Survival, quality of life and health resource use following hospitalisation for acute exacerbations of chronic obstructive pulmonary disease

Predicting outcomes following exacerbations of COPD

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Thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy

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March 2013

DECLARATION

I hereby declare that this thesis is my own work and effort and has not been submitted for a degree or other qualification in this or any other university. Where other sources of information have been used, they have been acknowledged.

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March 2013

THESIS ABSTRACT

Background

Hospital admissions with acute exacerbations of chronic obstructive pulmonary disease are common and associated with high mortality rates, frequent readmission and worse quality of life. An ability to identify patients at risk of subsequent poor outcome is lacking and the longitudinal change in quality of life following discharge is uncertain.

Methods

The study consisted of two parts:

1) Clinical data were collected on 920 consecutive patients hospitalised with exacerbations. The ability of a novel modification of the traditional MRC dyspnoea scale (the extended MRC dyspnoea scale, eMRCD) to identify patients at risk of poor outcome was assessed. Independent predictors of important clinical outcomes were recorded and clinical prediction tools derived.
2) A subgroup of 183 patients underwent longitudinal assessment of quality of life following hospital discharge and predictors of quality of life decline were identified.

Results

The study population was similar to that reported in UK national audits. 96 (10.4%) patients died in-hospital and 37.3% were readmitted to hospital, or died without being readmitted, within 90-days of discharge.

The eMRCD was a better predictor of outcome than the traditional scale and, compared to all clinical variables, was the single strongest predictor of mortality and readmission

Strong independent predictors of many important clinical outcomes were identified and, notably, the DECAF (dyspnoea, eosinopenia, consolidation, acidaemia, atrial

fibrillation) predictive tool was derived and shown to be an excellent, and internally valid, mortality predictor (area under ROC curve = 0.858).

Most patients who survived to discharge reported an improvement in respiratory symptoms and quality of life during follow-up. We defined a subgroup of patients who experienced poor post-discharge quality of life and identified robust, simple-to-measure predictors of poor quality of life.

Conclusions

Important patient outcomes can be accurately predicted in this population. Application of our results may reduce morbidity and mortality in this common and frequently fatal condition by improving clinical decision making regarding appropriate level of care, location of care and resource allocation.

GLOSSARY OF ABBREVIATIONS

6MWT	6-minute walk test
ACE	angiotensin converting enzyme
ADL	activity of daily living
AECOPD	acute exacerbation of COPD
AF	atrial fibrillation
ANOVA	analysis of variance
APACHE	acute physiology and chronic health evaluation (predictive tool)
ARF	acidaemic respiratory failure
ATS	American Thoracic Society
AUROC	area under the receiver operator characteristic curve
B	regression coefficient
BAP-65	blood urea nitrogen, altered mental status, pulse rate, age greater than 65 (predictive tool)
BDP	beclomethasone diproprionate
BE	base excess
BMI	body mass index
BNP	N-terminal pro-brain natriuretic peptide
BODE	body mass index, airflow obstruction, dyspnoea, exercise capacity (predictive tool)
BP	blood pressure
BPQ	breathing problems questionnaire
BTS	British Thoracic Society
CAP	community acquired pneumonia
CAPS	COPD and asthma physiology score (predictive tool)
CCI	Charlson comorbidity index
CI	confidence interval
CKD	chronic kidney disease
COPD	chronic obstructive pulmonary disease
CPI	COPD prognostic index
CPY	cigarette pack year
CRP	C-reactive protein
CRQ	chronic respiratory questionnaire
CT	computer tomography
CURB-65	confusion, urea, respiratory rate, blood pressure, age greater than 65 (predictive tool)
CVD	cardiovascular disease
CXR	chest radiograph
DNACPR	do not attempt cardiopulmonary resuscitation
ECG	electrocardiograph
ED	emergency department

EM	expectation-maximisation (algorithm)
eMRCD	extended Medical Research Council Dyspnoea (scale)
ERS	European Respiratory Society
ESD	early supported discharge
FEV_1	forced expiratory volume in one second
F_iO_2	fraction of inspired oxygen
FFM	fat free mass
FN	false negative
FP	false positive
FRC	functional residual capacity
(F)VC	(forced) vital capacity
GCS	Glasgow coma scale
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General Practitioner
HADO	health-activity-dyspnoea-obstruction (predictive tool)
HADS	hospital anxiety and depression scale
Hb	haemoglobin
HCO_3^-	bicarbonate
HLGFT	Hosmer-Lemeshow goodness of fit test
HR	heart rate
HRQoL	health-related quality of life
IBW	ideal body weight
IC	inspiratory capacity
ICS	inhaled corticosteroids
ICU	intensive care unit
IHD	ischaemic heart disease
IHM	in-hospital mortality
IPPV	invasive (intermittent positive pressure) ventilation
IQR	inter-quartile range
JVP	jugular venous pressure
LACE	length of stay, emergent admission, comorbidity, previous ED visits (predictive tool)
LTOT	long-term oxygen therapy
LV	left ventricular
LVEF	left ventricular ejection fraction
LVF	left ventricular failure / dysfunction
LVRS	lung volume reduction surgery
MAR	missing at random
MCAR	missing completely at random
MCID	minimally important clinical difference
MEWS	modified early warning score

MNAR	missing not at random
MODS	multi-organ dysfunction syndrome
MRCD	(modified) Medical Research Council dyspnoea (scale)
MTCSA	mid-thigh cross sectional area
MUST	malnutrition universal screening tool
NEADL	Nottingham extended activity of daily living (scale)
NH	nursing home
NHP	Nottingham health profile
NHS	National Health Service
NIV	non-invasive ventilation
npAECOPD	non-pneumonic acute exacerbation of COPD
NTGH	North Tyneside General Hospital
OR	odds ratio
OSA	obstructive sleep apnoea
P_aCO_2	partial pressure of carbon dioxide in arterial blood
pAECOPD	pneumonia acute exacerbation of COPD
P_aO_2	partial pressure of oxygen in arterial blood
PARR	the patients at risk of hospitalisation (predictive tool)
PASP	pulmonary artery systolic pressure
PCT	procalcitonin
PEFR	peak expiratory flow rate
PVD	peripheral vascular disease
QoL	quality of life
ROC	receiver operator characteristic
RR	respiratory rate
RSpN	respiratory specialist nurses
RV	residual volume
RVH	right ventricular hypertrophy
SAPS	simplified acute physiology score (predictive tool)
SD	standard deviation
SF-36	36-item short form health survey
SGRQ	St. George's respiratory question
SIP	sickness impact profile
SOLDQ	Seattle obstructive lung disease questionnaire
S_pO_2	transcutaneous arterial oxygen saturation
SUPPORT	the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments
TLC	total lung capacity
TN	true negative
TP	true positive
VIF	variance inflation factor

VO_{2MAX}	maximum oxygen consumption per minute per kilogram
WBC	white blood cell count (in serum)
WGH	Wansbeck General Hospital
WHO	World Health Organisation

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THESIS OUTLINE

The ability to identify patients at risk of poor outcomes in patients hospitalised with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) is suboptimal at present. Previous research has focused on the prediction of outcome in patients with stable COPD and, with the exception of mortality prediction (Table 2.1), discussion of prognostication in stable disease is not included in this thesis.

This thesis details a research project whose main aim was to define and predict outcomes in a large cohort of patients hospitalised with exacerbations of chronic obstructive pulmonary disease.

The first section thoroughly reviews the published literature on the prediction of mortality, readmission and subsequent quality of life in this patient group and evidences the assertion that improved prognostication is needed. In the next section, the aims and methodology are outlined and explained.

The results and discussion follow and are separated in two sections:

Part 1. The prediction of important patient outcomes in a large cohort of patients hospitalised with COPD exacerbations (n = 920), including the description of a novel modification of the traditional MRC dyspnoea score, the extended MRC Dyspnoea score (eMRCD).

Part 2. The description of longitudinal quality of life change in a subgroup of 183 patients surviving to discharge following hospitalisation with AECOPD, including the identification of predictors of poor subsequent quality of life.

After discussion of the potential clinical impact of this thesis and suggestions for future research, the appendices and references are listed.

BACKGROUND

CHAPTER 1 INTRODUCTION

1.1 STABLE COPD

1.1.1 DEFINITION

Chronic obstructive pulmonary disease (COPD) is a multisystem condition defined as "a preventable and treatable disease with some significant extra-pulmonary effects that may contribute to the severity in individual patients."[1] Its pulmonary component is characterised by airflow obstruction that is usually progressive and not fully reversible. In the western world, COPD is typically caused by long-term exposure to tobacco smoke.

1.1.2 BURDEN OF DISEASE

1.1.2.1 PREVALENCE

Estimates of COPD prevalence vary, largely due to differing diagnostic criteria. Surveys relying on physician reported diagnosis alone frequently under report the prevalence of COPD, and studies of patient-reported symptoms (without lung function verification) will overdiagnose COPD.[1]

Considerable geographic variation in COPD prevalence exists. The estimated UK COPD prevalence varies between 2% and 4%,[2] whereas in North-East England, in adults between 45 and 69 years old, the prevalence of COPD lies between 10 and 25% (depending on diagnostic criteria).[3] Over 900,000 people have been diagnosed with COPD in the UK,[4] but it has been estimated that only 30% of patients with COPD have been diagnosed.[5, 6]

The prevalence of COPD is expected to rise due to an ageing population and the long-term cumulative effects of tobacco smoke. In the UK, between 1990 and 1997, the prevalence rate rose by 69% in women and 25% in men.[7]

1.1.2.2 SYMPTOM BURDEN

The worldwide burden of COPD, as expressed by disability life years and compared to other conditions, was expected to rise from eighth in men and seven in women in 1996, to fifth for both sexes in 2020.[8]

In the general population, symptoms of chronic bronchitis have been found to be present in 8.9% of males and 4.1% of females, and symptoms of breathlessness in 13.6% of males and 16.4% of females.[9] As the severity of COPD worsens, the burden of symptoms increases: patients with very severe airflow obstruction (forced expiratory volume in 1 second, FEV_1 < 30% predicted) usually have disabling breathlessness at rest.[10]

1.1.2.3 HEALTH RESOURCE USE

Respiratory disease is the commonest reason for an individual to contact their General Practitioner, and of all respiratory diseases, COPD is the 2nd most frequent reason for contact with the GP.[11] COPD is the second largest cause of emergency hospital admissions in the UK, responsible for over 130,000 admissions - 1/5 of all bed days used for respiratory disease.[11, 12]

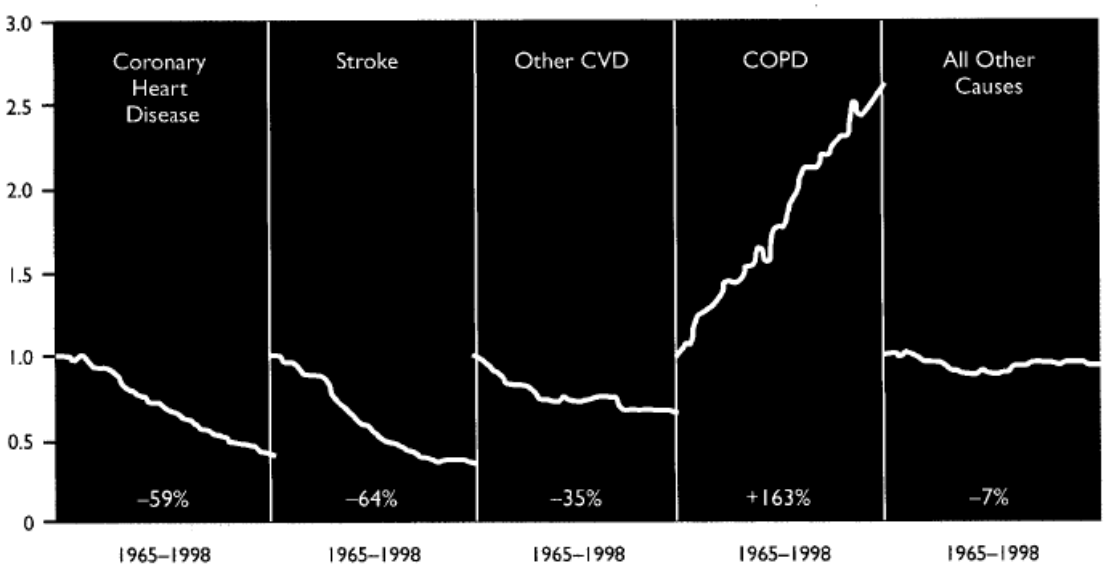
A telephone survey of 3245 individuals with COPD showed that a quarter of patients had reported ever being hospitalised with COPD and 14% had required a hospital admission in the preceding 12 months. 12% had attended the hospital emergency department for treatment of their COPD in the previous year.[13] Following discharge, 33% of patients are readmitted to hospital within 3 months,[12] and up to 55% within one year following discharge.[14, 15]

1.1.2.4 MORTALITY

Due to imprecise diagnostic criteria and significant underreporting, worldwide mortality figures for COPD need to be interpreted with caution and are likely to underestimate the true mortality burden of COPD. In spite of this, the World Health Organisation (WHO) Global Burden of Disease Study identified COPD as the 6th leading

cause of death worldwide in 1990, and projected that it would rise to third by 2020.[8] The British Thoracic Society Burden of Lung Disease reported in 1999 and 2006 [11, 16] and identified COPD as the 5th most common cause of overall mortality in England and Wales (in 1999), and the third leading cause of respiratory death (in 2004). The mortality rate associated with COPD is increasing in the developed world particularly when compared to other common chronic diseases (Figure 1.1)

Figure 1.1 Percentage change in age-adjusted death rates in the United States, 1965-1998



CVD – cardiovascular disease. [17]

1.1.2.5 COST

Britton [13] calculated that the annual direct per patient cost of COPD in the UK was £819.42 (rising substantially in patients with severe disease)[18] and the total direct cost to the NHS is estimated to be £810-£930 million per year.[11] A major proportion of the costs related to COPD is secondary to the treatment of acute exacerbations, particularly if hospitalisation is required (section 1.2.2.2).

