] excluded patients with pCO₂ below 50 mmHg and thus is unrepresentative of AECOPD admissions in general. Unlike some studies [19, 20], we did not find co-morbidity to be a mortality predictor, perhaps because we did not use a standard measure of co-morbidity [23] or (as also applies to some of our other negative findings) because of the relatively small numbers of patients studied.

The possibility that disability is an independent mortality predictor in COPD has been examined previously. Anthonisen et al. [22], in a large study of relatively young stable COPD patients, found that self-perception of disability was a long-term mortality predictor. Seneff [13] showed that ADL limitation was a mortality predictor at 12 months even in those ill enough to require admission to intensive care. Others have confirmed this in similar populations [24]. Connors et al. [15], confirmed that prior functional status was a highly significant mortality predictor. Similar findings were reported by Almagro [20]. In the recent British Thoracic Society AECOPD Audit, poor ‘performance status’ was the strongest predictor of 3-month mortality [18]. Long-term mortality in patients receiving LTOT is predicted by functional status [25].

Until recently no disease-specific ADL scale existed for COPD patients. Use of a disease-specific scale is likely to improve the detection of significant relationships between disability and other variables and outcomes [20]. Whether disability per se is an independent predictor of mortality or whether (like LTOT or readmission) it is merely a surrogate for disease severity is a moot point, though a consensus is emerging that disability is a powerful independent mortality predictor [15, 18, 20, 22, 25]. Similar arguments pertain to our finding and that of others that poor QoL is a mortality predictor [20, 21]. Indeed, in the present study there was significant co-linearity between disability and QoL measures, and QoL (BPQ) emerged as the only independent mortality predictor on multivariate multiple logistic regression analysis.
Few studies have examined the potential role of depressive illness in mortality prediction. Earlier studies have found no consistent relationship between mood disturbance and mortality [22, 23, 26], probably because only generic scales with a psychological component were utilised. Using a validated depression screening scale Almagro [20] reported similar results to ours with an even higher OR of 3.6. The prevalence of depression in the current study (56%) is only a little higher than that in our previous studies of stable COPD outpatients [9, 27], emphasising the importance of utilising validated depression screening instruments as part of the evaluation of COPD patients.

Given that depression is a factor in both disability and mortality [3, 4], an important question is whether alleviation of depression by psychological or pharmacological means will reduce mortality. Identification, acknowledgement and treatment of depression in COPD is difficult [28]. Nevertheless, antidepressants have been shown to be effective in a range of co-morbid disorders [29] and even brief psychological support in COPD may help [30].

In contrast to early studies where FEV1 was a predictor of long-term mortality in subjects with less severe COPD [22, 26], most authors have, in common with the present study, found that lung function does not predict short-medium term mortality in subjects with severe disease [16, 17, 20]. This is probably because the range of FEV1 values is low and compressed, reducing its discriminative power. Similarly, in the current study, age was not an independent predictive factor for survival. This finding is in agreement with Almagro [20], though most studies have found the converse [15, 19, 21, 22, 25]. In some cases, however, the subject population was unrepresentative young [22], other confounding variables such as disability, QoL and depression were not analysed [19, 21], or the predictive factor of increasing age was minor [25]. The age range of the subjects in the current study was representative of those admitted to hospital for AECOPD in the UK. Indeed, subjects were typical, save that we excluded those who had been ventilated.

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References


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