Predicting outcomes following hospitalization for acute exacerbations of COPD

J. STEER1, G.J. GIBSON2 and S.C. BOURKE1,2

From the 1Department of Respiratory Medicine, North Tyneside General Hospital, Northumbria Health NHS Foundation Trust, Rake Lane, North Shields, Tyne and Wear, NE29 8NH and 2Institute of Cellular Medicine, Newcastle University, Framlington Place, Newcastle-upon-Tyne, NE2 4HH, UK

Address correspondence to Dr J. Steer, North Tyneside General Hospital, Northumbria Health NHS Foundation Trust, Rake Lane, North Shields, Tyne and Wear, NE29 8NH, UK.
email: john.steer@northumbria-healthcare.nhs.uk

Summary

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are a frequent cause of hospital admission and are associated with significant morbidity, mortality, high readmission rates and high resource utilization. More accurate prediction of survival and readmission in patients hospitalized with AECOPD should help to optimize clinical management and allocation of resources, including targeting of palliative care and strategies to reduce readmissions. We have reviewed the published retrospective and prospective studies in this field to identify the factors most likely to be of value in predicting in-hospital and post-discharge mortality, and readmission of patients hospitalized for AECOPD. The prognostic factors which appear most important vary with the particular outcome under consideration. In-hospital mortality is related most clearly to the patient's acute physiological state and to the development of acute comorbidity, while post-discharge mortality particularly reflects the severity of the underlying COPD, as well as specific comorbidities, especially cardiac disease. Important factors influencing the frequency of readmission include functional limitation and poor health-related quality of life. Large prospective studies which incorporate all the potentially relevant variables are required to refine prediction of the important outcomes of AECOPD and thus to inform clinical decision making, for example on escalation of care, facilitated discharge and provision of palliative care.

Introduction

Worldwide, chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality. It was the 5th leading cause of mortality in the UK in 2005,1 and is projected to become the 3rd leading cause of death worldwide by 2020.2 Individuals with COPD typically experience acute exacerbations (AECOPD), which may result in hospitalization. The annual cost of managing COPD in the UK is over £800 million,3 with hospitalization responsible for up to 60% of the total.3,4 AECOPD is defined as ‘an acute worsening of the patient’s condition from the stable state, which is sustained and may warrant the patient to seek additional treatment’.5 AECOPD cluster in time, with a high risk of recurrence within 8 weeks of recovery,6 and increasing frequency as the disease progresses.7
Reported in-hospital mortality ranges from 2.5% to 25%,\textsuperscript{8,9} while, of those who survive, 25–55% will be readmitted\textsuperscript{10,11} and 25–50% die\textsuperscript{11,12} within 1 year. Hospitalization provides an opportunity to identify patients at high risk of subsequent readmission or death.

The severity of COPD is defined by the forced expiratory volume in one second (FEV\textsubscript{1}), but FEV\textsubscript{1} is a limited predictor of mortality in severe, stable disease.\textsuperscript{13,14} As no single index accurately and reliably predicts mortality, prognostic tools derived from several indices have been developed.\textsuperscript{15,16}

One example is the BODE index\textsuperscript{15} that, in stable disease, is a better predictor of mortality than FEV\textsubscript{1} alone. However, the relevance of such scores to patients at the time of hospitalization with AECOPD is uncertain. Some authors have attempted to develop prognostic instruments for hospitalized patients but they have either only studied patients with severe disease\textsuperscript{17–19} or the instruments have not been validated\textsuperscript{20–22} and therefore the models may not be applicable to the wider population hospitalized with AECOPD. These studies are discussed in greater depth below (Table 1).

In community acquired pneumonia, widespread use of a clinical prediction instrument (CURB-65 tool\textsuperscript{23}) has improved patient care, including choice of antibiotics and optimal location of care.\textsuperscript{24} Similar prognostic tools in COPD could help to direct resources to those most in need, reduce (re)hospitalization and improve patient care. This is especially true in patients hospitalized with AECOPD given the high rates of mortality and readmission.

### Methods

We searched Medline, CINAHL and EMBASE using the following search terms: chronic obstructive pulmonary disease, exacerbation, hospitalization, mortality and patient readmission. Articles reporting empirical quantitative research focusing on the identification of factors associated with subsequent mortality or hospital readmission of patients with an acute exacerbation of COPD requiring treatment in hospital were included. Publications were retrieved if, firstly the title and secondly the abstract, suggested that it was pertinent to our review question. We screened the reference lists of retrieved publications and relevant articles not previously identified were also included.