COPD is a major cause of work absence. 38% of patients with COPD reported their work being affected by their disease, with a mean number of 12 work days lost per patient per year.[13] It has been estimated that COPD results in 24 million lost working

days per annum,[19] and this costs the UK economy over £3.8 billion in lost productivity.[13]

1.1.3 COPD DIAGNOSIS

Traditionally, the terms ‘chronic bronchitis’ and ‘emphysema’ were used to describe the condition now classified as COPD. Chronic bronchitis is a symptom based definition that refers to the presence of cough and sputum production for at least 3 months in 2 or more consecutive years. Emphysema is a pathological term referring to “permanent, destructive enlargement of airspaces distal to the terminal bronchioles without evidence of fibrosis”,[20] but it only refers to one of many pathological abnormalities present in COPD.

The diagnosis of COPD is dependent on: the presence of characteristic symptoms; the identification of an appropriate risk factor (principally tobacco smoke); and the presence of airflow obstruction,[1] which is best assessed by spirometry (section 1.1.3.2). An additional characteristic of COPD is that it is accompanied by a high rate of comorbidity (section 1.1.3.5).

1.1.3.1 SYMPTOMS OF COPD

Although COPD can be considered a systemic disease, the majority of individuals seek medical attention because of respiratory symptoms. In its early stages, COPD can be asymptomatic, although the commonest symptoms are cough, sputum production, dyspnoea and wheeze / chest tightness. These symptoms are highly variable, vastly under-reported and not universally present, even in individuals with severe disease.[21]

Several systemic features have been identified in individuals with COPD and they appear more prevalent in those with severe disease. The systemic features of COPD include: skeletal muscle wasting and loss of free fat mass (resulting in weight loss and low body mass index – BMI), anaemia, osteoporosis and fatigue.[1]

1.1.3.1.1 DYSPNOEA

Dyspnoea is usually defined as an uncomfortable awareness of breathing. It is a major cause of disability and anxiety, and the reason that most patients with COPD seek medical attention.[1] Patients with COPD use a variety of terms to describe the symptoms that they experience when breathless and this makes objective, reproducible assessment of the degree of dyspnoea difficult. Smith et al [22] identified, in patients with COPD, that the best subjective descriptors of individuals' symptoms on exercise was the feeling of 'air-hunger', whereas at rest, descriptions with emotional connotations ('suffocating', 'fighting for breath') were most applicable.

In an attempt to standardise the assessment of dyspnoea, instruments have been developed that assess the effects that breathlessness causes on the ability to undertake certain activities of daily living (ADL) (discussed below) or on the effect that dyspnoea has on an individual's quality of life (section 4.3). The modified Medical Research Council Dyspnoea Scale (MRCD) (Table 1.1) assesses the impact of dyspnoea on the ability to perform ADLs and has been shown to be associated with exercise capacity, quality of life, mood state and level of disability.[23] However, MRCD and the forced expiratory volume in 1 second (FEV_1, section 1.1.3.2) are not closely associated,[23] and the severity of dyspnoea according to MRCD is a more accurate predictor of mortality and readmission than FEV_1 (section 2.1).[24-26] The MRCD performs equally as well as other clinical dyspnoea rating tools (e.g. Baseline Dyspnoea Index, dyspnoea component of Chronic Respiratory Questionnaire (CRQ), and activity component of St. George's Respiratory Questionnaire (SGRQ)) in evaluating dyspnoea in individuals with COPD.[27]

Table 1.1 The modified MRC Dyspnoea Score [23]

Grade	Degree of breathlessness related to exercise
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying or walking up a slight hill
3	Walks slower than contemporaries on level ground because of breathlessness, or has to stop for breath when walking at own pace
4	Stops for breath when walking about 100m or after a few minutes on level ground

5	Too breathless to leave the house

1.1.3.1.2 NUTRITIONAL DEPLETION IN COPD

It is well-established that many patients with COPD are underweight, and malnourishment becomes more common as COPD severity worsens.[28] This may in part be due to a reduction in calorific intake, but the increased work of breathing and systemic inflammation that is associated with this condition also contribute.

Nutritional depletion has a variety of definitions. The WHO defines nutritional status according to body mass index (BMI): weight (kg) / height $(m)^2$ (Table 1.2).

Table 1.2 International classification of adult nutritional status according to BMI [29]

Classification	BMI (kgm^{-2})
Underweight	<18.5
Normal	18.5 – 24.99
Overweight	≥25
Obese	30 – 39.99
Morbidly obese	≥40

Epidemiological studies in individuals with COPD have used various criteria to define poor nutrition and hence the prevalence rate varies (Table 1.3). Although fat free mass (FFM) appears to be a more accurate marker of undernutrition, and a better prognostic indicator, than BMI (section 2.1),[28] its accurate measurement is complex and largely confined to specialist centres. BMI is simple to measure and therefore is the nutritional index most commonly evaluated in COPD.

Table 1.3 Summary of different definitions of undernourishment and their respective prevalence rates in patients with COPD.

Author	Definition of undernutrition	Prevalence
Vermeeren et al [30]	BMI ≤ 21kgm^{-2} and / or FFMI ≤ 16 kgm^{-2}	27%
Gray-Donald et al [31]	BMI < 20 kgm^{-2} (males); < 18.8 kgm^{-2} (females)	18%
Wilson et al [32]	< 90% of ideal body weight	24%*
Schols et al [28]	BMI < 21 or FFMI < 16 kgm^{-2}	43.7%
Hallin et al [33]	BMI < 20 kgm^{-2}	19%$^{\Delta}$
Giron et al [34]	BMI < 20 kgm^{-2} or FFMI ≤ 16 kgm^{-2}	38%$^{\Delta}$

IBW – ideal body weight, FFMI – fat free mass index, * 24% in all patients, 50% in patients with FEV_1 <35% predicted, $^{\Delta}$in patients hospitalised with acute exacerbations of COPD.

It is well established that low BMI is associated with increased all-cause and COPD-related mortality, independent of disease severity.[35] It has also been shown that an elevated BMI is protective against mortality, particularly in patients with severe airflow obstruction, with the lowest risk of mortality in the overweight population (BMI 25 to 30 kgm^{-2}).[33] This relationship is in contrast to the general population where increased BMI is associated with reduced life expectancy, independent of smoking status and comorbidity.[36] This has been termed the 'obesity paradox' and has been reported in other chronic conditions (for example, end-stage renal disease, cardiac failure and rheumatoid arthritis) [37, 38] although the mechanisms of the relationship are unknown.

Nutritional depletion is possibly more common in patients hospitalised with acute exacerbations of COPD and is an adverse prognostic indicator in this population (section 2.2.4.1). Periods of hospitalisation are associated with weight loss and malnutrition,[39] and in acute exacerbations of COPD, weight loss is associated with increased risk of readmission following discharge.[34] However, the prevalence of undernutrition and weight loss has not been closely examined in patients hospitalised with COPD exacerbations.

The Malnutrition Universal Screening Tool (MUST) is a nutritional assessment instrument, which combines both BMI and recent unexplained weight loss into a screening tool which aims to improve the recognition and treatment of malnutrition in

the hospital setting (Table 5.2). It has excellent reproducibility between users [40] and also predicts mortality more reliably than BMI in elderly acute general medical admissions.[39, 41] Its use, however, has not been investigated in patients hospitalised with acute exacerbations of COPD (AECOPD) although its component variables suggest that it may be a prognostically useful tool.

1.1.3.2 SPIROMETRY

Spirometry assesses the volume of air that an individual can expel from their lungs in a single expiration from maximal inspiration.[42] The two indices measured are: the volume of air expelled in one second during a forced expiration (forced expiratory volume 1 - FEV_1) and the total volume of air expelled during a single expiration (vital capacity – VC). The vital capacity can be measured during a forced manoeuvre (FVC) or during a relaxed expiration (VC) however, during forced expiration, dynamic collapse of the small airways can result in an underestimation of vital capacity.[21] Values are measured in litres and compared to 'normal' values based on age, sex, height and ethnic origin [43] and are expressed as a percentage of predicted.

The volume of forcibly expelled air during the first second of expiration relative to their vital capacity (FEV_1 / FVC) provides a simple assessment of airflow limitation, with lower values (< 0.70) indicating airflow obstruction and being necessary for the diagnosis of COPD to be made.[44] Although recommended by all major expert bodies, using a fixed FEV_1 / FVC ratio for the diagnosis of COPD has limitations as it overestimates the prevalence of airflow obstruction in the elderly.[45]

At least three acceptable spirograms need to be obtained from the patient by a trained professional. The two largest values for VC and FEV_1 must be within 150ml of each other. Only when these criteria are met can the test be deemed to be acceptable.[46] The presence of bronchodilator reversibility may be useful in helping distinguish COPD from asthma but this is not routinely recommended for the diagnosis of COPD.[44]

1.1.3.3 STAGES OF COPD

A simple staging system for the severity of COPD is useful both practically, as a general indication to the approach to management, and educationally. However, it is very difficult to identify easily measurable clinical indices that accurately describe symptom severity as well as predicting outcomes. FEV_1 is typically used to stage COPD however: there is an imperfect relationship between the degree of lung function impairment and the severity of an individual's symptoms;[1, 24] FEV_1 does not consistently predict outcome; and although low FEV_1 is significantly associated with mortality in the population as a whole, in individuals with severe disease, where the range of FEV_1 values is narrow, the relationship weakens or disappears.[47, 48] Recent national guidelines [44] reflect this difficulty and recommend a comprehensive assessment of severity including the degree of airflow obstruction (Table 1.4) and disability, the frequency of exacerbations and a number of easily measurable known prognostic factors (e.g. BMI, MRCD scale, quality of life).

Despite the known problems, categorising FEV_1 provides a reproducible measure of the severity of airflow obstruction which in turn reflects an important component of disease severity. Therefore, the following classification describes the severity of airflow obstruction and has been endorsed by all the major international specialist advisory organisations (GOLD, BTS, ERS and ATS):

Table 1.4 Classification of severity of airflow obstruction in COPD [44]

Stage	FEV_1 / VC ratio	FEV_1 % predicted
Stage 1 – mild COPD	< 0.70	≥ 80
Stage 2 – moderate COPD	< 0.70	50 ≤ FEV_1 < 80
Stage 3 – severe COPD	< 0.70	30 ≤ FEV_1 < 50
Stage 4 – very severe COPD	< 0.70	< 30*

*or, FEV_1 < 50% + presence of chronic respiratory failure

1.1.3.4 ASTHMA & COPD

Similarly to COPD, asthma is a chronic condition causing airflow obstruction as a result of airway inflammation. A key component of asthma, and one that helps differentiate

the condition from COPD, is that the airflow obstruction is variable and often fully reversible. However, both conditions may coexist and there is an overlap between the two diseases: certain individuals with longstanding asthma can develop fixed, irreversible airflow obstruction and clinical symptoms similar to COPD [49] making the differentiation between asthma and COPD difficult. Despite a clinical picture similar to COPD, individuals with chronic asthma and fixed airflow obstruction have a pattern of airway inflammation that is different to those with COPD [1] as well as a more favourable prognosis.[50] Individuals with chronic asthma, compared to those with COPD, also show greater lung function reversibility to oral prednisolone although their response to inhaled bronchodilators may be similar [51]. In clinical practice it can be difficult to differentiate between individuals with COPD and individuals with chronic asthma, and they may co-exist. A careful history aimed at identifying the presence, or absence, of longstanding asthmatic symptoms coupled with demonstrating airflow obstruction during disease stability are important to help differentiate COPD from asthma.

1.1.3.5 COMORBIDITY

Comorbidity is defined as the presence of other chronic medical conditions in an individual in addition to the condition of primary interest.[52] Comorbidities are common in COPD but their reported prevalence varies significantly between studies. Mapel et al [53] reported that only 6% of individuals with COPD did not have another chronic medical condition, and van Manen et al [54] showed that 50% of patients with COPD had 1-2 comorbidities, 15% had 3-4, and 7% had ≥ 5.

The strong association between COPD and comorbidity may be because COPD shares a common risk factor (i.e. tobacco smoking) with other chronic conditions, or because the systemic effects of COPD predispose to certain medical conditions. Irrespective of the aetiology, managing an individual's comorbidity is important when managing their COPD. Huiart et al [55] reported that, in individuals with COPD, cardiovascular disease is a more frequent reason for hospitalisation and death than COPD. Zvezdin et al [56] retrospectively reviewed the autopsy results of 43 patients who had died within 24

hours of hospitalisation for acute exacerbations of COPD (AECOPD). Cardiac failure was the primary cause of death in 37%, pulmonary embolism caused death in 21% and respiratory failure secondary to COPD resulted in death in only 14%. Similarly, in 3343 patients with stable COPD followed up for up to 5 years, 2/3 of the 550 recorded deaths were due to non-respiratory disease.[57]

Furthermore, the overall comorbidity burden is important in the management of patients with COPD and is a strong independent predictor of mortality.[58] The Charlson Comorbidity Index (CCI, Table 17.1) [59] is a comorbidity assessment tool which quantifies an individual's comorbidity burden. The CCI grades 15 chronic diseases according to their severity: mild diseases are assigned lower scores than severe diseases, and a higher score indicates a greater comorbidity burden.

