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Predicting end-of-life in patients with an exacerbation of COPD by routine clinical assessment

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Summary
The purpose of this study was to determine if routine clinical assessment could reliably predict in-hospital death in patients admitted with acute exacerbation of COPD (AECOPD).
Methods: In a case-crossover study the case records of AECOPD related deaths were reviewed. Clinical and laboratory variables including performance status (WHO-PS) and a composite physiological score (early warning score, EWS) at initial clinical assessment on final admission (FA) and penultimate admission (PA) for AECOPD were compared.
Results: Sixty patients included in study, female 60%, mean age (SD) 75 (8.7) years. 98% had $\geq$2 admissions for AECOPD. On univariate analysis variables associated with death were: Charlson score, WHO-PS, EWS, pH $<$ 7.35, Urea and CRP. On multivariate analysis predictors of mortality were: WHO-PS (OR 95% CI: 4.9 (1.06–22.61); $p = 0.04$) and EWS (OR 95% CI: 3.39 (1.56–7.41); $p = 0.002$). ROC analysis of relationship between combined WHO-PS/EWS score and death gave AUC 0.86; a total score $\geq$ 6 had sensitivity 78% and specificity 86.2% and on multivariate analysis OR (95% CI) for death was 19.3 (4.3–86.2); $p < 0.0005$.
Conclusion: In-hospital deaths from AECOPD may be predicted by assessment of WHO-PS and EWS on admission to hospital.

Introduction

Approximately 10% of the UK population over the age of 40 years suffers from chronic obstructive pulmonary disease (COPD) and acute exacerbation of COPD (AECOPD) is the single most common cause for emergency medical admission to hospital.[1,2] In the UK there are over 31,000 deaths due to COPD annually although the numbers may be considerably higher.[3] The inpatient mortality from AECOPD is approximately 10–20% and the mortality within 12 months of an exacerbation is up to 49%.[4]

In stable COPD the risk of death increases with severity of airflow obstruction, in the presence of hypoxaemia or

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hypercapnia, poor exercise capacity, a high degree of functional breathlessness, low body mass index and frequent exacerbations.[5–15] The BODE Index a composite score of body mass index, airflow obstruction, dyspnoea and exercise capacity, has been shown to be highly predictive of mortality.[16]

In patients admitted to hospital with AECOPD there are a number of poor prognostic indicators including severity of hypoxia, presence of hypercapnia, pH $<$ 7.35 and raised CRP level.[17–22] There is, however, no reliable predictor of the terminal stage of the disease in individual patients. The prognostic models used in the SUPPORT study, which were based on the Acute Physiology and Chronic Health Evaluation II, highlighted this difficulty.[23]

The prevalence of COPD is increasing, and by the year 2020 it is expected to become the third leading cause of death in the world; therefore, there is increasingly a need for tools that can reliably identify patients that are in the terminal stages of the disease.[24]

As most COPD patients have multiple AECOPD related hospital admissions prior to death an interval change in clinical and laboratory variables, between the penultimate and final (fatal) admission for AECOPD may help identify the terminal stage of the disease. The purpose of this study was to determine if routine clinical assessment that includes a simple assessment of global performance and a composite score of physiological impairment could provide reliable predictors of death in hospital.

Methods

Study design and patient population

The study was a case-crossover design in which the study subjects were patients that died in hospital from AECOPD, and each subject served as his/her own control. We compared clinical and laboratory variables when the patients were admitted and died from AECOPD (case) with their penultimate admission for AECOPD (control).

In-hospital deaths (2004–2007) from COPD were identified from the hospital admissions database. Patients were included if the diagnosis of COPD had been confirmed previously by spirometry, AECOPD was the reason for hospital admission and clinical features satisfied accepted definitions of AECOPD ($\geq$2 of: increased dyspnoea, increased sputum volume, increased sputum purulence), and there was no other plausible cause of death.[25,26]

Data collected

On admission to hospital patients were assessed using a standard proforma that included an evaluation of the patients' social circumstances (living alone or with carer) and assessment of functional status from which we derived the WHO-ECOG performance score (WHO-PS: 0 – Asymptomatic and normal activity. 1 – Symptomatic but normal activity other than physical work. 2 – Symptomatic; some limitation of normal activity but up and about $>$50% of time during day; self-caring. 3 – Symptomatic; in bed/chair $>$ 50% of time during day; requires some help with self-care. 4 – Chair/Bedbound; cannot carry out any self-care).[27]

