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Review

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The prognostic variables predictive of mortality in patients with an exacerbation of COPD admitted to the ICU: an integrative review

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Summary

Introduction: Chronic Obstructive Pulmonary Disease (COPD) frequently presents with an acute exacerbation (AECOPD). Debate exists as to whether these patients should be admitted to intensive care units (ICUs). An integrative review was performed to determine whether clinical variables available at the time of ICU admission are predictive of the intermediate-term mortality of patients with an AECOPD.

Methods: An integrative review was structured to incorporate a five-stage review framework to facilitate data extraction, analysis and presentation. The quality of the studies contributing to the integrative review was assessed with a novel scoring system developed from previously published data and adapted to this setting.

Results: The integrative review search strategy identified 28 studies assessing prognostic variables in this setting. Prognostic variables associated with intermediate-term mortality were low Glasgow Coma Scale (GCS) on admission to ICU, cardiorespiratory arrest prior to ICU admission, cardiac dysrhythmia prior to ICU admission, length of hospital stay prior to ICU admission and higher values of acute physiology scoring systems. Premorbid variables such as age, functional capacity, pulmonary function tests, prior hospital or ICU admissions, body mass index and long-term oxygen therapy were not found to be associated with intermediate-term mortality nor was the diagnosis attributed to the cause of the AECOPD.

Discussion: Variables associated with intermediate-term mortality after AECOPD requiring ICU admission are those variables, which reflect underlying severity of acute illness. Premorbid and diagnostic data have not been shown to be predictive of outcome. A scoring system is proposed to assess studies of prognosis in AECOPD.

Introduction

Chronic obstructive pulmonary disease (COPD) is a common disease that frequently presents with respiratory failure. COPD-related deaths were the fourth leading cause of death worldwide in 2004.[1] Acute exacerbations of COPD (AECOPD) are a common cause of admission to Intensive Care Units (ICUs)[2] but debate exists amongst critical care practitioners as to the appropriate level of treatment of patients presenting to ICU with AECOPD. Some argue that ICU admission and invasive ventilation should be the default for all COPD patients presenting with acute respiratory failure,[3] while others suggest that invasive ventilation should only be offered as a last resort.[4–6] Uncertainty as to whether to consider invasive ventilation in COPD patients is in part driven by an individual clinician's ability to confidently decide whether the intubation of patients

with AECOPD is appropriate and which prognostic variables are predictive of poor outcome after ICU admission.[7,8]

The clinical equipoise relating to whether to admit a patient with AECOPD to ICU and offer mechanical ventilation is further fuelled by the conflicting evidence pertaining to the mortality of these patients. The short to intermediate term mortality of patients with AECOPD compare well to other cohorts of critical care patients[2,9] but longer term mortality remains high, with 5-year survival rates comparing poorly to those of many cancers.[10,11]

A number of clinical variables exist that may be of prognostic importance in the management of COPD patients with an acute exacerbation and respiratory failure. Potential prognostic variables include premorbid factors, the diagnosis associated with an AECOPD and acute physiological or laboratory parameters. Expert opinion has informed UK guidelines in suggesting that age, FEV_1, previous ICU admissions, prior functional status, body mass index, requirement for oxygen when stable and co-morbidities may be important prognostic variables.[12] Several groups have made survival prediction models based on; patients with AECOPD,[13] patients with AECOPD and hypercapnic respiratory failure[14] and patients with AECOPD admitted to ICU.[15,16] However, the overall effect of previously investigated prognostic variables has not been subject to rigorous evaluation and the importance of these variables in predicting outcome in patients with AECOPD requiring ICU admission remains uncertain.

In light of conflicting data and opinion in the literature, there is a scientific need to systematically evaluate the clinical variables associated with a poor prognosis for patients presenting with an AECOPD and acute respiratory failure. An understanding of these prognostic variables could aid critical care practitioners involved in decision-making and resource allocation processes as to whether an individual COPD patient should be considered for ICU admission and offered intubation and invasive ventilation.

Methods

Initial review of the evidence revealed significant variation in methodology and data presentation between studies. The primary data did not lend themselves to a systematic review with a meta-analysis. An integrative review was therefore carried out.

The integrative review was structured to incorporate the five-step review framework described by Whittemore and Knafl:[17]

1. problem identification;
2. literature search;
3. data evaluation;
4. data extraction, synthesis and analysis and
5. presentation of results.

Problem identification

To systematically evaluate the variables predictive of outcome in patients with AECOPD admitted to ICU.