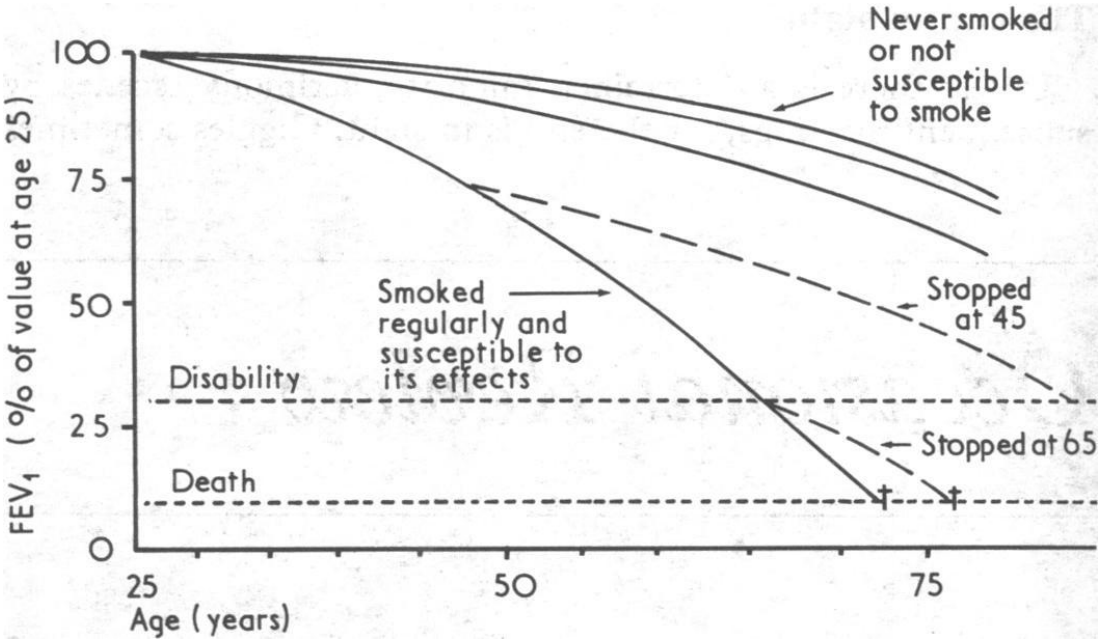
1.1.4 NATURAL HISTORY

COPD has a variable natural history but generally, there is a gradual decline in lung function and it is estimated that approximately 50% of individuals aged over 70, who continue to smoke, will develop COPD.[45] Similarly to the decline in lung function, patients with all stages of COPD have been shown to experience a progressive linear deterioration in quality of life (measured using the SGRQ) and this decline is independent of smoking status.[60]

The rate of decline in lung function is independently predictive of morbidity and mortality [61] although the rate of decline varies between individuals and is difficult to predict. The observation that different populations (i.e. susceptible smokers, non-susceptible smokers, ex-smokers and never smokers) experience varying declines in lung function was first identified by Fletcher and Peto in a prospective cohort study of working men in London.[62] They identified a gradual decline in lung function (FEV_1) with ageing in individuals who never smoked. The decline was accelerated in individuals who smoked regularly, whilst in those who stopped smoking, lung function did not improve but the rate of decline in lung function returned to normal. This is an oversimplification of the natural history in COPD but provides a useful schematic to

depict the harmful effects of tobacco smoke and the progressive decline frequently observed in patients (Figure 1.2).

Figure 1.2 The natural history of lung function decline in COPD



The dashed lines indicate the effects of smoking cessation at different ages.[62]

As well as the decline in lung function varying between populations of individuals, there is considerable variation in individuals within the populations with some individuals who continue to smoke experiencing no lung function decline over a number of years.[63] COPD is also characterised by a propensity to episodic acute deterioration in an individual's clinical condition. These episodes of sudden deterioration are termed acute exacerbations of COPD are the main focus of this thesis and are defined in section 1.2.

1.1.5 MANAGEMENT OF STABLE DISEASE

The goals of treatment in stable disease are to: improve patient understanding of their condition; address patient symptoms and improve individual quality of life; prevent exacerbation and hospitalisation; slow disease progression and improve survival.

Important educational interventions include: smoking cessation advice (and treatment) which reduces both lung function decline (Figure 1.2) and mortality;[64]

and providing patients with the means to self-manage episodes of AECOPD which shortens recovery time [65] and reduces hospital admissions.[66]

Vaccination plays an important role in the management of stable COPD. Influenza and pneumococcal vaccines reduce the risks of hospitalisation, serious illness and death in individuals with COPD.[67, 68]

A number of inhaled medications have been shown to improve symptoms or quality of life, or to reduce exacerbation frequency. These include: β_2-agonists;[69] anticholinergics;[70] and inhaled corticosteroids (ICS) (in combination with long acting β_2-agonists) in moderate-to-severe disease.[71] Other agents include oral mucolytic therapy, long-term anti-inflammatory macrolide therapy and phosphodiasterase-4 inhibitors which may all reduce exacerbation frequency in selected individuals.[72-75]

Pulmonary rehabilitation is a non-pharmacological intervention for individuals with COPD that can interrupt the vicious cycle of breathlessness, exercise deconditioning, immobility, social isolation and depression. It can also address problems of muscle wasting and weight loss. Pulmonary rehabilitation is cost effective and has been shown to improve exercise capacity, health-related quality of life and reduce hospitalisations.[44]

In individuals with severe chronic hypoxaemia, pulmonary hypertension and cor pulmonale can develop. Cor pulmonale is characterised by signs and symptoms of right heart failure (peripheral oedema and raised venous pressure) secondary to chronic lung disease in patients who have no other cause of ventricular dysfunction.[44] Treatment of cor pulmonale is to correct hypoxia and, in all individuals with chronic severe hypoxia (with or without cor pulmonale), treatment with long term oxygen therapy (LTOT) for at least 15 hours per day has been shown to increase survival.[76] This is, in part, through the prevention of pulmonary hypertension [77] although it also has benefits on mental state and haemodynamics.[78] In patients whose oxygen saturations significantly fall on exertion, supplemental oxygen administered during exercise (ambulatory oxygen) may increase the duration of physical activity,[79] and

oxygen is sometimes used in short bursts to relieve symptoms of breathlessness,[80] although controversy exists regarding the benefits of short burst therapy.[44, 81]

In carefully selected individuals with COPD, surgical intervention in the form of lung volume reduction surgery (LVRS) [82] or lung transplantation [83] can improve quality of life, functional status and survival (in the case of LVRS). In a small proportion of patients with chronic hypercapnic respiratory failure who are hypercapnic or acidaemic on LTOT, long-term non-invasive ventilation (NIV) may be of benefit.[44]

1.1.5.1 PALLIATIVE CARE IN COPD

Palliative care involves the care of patients and their families when the individual's disease no longer responds to curative treatment,[44] and is defined by the WHO as "patient and family-centred care that optimizes quality of life by anticipating, preventing, and treating suffering."[84] Palliative care and terminal care are not synonymous and the main foci of palliative care are: symptom control; maintenance of quality of life and independence; improved, open communication; and psychological, emotional and spiritual support for patient and carers.[85] Traditionally, palliative care programmes have focused on the needs of patients with cancer. However, given that COPD is typically a progressive condition that results in significant morbidity and mortality, and that there are few treatments available to alter the natural history of the condition, palliative care is an important aspect of the management of patients with (severe) COPD.

In spite of national recommendations that access to palliative care services should be available to all with advanced COPD,[44] many patients do not receive such support as they approach the end of their life. This is despite evidence that the palliative care needs of patients with COPD may exceed those of individuals with lung cancer. Gore et al [86] compared the quality of life of a group of 50 patients with severe COPD with 50 patients with unresectable lung cancer. Patients with COPD had significantly worse physical, social and psychological function, as well a greater burden of anxiety or depression (90% COPD versus 52% lung cancer). Of those with lung cancer, 30% were in receipt of palliative care input and a further 56% had been offered input from, or

were aware of the availability of, these services. In contrast, none of the COPD patients were in receipt of, or had been offered, palliative care input.

Also, the care of patients with COPD at the end of their life results in health resource use that is not in line with their needs or wishes. Compared to individuals who had died of lung cancer, Au et al [87] showed that, in the last six months of life, patients who had died of COPD were more likely to be invasively ventilated and were less likely to receive symptomatic treatment for dyspnoea and anxiety with benzodiazepines and opiates. This is despite evidence that patients with severe COPD experience more severe dyspnoea, and are as unwilling to receive life-prolonging treatments with little hope of meaningful recovery, as those with lung cancer.[88, 89]

The palliative care needs of patients with severe COPD remain unmet and there are many plausible reasons for this. Perhaps most important is the difficulty in accurately predicting prognosis in patients with COPD: in one study,[90] for patients later found to be in their last week of life, their physicians had estimated a 40% likelihood of at least 6 months survival.

The pattern of decline as an individual approaches death is termed the 'illness trajectory'. The illness trajectory of individuals who die from cancer characteristically follows a predictable pattern: a period of gradual decline (over weeks, months or years) is followed by an accelerated decline, once treatment options are exhausted or withdrawn, until death (Figure 1.3). COPD, however, does not follow the same pattern. Instead, patients are ill for many years with their condition punctuated by occasional acute exacerbations. Exacerbations cluster in time,[91] but the interval between exacerbations is difficult to predict, and although each exacerbation may result in death, the patient usually survives (Figure 1.4). Also, associated comorbidities, such as coronary artery disease, may result in sudden death causing the accurate prediction of mortality even more problematic.

Figure 1.3 Illness trajectory of individuals who die from cancer [92]

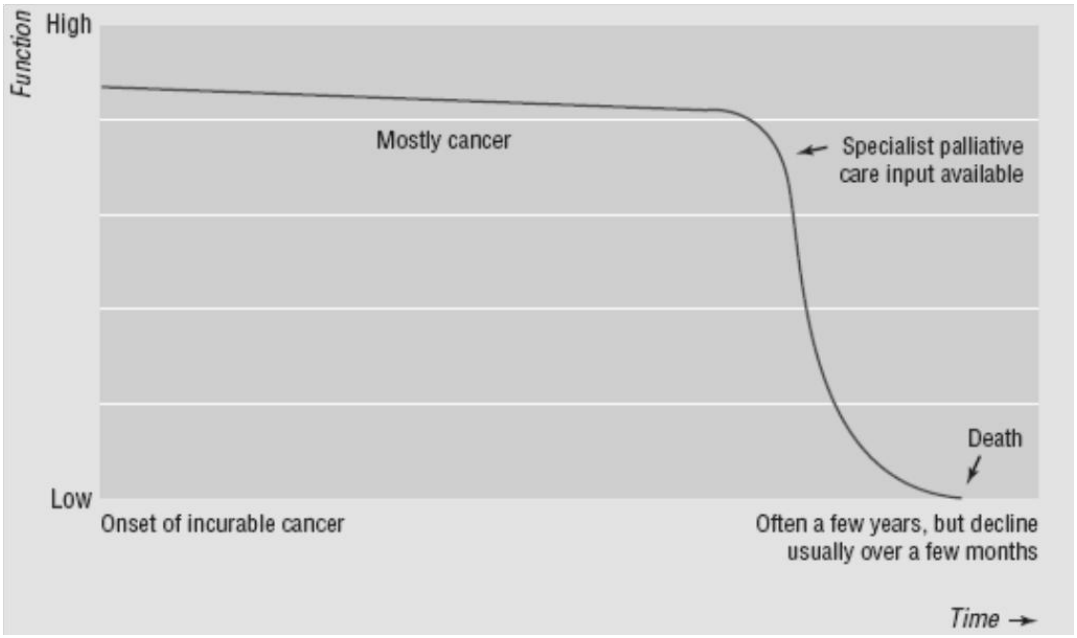
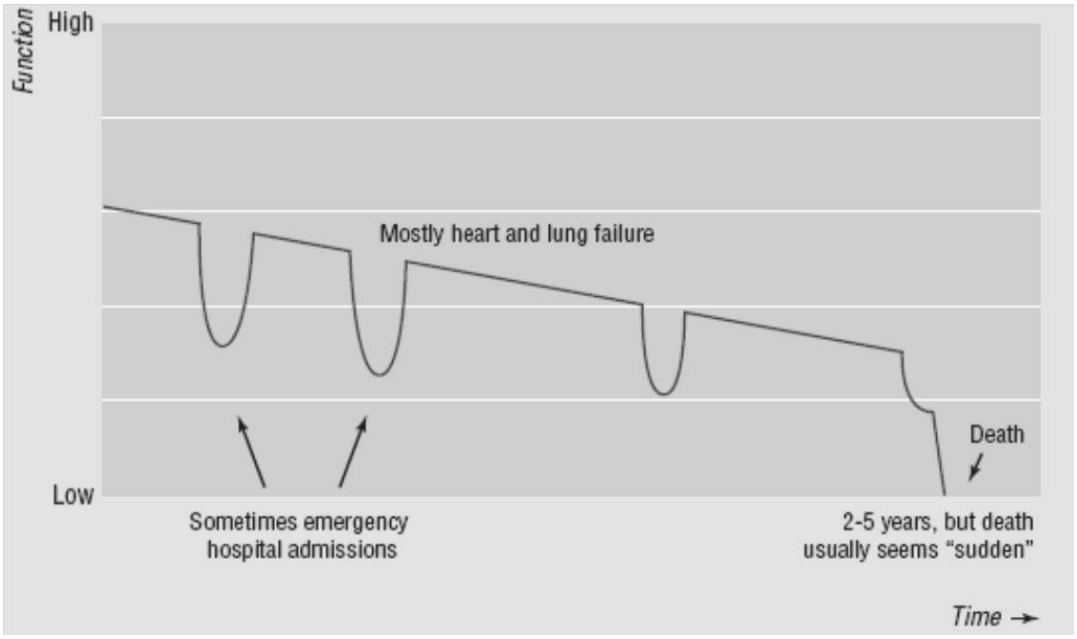


Figure 1.4 Illness trajectory of individuals who die from chronic disease (e.g. COPD or heart failure)[92]



Although palliative care is not synonymous with end-of-life care, attempts to predict the need for palliative care have focused on predicting end of life with no studies identifying predictors of poor quality of life. Furthermore, most studies have investigated predictors of palliative care need in malignant, rather than non-malignant, disease, and very few have examined patients with COPD.

Instruments such as the Palliative Performance Scale,[93] the Karnofsky Performance Scale,[94] and the Palliative Prognostic Index [95, 96], which are of prognostic use in malignant disease, have been infrequently studied in non-malignant disease: two studies [97, 98] have suggested they are prognostically useful in non-malignant disease, but in both studies only a small proportion of patients had COPD.

The Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT) aimed to predict six-month survival in seriously ill hospitalized adults.[99] Attempts to predict six-month mortality, and hence palliative care need, in the population of patients with COPD, have largely been unsuccessful,[100, 101] although Connors et al [102] derived a prognostic tool which showed promising performance, but it has not been validated outside of the study population.

Given the lack of robust predictors of medium-term prognosis in COPD (which will be discussed in greater detail in Chapter 2), perhaps the most pragmatic solution to identify those who may benefit from discussing palliative care options is the 'surprise' question: *"Would you be surprised if the patient died in the next 12 months?"*:[103] if the answer is *"No"* then a discussion around palliative care should be initiated. However, clinicians have difficultly accurately predicting prognosis and that they are often overly pessimistic in patients with COPD,[104] and therefore the 'surprise' question may over or under recognise patients potentially in need of palliative care.

It is important to recognise that all previous attempts to predict need for palliative care have focused solely on end of life with no reference to quality of life. Yet, given the difficulties in accurately identifying medium-term prognosis, prognostic markers for poor quality of life, or future decline in quality of life, may provide a more robust, and more patient-centred approach, to identifying those who may benefit from palliative care input.

1.2 ACUTE EXACERBATIONS OF COPD

1.2.1 DEFINITION AND PREVALENCE

As COPD progresses, it is typically punctuated by acute exacerbations (AECOPD) which often cluster in time.[91] There is no consensus definition for an exacerbation since they have a variety of causes, but a useful definition is that *"an exacerbation consists of an acute worsening of the patient's condition from the stable-state, which is sustained and may warrant the patient to seek additional treatment*".[105] This definition includes a wide variety of aetiologies and severities of exacerbation. Up to 50% of exacerbations are self-managed and never come to the attention of medical services,[106] whereas other acute exacerbations result in hospitalisation, respiratory failure and / or death. Studies suggest patients with COPD experience ≈1 AECOPD per annum,[71] and approximately 19% of AECOPD require hospitalisation for treatment.[44]

1.2.2 IMPACT OF AECOPD

1.2.2.1 PATIENT-CENTRED OUTCOMES

Exacerbations are important in the natural history and management of COPD: they cause a reduction in lung function and associated symptoms, resulting in deterioration in quality of life (QoL) [107-112], an increased need for healthcare interventions (for example, emergency hospitalisation), and an increased risk of mortality.[113-115] Admission to hospital for treatment of an acute exacerbation of COPD is associated with an in-hospital mortality rate of over 7.5% [12] and an annual mortality rate following discharge of up to 49%.

Recovery following AECOPD can be unpredictable and prolonged. In patients managed in the community with AECOPD, the recovery of lung function, symptoms and quality of life is most rapid during the initial four weeks, however a continued slow improvement is still apparent after six months, and some patients never recover to their pre-exacerbation level.[106, 116] The recovery of symptoms and lung function is

further prolonged in severe exacerbations or if a patient exacerbates during the recovery phase and therefore, in patients hospitalised with AECOPD, the median recovery time is likely to be significantly longer.[111] In some individuals, complete recovery is not achieved and therefore frequent exacerbations result in an accelerated decline in lung function,[117] symptoms and quality of life, [118] thus affecting the natural history of the disease.

Recovery following AECOPD managed in the community is well documented,[106, 119] but the time course of recovery following hospitalisation for AECOPD has been infrequently studied and requires clarification. Connors et al [102] showed that in patients with hypercapnia only 26% of patients were both alive and able to report a 'good' quality of life six months following discharge. Only a single study has assessed quality of life longitudinally, and this showed that health status continues to recover up to nine months following hospital discharge.[120]

The major risk factor for the development of AECOPD is a history of previous exacerbations,[91] and other risk factors include: low FEV_1; chronic mucus hypersecretion; higher age;[121] low health status; high comorbidity; high dyspnoea levels;[122] and a history of reflux or heartburn.[123] As COPD severity worsens, exacerbations become more frequent,[123-125] and those who experience frequent episodes of AECOPD are at a significantly increased risk of hospitalisation,[44] subsequent death,[113] low quality of life,[126] and a faster decline in lung function [117] and quality of life when compared to individuals who exacerbate less frequently.[118, 127]

Episodes of AECOPD, and in particular, episodes of AECOPD requiring hospitalisation, are therefore a key event in the natural history of COPD. They not only impact dramatically on patients' lives, but they may also signify a threshold in an individual's disease: following an exacerbation, and its associated slow or incomplete recovery, the patient is at risk of further episodes potentially requiring hospitalisation, thus resulting in an accelerated decline in their condition. Episodes of AECOPD therefore provide an opportunity to identify those patients at risk of subsequent exacerbation and disease decline, and to intervene early.

1.2.2.2 HEALTH RESOURCE USE AND COST

Acute exacerbations are the main reason for admission to hospital in COPD and are therefore a major reason behind the high financial burden associated with the management of COPD. There are variable estimates that unscheduled contact with the health service is responsible for between 35 and 63% of the total costs for COPD.[128, 129] The cost of AECOPD requiring hospitalisation varies from £2041 to £5298,[130] and the majority of the expenditure relates to length of stay and bed costs.[129, 131] It is estimated a small proportion of patients with COPD (approximately 10%) are responsible for over 70% of the costs associated with the disease, through unscheduled contact with the healthcare system for treatment of exacerbations.[132]

1.2.3 PATHOLOGY AND SYMPTOMATOLOGY

There are various aetiological agents implicated in AECOPD including both infective (bacteria and viruses) and non-infective (atmospheric pollution, pulmonary embolism, heart failure). It has been estimated that over 70% of AECOPD are due to an infective agent,[133] although in clinical practice a causative agent often remains unidentifiable.

Increased breathlessness is the main symptom of an exacerbation. Other symptoms may include wheeze, cough, sputum (either increased volume or purulence) or fever. Anthonisen [134] defined the severity of an acute exacerbation according to the symptoms at presentation (Table 1.5). Antibiotics are of clinical benefit in type 1 and type 2 exacerbations [134] and individuals with type 1 and type 2 exacerbations are at increased risk of in-hospital death, compared to type 3.[135]

Table 1.5 Anthonisen classification of acute exacerbations of COPD

Anthonisen Criteria	Symptoms & signs
Type 1	Increased dyspnoea, sputum volume and purulence
Type 2	Two of the above features present
Type 3	One of the above features present & at least one of the following: fever, increased wheeze, increased cough, or 20% increase in heart rate or respiratory rate compared to baseline

1.2.4 PNEUMONIA IN AECOPD

Community acquired pneumonia (CAP) is defined as an acute respiratory tract illness associated with radiographic consolidation on an admission chest radiograph consistent with infection, which is neither pre-existing nor due to another cause (for example, a known carcinoma or foreign body).[136] Pneumonia is a common complicating factor in patients hospitalised with AECOPD (termed pneumonic AECOPD, pAECOPD), and in patients hospitalised with CAP, COPD is the most common comorbidity.[137]

Estimates of the prevalence of radiographic consolidation in patients hospitalised with AECOPD vary considerably with quoted figures ranging from 10% to 70%.[135, 138-150] The most severe exacerbations (i.e. patients requiring ventilatory assistance) are typically associated with a higher prevalence. The varying prevalence rates are, in part, secondary to confusion regarding the terminology of patients with pneumonic AECOPD. Broadly, there are three approaches to defining the diagnosis in patients with AECOPD and complicating pneumonia: 1) AECOPD and CAP are separate entities and hence the presence of consolidation precludes the diagnosis of AECOPD; 2) the final diagnosis is AECOPD if the primary reason for admission is AECOPD rather than CAP and vice versa; and 3) the presence of consolidation is marker of a severe exacerbation of COPD, not a separate diagnosis, and if they coexist the diagnosis should be termed a pneumonic AECOPD (pAECOPD).

The approach of considering AECOPD and CAP as separate disease entities that cannot coexist is limited by a number of factors. Firstly, chest radiography has limited sensitivity for the diagnosis of pneumonia in both the critical care setting [151] and in general patients hospitalised with suspected pneumonia where it has been reported that up to 25% of patients with an initial negative chest radiograph (CXR) will have evidence of consolidation on computer tomography (CT) scanning,[152-154] and, of those with an initial negative CXR, over 50% will develop radiographic consolidation in the subsequent 48 hours.[154] Secondly, AECOPD is frequently diagnosed and managed in the community where chest radiographs are not routinely available:

therefore, excluding CAP from the diagnosis of AECOPD is not a reliable option. Lastly, including patients with both non-infective processes and infective bronchitis in the diagnosis of AECOPD, but excluding patients in whom the infection has progressed beyond the bronchial wall to cause pulmonary consolidation does not seem pathophysiologically consistent.

The second approach to diagnosing patients with COPD and CAP is limited on pragmatic grounds. In patients with underlying COPD, both an exacerbation of COPD and an episode of CAP will present with a similar clinical phenotype (dyspnoea, cough, purulent sputum production, wheeze and constitutional symptoms) and in the presence of coexistent pneumonia, it is often not possible to determine, using examination findings or simple investigations, that the admission episode is predominantly due to pneumonia rather than AECOPD, or vice versa.

Therefore, for this study, we have adopted the third approach listed above, which is supported by: most of the prognostic literature in AECOPD where patients with complicating pneumonia were not excluded;[139, 155-158] and the UK National COPD Audits which reported that pneumonia complicated 16% of all admissions with AECOPD [12] and 34.2% of patients with AECOPD requiring NIV.[159] In addition, Lieberman et al [141] compared the clinical characteristics of patients admitted with pAECOPD and non-pneumonic AECOPD (npAECOPD). They found that, compared to those with npAECOPD, patients with complicating pneumonia were similar in terms of sociodemographic details and severity of the underlying COPD, although they had more abnormal markers of acute clinical and physiological derangement, suggesting that consolidation identifies patients with a more severe acute illness, but does not signify a different disease process.

In CAP necessitating hospitalisation, the CURB-65 clinical prediction tool [160] is a six-point score (one point each for the presence of confusion, urea > 7mmol/L, respiratory rate (RR) ≥ 30min^{-1}, hypotension (systolic blood pressure < 90mmHg or diastolic blood pressure < 60mmHg) and age ≥ 65 years) which effectively predicts 30-day mortality. Although widely used in patients with AECOPD and coexistent pneumonia, its use in this cohort has not been specifically investigated. It has been shown that compared to

CAP, patients with pAECOPD are older and more breathless,[161, 162] and therefore the assessment of risk in patients with pAECOPD may be skewed and hence the expected mortality rates (Table 1.6) quoted in CAP may not be applicable in pAECOPD. CURB-65 is also sometimes used to guide clinical decisions in npAECOPD but only a single prospective study supports this.[163]

Table 1.6 CURB-65 severity classification for CAP

CURB score	Severity classification	Estimated mortality in CAP*
0 – 1	Low risk	1.5
2	Moderate risk	9.2
3 – 5	High risk	22.4

*from Lim et al [160]

1.2.5 MANAGEMENT OF ACUTE EXACERBATIONS IN HOSPITAL

The mainstay of treating acute exacerbations requiring admission to hospital is the administration of controlled oxygen therapy (if the patient is hypoxaemic),[164, 165] short acting bronchodilators and oral corticosteroids, as well as preventing complications of the disease and hospitalisation.[44] As discussed above, if Anthonisen criteria (Table 1.5) types 1 or 2 are fulfilled, then antibiotics are of clinical benefit: the number of patients needed to treat with antibiotics to prevent an episode of treatment failure or mortality is 3 and 8 respectively.[134, 166]

As part of the initial assessment, it is recommended [44] that all patients hospitalised with AECOPD should have arterial blood gases measured on a known, fixed concentration of inspired oxygen. Acidaemic respiratory failure (ARF) (pH < 7.35 and p_aCO_2 > 6kPa) is a marker of severe AECOPD and corresponds to an estimated in-hospital mortality rate of approximately 25%.[146] ARF occurs in approximately 20% of all hospital admissions with AECOPD,[146] and in these individuals, support with non-invasive or invasive ventilation is of benefit.[167]

1.2.6 NON-INVASIVE VENTILATION

Non-invasive ventilation (NIV) refers to the provision of ventilatory support without placing an endotracheal airway. Positive pressure ventilators are used in COPD and force air into the lungs by applying positive pressure to the airway via interfaces such as nasal and oro-nasal masks.

NIV can relieve the strain that the respiratory muscles experience during an exacerbation whilst conventional treatments aim to eradicate the acute cause. Invasive ventilation via tracheal intubation achieves this outcome but is associated with significant morbidity and mortality, and there may be difficulties weaning patients off invasive ventilation.[168] Compared to invasive ventilation, NIV avoids the need for sedation, can be applied intermittently and allows the patient to eat, drink and talk. Also, NIV reduces the risk of nocosomial pneumonia,[169] reduces the need for invasive ventilation, reduces mortality and reduces length of stay.[167] NIV can also be effectively used outside of the intensive care unit (ICU) [170] therefore relieving the burden on ICU beds.

NIV reduces the risk of treatment failure by more than 50%, when compared to conventional therapy, the number of patients needed to be treated with NIV to prevent one treatment failure of 5.[167] However, a significant proportion of individuals do not respond to treatment with NIV, with failure rates of up to 50% reported in some studies,[171] and in these patients escalating treatment to invasive ventilation has been shown to be associated with better outcomes than persevering with NIV.[172] NIV also has the potential to cause harm: the mask can be uncomfortable and can cause facial skin pressure necrosis, it causes gastric distension which may lead to vomiting, and bronchial toilet is difficult as the airway is not secured by an endotracheal tube.[173]

It is recommended that patients with mild to moderate respiratory failure ($7.26 \leq pH < 7.35$ and $P_aCO_2 > 6kPa$), or those with severe respiratory failure ($pH < 7.26$ and $P_aCO_2 > 6kPa$) who are deemed not appropriate for invasive ventilation, should receive treatment with NIV.[174] For those with severe respiratory failure ($pH < 7.26$ and

P_aCO_2 > 6kPa) it was previously recommended that invasive ventilation (IPPV) should be considered as first line treatment [44] although this is not standard practice in the UK.[146] Although previously recommended, it is not clear whether patients with severe acidosis respond better to invasive ventilation than NIV because most randomised controlled trials of NIV in AECOPD excluded patients with pH < 7.26. Two studies comparing NIV to invasive ventilation in patients with severe acidaemic respiratory failure secondary to AECOPD [149, 175] showed that there was no difference in risk of mortality between the two groups, and suggested that a trial of NIV, even in severe acidosis, may benefit the patient. Furthermore, McLaughlin et al [176] reported that managing patients with severe acidaemic respiratory failure (pH < 7.25) secondary to AECOPD with NIV resulted in 61% of patients surviving to discharge. Therefore, recently updated national COPD guidelines [44] have suggested that in acidaemic respiratory failure secondary to AECOPD, NIV should be considered the initial treatment of choice irrespective of pH.