Since prognostic studies in AECOPD have used varied methodology and case mix, it is not possible accurately to quantify the relative impacts of different prognostic variables, or rank their relative importance. Consequently, in this review we summarize the main findings and identify common themes within the data upon which future research can build. In order to enable comparison between different prognostic indices, the strength of the relationship between outcome and variable has been arbitrarily defined as follows: strong evidence—at least three studies showing an independent relationship; moderate evidence—two studies showing an independent relationship and weak evidence—one study showing an independent relationship.

### Results

#### Predicting mortality in hospital and after discharge with AECOPD

It is important to distinguish prediction of in-hospital and post-discharge mortality; although there is some overlap, the indices involved and their prognostic strength differ between the two outcomes (Table 2).

##### Patient demographics

Not surprisingly, older age is an independent predictor of both in-hospital and post-discharge mortality.\textsuperscript{8,11,20,22,25–30} However, disease duration may be a more important predictor of death following discharge than chronological age, which may act as a surrogate marker.\textsuperscript{31}

Although studies investigating the association of mortality with gender are frequently limited by a small number of female participants, a large retrospective analysis (including 31 039 females) showed that male gender was independently predictive of in-hospital death.\textsuperscript{8} Following discharge, male gender may also independently predict early mortality (within 30 days),\textsuperscript{32} but gender appears unrelated to long-term mortality.\textsuperscript{27,31,33–36}

##### Comorbidity

In stable COPD, the comorbidity burden (usually measured by Charlson Index, CI) is an established predictor of mortality.\textsuperscript{37–39} In AECOPD requiring hospitalization, the evidence is less consistent; CI was an independent predictor of death following discharge in one study,\textsuperscript{40} but three others showed no independent association with either in-hospital\textsuperscript{8,41} or post-discharge\textsuperscript{44} mortality. However, specific comorbidities, most notably ischaemic heart disease\textsuperscript{27,35,42,43} congestive cardiac failure,\textsuperscript{10,29,41,42} chronic liver disease,\textsuperscript{41} chronic renal failure\textsuperscript{22} and diabetes,\textsuperscript{42–45} independently predict in-hospital mortality, post-discharge mortality or both. A possible explanation for this apparent paradox is that all the conditions listed...
above are particularly liable to acute decompensation, and hence increased mortality, which more commonly occur during ill-health (such as during AECOPD) than clinical stability. In individuals hospitalized for AECOPD, acute comorbidity (for example, shock, pulmonary oedema, arrhythmia, stroke, renal insufficiency) is independently associated with a greater risk of in-hospital, and 6-month, mortality. In one study of patients with AECOPD requiring intensive care, it was not the severity of respiratory failure that predicted mortality, but the development of non-respiratory organ failure.

Prior treatment
An association exists between use of long-term oxygen therapy (LTOT) and in-hospital mortality, but there is no independent relationship suggesting that LTOT may act as a surrogate marker of disease severity. Use of maintenance oral corticosteroids independently predicts in-hospital death in patients requiring treatment in an intensive care unit (ICU), but has no impact on outcome in unselected patients with AECOPD. In those surviving to discharge, the use of maintenance oral corticosteroids, but not LTOT, independently predicts long-term mortality.

Smoking status
Some studies have shown that both current smoking and total smoking load are independently predictive of death, but many other studies have failed to replicate these findings.

Functional limitation and health-related quality of life
In stable COPD, inability to perform activities of daily living is independently predictive of mortality. The relationship between functional limitation and in-hospital mortality has only been studied in patients requiring non-invasive ventilation (NIV) or treatment in an intensive care unit (ICU), where no studies have found a significant independent relationship. However, treatment in ICU may not be considered appropriate for individuals with very severe disability and these results should therefore be interpreted with caution. In contrast, in those who survive to hospital discharge, functional impairment predicts both early and long-term mortality.

Greater social support prior to hospitalization does not independently predict mortality, whereas admission from a long-term care facility does. Following discharge, a need for social support is associated with long-term mortality but only marital status is an independent predictor (unmarried = increased risk of death), nor the amount of social care required, nor whether the individual lives alone.

The relation between quality of life or psychological well-being and in-hospital mortality has not been reported but poor health-related quality of life and depression at discharge are both independent predictors of mortality for up to 2 years.