Literature search

Studies were identified on 11 January 2010 using MEDLINE (1950–present), EMBASE (1980–present) and CINAHL (1981–present) via the NHS national library for health. The following search strategy was used: ((chronic AND obstructive AND (airways OR lung OR pulmonary) AND disease) OR COPD) AND (prognos* OR outcome OR mortality OR predict* OR survival OR death) AND ((intensive AND (care OR treatment OR therapy)) OR (high AND dependency) OR (critical AND care) OR (level AND (two OR three))). This was based in part on Altman's suggestion of an effective search strategy for prognostic studies on MEDLINE[18] and developed to be specific for studies about COPD and ICU.

Studies without an English title or abstract were excluded. A hand search was also performed of personal files, references suggested by experts contacted and reference lists of relevant review articles. Further snowballing from the reference lists of all relevant full-text studies identified from the electronic search was undertaken.

Data evaluation

Relevant studies were identified by title, then abstract and finally full text.

Studies were included for review if the following predefined inclusion criteria were met:

- patients with AECOPD;
- patients admitted to ICU; and
- studies analysed variables predictive of mortality up to 6 months after ICU admission.

Studies were excluded for review if the following predefined exclusion criteria were present:

- studies of prognostic variables in a non-ICU setting;
- studies which analysed prognostic variables for outcomes other than death;
- studies of prognostic variables, which would only become available to critical care practitioners after ICU admission e.g. the presence of a ventilator-associated pneumonia;
- no abstract available; and
- full text not available in English.

Definitions

The following definitions have been used

AECOPD: a deterioration in the respiratory status of a patient with COPD defined clinically by symptoms or signs or biochemically by arterial blood gas analysis.

ICU: a ward capable of delivering level three care as defined by the Intensive Care Society.[19]

AECOPD requiring admission to ICU: a deterioration in the respiratory status of a patient with COPD necessitating admission to ICU. It was expected that a proportion of patients were *invasively* ventilated though the selection of studies did not require 100% of patients to be treated in this way.

Intermediate-term mortality: mortality occurring up to and including 6 months after admission to ICU with AECOPD.

Data extraction, synthesis and analysis

For each study, data were extracted against predefined baseline variables to define study characteristics and determine study quality. A qualitative synthesis of the primary data was then undertaken. The quality of each eligible study was assessed by five criteria adapted from previously published work regarding the analysis of prognostic studies by Altman, Laupacis, Justice, Concato and Hayden as well as from recommendations from the centre of evidence-based medicine.[18,20–24] The five criteria used to assign a quality score for each study are given below.

- Criterion A: did the study include a representative and well-defined sample of patients at a similar point in disease?[18,20,23,24]
- Criterion B: did the study evaluate 'independent' predictors of mortality with the use of multi-variable analysis?[18,20,22–24]
- Criterion C: were the results validated? Validation could be either internal, using the population from which the data were gathered or prospective, using a different population of patients.[20,21,24]
- Criterion D: were the numbers patients recruited adequate to investigate the effect of the variables studied?[22,24]
- Criterion E: did the study present risk of mortality according to 'ranges' of the variable being evaluated?[22,23]

One point was awarded for the presence for each of the above criteria giving a maximum quality score of five. High-quality studies were those assigned a quality score of three or more and low-quality studies were those assigned a quality score of less than three.

Variables were divided into the following three prognostic categories:

- Variables that predict intermediate mortality in patients with AECOPD requiring ICU admission. This was defined when the prognostic value of the variable was supported by at least one high-quality study or at least three low-quality studies with fewer *and* lower quality conflicting studies.
- Variables that do not predict intermediate mortality in patients with AECOPD requiring ICU admission. This was defined when the prognostic value of the variable was refuted by at least one high-quality study or at least three low quality studies with fewer *and* lower quality conflicting studies *or* when the variable was associated with mortality in some studies and 'survival' in other studies.
- Variables that have been insufficiently studied. This was defined when fewer than two studies had investigated the variable.

Presentation of results

To facilitate data analysis and presentation, the prognostic variables were divided into the following pre-specified groups:

- premorbid variables e.g. age and functional capability;
- diagnosis associated with AECOPD e.g. pneumonia and
- acute physiological variables e.g. heart rate or laboratory variables e.g. arterial blood gas analysis.

Data are presented qualitatively in tabular form to highlight the importance of the prognostic variables.