Clinical guidelines regarding the use of NIV [174] stipulate certain contraindications to its use, including an altered level of consciousness. Avoiding NIV in patients with altered consciousness is recommended because NIV is thought to be less effective in uncooperative patients and also may increase the risk of pulmonary aspiration, however, most randomised trials have excluded such patients. A case-control study [148] has shown that NIV can be successfully used in patients with impaired consciousness and, furthermore, it has been shown that invasive ventilation does not add any further benefits in patients with severe altered consciousness compared to NIV.[175] Therefore, more robust predictors of NIV failure are needed because current recommendations do not appear to be supported by the published literature.

National guidelines also state that NIV should be considered if there *is "potential for recovery to a quality of life acceptable to the patient"*.[174] This subjective assessment is very difficult to perform in an acutely unwell patient and the difficulties associated with interpreting what an 'acceptable quality of life' is leads to considerable variability in the use of NIV. Furthermore, there are conflicting results from published evidence. Connors et al reported that, in patients with a severe exacerbation treated in hospital,

only 26% of patients were alive and reported 'good' quality of life at six months following hospital discharge,[102] however, a more recent study showed that, in patients with AECOPD requiring treatment on ICU, over two thirds of patients felt that their health was the same or better than prior to admission.[177]

A consequence of the uncertainty with regards to survival and quality of life following NIV is that clinicians exhibit prognostic pessimism [104] and therefore patients who may benefit from ventilatory support might not receive it. In addition, clinicians may be failing to identify patients where treatment with NIV has a low chance of short-term survival and is not associated with sustained long-term clinical improvements, but instead is saving them for a future life of recurrent hospitalisations, a heavy symptom burden and a poor quality of life.

Therefore, simple, objective measurements that help identify patients who are unlikely to benefit from treatment with NIV would ensure that they are spared the potential discomfort of treatment with NIV, and that they can either be considered for invasive ventilation or symptom palliation. There is also a lack of clarity regarding the potential for recovery in quality of life following discharge and an inability to accurately identify patients at risk of poor recovery. Therefore, further data on the expected recovery following treatment with NIV as well as the identification of independent predictors of poor outcome, could help patients and clinicians decide on the appropriate use of NIV.

1.3 CHAPTER SUMMARY

COPD is a common cause of morbidity and mortality and its prevalence is increasing. The treatment of COPD and its complications places an enormous burden on health resources and the burden increases as individuals approach end of life. Most of the COPD disease burden (morbidity, mortality and economic) relates to hospital admissions for treatment of AECOPD and therefore, an ability to identify individuals at risk of in-hospital death and readmission following discharge would enable healthcare providers to direct resources at those most in need. This might improve the survival, reduce readmission and relieve the financial burden of patients with AECOPD.

Patients with COPD have significant unmet palliative care needs and this is, in part, due to difficulties in identifying individuals either approaching the end of their life or at risk of a decline in quality of life unacceptable to the patient who may be in need of palliative care input. A simple clinical tool which accurately and reliably predicts poor quality of life, and poor short and medium term prognosis, would be useful in helping identify which patients could be considered for referral to the palliative care services.

CHAPTER 2 PREDICTING MORTALITY IN COPD

2.1 PREDICTING MORTALITY IN STABLE DISEASE

There is a considerable and conflicting literature base regarding prognostic indices in stable COPD and application of the results to clinical practice is difficult. Typically, each study includes a different set of covariates in their regression analyses and therefore, the independent predictors identified by one study are not comparable with the predictors from other studies, because potential confounders may have been omitted in one, or both, studies. Furthermore, very few papers provide detail on the strength and validity of regression models, therefore identified predictors can only be said to be independent of the other confounders included in the model and it is not possible to assess the strength of their relationship with outcome, or to generalise outside the study population.

Therefore, Table 2.1 attempts to summarise extensive published data so that it can be interpreted in the context of other studies and some conclusions can be made outside the study populations. Table 2.1 shows not only how frequently a variable predicts mortality, but also how often has it been investigated and not been found to be a prognostic factor. Studies of unselected groups of patients with stable COPD are included and for each prognostic index: its relationship with mortality is described; the number of studies that have clearly investigated the relationship with mortality is shown; the number of studies identifying an association on univariate analysis is recorded; and finally, the number of studies identifying an association with mortality on multivariate analysis (numerator) is compared with the total number of studies which have investigated that index using multivariate methodologies (denominator).

This table helps illustrate that factors such as higher age, more severe dyspnoea, poor quality of life, low FEV_1, low BMI, more severe hypoxaemia, high levels of comorbidity, and short distances walked in the 6-minute walk test (6MWT) are consistently found to be independently predictive of mortality in stable COPD. Many of the other variables have been studied infrequently and therefore it is difficult to come to firm conclusions

on the prognostic value of these indices in a general population of individuals with stable COPD.

The data regarding the relationship between sex and mortality is contradictory. In unselected patients, survival of females is longer than males, independent of FEV_1.[178] However, in patients requiring LTOT, and therefore with severe COPD, the length of survival of females is less than males.[179] Although the selection criteria for LTOT are the same for females as males, it is unclear whether there is the same level of recognition of the need for LTOT in males and females and therefore this may bias the results. However, it has been shown that women are more prone to the systemic effects of severe COPD with significantly higher rates of depression [180] and body fat depletion,[30] and this may therefore explain an increased risk of death in females with severe COPD.

It is of interest that certain indices, such as low vital capacity and anaemia, are associated with mortality on univariate analysis but fail to act as independent predictors of death. It is also of interest that low FEV_1 is almost universally associated with mortality on univariate analysis but it acts less frequently as an independent predictor on multivariate analysis. This is mostly due to studies that included detailed assessments of lung function or exercise capacity where they have identified complex or difficult to measure variables which are stronger predictors of mortality and therefore limit the predictive ability of FEV_1. It is also because the predictive capacity of FEV_1 is constrained by the limited range of FEV_1 values that are present when this is used as the defining criterion for inclusion in the study.

Not all of the published research on this topic details all of the indices included in data analysis and therefore the above table will underestimate the number of times that the above listed indices have failed to demonstrate an association with mortality.

Table 2.1 Summary of prognostic indices associated with mortality in stable COPD – see text for explanation

Index	Positive or negative correlation with outcome	Number of studies investigating index	Association identified on univariate analysis	Association identified on multivariate analysis
Sociodemographic details,				
Age	Positive	41	25	19/24
Sex	Male sex at increased risk of death	25	7	3/12
Smoking load	Positive	6	1	0/1
Years of education	Negative	2	1	1/2
Socioeconomic class	Lower socioeconomic class associated with increased death	5	0	0
History and examination,				
Mucus hypersecretion	Positive	7	4	1/3
Pedal oedema	Positive	1	0	1/1
Exacerbation frequency in past year	Positive	4	3	2/2
Previous admissions in past year	Positive	3	1	0/1
Dyspnoea	Positive	18	11	6/10
Cor pulmonale	Positive	2	2	0
Heart rate at rest	Positive	3	2	1/2
ECG evidence of right heart strain	Positive	4	2	1/1

Index	Positive or negative correlation with outcome	Number of studies investigating index	Association identified on univariate analysis	Association identified on multivariate analysis
Disability	Inability to perform ADLs associated with increased risk of death	1	1	1/1
Health status assessment,				
Quality of life	Negative	14	11	6/9
Cognitive impairment	Positive	4	3	2/4
Depression	Positive	4	3	1/3
Lung Function,				
FEV_1	Negative	44	32	13/23
VC	Negative	17	11	0/7
FEV_1/FVC	Negative	6	4	0/2
IC	Negative	2	2	1/1
TLC	Positive	4	3	1/3
IC/TLC	Negative	4	4	2/2
RV	Positive	1	1	1/1
RV/TLC	Positive	6	4	0/1
FRC	Negative	1	0	
Gas transfer	Negative	9	6	4/4
Bronchodilator reversibility	Negative	6	3	2/4
FEV_1 rate of decline	Positive	2	2	0

Index	Positive or negative correlation with outcome	Number of studies investigating index	Association identified on univariate analysis	Association identified on multivariate analysis
Arterial blood gas,				
S_pO_2	Negative	5	4	0/2
P_aO_2	Negative	18	13	5/9
P_aO_2/F_iO_2	Negative	2	2	0/2
P_aCO_2	Positive	17	12	4/10
Exercise capacity,				
Self-reported activity level	Negative	1	1	1/1
6MWT	Negative	17	16	8/10
VO_{2max} §	Negative	4	2	2/3
Nutritional assessment,				
BMI	Negative	34	19	10/20
Weight loss	Positive	2	2	1/1
Fat free mass	Negative	4	2	2/3
Mid arm muscle area	Negative	1	1	1/1
Quadriceps strength	Negative	1	1	1/1
Thigh circumference	Negative	1	1	0/1
MTCSA	Negative	1	1	1/1
Blood tests,				
Haemoglobin	Negative	6	4	0/3

Index	Positive or negative correlation with outcome	Number of studies investigating index	Association identified on univariate analysis	Association identified on multivariate analysis
Albumin	Negative	4	4	0/1
CRP	Positive	3	1	2/3
BNP	Positive	1	1	1/1
Comorbidity,				
CCI	Positive	13	8	5/8
Number of comorbidities	Positive	1	0	0/1
Ischaemic heart disease	Positive	8	2	1/2
Cardiac failure	Positive	2	1	1/1
Cerebrovascular disease	Positive	2	2	2/2
Diabetes	Positive	2	0	0
Medication,				
LTOT	Positive	7	3	2/4
Oral corticosteroids	Positive	3	1	1/1
Inhaled corticosteroids	Negative	2	1	1/1
Influenza vaccine	Negative	1	1	1/1

References - [24, 26, 28, 35, 61, 178, 181-234]

ECG – electrocardiograph; ADL – activities of daily living; QoL – quality of life; IC – inspiratory capacity; TLC – total lung capacity; RV – residual volume; FRC – functional residual capacity; S_pO_2 – transcutaneous oxygen saturation; P_aO_2 – arterial partial pressure of O_2; F_iO_2 – fraction of inspired oxygen; P_aCO_2 – arterial partial pressure of CO_2; 6MWT – six minute walk test; VO_{2MAX} – maximum oxygen consumption per minute per kilogram; BMI – body mass index; MTCSA – midthigh cross-sectional area; CRP – C reactive protein; BNP – brain natriuretic peptide; CCI – Charlson comorbidity index; LTOT – long term oxygen therapy; § - on cardiopulmonary exercise testing

2.1.1.1 CLINICAL PREDICTION TOOLS IN STABLE COPD

Many authors have attempted to develop multivariable prediction tools that can help clinicians to accurately predict prognosis, however the developed tools are often complex and include prognostic variables that are difficult to measure in routine clinical practice. Importantly, for the purposes of my study, none of the tools have been studied in exacerbations of COPD requiring hospitalisation.

Celli et al [26] identified four indices that predicted increased mortality risk: **B**MI; airflow **O**bstruction; MRC **D**yspnoea scale; and **E**xercise capacity (measured by 6MWT). Each variable is assigned a score and the total score (out of 10) is termed the BODE index (Table 2.2). A high BODE index score is associated with a worse prognosis: a BODE index score of 7-10 is associated with a 52-month mortality rate of 80%.[26] This instrument has been shown to be a more accurate predictor of mortality than FEV_1, and has also been shown to accurately predict the risk of AECOPD [235] and hospitalisation due to AECOPD.[25] The BODE index score correlates well with measures of quality of life [236] and has been shown to be a useful measure of assessing response to certain treatments.[237, 238]

Table 2.2 The BODE index [26]

Variable	BODE score			
	0	1	2	3
FEV_1 (% predicted)	>65	50-65	35-49	<35
MRCD scale	1-2	3	4	5
6MWT (metres)	>350	250-349	150-249	<149
BMI	>21	<21		

MRCD – MRC Dyspnoea Scale; 6MWT – six minute walk distance; BMI – body mass index

Briggs et al [199] developed the COPD Prognostic Index (CPI) which aimed to accurately predict death, hospitalisation and exacerbation (Table 2.3). High scores indicate increased risk of mortality, hospitalisation and exacerbation. The derivation study estimated that a CPI score of 90 equates to a 30% three-year mortality rate, a 60% three-year hospitalisation rate, and 9 expected exacerbations within three years.[199] The initial cohort was split with one third reserved for internal validation of the developed instrument, but it has not undergone external independent validation.

Table 2.3 The COPD Prognostic Index (CPI)[199]

Prognostic factor		Addition to risk score			
Either:	CRQ total	<68	68 to <86	86 to <104	≥104
Or:	SGRQ total	>64	<47 to 64	<30 to 47	≥30
	Score	**18**	**13**	**7**	**0**
	FEV_1 % predicted	<30	30 to 49	50 to 59	≥60
	Score	**24**	**15**	**7**	**0**
	Age, years	<55	55 to 64	65 to 74	≥75
	Score	**0**	**7**	**14**	**20**
	Sex	Male		Female	
	Score	**0**		**1**	
	BMI <20	No		Yes	
	Score	**0**		**11**	
	History of ED visits / exacerbations *	No		Yes	
	Score	**0**		**20**	
	History of CVD	No		Yes	
	Score	**0**		**7**	

CRQ – Chronic Respiratory Disease Questionnaire; SGRQ – St. George's Respiratory Questionnaire; ED – emergency department; CVD – cardiovascular disease. * within past 12 months.