Previous hospitalizations
Patients admitted to hospital in the previous year, for COPD or non-COPD, have a higher risk of death following discharge. The relationship between prior hospitalization and in-hospital mortality is more complex: prior hospitalization for AECOPD, particularly if complicated by respiratory failure, is an independent predictor of in-hospital mortality, whereas prior hospitalization for any cause is not. Individuals with COPD who frequently exacerbate (and therefore have a higher risk of hospitalization) also have more severe underlying disease and a higher mortality. Prior hospitalization for any cause is likely to reflect comorbidity, but, as discussed above, specific comorbid conditions are stronger predictors of outcome, and these covariates may explain why previous hospital admissions for any cause do not independently predict mortality.

Symptoms and signs during hospital admission
Poor nutritional status (measured by BMI or other anthropometrics) is predictive of mortality both in-hospital and following discharge. The severity of dyspnoea during the stable state also independently predicts both in-hospital and post-discharge mortality. In one study of patients admitted to an Emergency Department with AECOPD, the presence of acute neurological impairment and the use of inspiratory, accessory muscles were independently predictive of in-hospital mortality, but the subjective nature of these findings limits their widespread clinical application.

The presence of pedal oedema, which can imply the presence of cor pulmonale and severe disease, is independently associated with mortality following discharge rather than in hospital. Thus, a feature associated with severe disease predicts long-term mortality, while signs or symptoms related to the severity of the acute illness better predict in-hospital mortality.
In patients with community-acquired pneumonia, the presence of coexisting COPD increases the risk of mortality. The impact of pneumonia on mortality, in patients hospitalized with AECOPD, is less clear. In part, this is because the presence of pneumonia is often not documented or is a criterion for exclusion from the study. Most studies either show no association between pneumonia and mortality, or an association on univariate analysis, not confirmed on multivariate analysis. However, a large retrospective analysis of coded admission diagnoses in 265,200 patients hospitalized with AECOPD showed that an admission diagnosis of ‘pneumonia or influenza’, in addition to AECOPD, independently predicted in-hospital mortality.

Other clinical findings independently predictive of in-hospital mortality include: hypotension, tachycardia and the severity of the acute exacerbation (Anthonisen criteria). In patients with AECOPD requiring NIV or intensive care, acute physiology scores (APACHE II and SAPS), increased respiratory rate and reduced Glasgow Coma Score (GCS) are all independently associated with in-hospital mortality. A study in AECOPD requiring admission to ICU showed that respiratory physiological variables (respiratory rate, pH, PaCO2, PaO2 and alveolar–arterial gradient) were not related to in-hospital mortality but did independently predict 6-month mortality. Variables related to non-respiratory system function, however, were strong independent predictors of both in-hospital and 6-month mortality. This suggests that the main factor determining in-hospital mortality in the ICU setting is the development of dysfunction of other bodily systems, with the severity of the underlying respiratory condition more important in relation to long-term prognosis. This is consistent with the data on comorbidity where non-respiratory conditions prone to acute decompensation during hospitalization are stronger predictors of mortality during, rather than after, admission.

**Arterial blood gas measurements**

**Hypoxaemia.** In studies in which FiO2 is not standardized, it is not surprising that no relation between low PaO2 and mortality is found. However, hypoxaemia breathing air or an increased alveolar–arterial gradient on admission are independently associated with in-hospital mortality, and a low PaO2/FiO2 ratio independently predicts 6-month mortality. These indices probably reflect the severity of both the acute illness and the underlying condition.

**Hypercapnia.** In stable COPD, hypercapnia is a strong independent predictor of mortality. In acute exacerbations, however, high PaCO2 values on admission have not been shown to independently predict in-hospital death. In AECOPD requiring NIV, a very high PaCO2 is predictive of treatment failure but it is not clear whether severe hypercapnia predicts in-hospital mortality. Hypercapnia is likely to signify severe COPD as well as a severe acute exacerbation, and it may therefore appear surprising that it is not related to short-term mortality. However, in many studies, the participants’ mean PaCO2 is high (often >7 kPa), which is likely to limit its discriminative value. A sub-group analysis of hospitalized patients with AECOPD, the majority of whom (82%) had PaCO2 < 6.0 kPa, showed that hypercapnia independently predicted in-hospital death, and two further studies with mean PaCO2 closer to normal (mean < 6.5 kPa) showed an association between hypercapnia and in-hospital mortality.