The presence of co-morbidity was recorded and quantified according to the index of Charlson et al.[28,29] The most recent body mass index (BMI), drug therapy for COPD, use of long-term oxygen therapy (LTOT), most recent FEV_1, arterial blood gas data (on admission and at 24 h), serum urea and creatinine and C-reactive protein (CRP) were recorded. Severity of COPD was graded according to the *Global Initiative on Obstructive Lung Disease* (GOLD) staging classification (2003).[30] A composite score of physiological impairment the Early Warning Score (EWS derived from: Heart Rate, Systolic Blood Pressure, Respiratory rate, Temperature, CNS score, and Urine output) was recorded on admission and at intervals thereafter (Appendix 1).[31,32] The highest value of the EWS in each 24 h period was used in the analysis.

Analysis

Data was analysed using SPSS software (SPSS Inc., Chicago, IL). Comparisons were made between the final (case) and penultimate (control) admissions. Continuous data are presented as means and standard deviation (SD) or as medians and range unless otherwise stated. Continuous variables were compared by matched pair *t*-test. Chi-squared was used to compare categorical variables in bivariate analysis. The relationship between variables and death was examined by conditional logistic regression on matched data. Variables that were significant on univariate analysis ($p < 0.05$) were included in the multivariate analysis. The intervals between admission and from admission to death was analysed by the Kaplan–Meier method and Cox proportional hazards regression analysis.

Results

Of 100 patients initially identified 60 satisfied the inclusion criteria. A total of 97% had $\geq$2 admissions for AECOPD. The median (IQ) number of previous admissions for AECOPD in the 12 months prior to death was 1 (0–2) and median (IQ) interval between penultimate (PA) and final admission (FA) was 14 (5–62) weeks. After controlling for social circumstances (Lives alone: FA: 51.6%) and WHO-PS (FA) the interval between admissions was shorter in patients receiving LTOT (HR 2.61 (95% CI: 1.38–4.9) $p = 0.003$; Fig. 1).

Clinical and laboratory variables on admission to hospital are shown in Table 1. Sixty percent of patients were female; the mean age at death was 75.3 (8.6) years. Most patients had GOLD stage IV COPD (PA 89.6% *v* FA 90.0%) and more than half were receiving LTOT (PA 50% *v* FA 58%). Co-morbidity was common particularly congestive cardiac failure and there was a significant increase in Charlson co-morbidity index on the final admission. Fifty percent of patients were described as cachectic and/or had a BMI $\leq$ 20 kg/m^2.

The frequency and number of days spent in hospital for AECOPD related admissions in the previous 12 months were greater on the final admission. Differences in maintenance therapy for COPD between admissions included greater use of inhaled corticosteroids (ICS) and tiotropium on the final admission (ICS, PA 62% *v* FA 82%; $p < 0.05$; Tiotropium, PA 14% *v* FA 32%; $p < 0.05$). There were no differences in the use of oral corticosteroid maintenance therapy (38%), benzodiazepines (12%) or opiates (5%).

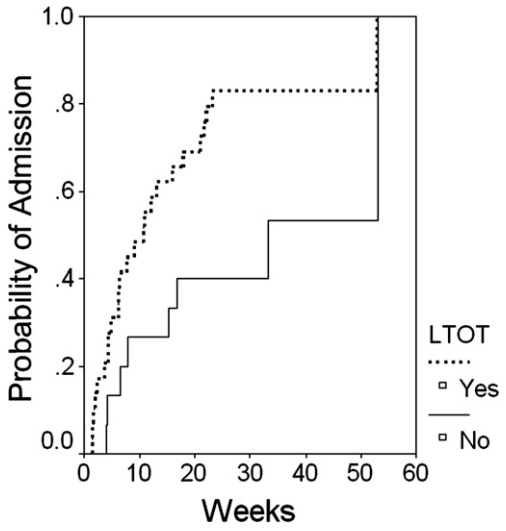

Figure 1 Interval between admissions to hospital for AECOPD. (Kaplan–Meier curve) for patients receiving long-term oxygen therapy (LTOT; broken line) *v* no LTOT (solid line); censored at 52 weeks. Cox proportional hazards analysis included: social circumstances and WHO-PS as covariates. *Hazard Ratio* for LTOT 2.61 (95% CI: 1.38–4.9) $p = 0.003$.