Results

Search results

The search returned a total of 1587 references (175 from CINAHL, 794 from EMBASE, 615 Medline, 3 from references of reviewed studies). The flow diagram of literature search results is shown in Figure 1. One hundred and twenty studies were retrieved and reviewed by abstract. Sixty-one studies underwent full-text review and of these 28 were included in the review.[2,15,25–50]

Study characteristics

The major characteristics of each study included in the integrative review are summarized in Table 1.

Assessment of study quality

Study quality is summarized in Table 2. The quality score assigned to the studies ranged from 0 to 5, with 4 studies of high quality[2,15,27,28] and 24 low quality.[25,26,29–50]

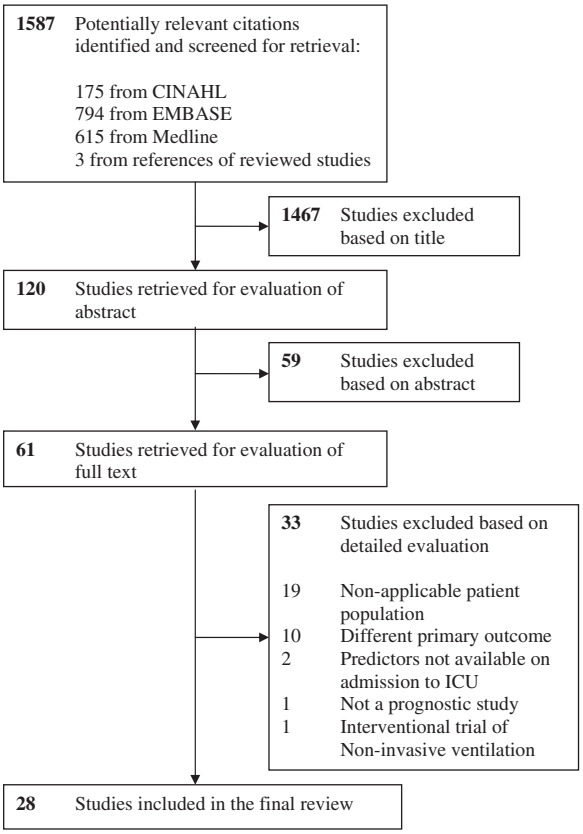

Figure 1. Flow Diagram of literature search results.

Prognostic variables predictive of intermediate-term mortality

The only premorbid prognostic variable predictive of intermediate-term mortality was hospital stay prior to ICU admission.[2,15,46] Five acute physiological or laboratory variables were predictive of intermediate-term mortality: admission to ICU following cardio-respiratory arrest;[2,35,44] admission with a low GCS;[15,33,37,38,47] the presence of dysrhythmia on admission;[15,33,49] an abnormally high acute physiology score (either APACHE II or COPD and Asthma Physiology Score) on 'admission' to the ICU;[15,25,34,37,39,44] low serum bicarbonate or inadequate metabolic compensation for respiratory acidosis on admission to ICU.[26,27,33,37,44]

These data are summarized with odds ratios for effect where available in Table 3.

Prognostic variables which are not predictive of intermediate-term mortality

These data are summarized in 'Table 4'.

Other prognostic variables have not been adequately investigated to make conclusions.

Discussion

Knowledge of the prognostic variables that can predict outcome in patients with AECOPD presenting with acute respiratory failure is important because decisions about admission to ICU and consideration for intubation and invasive ventilation can be potentially based upon these variables if they are proved to be accurate and reliable. Additionally, refusal of admission to critical care should be on the basis of rigorously investigated variables to reduce the potential for patients without adverse prognostic variables being inappropriately refused access to critical care services. This integrative review has highlighted variables predictive of intermediate-term mortality, which may represent physiological markers of severity of illness or organ dysfunction.

Most premorbid variables have not been shown to predict intermediate-term mortality; neither has the diagnosis causing the AECOPD.

The UK guidelines recommend age, FEV_1, previous ICU admissions, prior functional status, body mass index, requirement for oxygen when stable, co-morbidities and previous ICU admissions as important variables to consider when assessing the appropriateness of ICU admission and invasive ventilation.[12] The UK guidelines use three papers as the evidence base for predictive variables and all three papers have been included in the integrative review.[41,46,47] Two papers[46,47] support the use of age as a variable which predicts mortality but only one of these[46] found age to be an independent predictor of mortality and the other paper only found age to predict mortality in a subgroup of 19 patients with less severe COPD.[47] One paper[41] found that the presence of an APACHE II co-morbidity was a significant predictor of hospital mortality. The other factors listed above are not supported by the evidence in the three papers quoted.