Using a large outpatient database of patients with COPD, Schembri and colleagues [57] developed a risk score that predicted a composite outcome of hospitalisation or death. Risk factors within the score were: increased age; low BMI; MRCD; FEV_1 % predicted; previous healthcare utilisation; and whether the patient had received influenza vaccination. The lack of external validation and the complex calculation required to calculate an individual's risk of outcome mean the utility of this instrument in clinical practice is uncertain.

Esteban et al [206] developed a clinical prediction tool using a population of 600 unselected individuals with stable COPD. Using a subjective assessment of physical activity, dyspnoea and health status, as well as measurement of FEV_1 % predicted, the Health-Activity-Dyspnoea-Obstruction (HADO) score was developed. This score reliably and independently predicted the risk of death at three years more accurately than the FEV_1. This score has not been externally validated.

Kostianev et al [234] derived a multidimensional prognostic score (the DOREMI BOX score) in 84 young patients with stable COPD and subsequently validated the score in a separate population of 68 COPD patients. The DOREMI BOX score had similar performance to the BODE score for the prediction of mortality, however the relatively small derivation and validation cohorts and the uncertain variable selection methodology used mean that this tool has not been investigated further or used in routine clinical practice in the United Kingdom.

2.1.1.2 SUMMARY OF PROGNOSTICATION IN STABLE COPD

The prognostic tools discussed have been derived using varied methodologies and have frequently not undergone external validation and hence their clinical application is limited. Furthermore, in spite of frequent poor outcomes, there has been less interest in prognostication following admission for AECOPD. Given the different pathophysiological processes that occur in stable COPD and AECOPD, many of the indices, and predictive tools identified in stable disease may not be relevant during an acute exacerbation. They may also be difficult to measure during a hospital stay and may therefore be of limited use. The prognostication of AECOPD and stable COPD should therefore be treated separately and the evidence surrounding prognostication following admission for AECOPD will be discussed in section 2.2.

2.2 PREDICTING MORTALITY FOLLOWING HOSPITALISATION FOR AECOPD

Most studies evaluating prognostic indices in COPD refer to assessments performed during a stable state (Table 2.1). There is a lack of robust data, using a prospective methodology, assessing prognostic indices in AECOPD requiring hospital admission. Prognostication in stable COPD was discussed in section 2.1 and I will now review the literature relating to hospitalised patients with AECOPD. Many individual prognostic factors are closely related (e.g. FEV_1 to exercise performance) and therefore it is particularly important to differentiate independent predictors of mortality (identified using multivariate analysis) from variables associated with mortality on univariate analysis alone. If a variable is independently predictive of death then this is mentioned in the text, or it is highlighted in italics in the summary tables.

It is unlikely that the same indices predict both acute and longer-term mortality. Therefore, in the following text, indices predictive of in-hospital mortality, and indices predictive of mortality following hospital discharge have been identified and distinguished in both the text and tables.

2.2.1 SOCIODEMOGRAPHIC DETAILS

2.2.1.1 AGE

A retrospective analysis of 71,130 patients with a discharge diagnosis, or cause of death, of AECOPD showed that increasing age is independently predictive of in-hospital mortality.[239] This association has been replicated in several other large retrospective [114, 240-242] and prospective [135, 156, 243] studies. Increasing age is also independently predictive of mortality following hospital discharge.[15, 242, 244-246] However, disease duration may be a more important predictor of death following discharge than chronological age, which may act as a surrogate marker.[247]

2.2.1.2 SEX

Most participants in clinical COPD research are male, reflecting the underlying demographics of the disease population. Conclusions regarding the role of sex in the prediction of in-hospital mortality are conflicting. Although smaller studies disagree,[15, 248] large retrospective analyses suggested that male patients have higher in-hospital mortality.[239, 240] The effect of male sex on mortality following discharge is uncertain with some articles suggesting an increased risk of death,[14, 246] others finding no association, [233, 242, 247, 249-251] and a single study suggesting an increased long-term mortality rate in females.[252]

2.2.1.3 INCOME AND EDUCATION

In stable disease, income and years in education typically demonstrate a negative relationship with mortality.[253] However, in patients hospitalised with exacerbations, Patil et al [239] suggested that high incomes were independently predictive of mortality although the authors advise cautious interpretation of this finding and

suggest that there may have been different thresholds for admission for individuals with different incomes. Faustini et al [240] suggested that a lower level of education (< 5 years formal education) was predictive of death after discharge on univariate analysis but this finding was not confirmed in a prospective analysis of patients with AECOPD.[58]

2.2.1.4 SOCIAL SUPPORT AND MARITAL STATUS

Greater social support prior to hospitalisation does not independently predict mortality,[156, 254] whereas admission from a long-term care facility does.[239] 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), not the amount of social care required,[58] nor whether the individual lives alone.[255] The protective effect of marital status is consistent with research in other diseases [256] and it may be due to better compliance with prescribed medication in married individuals with COPD.[257]

2.2.2 CLINICAL HISTORY

2.2.2.1 PRE-ADMISSION LEVEL OF FUNCTION

The relationship between functional limitation and in-hospital mortality has most frequently been studied in individuals requiring NIV or ICU treatment where functional limitation has not been shown to be associated with in-hospital mortality.[147, 248, 258, 259] However, treatment with NIV or on ICU is frequently not offered to individuals with severe functional limitation and therefore these results should be interpreted with caution. A single study of a selected population of patients who died in-hospital due to AECOPD,[260] which compared indices collected from the admission which resulted in death with the patient's previous admission, has suggested that functional limitation (measured using the Performance status, Table 4.1) independently predicts in-hospital mortality, but it is uncertain whether this result generalises to all patients hospitalised with AECOPD.

However, in patients surviving to discharge, the level of functional impairment, at two weeks prior to admission, measured informally [246, 254, 258] or formally using validated instruments,[58, 102, 249, 250, 254] is predictive of mortality up to 1 year.

2.2.2.2 QUALITY OF LIFE AND PSYCHOLOGICAL WELLBEING

Poor quality of life or psychological wellbeing are well established predictors of mortality in stable disease.[181, 186, 261] The impact of depression and impaired quality of life on in-hospital mortality in AECOPD has not been described due to difficulties performing assessments in acutely unwell patients.

However, it is estimated that, at discharge following admission for AECOPD, 40% of patients are depressed.[262] Following discharge, depression acts as an independent predictor of mortality.[58, 249, 262]

Gudmundsson et al [255] undertook a large prospective multicentre study of AECOPD. Health status was assessed at discharge using the St. George's Respiratory Questionnaire. All components of the SGRQ (symptoms, activities, impacts and total score) were associated with increased mortality at 2 years, although only the total and impacts scores were independent predictors. Almagro et al [58] suggested that only the activity component of SGRQ independently predicted mortality and Yohannes et al [249] demonstrated that low quality of life (measured using the Breathing Problems Questionnaire) was predictive of 1-year mortality.

2.2.2.3 DYSPNOEA

The MRCD scale (Table 1.1) was associated with, but not independently predictive of, in-hospital mortality in a prospective cohort of 284 consecutive admissions with AECOPD,[157] and was found to be independently predictive of in-hospital mortality in a study of 794 patients presenting to the emergency department (ED) with AECOPD.[156] Following discharge, the severity of self-reported dyspnoea predicts mortality.[58, 233, 263, 264]

2.2.2.4 PRIOR HOSPITALISATION AND EXACERBATION

A previous hospitalisation for AECOPD,[114, 156] particularly if complicated by respiratory failure,[240, 248] has been shown by many to be an independent predictor of in-hospital mortality. However, Faustini et al [240] suggested a more complex relationship. They showed that two or more hospitalisations within the preceding two years, for AECOPD without respiratory failure, increased the risk of mortality after discharge but not during admission. In fact, in their retrospective review, individuals with no prior hospital admissions were at a greater risk of in-hospital death than of dying soon after discharge. The reasons for this are unclear. Individuals without previous hospitalisations may only seek medical attention during a severe exacerbation and hence have greater in-hospital mortality. It may also reflect the higher level of post-discharge support that is frequently offered to individuals with a past history of frequent admissions.

Hospital admissions for COPD and for non-COPD, both before and after the index admission, have been shown to be independently predictive of short and long-term mortality following discharge.[14, 58, 242, 265, 266]

2.2.2.5 SMOKING STATUS

A retrospective cohort study of 786 elderly patients (mean age 75 years) admitted with AECOPD demonstrated that active smokers (tobacco smoking within the past 6 months) had significantly higher in-hospital and post-discharge mortality.[242] In individuals requiring admission to ICU, the poor prognostic effects of active smoking do not appear to persist.[248] Goel [267] suggested that a smoking history of greater than 60 cigarette pack years was independently associated with long-term mortality following discharge for AECOPD. However, many other studies have failed to replicate these findings,[31, 33, 58, 125, 247, 249, 255] and the prognostic value of smoking status must therefore be questioned.

A summary of the significant findings discussed so far is shown in Table 2.4.

Table 2.4 Summary of main prognostic indices associated with mortality following hospitalisation for AECOPD (*Italics indicate - significance persists on multivariate analysis*)

Study	Design[a]	Outcomes & mortality rate[b]	Sociodemographic details	Pre-admission level of function	QoL and psychological wellbeing	Stable-state dyspnoea	Episodes of AECOPD
Patil [239]	Retrospective. n=71,130	IHM – 2.5%	*Older age, male sex, higher income*	*Admission from long-term care facility*			
Roche [156]	Prospective. ED attendees with AECOPD. n=794	IHM – 7.4%	*Older age*	Home support / institutionalisation prior to admission		*More severe dyspnoea*	Previous hospitalisation for AECOPD
Ai-Ping [248]	Retrospective. AECOPD requiring ICU. n=57	IHM – 24.5%	*Older age*				*Previous hospitalisation requiring IPPV*
Bustamente-Fermosel [135]	Retrospective. n=972	IHM – 6.4%	*Older age*				
Murphy [260]	Retrospective. Deaths secondary to AECOPD. n=60	IHM		*Poor performance status*			
De la Iglesia [157]	Prospective. n=284	IHM – 3.9%				More severe dyspnoea	
Dransfield [114]	Retrospective. n=825	IHM – 5.2%	*Older age*				*Previous hospitalisation for AECOPD*[>]

Study	Design[a]	Outcomes & mortality rate[b]	Sociodemographic details	Pre-admission level of function	QoL and psychological wellbeing	Stable-state dyspnoea	Episodes of AECOPD
Faustini [240]	Retrospective. n=26,039	IHM – 2.9% 30-day mortality – 3.6%	*Older age, male sex, admission to inappropriate ward**				*Previous hospitalisation for AECOPD*
Fruchter [242]	Retrospective. Elderly patients with AECOPD. n=786	IHM – 7.2% 12-month mortality – 28%	*Older age*				*Subsequent hospitalisation for AECOPD*
Gunen [247]	Prospective. n=205	12-month mortality – 33%	*Longer duration of disease (years)*				
Roberts [254]	Retrospective. n=1221	3-month mortality – 14%	Older age	Institutional care prior to admission, *Worse performance status^*			
Almagro [58]	Prospective. n=135	12-month mortality – 22%	Older age, *Unmarried*	*High functional dependenceº / limitation in activity~*	Increased levels of depression[#]		
Ranieri [250]	Prospective. n=244	6-month mortality – 20%		*Increased functional dependence [%]*			

Study	Design[a]	Outcomes & mortality rate[b]	Sociodemographic details	Pre-admission level of function	QoL and psychological wellbeing	Stable-state dyspnoea	Episodes of AECOPD
Yohannes [249]	Prospective. Discharged following AECOPD. n=100	12-month mortality – 36%		Increased functional dependence	Depression, *low quality of life*		Subsequent hospitalisation for AECOPD
Groenewegen [15]	Prospective. Discharged following AECOPD. n=171	12-month mortality – 23%	*Older age*				
Gudmundsson [255]	Prospective. Discharged following AECOPD. n=416	2-year mortality – 29.3%	*Older age,* male sex	More limitation in physical activity~	*Low quality of life*		≥ 2 hospitalisations in previous 12 months
Ng [262]	Prospective. Discharged following AECOPD. n=376	Mortality following discharge			*Increased levels of depression*‡		
Chu [264]	Prospective. AECOPD discharged following NIV. n=110	12-month mortality – 49%		Increased functional dependenceº		*More severe dyspnoea*	Previous hospitalisations
Antonelli-Incalzi [244]	Prospective. Discharged following AECOPD. n=270	Long-term mortality	*Older age*				
Wildman [246]	Prospective. AECOPD requiring HDU/ITU. n=832	180-day mortality – 37.9%	*Older age, male sex*	*Increased functional dependence*			

Study	Design[a]	Outcomes & mortality rate[b]	Sociodemographic details	Pre-admission level of function	QoL and psychological wellbeing	Stable-state dyspnoea	Episodes of AECOPD
Tsimogianni [263]	Prospective. Discharged following AECOPD. n=81	3-year mortality – 41%				*More severe dyspnoea*	
Almagro [233]	Prospective. Discharged following AECOPD. n=316	3-year mortality – 42.4%	*Older age*			*More severe dyspnoea*	
Kim [265]	Retrospective. ED attendees with AECOPD. n=482	60-day mortality – 9%	*Older age*				*Previous hospitalisation for AECOPD*
McGhan [14]	Retrospective. Discharged following AECOPD. n=51,353	12-month mortality – 21%	*Older age, male sex*, non-Caucasian ethnicity				*Previous hospitalisation for AECOPD*

[a] Study involves unselected patients admitted with AECOPD unless otherwise stated; [b] IHM – in-hospital mortality; † according to Anthonisen criteria; * inappropriate ward – non-respiratory or non-ICU; ^ Performance status – assessment of ability to mobilise and perform self-care; º measured by Katz index; # measured by Yesavage scale; ~ measured by SGRQ activity subscale; % measured by Barthel index; ~ only predictive of 12-month mortality; ‡ measured by Hospital Anxiety and Depression Scale; > during 7 year study period; QoL – quality of life; IHM – in-hospital mortality; ED – emergency department

2.2.2.6 MEDICATION AND OXYGEN THERAPY

A number of authors have investigated the ability of medication taken at admission to predict in-hospital mortality with conflicting results (Table 2.5).