Significant differences between admissions were seen for Charlson score, WHO-PS, EWS, Urea, CRP and arterial pH. There were no differences in coma score and respiratory rate between admissions (other components of the EWS were not included in the analysis). The degree of hypoxia and frequency of hypercapnia were non-statistically greater on the final admission. Twice as many patients required non-invasive ventilation on the final admission (PA 20% *v* FA 40%; $p < 0.05$). However, although the pH normalised within 24 h in response to treatment the EWS remained higher on the final compared to the penultimate admission (Fig. 2).

Variables that were significant on univariate analysis (Charlson score, WHO-PS, EWS on admission (EWSo/a), pH, Urea and CRP) were included in a multivariate analysis of factors associated with death. The pH and urea were converted to dichotomous variables (pH < 7.35 and urea > 7.0 mmol/l). In the multivariate analysis only WHO-PS and EWSo/a were independently predictive of death from AECOPD (Table 2).

Receiver operating characteristic (ROC) curve analysis was used to define the best cut-off value for a combined (WHO-PS plus EWSo/a) score in relation to death. A value of 0.80 for the area under the curve (AUC) was considered to represent good discrimination. The sensitivity and specificity of the *combined score* was calculated at various cut-off points. ROC curve analysis showed the combined

Table 1 Clinical and laboratory variables on admission to hospital. GCS, Glasgow coma score; EWSo/a, Early warning score on admission; CR, creatinine; Aa-gradient, Alveolar–arterial oxygen gradient; and NS, $p \geq 0.05$.

	Penultimate ($n = 58$)	Final ($n = 60$)	*p*-Value
M:F	23:35	24:36	NS
Age, median (range) yrs	75 (53–93)	76 (53–94)	NS
Admission rate, mean (SD)/yr	1.45 (1.52)	1.97 (1.47)	$p < 0.05$
Days in hosp/yr, mean (SD)	14.2 (18)	20.6 (20)	$p < 0.001$
FEV_1, mean (SD) L	0.72 (0.32)	0.74 (0.34)	NS
FEV_1% predicted, mean (SD)	33.4 (15.4)%	34 (16.8)%	NS
COPD severity by GOLD stage *n* (%)			
Stage 2 ($FEV_1 < 80$% predicted)	2 (3.4%)	2 (3.3)	
Stage 3 ($FEV_1 < 50$% predicted)	4 (7%)	4 (6.6%)	
Stage 4 ($FEV_1 < 30$% pred. or <50% pred. + chronic respiratory failure)	52 (89.6%)	54 (90%)	
Additional co-morbidity *n* (%)	33 (57%)	37 (61.6%)	NS
Congestive cardiac failure	17 (29.3%)	23 (38.3%)	NS
Myocardial infarction	5 (8.6%)	5 (8.3%)	
≥Stage 3 renal impairment	6 (10.3)%	8 (13%)	
Malignancy	2 (3.4%)	3 (5%)	
Charlson index, mean (SD)	4.90 (1.57)	5.14 (1.40)	$p < 0.01$
WHO-PS, median (range)	2 (1–3)	3 (2–4)	$p < 0.001$
Resp. rate, mean (SD)/min	23.3 (9.34)	24.8 (6.5)	NS
GCS, median (range)	15 (11–15)	15 (5–15)	NS
EWSo/a, median (range)	2 (0–5)	4 (1–8)	$p < 0.001$
Hb, mean (SD) g/dl	13.52 (2.16)	13.19 (2.32)	NS
Urea, mean (SD) mmol/l	8.9 (5.11)	12.3 (8.91)	$p < 0.05$
CR, mean (SD) mmol/l	106.6 (31.9)	129.2 (83.5)	NS
CRP, mean (SD) mg/l	33.0 (36.7)	86.1 (116.7)	$p < 0.05$
Arterial pH, mean (SD)	7.34 (0.09)	7.28 (0.12)	$p < 0.05$
Aa-gradient, mean (SD) KPa	5.49 (10.58)	12.31 (8.40)	NS
Hypercapnia ($PCO_2 > 6.0$ KPa) *n* (%)	39 (67.2%)	46 (76.60%)	NS