It is very important that patients are not denied critical care admission on the basis of the variables quoted in the UK guidelines without further study of these variables.

Integrative review methodology

Due to heterogeneity between the methodology of studies and data presentation, an integrative review was carried out with a structured methodology, which enabled a more rigorous synthesis than a narrative review while the primary data did not support the use of a meta-analysis.[17] Structuring the integrative review facilitated the synthesis, analysis and presentation of heterogeneous information from the studies evaluated.

Table 1 Study characteristics and patient demographics of studies of prognostic variables predicting intermediate-term mortality in AECOPD patients admitted to ICU

References	Country	Multi-centre	Setting[a]	Study type	N[b]	Age	Male (%)	APACHE score[c]	Intubated (%)	NIV[d] (%)	Mortality
Motiani *et al.*[25]	India	No	ICU	Retrospective/Prospective	63	57.8[e]	74.6	23.8[e]	93.7	15.9	41.3%[h]
Rammaert *et al.*[26]	France	No	ICU	Prospective	116	67[e]	79	43[e] (SAPS)	100	46	25%[i]
Wildman *et al.* [15]	UK	Yes	ICU/MCCU	Prospective	832	n/s	52	n/s	54	n/s	37.9%[g]
Ucgun *et al.*[27]	Turkey	No	RICU	Prospective	213	65[e]	74.6	22.2[e]	57.7	n/s	24.9%[i]
Berkius *et al.*[28]	Sweden	Yes	ICU	Retrospective	1009	70.2[e]	38.5	20.2[e]	n/s	n/s	7.8%[i] 26%[f]
Rello *et al.*[29]	Spain	Yes	ICU	Prospective	176	67.1[e]	85.2	12.6[e] (APS)	73.3	28.4	30.1%[i]
Gursel[30]	Turkey	No	RICU	Retrospective	93	67.1[e]	74.2	18.7[e]	100	35	29.0%[i]
Rivera-Fernandez *et al.*[31]	Spain	Yes	ICU	Prospective	742	65.2[e]	n/s	66.6[e] (III)	75.1	n/s	23%[h]
Mohan *et al.*[32]	India	No	MICU	Prospective	116	62.1[e]	87.9	n/s	15.5	n/s	13.7%[h]
Ucgun *et al.*[33]	Turkey	No	RICU	Prospective	151	65.1[e]	74.4	23.7[e]	57.6	14.6	33.1%[h]
Wildman *et al.*[2]	UK	Yes	ICU/MCCU	Retrospective	3752	67.8[f]	51.8	19.4[e] 19[f]	73.9	n/s	38.3%[h]
Ai-Ping *et al.*[34]	Singapore	No	ICU	Retrospective	57	70.0[e]	80.7	22[e]	94.7	29.8	24.5%[h]
Raurich *et al.*[35]	Spain	No	ICU	Retrospective	101	70[e]	90	38.8[e] (SAPS)	100	n/s	25.7%[h]
Yang *et al.*[36]	Singapore	No	ICU	Retrospective	102	72[e]	82.4	18.5[e]	66.7	27.4	18%[h]
Khilnani *et al.*[37]	India	No	ICU	Prospective	82	60[e]	n/s	13[e]	84.1	20.7	36.6%[h]
Baillard *et al.*[38]	France	Yes	ICU	Prospective	71	71.1[f]	n/s	n/s	34	51	25%[h]
Breen *et al.*[39]	Australia	No	ICU	Retrospective	74	65.5[e] 65[f]	59.5	22[e] 20[f]	85.1	0	20.3%[h]
Afessa *et al.*[40]	USA	No	ICU	Prospective	180	63.1[e]	59	19.0[e]	61.2	40	21%[h]
Nevins and Epstein[41]	USA	No	ICU	Retrospective	166	67[e]	62	15[e]	100	1	28%[h]
Faisy *et al.*[42]	France	No	ICU	Retrospective	51	69[e]	82.4	13[e] (SAPS)	58.8	n/s	19.6%[i]
Anon *et al.*[43]	Spain	No	ICU	Prospective	20	64[f]	90	20[f]	100	n/s	35%[i] 50%[h]
Hill *et al.*[44]	UK	No	ICU	Retrospective	46	68[f]	51	14.2[f]	100	n/s	49%[h]
Moran *et al.*[45]	Australia	No	ICU	Retrospective	75	68.5[e]	68	18[e]	43	n/s	11%[h] 25%[g]
Seneff *et al.*[46]	USA	Yes	ICU	Prospective	362	66[e]	56	57[e] (III)	47	n/s	23.8%[h] 48%[g]
Rieves *et al.*[47]	USA	No	MICU	Prospective	33	65.1[e]	100	n/s	100	n/s	43.6%[i]
Portier *et al.*[48]	France	Yes	ICU	Prospective	322	65.5[e]	69.9	11.8[e] (SAPS)	52	n/s	14%[j]
Ying-Huang *et al.*[49]	Taiwan	No	MICU	Retrospective	121	67.5[e]	66.1	n/s	100	n/s	35.5%[i]
Kaelin *et al.*[50]	Switzerland	No	ICU	Prospective	35	65.4[e]	64.1	n/s	100	n/s	36%[g]