The severity of hypercapnia on admission is more clearly related to long-term mortality. Almagro et al., however, suggested that hypercapnia at discharge, rather than admission, was the more important predictor, a proposal corroborated by a prospective cohort study, which showed that individuals with hypercapnia at admission and discharge (‘irreversible hypercapnia’) had significantly higher 5-year mortality rates than those in whom hypercapnia resolved during their hospital stay. These findings support the recommendation by the British Thoracic Society that all patients with AECOPD complicated by respiratory failure should have arterial blood gas (ABG) recorded before hospital discharge.

**Acidaemia.** Acidaemia usually implies a severe acute exacerbation of COPD. In AECOPD requiring hospitalization, the severity of acidaemia predicts both in-hospital and 30-day mortality. While it has not been shown to predict long-term mortality, the range of pH values in the relevant studies was narrow, which may have influenced results: one study involved patients with severe acidaemia (mean pH 7.24) requiring NIV, while the other included few acidaemic patients (mean pH 7.41).

**Laboratory investigations**

Biochemical and haematological abnormalities commonly associated with a severe acute illness,
Predicting outcomes in acute exacerbations of COPD

or the severity of the acute illness, are predictive of in-hospital mortality in AECOPD. These indices include: hyperglycaemia,\textsuperscript{69,81} renal dysfunction,\textsuperscript{17,21,48} hypoalbuminaemia,\textsuperscript{9,17,74} anaemia,\textsuperscript{73} leucocytosis/leucopenia,\textsuperscript{17} inadequate metabolic compensation for respiratory acidosis (low serum bicarbonate)\textsuperscript{73} and elevated serum procalcitonin\textsuperscript{82} and troponin.\textsuperscript{65}

Biochemical and haematological indices which indicate the presence of comorbidity, chronic organ dysfunction or the severity of underlying respiratory disease predict mortality after discharge. For example, hypoalbuminaemia occurs as an acute response to severe infection as well as being a marker of poor synthetic liver function, which may explain its ability independently to predict post-discharge mortality.\textsuperscript{19,31} Elevated serum troponin may result not only from acute cardiac dysfunction during the hospital stay, but also relates to ongoing cardiac comorbidity. As cardiac disease is the most frequent cause of death in patients with COPD,\textsuperscript{81,84} it is unsurprising that elevated troponin independently predicts death following discharge.\textsuperscript{43,85} The presence of anaemia may reflect severe underlying COPD, or it may be a sign of comorbidity. Either, or both, might explain why anaemia independently predicts higher mortality following hospital discharge.\textsuperscript{43} Hence, the same abnormality can influence both short- and long-term outcomes, though not necessarily via the same mechanism.

**Spirometry**

In stable disease, the FEV\textsubscript{1} is used to classify the severity of COPD and lower values are associated with higher mortality.\textsuperscript{15,53,86} There is, however, varying evidence surrounding its value as a predictor of in-hospital death in AECOPD. In many retrospective studies, missing FEV\textsubscript{1} data may explain why no association was found between FEV\textsubscript{1} and in-hospital survival.\textsuperscript{25,54,81} The results from one study of patients treated with NIV\textsuperscript{46} suggested that low FEV\textsubscript{1} was independently predictive of treatment failure (death or need for invasive ventilation), but others have found no such relationship.\textsuperscript{9,70,87} The lack of consistency about the prognostic value of FEV\textsubscript{1} is emphasized by one study\textsuperscript{88} in which, counterintuitively, a higher baseline FEV\textsubscript{1} was associated with higher in-hospital mortality.

Unlike in-hospital mortality, most studies investigating prognosis post-discharge are prospective and benefit from fewer missing FEV\textsubscript{1} values. Three studies\textsuperscript{22,36,41} showed that individuals with low FEV\textsubscript{1} are at increased risk of death following discharge, but three others\textsuperscript{11,31,40} found no such association. Closer analysis of the positive studies suggest that FEV\textsubscript{1} is predictive of mortality either when very low (FEV\textsubscript{1} <590 ml)\textsuperscript{22} or when the population on average has relatively well preserved lung function (mean FEV\textsubscript{1} \~50% predicted).\textsuperscript{27} It is therefore likely that patients with the most severely impaired lung function have a higher likelihood of death, but FEV\textsubscript{1} lacks discriminatory power because most patients hospitalized with AECOPD have severe COPD and a narrow range of FEV\textsubscript{1}.

**Clinical prediction instruments**

Studies aimed at developing clinical prediction tools to improve prognostication in AECOPD are summarized in Table 1.