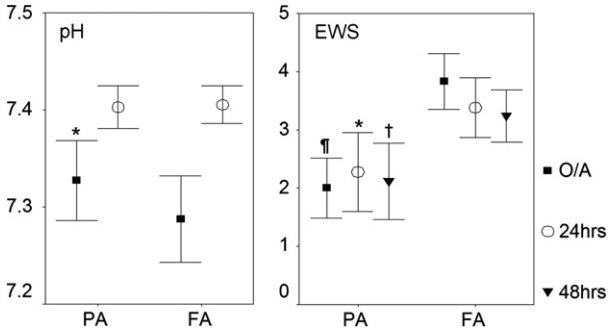

Figure 2 Effect of treatment on pH and Early Warning Score (EWS). Mean (95% CI); penultimate (PA) *v* final admission (FA): EWS on admission (*O*/*A*) and after 24, and 48 h. *$p < 0.05$; †$p < 0.005$; and ¶$p < 0.001$.

WHO-PS/EWS score had good discriminative capability for death with an AUC of 0.86. A total score of 6 had a sensitivity of 78% and specificity of 86.2% (Fig. 3). When included in the regression as an 'indicator variable' (WHO-PS/EWS ≥ 6) it was the only independent predictor of death (OR 95% CI: 19.3 (4.3—86.2) $p < 0.0005$).

Time to death (in hospital) showed a bimodal distribution with early deaths (ED) occurring at a median (range) of 2 (1—7) days and late deaths (LD) 18 (8—52) days after admission. Early death was associated with decompensated acidosis on admission (pH < 7.35: ED 67.6% *v* LD 17%; $p < 0.001$). Fig. 4 shows survival after admission to hospital (covariates: Charlson score, WHO-PS, EWSo/a, Urea > 7.0, pH < 7.35, CRP).

Discussion

The mortality rate for patients admitted to hospital with AECOPD is up to 49% within 2 years and rises with the number of exacerbations.[4,14] The prognosis for end-stage COPD is comparable to that of inoperable non-small cell lung cancer (NSCLC) but COPD patients receive substantially less palliative and end-of-life care.[33,34] One of the reasons for this is the difficulty in determining the terminal phase of the illness. Patients with end-stage COPD are likely to experience several hospital admissions for AECOPD before death and although a number of variables are associated with poor prognosis in AECOPD these lack the sensitivity or specificity required to identify patients dying from the disease. It is, therefore, inevitable that in most cases physicians continue active life-prolonging treatment, however, seemingly futile.

Many of our findings are in keeping with observations that have been previously reported by others. The risk of death in patients with COPD increases with the severity of airflow obstruction[5]; 90% of patients in this study had very severe (GOLD stage 4) COPD. The frequency of AECOPD is also an important prognostic factor.[14,15] In the study by Soler-Cataluña et al. patients with frequent exacerbations had a risk of death 4.3 times greater (95% CI: 2.62—7.02) than patients not requiring hospital admission. All but two of our patients had at least one previous admission for AECOPD and there was a significant increase in the annualised rate of admission for AECOPD in the final 12 months of life. However, the number and interval between exacerbations varied widely and was greater than 12 months in some patients. The shorter interval between admissions for patients receiving long-term oxygen therapy (LTOT) is in keeping with previous studies that found LTOT to be a marker for readmission.[35] The increased frequency of prescriptions for inhaled corticosteroids and tiotropium on the final admission probably reflects the increased severity of the disease.[36]

BMI has been shown to be an independent predictor of long-term prognosis in COPD.[12,13] Landbo et al. observed a relative risk of death of 7.1 (range: 2.97—17.05) in patients with severe COPD and a BMI < 20 kg/m^2 compared with obese subjects. However, in the present study BMI did not differ between the two admissions. Indeed although 50% of our patients were described as cachectic or had a BMI $\leq$ 20 kg; the average BMI (recorded) was within the normal range.