[a]RICU/MCCU: Respiratory ICU/Mixed Critical Care Unit.
[b]Number of patients included in the study.
[c]APACHE score is APACHE II unless indicated with (III) for APACHE III, (SAPS) for Simplified Acute Physiology Score or (APS) for Acute Physiology Score of APACHE II score.
[d]NIV is the percentage of AECOPD patients treated with Non-Invasive Ventilation.
[e]Mean.
[f]Median.
[g]Six month mortality.
[h]Hospital mortality.
[i]ICU mortality.
[j]30 day mortality.
n/s: not stated.

Table 2 Quality score of studies of prognostic variables predicting intermediate-term mortality in AECOPD admitted to ICU

Study	A	B	C	D	E	Overall quality score (/5)
Wildman *et al.*[15]	+	+	+	+	+	5
Berkius *et al.*[28]	+	+	−	+	+	4
Wildman *et al.*[2]	+	+	−	+	+	4
Ucgun *et al.*[27]	+	+	−	−	+	3
Rammaert *et al.*[26]	+	+	−	−	−	2
Rivera-Fernandez *et al.*[31]	−	+	−	+	−	2
Gursel[30]	+	+	−	−	−	2
Mohan *et al.*[32]	+	+	−	−	−	2
Ucgun *et al.*[33]	+	+	−	−	−	2
Ai-Ping *et al.*[34]	+	+	−	−	−	2
Raurich *et al.*[35](2004)	+	+	−	−	−	2
Yang *et al.*[36]	+	+	−	−	−	2
Khilnani *et al.*[37]	+	+	−	−	−	2
Baillard *et al.*[38]	+	+	−	−	−	2
Afessa *et al.*[40]	+	+	−	−	−	2
Breen *et al.*[39]	+	+	−	−	−	2
Moran *et al.*[45]	+	+	−	−	−	2
Seneff *et al.*[46]	+	+	−	−	−	2
Rieves *et al.*[47]	+	+	−	−	−	2
Ying-Huang *et al.*[49]	+	−	−	+	−	2
Kaelin *et al.*[50]	+	+	−	−	−	2
Motiani *et al.*[25]	+	−	−	−	−	1
Rello *et al.*[29]	−	+	−	−	−	1
Nevins and Epstein[41]	−	+	−	−	−	1
Faisy *et al.*[42]	+	−	−	−	−	1
Hill *et al.*[44]	+	−	−	−	−	1
Portier *et al.*[48]	−	+	−	−	−	1
Anon *et al.*[43]	−	−	−	−	−	0

Criterion A. Representative and well-defined sample of patients at a similar point in disease?
Criterion B. Independent predictors evaluated with the use of multi-variable analysis?
Criterion C. Results validated?
Criterion D. Were the patient numbers adequate? Studies of prognostic variables predictive of death should have 10 or more deaths per variable studied.
Criterion E. Did the study present risk of mortality according to ranges of the variable being evaluated?

The integrative review only encompassed studies that included patients admitted to ICUs. These patients were included to focus the reader on prognostic variables important in the most unwell of hospital in-patients.

Variables were chosen that would be known to critical care practitioners prior to ICU admission rather than variables that would only become available during ICU stay such as length of time ventilated. These are not included in the review as its purpose is to aid clinicians in making decisions regarding the likelihood of an individual patient receiving a sustained benefit from ICU admission rather than to assist in guiding treatment subsequent to ICU admission.