Treatment with long term maintenance corticosteroids independently predicts higher in-hospital mortality in patients requiring treatment in ICU,[248] but has no impact on outcome in unselected patients with AECOPD.[156] However, in patients surviving to discharge, maintenance oral corticosteroid therapy independently predicts subsequent mortality.[15, 185, 242] Soyseth et al [245] suggested that treatment with statins reduced mortality following AECOPD but this was not a randomised controlled trial so the validity of its conclusions are uncertain.

LTOT has been shown to be associated but not independently predictive of long-term mortality.[58, 135, 247] Some authors suggest LTOT may independently predict in-hospital mortality,[157] whereas others suggest that it is a surrogate marker of disease severity.[156]

2.2.2.7 COMORBIDITY

In stable COPD, the comorbidity burden (usually measured by the Charlson Comorbidity Index (CCI), Table 17.1) is an established predictor of mortality.[194, 195, 268] In AECOPD requiring hospitalisation, the evidence is less consistent; CCI was an independent predictor of death following discharge in one study,[58] but three others showed no independent association with either in-hospital [114, 239] or post-discharge [250] mortality. However, specific comorbidities, most notably ischaemic heart disease,[242, 245, 251, 269, 270] congestive cardiac failure,[14, 114, 245, 265] chronic liver disease,[114] chronic renal failure [244] and diabetes,[33, 245, 255, 269] 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, and these more commonly occur during ill-health (such as during AECOPD) than clinical stability.

Further emphasizing this point, many authors have shown that acute comorbidity (for example, shock, pulmonary oedema, arrhythmia, stroke, renal insufficiency) is independently associated with a greater risk of in-hospital, and six-month, mortality.[135, 147, 161, 271, 272] In one study [259] 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. This association appears in a similar study by Seneff [258] where evidence of non-respiratory physiological derangement was significantly predictive of in-hospital death whereas derangement of respiratory physiology was not.

The relevant findings are summarised in Table 2.5.

Table 2.5 Studies of AECOPD identifying an association between comorbidity or medication and mortality (*Italics indicate - Significance persists on multivariate analysis*)

Study	Design & patient group[a]	Outcomes[b]	Mortality rate	Comorbidity	Medication
Patil [239]	Retrospective. n=71,130	IHM	2.5%	CCI	
Dransfield [114]	Retrospective. n=825	IHM	5.2%	CCI, *congestive heart failure, cerebrovascular disease, chronic liver disease*	Patients not in receipt of B-blockers
Fruchter [242]	Retrospective. Elderly medical admissions with AECOPD. n=786	IHM and 6-year mortality	7.25% in-hospital	*Ischaemic heart disease*, congestive cardiac failure	*Oral maintenance corticosteroids*
Bustamente-Fermosel [135]	Retrospective. n=972	IHM	6.4%	*Acute complication developed during hospital stay**	LTOT
Raurich [271]	Retrospective. AECOPD requiring invasive ventilation. n=101	IHM	25.7%	*MODS*	
Liu [259]	Retrospective. AECOPD requiring invasive ventilation. n=138	IHM	39.9%	*MODS*	
Scala [147]	Prospective. AECOPD requiring NIV. n=120	IHM	10% in-hospital	*Acute non-respiratory comorbidity*	
Fuso [243]	Retrospective. n=590	IHM	14.4%	Previous myocardial infarction	Digoxin
Roche [156]	Prospective. AECOPD attending ED. n=794	IHM	7.4%		LTOT
De la Iglesia [157]	Prospective. n=284	IHM	3.9%		*LTOT*
Ai-Ping [248]	Retrospective AECOPD requiring ICU. n=57	IHM	24.5%	Cardiac disease	*Oral maintenance corticosteroids*

Study	Design & patient group[a]	Outcomes[b]	Mortality rate	Comorbidity	Medication
Seneff [258]	Prospective. AECOPD requiring intensive care	IHM and 1-yr mortality	24% IHM	*Acute non-respiratory comorbidity*	
Faustini [240]	Retrospective. n=26,039	30-day mortality	3.6%	*Total number of comorbidities >1*	
Niewoehner [273]	Prospective. n=271	30-day mortality	7%		Theophylline
Molinos [161]	Prospective. Admissions with AECOPD and pneumonia. n=244	30-day mortality	9%	*Septic shock, acute renal failure*	
Kim [265]	Retrospective. ED attendees with AECOPD. n=482	Early mortality	9% 60-day mortality	*Congestive cardiac failure, metastatic cancer*	
Ranieri [250]	Prospective. n=244	6-month mortality	20%	CCI	
Groenewegen [15]	Prospective. n=171	1-year mortality	23%		*Oral maintenance corticosteroids*
McGhan [14]	Retrospective. Discharged following AECOPD. n=51,353	6-year mortality	21% 1-year	*Malignancy, pulmonary hypertension, heart failure*	
Fruchter [251]	Retrospective. Admissions with AECOPD with troponin measured. n=178	Long-term mortality	46% 3-year mortality	*IHD,* chronic renal failure	
Almagro [58]	Prospective. Discharged following AECOPD. n=135	Long term mortality	22% 1-year	*CCI*	LTOT, total number of drugs per day
Soyseth [245]	Retrospective. Discharged following AECOPD. n=854	Long term mortality	Not quoted	*IHD, congestive heart failure, atrial fibrillation, diabetes, venous thromboembolism, cancer*	*Statins and inhaled corticosteroids reduce risk*

Study	Design & patient group[a]	Outcomes[b]	Mortality rate	Comorbidity	Medication
Antonelli-Incalzi [244]	Prospective. Discharged following AECOPD. n=288	Long term mortality	Median survival 3.1 years	*Chronic renal failure*, chronic liver disease, previous myocardial infarction	
Hallin [33]	Prospective. Discharged following AECOPD. n=261	2-year mortality	19%	*Diabetes*	
Gudmundsson [255]	Prospective. n=416	2-year mortality	29.3%	*Diabetes*	
Brekke [269]	Retrospective. Admissions with AECOPD and pneumonia. n=897	Long-term mortality	24.4% 1-year	*IHD, diabetes, malignancy*	

[a] Study involves unselected patients hospitalised with AECOPD unless otherwise stated; [b] IHM – in-hospital mortality; * 'acute complication' undefined in study; CCI – Charlson Comorbidity Index; LTOT – long-term oxygen therapy; IHD – ischaemic heart disease; MODS – multi-organ dysfunction syndrome

2.2.3 CLINICAL FINDINGS ON ADMISSION

2.2.3.1 HISTORY AND EXAMINATION FINDINGS

Cor pulmonale is independently associated with long-term mortality in patients hospitalised with AECOPD,[102, 270] and the presence of pedal oedema, which can imply the presence of cor pulmonale, is similarly independently associated with mortality following discharge.[102, 254] A single study [271] has shown cor pulmonale to be independently predictive of in-hospital mortality in patients requiring intensive care but others have found no association.[156]

Roche et al [156] showed that, on admission to hospital with AECOPD, the presence of neurological impairment and the use of inspiratory accessory muscles both independently predicted in-hospital mortality. Neurological impairment (a reduced Glasgow Coma Scale, GCS) has repeatedly been found to independently predict in-hospital mortality in patients requiring treatment on ICU or in those with co-existent pneumonia.[139, 150, 161, 274]

In a prospective cohort study of 972 individuals hospitalised for AECOPD, Bustamante-Fermosel [135] classified exacerbations using Anthonisen's criteria (Table 1.5) as 'moderate to severe AECOPD' (type 1 and type 2) and 'mild AECOPD' (type 3). This sub-classification revealed that a moderate to severe exacerbation was independently predictive of in-hospital mortality. The mortality rate associated with a mild AECOPD was 0.3% compared to 9.3% in moderate and severe exacerbations ($p < 0.05$).

2.2.3.2 BEDSIDE OBSERVATIONS

A number of investigators have attempted to identify simple bedside physiological observations that are predictive of in-hospital mortality. Hypotension [150, 158, 161, 275] and tachycardia [158] (measured within 24 hours of admission) have been shown to independently predict in-hospital mortality, whereas tachypnoea is only found to be an independent predictor in patients requiring assisted ventilation or in those with co-

existent pneumonia.[138, 139, 161] Lower transcutaneous arterial oxygen saturation (S_pO_2) has been found to be associated with, but not independently predictive of, in-hospital [247, 254] and 3 month [254] mortality. Seneff et al [258] showed that in patients requiring intensive care, non-respiratory physiological abnormalities (for example, heart rate, blood pressure, temperature) were strongly predictive of both in-hospital and six-month mortality, whereas respiratory physiological abnormalities were predictive of six-month mortality alone. Similarly, Høiseth et al [252] showed tachycardia to be an independent predictor of long-term mortality following hospitalisation for AECOPD.

Studies that demonstrate an association between clinical signs and mortality are summarized in Table 2.6:

Table 2.6 Clinical signs associated with mortality following admission for AECOPD (*Italics indicate - significance persists on multivariate analysis)*

Study	Design[a]	Outcomes[b]	Mortality rate	Predictors of mortality
Roche [156]	Prospective. AECOPD attending ED. n=794	IHM	7.4%	Central cyanosis, pedal oedema, asterixis, expiratory use of abdominal muscles, *neurological impairment*, *use of inspiratory accessory muscles*
Chandra [275]	Retrospective. n=94	IHM	12.8%	Central cyanosis, elevated JVP, *hypotension*
Wildman [158]	Retrospective. AECOPD or asthma requiring ICU. n=8,527	IHM	35.5%	*Tachycardia, hypotension*
Confalonieri [139]	Prospective. AECOPD requiring NIV. n=1,033	Need for IPPV or death	13.7% in-hospital	*Neurological impairment, tachypnoea*
Chakrabati [138]	Prospective. AECOPD requiring NIV. n=88	Need for IPPV or death	17% in-hospital	*Tachypnoea*
Ucgun [150]	Prospective. AECOPD requiring ICU. n=151	IHM	33.1%	*Hypotension, neurological impairment*
Levy [276]	Prospective. Patients requiring NIV with DNACPR order. n=114†	IHM	57%	*Weak cough*
De la Iglesia [157]	Prospective. n=284	IHM	3.9%	Tachypnoea, reduced conscious level
Bustamente-Fermosel [135]	Retrospective. n=972	IHM	6.4%	*Severity of exacerbation**
Seneff [258]	Retrospective. AECOPD requiring ICU. n = 362	IHM and six-month mortality	23.8% IHM	*Non-respiratory physiological abnormalities, respiratory physiological abnormalities*
Roberts [254]	Retrospective. n=1,400	3-month mortality	14%	*Pedal oedema*, low transcutanoeous oxygen saturation

Study	Design[a]	Outcomes[b]	Mortality rate	Predictors of mortality
Terzano [270]	Prospective. AECOPD surviving to discharge. n=288	Long-term mortality	19.4% 6-year	*Cor pulmonale*
Connors [102]	Prospective. Admissions with AECOPD and hypercapnia. n=1,016	6-month mortality	33%	*Cor pulmonale* ^, tachycardia
Wildman [246]	Prospective. AECOPD requiring ICU. n=832	6-month mortality	37.9%	*Glasgow Coma Score <8*
Høiseth [252]	Prospective. n=99	Long-term mortality	Median survival = 2.3 years	*Tachycardia*

[a] Study involves unselected patients hospitalised with AECOPD unless otherwise stated; [b] IHM – in-hospital mortality; *for classification of severity – see above; ^ presence of ≥2 of: pedal oedema; jugular venous distension; enlarged pulmonary arteries on CXR; ECG signs of RVH or RAE; ED – emergency department; ICU – intensive care unit; RVH – right ventricular hypertrophy; RAE – right atrial enlargement; JVP – jugular venous pressure; NIV – non-invasive ventilation; IPPV – invasive ventilation

2.2.3.3 ACUTE PHYSIOLOGY SCORES

Markers of acute physiological derangement can be combined in to a composite measure of acute illness severity. Common examples of acute physiology scores include the APACHE II (Acute Physiology and Chronic Health Evaluation), MEWS (Modified Early Warning Score), SAPS (Simplified Acute Physiology Score), and CAPS (COPD and Asthma Physiology Score). These scores were, in general, developed for use in patients admitted to acute medicine or ICU, however their use in AECOPD has also been assessed. In various reports of patients with AECOPD requiring NIV or intensive care, APACHE II,[138-140, 248, 272] SAPS,[277] modified early warning score (MEWS),[260] and CAPS,[158] have been independently associated with in-hospital mortality.

A study [258] of APACHE II in AECOPD requiring admission to ICU showed that respiratory physiological variables (respiratory rate, pH, P_aCO_2, P_aO_2, 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 six-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 hospitalisation are stronger predictors of mortality during, rather than after, admission.

2.2.4 INVESTIGATIONS

2.2.4.1 NUTRITIONAL STATUS

In stable COPD, poor nutritional status is associated with increased mortality.[35, 268, 278] Studies assessing predictors of in-hospital mortality have been less frequently studied but have shown similar findings; low BMI [157, 247, 279] and low percentage of ideal body weight [280] are negative prognostic indices.

Hallin et al [33] prospectively analysed the BMI of 261 individuals discharged following AECOPD. They identified a 'U-shaped curve' relationship between BMI and mortality, whereby low BMI (<20 kgm^{-2}) and obesity (BMI > 30kgm^{-2}) were shown to be independently associated with mortality at 2 years, and overweight patients (BMI 25-30) had the lowest risk of death. The protective effect of mild BMI elevation has been termed the 'obesity paradox' (section 1.1.3.1.2). The independent association between low BMI and post-discharge mortality is strong and has been confirmed in other prospective cohort studies.[102, 247, 250] Alternative measures of nutritional depletion, such as low mid arm muscle circumference [246] and unplanned weight loss [14] have also been shown to independently predict 180-day mortality.