The importance of co-morbidities in patients with COPD is well recognised, particularly cardiovascular and other smoking related diseases.[37] In a retrospective study of 71,130 patients admitted to hospital with AECOPD patients with a Charlson score of 5 were more than five times as likely to die in hospital compared with patients without co-morbidities.[38] However, in the prospective study by Groenewegen et al. of 171 patients hospitalised for ACOPD more than two-thirds had at least one co-morbid illness but the Charlson score was not independently associated with an increased risk of death.[18] Similarly in the present study co-morbidity was considerable but although there was a significant increase in the Charlson score between admissions it was not an independent predictor of death in our patients with end-stage disease.

Breathlessness and exercise capacity have both been found to be better predictors of mortality than FEV_1 in patients with COPD.[9—11] In the study by Nishimura a score of

Table 2 Multivariate analysis of association between variables and death. Forward conditional regression; variables significant ($p < 0.05$) on univariate analysis were included. *Odds Ratio* (95% CI) for 1 unit increase in value of variable.

	Variable	Odds Ratio	95% C.I.	*p*-Value
Step1	EWS(o/a)	3.45	1.59—7.50	0.002
Step 2	EWS(o/a)	3.39	1.56—7.41	0.002
	WHO-PS	4.91	1.06—22.61	0.041
Adjusted Odds Ratios for covariates not included in model				
	Charlson score	1.62	0.75—3.51	0.196
	pH < 7.35	0.95	0.13—6.49	0.740
	Urea > 7.0 mmol/l	1.39	0.18—10.70	0.684
	CRP	1.02	0.99—1.04	0.064

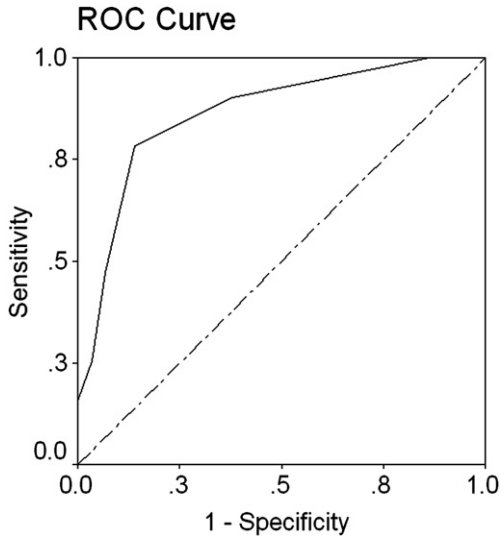

Figure 3 ROC curve analysis of combined WHO/EWS(o/a) score and death. AUC 0.86. The best cut-off value was combined WHO-PS/EWSo/a score = 6 (sensitivity of 78% and specificity of 86.2%).

5 on the modified MRC-dyspnoea score was highly predictive of long-term mortality with a relative risk compared to grade 2 dyspnoea of 61.3 (95% CI: 13.2—285.4).[9] Oga et al. found that exercise capacity measured by VO_2max was the best predictor of mortality.[10] Pinto-Plata et al. observed close correlation between six-minute walk distance (6MWD) and survival; those with a 6MWD < 100 m had a 1-year mortality > 60%.[11] Combining prognostic variables that reflect the systemic manifestations and functional impairment in COPD to create a severity score, the BODE index, has greater predictive power for mortality than individual variables.[16] However, in patients with very advanced disease it has limitations; a BODE score in the upper quartile is associated with a 12 month mortality of only 5% and is, therefore, of limited utility in identifying patients in the terminal stages of the disease.