Intermediate-term mortality was chosen as the outcome measure for the following reasons. Firstly, intermediate-term mortality encompasses all phases of a patient's intensive care pathway, which critical care practitioners might realistically expect to influence: pre-ICU management; management on the ICU; post-ICU discharge leading to hospital discharge and follow-up. Secondly, a study which examined variations in intubation decisions between physicians found that the estimated 6-month survival of a patient with AECOPD was the only significant predictor of whether a critical care practitioner would intubate such a patient.[7] Finally, in light of recent data from the UK exploring patient preferences and health-related quality of life at

Table 3 Variables that predict intermediate-term mortality in AECOPD requiring ICU admission

Variable	Study	Range/change of variable	Odds ratio[a]	Value/incidence in survivors vs. non-survivors	*P*-value/other
Hospital stay prior to ICU admission	Wildman *et al.*[2]	Per day	**1.02**	N/R[b]	
	Wildman *et al.*[15]	0–1 days	1	N/R	
		2–3 days	1.47		
		4–7 days	**3.36**		
		>7 days	**2.36**		
	Seneff *et al.*[46]			N/R	**33%**[c]
ICU admission post-arrest	Wildman *et al.*[2]	No	1	5.7% vs. 12.7%	
		Yes	**1.83**		
	Raurich *et al.*[35]		**4.4**[d]	0% vs. 15.4%	**0.0005**
	Hill *et al.*[44]			4.8% vs. 30%	**<0.05**
Glasgow Coma Score on ICU admission	Wildman *et al.*[15]	15	1	N/R	
		8–14	1.19		
		<8	**2.50**		
	Ucgun *et al.*[33]		**0.74**	13.2 vs. 10.3	**<0.001**
	Khilnani *et al.*[37]			12.8 vs 10.8	**0.003**
	Baillard *et al.*[38]		1.11	15 vs. 12	**0.02**
	Rieves *et al.*[47]			N/R	**0.04**[e]
	Portier *et al.*[48]			N/R	**<0.05**[f]
Dysrhythmia on ICU admission	Wildman *et al.*[15]	AF Absent	1	8.7% vs. 18.4%	
		AF Present	**2.37**[g]		
			1.58		
	Ucgun *et al.*[33]	Any dysrhythmia		13.9% vs. 32%	**0.016**
	Tsai *et al.*[49]	Multi-focal atrial tachycardia		3.8% vs. 46.5%	**<0.01**
High Acute physiology Score[h] on ICU admission	Wildman *et al.*[15]	Normal CAPS[i]	1	N/R	
		1 abnormal CAPS value	1.37		
		>1 abnormal CAPS value	**3.06**		
	Motiani *et al.*[25]			22.51 vs. 22.65	**0.033**
	Ai-Ping *et al.*[34]		**2.0**	21.0 vs. 24.9	**0.004**
	Khilnani *et al.*[37]		**1.32**	10.6 vs. 17.5	**0.001**
	Breen *et al.*[39]			N/R	**0.01**
	Hill *et al.*[44]			12. vs 16.5.	**<0.05**
Low bicarbonate (mmol/l) on ICU admission	Ucgun *et al.*[27]	<20 mmol/l	**0.552**	18.8% vs. 43.4%	**0.013**
	Rammaert *et al.*[26]		**0.938**[g]	31 vs. 28	**0.035**
	Ucgun *et al.*[33]		**0.14**[j]	28.6 vs. 24.2	**0.003**
	Khilnani *et al.*[37]			33.8 vs. 29.6	**0.035**

[a]Odds ratio quoted as multivariate unless stated otherwise.
[b]Not Reported.
[c]Percentage explanatory power for mortality.
[d]Relative Risk.
[e]Alert versus not alert (undefined) in subgroup of patients with FEV_1 >1 l.
[f]Presence of coma (undefined).
[g]Univariate analysis of odds ratio.
[h]APACHE II unless stated otherwise.
[i]COPD and Asthma Acute Physiology Score (CAPS).
[j]Inadequate compensation for respiratory acidosis (undefined).
Statistically significant results are in bold type. High-quality studies are the first studies presented within each variable.

Table 4 Variables which do not predict intermediate-term mortality in AECOPD requiring ICU admission