Wildman et al.\textsuperscript{17} developed two prognostic instruments to aid prediction of in-hospital and 6-month mortality\textsuperscript{18} from two large cohorts of patients with acute exacerbations of COPD or asthma admitted to an ICU. Both showed good discrimination in their derivation cohorts and both underwent internal validation. However, their utility in a population of patients hospitalized with AECOPD not requiring intensive care is uncertain.

Roche et al.\textsuperscript{20} recruited all patients admitted to the Emergency Department with AECOPD. Although the final tool showed good discrimination in development and validation cohorts, the use of subjectively defined clinical measurements potentially limits its widespread applicability.

Three further clinical prognostic instruments assisting the prediction of in-hospital\textsuperscript{21} and long-term\textsuperscript{22,61} mortality in AECOPD showed promise in their derivation studies but neither has undergone external validation and therefore their accuracy beyond their study populations is uncertain.

Ruiz-Gonzalez et al.\textsuperscript{51} investigated variables associated with a composite outcome of: mortality (in-hospital or 15 days following discharge); need for ICU care; or development of acute cardiac failure. The instrument has not been validated and the small number of deaths recorded (21) suggest that it is probably a stronger predictor of the other outcomes than of mortality.

Connors et al.\textsuperscript{19} analysed 1016 patients hospitalized with severe AECOPD (PaCO\textsubscript{2} >6.65 kPa) and developed an instrument aimed at predicting 6-month mortality. This showed fair discrimination in the subsequent validation by the same authors but no external validation has been reported.

Anton et al.\textsuperscript{88} and Confalonieri et al.\textsuperscript{57} aimed to develop equations predicting failure of treatment in individuals requiring NIV. The general applicability of the former is limited by the small number of participants (n = 44). The study by Confalonieri et al.,
<table>
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<tr>
<th>References</th>
<th>Design</th>
<th>Outcome</th>
<th>N</th>
<th>Variables included in model</th>
<th>Predictive ability of instrument&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Validated?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wildman et al&lt;sup&gt;.17&lt;/sup&gt;</td>
<td>Retrospective AECOPD and asthma requiring ICU</td>
<td>In-hospital mortality</td>
<td>8527</td>
<td>Heart rate, blood pressure, pH, sodium, urea, creatinine, albumin, WBC</td>
<td>AUROC 0.718</td>
<td>Internal validation</td>
</tr>
<tr>
<td>Roche et al&lt;sup&gt;.20&lt;/sup&gt;</td>
<td>Prospective ED attendances with AECOPD</td>
<td>In-hospital mortality</td>
<td>794</td>
<td>Age, clinical signs of severity, dyspnoea grade</td>
<td>AUROC 0.79</td>
<td>Internal validation</td>
</tr>
<tr>
<td>Mohan et al&lt;sup&gt;.21&lt;/sup&gt;</td>
<td>Prospective Admission with AECOPD</td>
<td>In-hospital mortality</td>
<td>151</td>
<td>Serum creatinine, serum sodium</td>
<td>AUROC 0.73</td>
<td>No</td>
</tr>
<tr>
<td>Anton et al&lt;sup&gt;.18&lt;/sup&gt;</td>
<td>Prospective AECOPD requiring NIV</td>
<td>Failure of NIV</td>
<td>59</td>
<td>Change in $P_{a}CO_2$ on NIV, initial pH, baseline FEV&lt;sub&gt;1&lt;/sub&gt; and initial $P_{a}CO_2$</td>
<td>Sensitivity 0.97, specificity 0.9</td>
<td>Internal validation</td>
</tr>
<tr>
<td>Ruiz-Gonzalez et al&lt;sup&gt;.51&lt;/sup&gt;</td>
<td>Prospective Admissions with AECOPD</td>
<td>Mixed&lt;sup&gt;b&lt;/sup&gt;</td>
<td>147</td>
<td>Confusion, CRP $\geq$50mg/l, $\geq$2 comorbidities, current smoking status</td>
<td>AUROC 0.80</td>
<td>No</td>
</tr>
<tr>
<td>Confalonie-ni et al&lt;sup&gt;.57&lt;/sup&gt;</td>
<td>Prospective AECOPD requiring NIV</td>
<td>Failure of NIV</td>
<td>1033</td>
<td>pH, respiratory rate, APACHE II score, GCS</td>
<td>AUROC 0.88</td>
<td>External validation</td>
</tr>
<tr>
<td>Connors et al&lt;sup&gt;.19&lt;/sup&gt;</td>
<td>Prospective Admissions with severe AECOPD</td>
<td>6-month mortality</td>
<td>1016</td>
<td>APACHE III, age, PaO2/FiO2, BMI, level of disability, albumin, CHF, cor pulmonale, comorbidity</td>
<td>AUROC 0.731</td>
<td>Internal validation</td>
</tr>
<tr>
<td>Tsimogian-ni et al&lt;sup&gt;.61&lt;/sup&gt;</td>
<td>Prospective admissions with AECOPD</td>
<td>3-year mortality</td>
<td>81</td>
<td>BMI, MRC Dyspnoea score</td>
<td>AUROC 0.83</td>
<td>No</td>
</tr>
<tr>
<td>Antonelli-Incalzi et al&lt;sup&gt;.22&lt;/sup&gt;</td>
<td>Prospective Discharged following AECOPD</td>
<td>5-year mortality</td>
<td>270</td>
<td>Age, ECG evidence of RVH, ECG evidence of IHD, chronic renal failure, FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Sensitivity 63%, specificity 77%</td>
<td>No</td>
</tr>
<tr>
<td>Wildman et al&lt;sup&gt;.18&lt;/sup&gt;</td>
<td>Prospective AECOPD and asthma requiring ITU or HDU</td>
<td>6-month mortality</td>
<td>832</td>
<td>CAPS, age, male, mid arm circumference, functional impairment, AF, days spent in hospital, GCS</td>
<td>AUROC 0.75</td>
<td>Internal validation</td>
</tr>
</tbody>
</table>