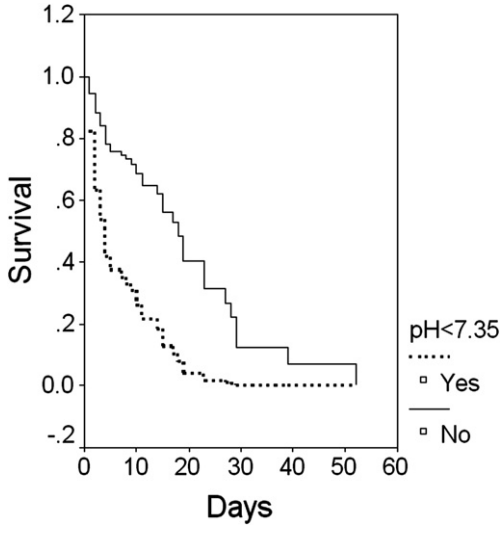

Figure 4 Kaplan—Meier Survival Curve on final admission to hospital. Decompensated acidosis (Broken line) *v* No acidosis (Solid line). Cox proportional hazards analysis included Charlson score, WHO-PS, EWSo/a, Urea > 7.0 mmol/l, CRP as covariates. *Hazard Ratio* for acidosis: 0.207 (95% CI: 0.076—0.566) $p = 0.002$.

Measurement of performance status is integral to the assessment of patients with COPD. The St. George's (SGRQ) and the Chronic Respiratory Disease Questionnaire (CRQ) are invaluable in studies of interventions; however, they are impractical for routine clinical use.[39,40] The WHO-PS provides a simple and reliable measure of global performance that most physicians are familiar with. We are unaware of any previous reports of the WHO-PS as an instrument for assessing this group or patients. However, in the UK National COPD Audit (2003) a very similar 5-point assessment of performance status was a better predictor of mortality (2% in the best category compared with 38% in the most severe; bed or chair bound) than the more respiratory specific factors.[41] This concurs with the finding of this study in which there is a threshold for mortality between a WHO-PS score of 2 (self-caring and up and about 50% of the time) and 3 (needing help with self-care and in bed/chair > 50% of the time during the day).

The Early Warning Score (EWS) is a tool for bedside evaluation based on six physiological parameters: pulse rate, systolic blood pressure, respiratory rate, temperature, CNS score and urine output (Appendix 1). The EWS, originally developed for surgical patients, has been validated for use in medical patients in whom a score > 3 on admission to hospital was associated with a mortality of about 25%.[31,32] The finding of a highly significant association between EWS and death in the present study is indicative of systemic physiological disturbance in end-stage COPD. This is reflected in the more severe biochemical derangement including lower pH and raised blood urea concentration.

The relationship between in-hospital mortality due to COPD and decompensated acidosis is well established.[19,21] In the UK national audit of COPD admissions (1997) risk of death was related to severity of acidosis (*Relative Risk* (95%CI) for pH 7.26—7.34, *RR* 1.9 (1.3—2.83); pH < 7.26, *RR* 3.8 (2.7—5.4)).[19] In the present study more patients were acidotic on the final admission and acidosis was associated with a shorter interval to death indicating that these patients are the most acutely unwell. However, in the terminally ill COPD patient pH improved with treatment whilst the EWS did not unlike on the penultimate admission. Furthermore respiratory specific variables were not associated with death implying that in patients dying from COPD there is more generalised systemic disturbance. This is supported by the finding of an increased urea on the final admission. An association between uraemia and death from COPD has been reported previously.[21] Jeffrey et al. also reported a relationship between death and systolic hypotension and intimated that these findings reflected the severity of systemic disturbance associated with an exacerbation. The EWS, based upon routine clinical observations, provides a useful measure of that systemic disturbance.

Systemic manifestations of COPD may be related to systemic inflammation which is increasingly recognised as a risk factor for complications of COPD[42]; patients with COPD have raised levels of CRP and other markers of systemic inflammation compared with healthy controls. The CRP level increases during AECOPD and has been

related to 'Anthonisen exacerbation type' with the highest levels in type 1 exacerbation.[43] In the present study CRP levels in both groups were in the range seen in type 1 exacerbations reported by Stolz et al. The level of CRP has also been related to mortality; Ruiz-González et al. observed an increased risk of adverse outcome including death in patients with a CRP $>$ 50 mg/l.[22] We also found higher CRP levels in relation to death but the frequency of CRP $>$ 50 mg/l did not differ significantly between admissions (PA 17.8% *v* FA 36%; $p = 0.09$).

Previous studies relating to mortality in COPD have been in patients with a wide range of severity of the condition and do not address the question of short-term prognosis. The benefit of the case-crossover design employed in this study is that it has enabled us to specifically investigate clinical changes over the final weeks of life in patients with end-stage COPD. We accept that the retrospective nature of the study has inherent shortcomings including selection bias. However, the differences observed over a short period (about 3—4 months in most cases) within a homogeneous cohort of patients are likely to be smaller than would have been the case in a broader range of patients.