Variable	Number of high-quality studies supporting an effect of the variable (*n*)[references]	Number of low-quality studies supporting an effect of the variable (*n*)[references]	Number of high-quality studies refuting an effect of the variable (*n*)[references]	Number of low-quality studies refuting an effect of the variable (*n*)[references]
Age	3[2,15,28]	4[34,35,46,47]	0	14[25,26,29,31,33,36,38–41,44,47,48,50]
Male Sex	3[2,15,28]	0	0	14[25,26,29,33–36,39–41,44,46,48,50]
Functional capacity	1[15]	1[48]	0	7[34,35,39,44–47]
Co-morbidity	0	3[32,33,41]	2[2,15]	6[26,29,30,35,45,46]
Any spirometric value	0	0	1[15]	9[34–36,39,41,43,45,47,50]
Oral steroid use	0	1[34]	1[2]	6[26,35,39,41,44,45]
Previous AECOPD admissions	0	0	1[15]	6[34,35,39,44,45,48]
Long-term oxygen therapy	0	0	1[15]	5[26,35,36,45,47]
Previous intubation	0	1[34]	1[15]	4[39,41,47,48]
Body mass index	0	0	1[15]	1[42]
Quality of life	0	1[31]	1[15]	0
Smoking status	0	0	0	7[25,29,34,36,41,44,45]
Ethnicity	0	0	0	3[36,40,46]
Long-term inhaled therapy	0	0	0	3[35,41,45]
Weight	0	0	0	3[42,45,50]
Source of admission	0	0	0	2[45,48]
Recent antibiotic use	0	1[26]	0	1[46]
Right heart failure	1[2]	1[35]	0	2[34,38]
Pneumonia	0	4[25,29,32,47]	2[2,15]	4[41,44,45,47]
Left ventricular failure	0	0	2[2,15]	2[38,41]
pH	1[27]	2[33,40]	0	4[26,39,41,44]
Creatinine	1[27]	1[33]	0	2[45,50]
Oxygenation	0	1[32]	1[27]	11[26,33,34,38–41,44,45,48,50]
Carbon dioxide levels	0	2[39,46]	1[27]	11[26,32–34,37,40,41,44,45,48,50]
Albumin	0	6[32,34,37,41–43]	1[27]	6[25,26,36,45,47,50]
Sodium	0	2[43,48]	1[27]	2[36,45]
Potassium	0	0	1[27]	2[33,45]
Respiratory rate	0	0	1[15]	1[33]
Swelling of ankles	0	0	1[15]	1[32]
Haemoglobin	0	3[33,41,47]	0	4[34,39,47,50]
Hypotension	0	3[33,37,48]	0	2[38,45]
Total protein	0	2[33,36]	0	2[25,50]
Tachycardia	0	2[32,37]	0	1[45]
Phosphate	0	1[48]	0	3[41,43,50]
Urea	0	1[48]	0	2[43,45]
C-reactive protein	0	1[33]	0	1[26]
White cell count	0	0	0	5[26,33,39,45,47]
Temperature	0	0	0	3[26,45,47]

6 months, there is evidence that COPD patients would consider 6-month survival a worthwhile objective.[51]

Variables which are predictive of intermediate-term mortality

Premorbid variables

Time spent in hospital prior to ICU admission has been demonstrated in three studies[2,15,46] to predict hospital or 6-month mortality and this may reflect treatment failure, more severe underlying exacerbation or the development of a hospital-acquired infection.

Wildman found an independent effect on mortality when hospital stay was >3 days prior to ICU admission.[15]

Acute physiological or laboratory variables

Acute physiological disturbances are important prognostic variables predictive of intermediate-term mortality after AECOPD. Admission following cardio-respiratory arrest may reflect the severity of

the underlying acute respiratory embarrassment.[2,35,44] Low GCS is independently predictive of intermediate-term mortality. This may reflect central nervous system dysfunction due to the severity of the underlying exacerbation.[15,33,37,38,47]

Cardiovascular dysfunction may be an important variable with the presence of cardiac dysrhythmia predictive of mortality.[15,33,49]

Low bicarbonate predicts mortality in this setting and may reflect metabolic acidosis and physiological decompensation or cardiovascular disturbance.[26,27,33,37,44]

Admission APACHE II score has been found by five studies to be predictive of intermediate-term mortality.[25,34,37,39,44] Although APACHE II has not been validated as a severity scoring system on admission to ICU, other studies analysed have found APACHE II and other acute physiology scores to be predictive of mortality when using data from the first 24 h of ICU admission.[28,29,31,34,38–41,46] Additionally, the COPD and Asthma Physiology Score (CAPS) calculated on admission has been shown by one high-quality study[15] to predict outcome when used to form a scoring system with other prognostic variables and is also prognostic when data are gathered during the first 24 h of ICU admission[16] and has been prospectively and independently validated. Finally, this mirrors work in the overall hospital population of COPD patients from the SUPPORT group who found that APACHE III acute physiology score on day 3 of hospitalization was the most important predictor of 6-month mortality.[14]