<sup>a</sup>AUROC: ‘area under the receiver operating characteristic curve’: a measure of predictive ability of instrument (0.5: no predictive ability; >0.70 = fair discrimination; >0.80 = good discrimination; 1: perfect discrimination)<sup>89</sup>; <sup>b</sup>Composite outcome of: mortality, need for ICU care, or development of acute cardiac failure; <sup>c</sup>assessed by Katz ADL score.

ED: emergency department; ADL: activities of daily living; BMI: body mass index; WBC: white blood cell count; CHF: congestive heart failure; IHD: ischaemic heart disease; CRP: C reactive protein; ECG: electrocardiogram; RVH: right ventricular hypertrophy; GCS: Glasgow Coma Score; CAPS: COPD Asthma PhysiologyScore; AF: atrial fibrillation; APACHE: Acute Physiology and Chronic Health Evaluation.
Predicting readmission following hospitalization for AECOPD

Several authors have investigated the risk of hospitalization in stable COPD, but few have studied variables associated with a high rate of readmission following hospitalization for AECOPD (Table 2). Clearly this is of importance to clinicians managing AECOPD in hospital and the available data are reviewed below.

Socio-demographic variables predictive of hospital readmission in patients admitted to hospital with AECOPD include: older age, male sex, low monthly income and being unmarried or widowed. Indices related to more severe underlying COPD are also independent predictors of readmission including: the number of prior admissions for AECOPD, lower FEV₁, duration of disease >5 years and hypercapnia at discharge.

As discussed above, markers of acute physiological derangement predict mortality during or after hospitalization for AECOPD, but hypoxaemia, acidaemia, low peak expiratory flow, high APACHE II score, higher respiratory rate, hypoalbuminaemia, renal impairment and high white cell count are not independently related to hospital readmission. Hence, while the severity of the acute illness predicts mortality, it does not appear to predict readmission following discharge.

The severity of functional impairment and poorer quality of life scores both independently predict readmission as well as mortality. However, the influence of anxiety or depression on readmission differs from their impact on mortality. Anxiety is independently predictive of readmission only in patients with a poor quality of life, and while depression predicts mortality, it is not an independent predictor of readmission. A depressed individual’s hopelessness and lack of motivation to change their circumstances may result in not seeking medical attention when unwell, a factor hypothesized to cause fewer readmissions but higher mortality following discharge.

Comorbidity influences hospital readmission in patients with AECOPD. Coexistent asthma or cardiac comorbidities, including pulmonary hypertension, are independently predictive of readmission, whereas diabetes is apparently protective. These findings contrast with those on mortality where the coexistence of diabetes is associated with a higher mortality, and asthma is protective. Perhaps the extensive community support available for patients with diabetes ensures that episodes of AECOPD are recognized and treated promptly, with hospital admission thereby averted. No relation has been found between the Charlson Index (CI) and hospital readmission. However, the total number of comorbidities, and a global measure of chronic disease burden, predict readmission. Possibly, the prognostic influence of individual comorbidities included in the CI conflicts, in a similar way that asthma and diabetes conflict, and this may explain why the CI has no association with readmission.