The purpose of this study was to determine if routine clinical assessment of patients with severe COPD admitted to hospital could identify the "tipping point" in the disease thereby facilitating the transition from life-prolonging treatment to end-of-life care. Our observations suggest that a combination of assessment of global performance status and a measure of acute systemic physiological impairment may enable this. In this study combining the WHO-PS and EWS scores gave an objective measurement that was highly specific for death in patients with very severe COPD admitted to hospital with an acute exacerbation. The EWS is used routinely in most hospitals in the UK and the WHO-PS could be readily incorporated into clinical assessment proformas. The potential utility of this is clear but prospective studies are required to confirm our findings.

Conflict of interest statement

The authors have no conflicts of interest.

Supplementary material

Supplementary material can be found, in the online version, at doi: 10.1016/j.rmed.2010.04.025.

References

1. Britton M. The burden of COPD in the U.K.: results from the Confronting COPD survey. *Respir Med* 2003;**97**(Suppl. C):S71—S79.
2. Pearson MG, Littler J, Davies PDO. An analysis of medical workload by speciality and diagnosis in Mersey: evidence of a specialist to patient mismatch. *JR Coll Physicians* 1994;**28**:230—4.
3. Partridge MR. Patients with COPD: do we fail them from beginning to end. *Thorax* 2003;**58**:373—5.
4. Connors AF, Dawson NV, Thomas C, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. *Am J Respir Crit Care Med* 1996;**154**:959—67.
5. Hodgkin JE. Prognosis in chronic obstructive pulmonary disease. *Clin Chest Med* 1990;**11**:555—69.
6. Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive pulmonary disease: a clinical trial. *Ann Intern Med* 1980;**93**:391—8.
7. The Intermittent Positive Pressure Breathing Trial Group. Intermittent positive pressure breathing therapy of chronic obstructive pulmonary disease: a clinical trial. *Ann Intern Med* 1983;**99**:612—20.
8. Gerardi DA, Lovett L, Benoit-Connors ML, Reardon JZ, ZuWallack RL. Variables related to increased mortality following outpatient pulmonary rehabilitation. *Eur Respir J* 1996;**9**:431—5.
9. Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. *Chest* 2002;**121**:1434—40.
10. Oga T, Nishimura K, Tsukino M, et al. Analysis of the factors related to mortality in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2003;**167**:544—9.
11. Pinto-Plata VM, Cote C, Cabral H, Taylor J, Celli BR. The 6-min walk distance: change over time and value as a predictor of survival in severe COPD. *Eur Respir J* 2004;**23**:28—33.
12. Schols AM, Slangen J, Volovics L, Wouters EF. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;**157**:1791—7.
13. Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP. Prognostic value of nutritional status in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;**160**:1856—61.
14. Soler-Cataluña JJ, Martínez-García MÁ, Román Sánchez P, et al. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax* 2005;**60**: 925—31.
15. Almagro P, Calbo E, Ochoa de Echagüen A, et al. Mortality after hospitalization for COPD. *Chest* 2002;**121**:1441—8.
16. Celli BR, Cote C, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004;**350**: 1005—12.
17. Fuso L, Incalzi RA, Pistelli R, et al. Predicting mortality of patients hospitalized for acutely exacerbated chronic obstructive pulmonary disease. *Am J Med* 1995;**98**:272—7.
18. Groenewegen KH, Schols AMWJ, Wouters E. Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. *Chest* 2003;**124**:459—67.
19. Roberts CM, Lowe D, Bucknall CE, et al. Clinical audit indicators of outcome following admission to hospital with acute exacerbation of chronic obstructive pulmonary disease. *Thorax* 2002;**57**:137—41.
20. Gunen H, Hacievliyagil SS, Kosar F, et al. Factors affecting survival of hospitalised patients with COPD. *Eur Respir J* 2005; **26**:234—41.
21. Jeffrey AA, Warren PM, Flenley DC. Acute hypercapnic respiratory failure in patients with chronic obstructive lung disease: risk factors and use of guidelines for management. *Thorax* 1992;**47**:34—40.
22. Ruiz-González A, Lacasta D, Ibarz M, et al. C-reactive protein and other predictors of poor outcome in patients hospitalized with exacerbations of chronic obstructive pulmonary disease. *Respirology* 2008;**13**(7):1028—33.
23. Claessens MT, Lynn J, Zhong Z, et al. Dying with lung cancer or chronic obstructive pulmonary disease: insights from SUPPORT. *J Am Geriatr Soc* 2000;**48**(Suppl. 5):S146—S153.
24. Murray CJL, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet* 1997;**349**:1269—76.
25. National Collaborating Centre for Chronic Conditions. Chronic obstructive pulmonary disease. National clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. *Thorax* 2004;**59**(Suppl. (1)):1—232.