Overall, the data support acute physiological derangement and organ dysfunction as being predictive of intermediate term outcome and other studies of ICU admission due to AECOPD support this hypothesis with other organ failure, particularly cardiovascular and renal having a negative prognostic implication when developing early during ICU course.[2]

Variables which are not predictive of intermediate-term mortality

Premorbid variables

Premorbid variables traditionally assigned prognostic significance have not been demonstrated to be predictive of intermediate-term mortality. These include: age, functional capacity, quality of life, male sex, oral steroid use, spirometry, previous hospital or ICU admissions, body mass index, smoking status and long-term oxygen therapy. However, a number of these variables have been shown to be associated with longer term poor outcome.[52]

When age is analysed as a predictive variable, most studies quote mean age in survivors and non-survivors and the majority of studies have not found a significant difference in age between survivors and non-survivors. However, where age is quoted, the mean age is higher in non-survivors than survivors in 19 out of 20 studies. It may also be true that mean age is not the most appropriate way of analysing the effect of age in studies of this nature, particularly as older patients may be denied admission, which could affect results. An important, high-quality study which found age to be predictive of mortality used ranges of age to assess the affect on mortality which may be a more appropriate analysis than comparing mean ages in survivors and non-survivors.[15] Although most studies have not found that functional capacity predicts intermediate-term mortality, this has never been objectively assessed as a prognostic variable with the use of previously documented 6-min walk tests. Finally, a potential confounding factor, which may limit the usefulness of studies in this area, is that patients with variables who are traditionally thought to be associated with a poor outcome such as long-term oxygen therapy might be denied admission and therefore, the variable would be inadequately investigated. However, nine studies quote the percentage of patients receiving long-term inhaled oxygen therapy and 43–100% of the patients in these were invasively ventilated including those patients receiving long-term oxygen therapy. Six studies have found that long-term oxygen therapy is not predictive of intermediate-term mortality.

Diagnosis associated with exacerbation of COPD

Pneumonia, left ventricular failure and right ventricular failure have not been consistently demonstrated to be associated with a worse prognosis.[2,15,25,29,32,34,35,38,41,44,45,47] In the case of pneumonia and left ventricular failure, this may reflect effective immediate treatments for these conditions. The case of right heart failure is less easy to explain though the SUPPORT group similarly found no evidence of an adverse prognostic effect of cor pulmonale. Indeed, their data suggest a 'protective' effect of cor pulmonale on 6-month mortality.[14]

Acute physiological and laboratory variables

Isolated physiological variables such as tachycardia have not been shown to be predictive of intermediate-term outcome in AECOPD.[32,37,45] A single physiological variable such as tachycardia

abnormality is non-specific in this setting with many possible causes such as drug therapy for AECOPD and hypovolaemia, which are not always related to the severity of the underlying exacerbation.

Similarly, isolated laboratory variables are not associated with intermediate-term mortality.

Measurements of oxygenation and carbon dioxide levels may reflect the severity of the respiratory failure but have not been shown to be predictive of outcome.[26,27,32–34,38–41,44,45,48,50] This may reflect the effective treatments readily available to the critical care practitioner to reverse these physiological derangements.

Discussion of scoring system for study quality

The integrative review has highlighted the variable quality of studies investigating prognostic variables predictive of intermediate-term mortality in patients with AECOPD admitted to ICU (Table 2). In order to rigorously study the prognostic variables predictive of intermediate-term mortality in patients with AECOPD admitted to ICU future studies would incorporate the quality criteria highlighted in this review. It is well-recognized that there has been no validated method of critically appraising prognostic research but McShane *et al*.[53] have developed a template for prognostic trial design in the specific setting of the use of biomarkers in cancer. The quality criteria used in this review are developed from published work, recommendations and quality scoring systems which have been previously proposed. The criteria have been selected as being most pertinent to studies investigating predictors of mortality after AECOPD.

Conclusions

The most important variables that are predictive of intermediate mortality after AECOPD requiring ICU admission are those which reflect acute physiological disturbance and severity of acute disease. Variables that reflect chronic health status are less important as is the cause of decompensation leading to AECOPD. These results do not support current UK guidelines regarding which factors may be important to consider when considering a patient for ICU admission and invasive mechanical ventilation. Strict adherence to these guidelines may result in patients being inappropriately denied critical care resources. The discrepancy between the published evidence and the UK guidelines should prompt further studies to validate previously published high-quality studies in this area.[15]

Studies that have investigated this subject are often of poor quality and a quality scoring system based on previously published data is proposed.

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