BMI is a strong independent predictor of mortality in both stable COPD and AECOPD, but low BMI is not independently predictive of hospital readmission. Respiratory muscle overload at discharge independently predicts readmission, and low fat free mass and muscle mass are associated with rehospitalization within 3 months, but not independent of other variables.

At discharge, patients prescribed high dose inhaled corticosteroids, oral theophylline and maintenance oral corticosteroids are at an increased risk of hospital readmission, independent of other variables. LTOT or home nebulized bronchodilators have frequently been shown to be predictive of readmission, but LTOT was an independent predictor in only a single study. Although one study showed an association between inhaled anti-cholinergics and readmission, others have not confirmed this finding.

Conclusions

Some indices are of value in predicting all the outcomes discussed: older age; previous admissions for AECOPD; and comorbidity (although the relationship to comorbidity differs depending on the outcome of interest).

Clinical practice is often influenced by the assumption that patients with more severe underlying disease are likely to have worse in-hospital outcomes. For example, decisions regarding appropriateness of invasive ventilation are often made on the basis of the severity of underlying COPD. In general, the results from the studies included in this review support this approach. Although markers of disease severity such as low FEV₁ or hypercapnia do not predict in-hospital mortality, their discriminative value is limited by the narrow range seen in the hospitalized population, most of whom have
Table 2 Relationships between different variables and outcomes following hospitalization for AECOPD

<table>
<thead>
<tr>
<th>In-hospital mortality</th>
<th>Post-discharge mortality&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Hospital readmission</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strong evidence&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td>• Older age</td>
<td>• Older age</td>
</tr>
<tr>
<td>• Poor nutritional status</td>
<td>• Poor nutritional status</td>
<td>• Low FEV&lt;sub&gt;1&lt;/sub&gt;</td>
</tr>
<tr>
<td>• Acute comorbidity</td>
<td>• Cardiac comorbidity</td>
<td>• Functional limitation</td>
</tr>
<tr>
<td>• Elevated acute physiology scores</td>
<td>• Diabetes</td>
<td>• Poor quality of life</td>
</tr>
<tr>
<td>• Acidaemia</td>
<td>• Functional limitation</td>
<td></td>
</tr>
<tr>
<td>• Impaired consciousness</td>
<td>• Poor quality of life</td>
<td></td>
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<tr>
<td>• Prior hospitalizations for AECOPD</td>
<td>• Prior hospitalizations</td>
<td></td>
</tr>
<tr>
<td>• Hypoxaemia&lt;sup&gt;c&lt;/sup&gt;</td>
<td>• Cor pulmonale&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>• Renal impairment</td>
<td>• Maintenance oral corticosteroids</td>
<td></td>
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<tr>
<td>• Hypotension</td>
<td>• Hypoalbuminaemia</td>
<td></td>
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<tr>
<td>• Hypoalbuminaemia</td>
<td>• Elevated troponin</td>
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| **Moderate evidence<sup>b</sup>** | • Tachypnoea | • Depression | • Male gender |
| • Hyperglycaemia | • Hypoalbuminaemia | • Hypoxaemia<sup>c</sup> | • Cor pulmonale<sup>d</sup> |
| • Hypercapnia<sup>a</sup> | • Dyspnoea | • Disease duration | • Comorbidity burden<sup>f</sup> |

| **Weak evidence<sup>b</sup>** | • Male gender | • Depression | • Male gender |
| • Low monthly income | • Hypoalbuminaemia | • Hypoxaemia<sup>c</sup> | • Long duration of COPD |
| • Current smoking | • Disease duration | • Low serum bicarbonate | • Unmarried/widowed |
| • Admission from long-term care facility | • Current smoking | • Anaemia | • Hypercapnia |
| • Elevated troponin | • >60 cigarette pack years | • Hypoxaemia<sup>c</sup> | • Anxiety |
| • Severity of acute exacerbation<sup>i</sup> | • Anaemia | • Unmarried | • Asthma |
| • Tachycardia | • Hypoxaemia<sup>c</sup> | • CI | • Oral theophylline |
| • Dyspnoea | • Asthma | | • High dose ICS |
| • Cerebrovascular disease | | | • Inhaled anti-cholinergics |
| • Chronic liver disease | | | • Respiratory muscle overload<sup>h</sup> |
| • Congestive cardiac failure | | | • Cardiac comorbidity |
| • Maintenance oral corticosteroids | | | |
| • Low FEV<sub>1</sub><sup>e</sup> | | | |
| • Pneumonia | | | |
| • Low serum bicarbonate | | | |
| • Anaemia | | | |
| • Elevated procalcitonin | | | |