26. Hurst JR, Wedzicha JA. Chronic obstructive pulmonary disease: the clinical management of an acute exacerbation. *Postgrad Med J* 2004;**80**:497—505.
27. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;**5**: 649—55.
28. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;**40**:373—83.
29. Hall WH, Ramachandran R, Narayan S, Jani AB, Vijayakumar S. An electronic application for rapidly calculating Charlson comorbidity score. *BMC Cancer* 2004;**4**:94. doi:10.1186/1471-2407-4-94.
30. Fabbri LM, Hurd SS, for the GOLD Scientific Committee. Global strategy for the diagnosis, management and prevention of COPD: 2003 update. *Eur Respir J* 2003;**22**:1—2.
31. Gardner-Thorpe J, Love N, Wrightson J, Walsh S, Keeling N. The Value of Modified Early Warning Score (MEWS) in surgical in-patients: a prospective observational study. *Ann R Coll Surg Engl* 2006;**88**(6):571—5.
32. Subbe CP, Kruger M, Rutherford P, Gemmel L. Validation of a modified Early Warning Score in medical admissions. *QJM* 2001;**94**:521—6.
33. Gore JM, Brophy CJ, Greenstone MA. How do we care for patients with end stage chronic obstructive pulmonary disease (COPD)? A comparison of palliative care and quality of life in COPD and lung cancer. *Thorax* 2000;**55**:1000—6.
34. Curtis JR. Palliative and end-of-life care for patients with severe COPD. *Eur Respir J* 2008;**32**:796—803.
35. Gudmundsson G, Gislason T, Janson C, et al. Risk factors for rehospitalisation in COPD: role of health status, anxiety and depression. *Eur Respir J* 2005;**26**:414—9.
36. Garcia-Aymerich J, Farrero E, Félez MA, et al. Risk factors of readmission to hospital for a COPD exacerbation: a prospective study. *Thorax* 2003;**58**:100—5.
37. Sin DD, Anthonisen NR, Soriano JB, Agusti AG. Mortality in COPD: role of comorbidities. *Eur Respir J* 2006;**28**:1245—57.
38. Patil SP, Krishnan JA, Lechtzin N, Diette GB. In-hospital mortality following acute exacerbations of chronic obstructive pulmonary disease. *Arch Intern Med* 2003;**163**:1180—6.
39. Jones PW, Quirk FH, Baveystock CM. The St. George's Respiratory Questionnaire. *Respir Med* 1991;**85**(Suppl. B):25—31 [discussion 3—7].
40. Larson JL, Covey MK, Berry JK, et al. Reliability and validity of the Chronic Respiratory Disease Questionnaire. *Am Rev Respir Dis* 1993;**147**:A530.
41. Price LC, Lowe D, Hosker HSR, , et alon behalf of the British Thoracic Society and the Royal College of Physicians Clinical Effectiveness Evaluation Unit (CEEU). UK National COPD Audit 2003: impact of hospital resources and organisation of care on patient outcome following admission for acute COPD exacerbation. *Thorax* 2006;**61**:837—42.
42. Gan WQ, Man SFP, Senthilselvan A, et al. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax* 2004;**59**:574—80.
43. Stolz D, Christ-Crain M, Morgenthaler NG, Leuppi J, Miedinger D, et al. Copeptin, C-reactive protein, and procalcitonin as prognostic biomarkers in acute exacerbation of COPD. *Chest* 2007;**131**:1058—67.