<sup>a</sup>Excluding studies investigating mortality within 30 days of discharge; <sup>b</sup>Strong evidence—at least three studies showing independent relationship; moderate evidence—two studies showing independent relationship; weak evidence—one study showing independent relationship. <sup>c</sup>Hypoxaemia on ABG, low alveolar–arterial gradient, low PaO<sub>2</sub>/FiO<sub>2</sub> ratio; <sup>d</sup>Clinical diagnosis of cor pulmonale, pulmonary hypertension on echocardiogram, or presence of bilateral pedal oedema; <sup>e</sup>Predictive of NIV failure; <sup>f</sup>High total number of comorbidities or high chronic disease score<sup>105</sup>; <sup>g</sup>According to Anthonisen Criteria; <sup>h</sup>Measured non-invasively using pressure-time index. ICS: inhaled corticosteroids.
severe COPD. Other variables reflecting severe underlying disease do have an important influence on in-hospital mortality. These include: the number of prior hospitalizations for AECOPD; the severity of dyspnoea; and low BMI.

Although in-hospital mortality is related to the severity of underlying disease, the main influence on in-hospital mortality appears to be the severity of the acute illness. Markers of acute physiological impairment, especially non-respiratory variables, acute non-respiratory comorbidity or organ dysfunction, and the presence of acidemia are all strong independent predictors of in-hospital mortality.

If patients survive to discharge, the severity of the acute illness has less impact on subsequent mortality with the severity of the underlying disease becoming the more important factor. Functional disability and impairment of quality of life also independently predict long-term mortality. When hospital readmission is the outcome of interest, functional disability and impaired quality of life assume particularly important prognostic roles.

The strength of the relationships between relevant variables and outcome in patients hospitalized with AECOPD is summarized in Table 2.

Potential prognostic variables, excluding the presence of chronic comorbid conditions and increased age which have been shown to predict all three outcomes, can be broadly classified in to the following categories: markers of the severity of acute illness (e.g. acidemia, hypoxaemia, presence of acute comorbidity); markers of underlying disease severity (e.g. low FEV1, previous hospitalization, cor pulmonale) and poor health status (e.g. low quality of life, impaired functional status). Their relative impacts on the outcomes discussed here (in-hospital mortality, post-discharge mortality and hospital readmission) vary, as depicted schematically in Figure 1.

Despite considerable research on patients hospitalized with AECOPD, we are still unable accurately to predict the important clinical outcomes in an individual patient. Models that have shown promise in their derivation cohort have frequently not been validated, or have only undergone internal validation, which often provides an over-optimistic assessment of the performance of the original model.109

Palliative care is an important part of the management of advanced COPD and should be considered not only at the end of life. Compared to patients with unresectable non-small cell lung cancer, patients with advanced COPD have significantly worse health status, higher functional dependence and more anxiety and depression.110 They, however, are less likely to receive specialist palliative care input than those with malignant disease,110,111 despite the specific concern expressed by patients with advanced COPD that non-specialist palliative care would not sufficiently address their needs.112 Under-provision of palliative care may reflect a combination of difficulty in predicting end of life in COPD, failure to recognize poor symptom control and quality of life and a greater emphasis on providing palliative care for malignant, rather than non-malignant diseases.

Hospitalization for AECOPD becomes more frequent with severe disease and places an enormous burden upon the patients and the healthcare system. Large prospective studies to develop tools which accurately predict in-hospital death and outcomes following discharge (including readmission, symptom control and quality of life) would help to inform clinical decisions, such as the appropriate escalation of care and optimum utilization of resources for safely facilitating early discharge and reducing readmissions, as well as better identifying patients with unmet palliative care needs. This would help to direct healthcare resources to those most likely to benefit and to reduce the significant burden of morbidity in this disease.

Conflict of interest: None declared.

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Figure 1. Schematic representation of relative impact of three main groups of variables on different outcomes.


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