2.2.4.2 LUNG FUNCTION

The forced expiratory volume in 1 second is a well established independent predictor of mortality in stable disease (low FEV_1 = increased mortality).[26] However, in AECOPD, many studies are retrospective with a high proportion of missing spirometry data, potentially biasing results. For example, Baker et al [281] retrospectively identified 348 individuals admitted with AECOPD. Spirometric data (during a period of clinical stability up to two years prior to admission) were only available in 34% and low FEV_1 did not predict in-hospital mortality. Similarly, Bustamente-Fermosel et al [135] only obtained spirometric data in a small minority and no association could be shown between FEV_1 and in-hospital survival.

The results from one study of patients treated with NIV [147] suggested that low FEV_1 was independently predictive of treatment failure (death or need for invasive ventilation), but others have found no such relationship.[145, 248, 282] The lack of consistency about the prognostic value of FEV_1 is emphasised by one study [283] in which, counterintuitively, a higher baseline FEV_1 was associated with higher in-hospital mortality.

Studies investigating mortality following discharge typically contain fewer missing results. Despite this, there is still disagreement regarding the influence of FEV_1 on mortality. A number of studies [31, 242, 244, 269, 270] have shown that individuals with low FEV_1 are at increased risk of death following discharge, but others [15, 58,

247] have found no association. Closer analysis of the positive studies suggests that FEV_1 is predictive of mortality either when very low (FEV_1 < 590ml)[244] or when the population on average has relatively well preserved lung function (mean FEV_1 ≈ 50% predicted).[242, 270] It is therefore likely that patients with the most severely impaired lung function have a higher likelihood of death, but FEV_1 lacks discriminatory power because most patients hospitalised with AECOPD have severe COPD and a narrow range of FEV_1.

In the acute setting, spirometry is not one of the recommended investigations,[44] and it is infrequently performed. This has prompted investigators to investigate potential associations between mortality and peak expiratory flow rate (PEFR). De la Iglesia and colleagues [157] identified admission PEFR as an independent predictor of in-hospital mortality on multivariate analysis. Roberts [254] confirmed this finding but given that the majority of patients (54%) had missing PEFR data, this finding should be interpreted with caution.

2.2.4.3 ARTERIAL BLOOD GASES

2.2.4.3.1 HYPOXAEMIA

In studies in which F_iO_2 is not standardised, it is not surprising that no relation between low P_aO_2 and mortality is found.[150, 242, 243, 248] However, hypoxaemia breathing air,[161, 247, 270] an increased alveolar-arterial gradient,[243] and a low P_aO_2 / FiO_2 ratio [102] are all independently associated with in-hospital or six-month mortality.

2.2.4.3.2 HYPERCAPNIA

In stable COPD, hypercapnia is a strong independent predictor of mortality.[48, 113, 195] In all patients hospitalised with AECOPD, however, high P_aCO_2 values on admission have only been shown to predict in-hospital mortality in a single study,[279] whereas many other authors have failed to replicate this finding.[157, 243, 247, 258, 272] In AECOPD requiring NIV, a very high P_aCO_2 is predictive of a combined outcome of treatment failure or death.[139, 284] Hypercapnia is likely to signify severe COPD as well as a severe acute exacerbation, and it may therefore appear surprising that it is

not consistently related to short term mortality. However, in many studies, the participants' mean P_aCO_2 is high (often > 7kPa), which is likely to limit its discriminative value. A subgroup analysis of hospitalised patients with AECOPD, the majority of whom (82%) had P_aCO_2 < 6.0kPa, showed that hypercapnia independently predicted in-hospital death,[161] and three further studies [161, 242, 247] with mean P_aCO_2 closer to normal (mean < 6.5kPa) showed an association between hypercapnia and in-hospital mortality.

The severity of hypercapnia on admission is more clearly related to long-term mortality.[15, 242, 251] Almagro et al,[58] however, suggested that hypercapnia at discharge, rather than admission, was the more important predictor, a proposal corroborated by a prospective cohort study [285] 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 ABG recorded before hospital discharge.[286]

2.2.4.3.3 ACIDAEMIA

Acidaemia usually implies a severe acute exacerbation of COPD. In AECOPD requiring hospitalisation, the severity of acidaemia predicts both in-hospital and 30-day mortality.[158, 254, 274, 287] Whilst it has not been shown to predict long-term mortality,[247, 264] 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,[264] while the other included few acidaemic patients (mean pH 7.41).[247]

2.2.4.4 BIOCHEMICAL & HAEMATOLOGICAL ANALYSIS

In patients with severe AECOPD requiring treatment on ICU, low serum albumin identifies a group of individuals at increased risk of death in-hospital,[140, 158, 248] however in general patients with AECOPD, hypoalbuminaemia predicts mortality post-discharge not in-hospital.[102, 247] In all patients hospitalised with AECOPD, renal

dysfunction,[158, 161, 288] and hyperglycaemia [138, 281] independently predict in-hospital mortality. There is conflicting data surrounding the relationship between the presence of anaemia and the risk of death. Studies including individuals with pneumonia and AECOPD have shown an independent association between anaemia and mortality, both in-hospital [150] and following discharge.[250, 269] Other research, which excluded individuals with evidence of pneumonia, showed that the presence of anaemia does not predict death after admission for AECOPD.[248, 259, 288] Anaemia may therefore act as a marker of severe pneumonia, in individuals with COPD, rather than severe AECOPD. Holland et al [289] showed, in a small retrospective study, that patients with eosinopenia on admission were at an increased risk of death compared to those with normal eosinophil counts, but important confounders were not included in their analysis and the findings have not yet been reproduced.

Table 2.7 summarises the data regarding the association between biochemical and haematological indices and mortality following admission for AECOPD.

Table 2.7 Relationship between biochemical and haematological indices and mortality (*Italics indicate - significance persists on multivariate analysis)*

Study	Design & patient group[a]	Outcomes[b]	Mortality rate	Biochemical index associated with mortality	Haematological index associated with mortality
Baker [281]	Retrospective. n=348	IHM	18%	*Hyperglycaemia*	
Chakrabati [138]	Prospective. AECOPD requiring NIV. n=88	Failure of NIV	17%	*Hyperglycaemia*	
Wildman [158]	Retrospective. ICU admissions with AECOPD or asthma. n=8527	IHM	35% in-hospital	*Low sodium, high urea, high creatinine, hypoalbuminaemia*	*WBC <4x10^9, WBC >20x10^9*
Holland [289]	Retrospective. n=65	IHM	7.6%		Eosinopenia
Ai-Ping [248]	Retrospective. AECOPD requiring ICU. n=57	IHM	24% in-hospital	*Hypoalbuminaemia*	
Ucgun [150]	Prospective. AECOPD requiring ICU. n=151	IHM	33.1%	Hypoalbuminaemia, elevated CRP, high creatinine	*Anaemia*
Baillard [290]	Prospective. AECOPD requiring ICU. n=71	IHM	25%	*Elevated troponin*	
Molinos [161]	Prospective. Admissions with AECOPD and pneumonia. n=244	IHM	9%	*Elevated creatinine*	
Mohan [288]	Prospective. n=151	IHM	25%	*High urea*, creatinine. Hypoalbuminaemia, *low sodium*	
Rammaert [291]	Prospective. AECOPD requiring IPPV. n=116	Intensive care mortality	25%	Low HCO_3^-, *elevated PCT*	Elevated WBC
Chang [279]	Prospective. n=250	30-day mortality	8.5%	*Elevated BNP,* elevated troponin	

Study	Design & patient group[a]	Outcomes[b]	Mortality rate	Biochemical index associated with mortality	Haematological index associated with mortality
Connors [102]	Prospective. Admissions with severe AECOPD. n=1016	180-day mortality	33% 180-day	*Hypoalbuminaemia*	
Ranieri [250]	Prospective. Elderly admissions with AECOPD. n=244	6-month mortality	20% 6-month	High cholesterol	Anaemia
Gunen [247]	Prospective. n=205	Long-term mortality	33% 1-year	*Hypoalbuminaemia*	
Brekke [269]	Retrospective. n=897	Long-term mortality	24% 1-year	*Elevated troponin*	*Anaemia*

[a] Study involves unselected patients hospitalised with AECOPD unless otherwise stated; [b] IHM – in-hospital mortality; WBC – white blood cell count; BNP – N-terminal pro-brain natriuretic peptide

2.2.4.5 MICROBIOLOGICAL ANALYSIS

An infective agent was implicated in 78% of admissions to hospital with a severe AECOPD in one study.[133] However, in clinical practice, many patients suffer exacerbations where no pathogen can be identified. Mohan et al [288] and Bustamente-Fermosel [135] conclude that if a pathogenic organism is identified, there is an increased risk of in-hospital mortality. In a prospective cohort of patients requiring treatment with NIV, airway colonisation with gram-negative bacilli was associated with increased in-hospital mortality,[292] perhaps reflecting more severe disease and the development of secondary bronchiectasis. This is consistent with data from patients with stable disease where the isolation of non-usual pathogens (including gram-negative bacilli) was independently associated with long-term mortality.[232]

2.2.4.6 CARDIAC INVESTIGATIONS

In individuals with COPD, cardiovascular disease more frequently causes death than COPD itself.[55] The presence of atrial fibrillation or ventricular arrhythmias on the admission ECG was shown by Fuso et al [243] to be predictive of in-hospital death. Raurich et al [271] suggested that ECG evidence of cor pulmonale was associated with in-hospital death in patients with AECOPD undergoing mechanical ventilation. A prospective cohort study of 263 patients surviving AECOPD to discharge showed that individuals with ≥1 signs of cor pulmonale on ECG at discharge had an increased risk of long-term mortality.[293] It was also demonstrated that electrocardiographic evidence of right ventricular hypertrophy and right atrial overload, were independently predictive of long-term mortality.

Impairment of left ventricular function (ejection fraction < 45% on transthoracic echocardiography) is also predictive of higher mortality following AECOPD.[135]

Acute exacerbations result in significant physiological disturbance and place a significant burden on, what may be an already impaired, heart. Troponins are released by injured myocardial cells and act as a biomarker of myocardial damage. In patients admitted with AECOPD requiring admission to ICU, elevated troponin I was a strong

independent predictor of in-hospital death.[290] It is unclear whether it is the severity of the exacerbation, and resultant hypoxia and hypotension, which results in myocardial damage and increases mortality, or whether elevated troponin identifies a high risk subgroup of patients with co-existent cardiac disease and hence increased mortality. This study did not record any markers of acute heart failure and therefore the presence of coexistent cardiac disease may explain the elevated troponin and the increased mortality rates identified. Three further studies have shown that elevated troponin on admission predicts long-term mortality following discharge,[252, 269, 294] although two of these studies [269, 294] retrospectively studied patients hospitalised with AECOPD in whom a troponin was measured. Therefore, the unavoidable selection bias in these analyses means the findings need to be interpreted with caution and require additional prospective research.

2.2.4.7 RADIOLOGICAL INVESTIGATIONS

In individuals admitted to hospital with pneumonia, the presence of COPD has been found to be associated with increased in-hospital mortality,[161, 295, 296] and in AECOPD the presence of pneumonia is often seen to be a marker of a severe exacerbation. However, the relationship between pneumonia and mortality in patients with AECOPD has been infrequently studied. This is in part because the presence of radiographic consolidation on admission often precludes entry in studies of AECOPD. Two previous studies [135, 141] which have included unselected patients with AECOPD, including those with pneumonic exacerbations, have shown an association between pneumonia and mortality, but no independent relationship. A large retrospective study in patients with AECOPD showed that a diagnostic code of ‘pneumonia-influenza’ was independently associated with an increased risk of death in hospital.[297] However, the diagnosis of COPD and the meaning of the diagnosis ‘pneumonia-influenza’ are uncertain and therefore the true relationship between pneumonia and mortality in AECOPD remains unestablished. A single prospective study showed radiographic evidence of coexistent left ventricular failure to be independently predictive of long-term mortality.[252]

2.2.5 DEVELOPMENTS DURING HOSPITAL ADMISSION

Several authors have shown that the development of acute non-respiratory medical complications during the hospital stay is associated with increased in-hospital and post-discharge mortality. This has been discussed in section 2.2.2.7.

Antonelli-Incalzi [244] showed that a longer hospital stay (highest quartile versus lowest quartile) independently predicted long term mortality following discharge. The location of care has also been found to be a predictor of in-hospital and 30-day mortality in a large retrospective study.[240] In the latter study, admission to wards other than respiratory or ICU (for example, general medicine, elderly care and surgical wards) occurred in 85% of cases and was associated with an increased risk of in-hospital mortality independent of confounders. This is relevant to current UK practice where only 30% of patients are admitted under the care of a respiratory or ICU physician.[12]

2.2.6 PREDICTING MORTALITY IN AECOPD TREATED WITH ASSISTED VENTILATION

In the discussion above, indices which predict outcome in AECOPD requiring ventilatory assistance have not been separated from those which predict outcome in patients with AECOPD without respiratory failure. This is because AECOPD requiring NIV is now commonly managed on general respiratory or medical wards and should be viewed as a severe variant of AECOPD but not as a different entity. Also, in a patient hospitalised with AECOPD, all of the indices discussed above are potentially relevant. However, once a patient has developed acidaemic respiratory failure requiring ventilatory assistance, it is important to consider specific prognostic variables for this patient group.

Although some agreement between prognostic studies in exacerbations requiring assisted ventilation is found, there have been few robust prognostic markers identified. This reflects differences in participants' disease severity, and in the study outcomes used. Furthermore, typically a composite outcome of either need for invasive ventilation or death is used and given that there are frequently a small

number of deaths, the prognostic factors probably predict the need for invasive ventilation rather than mortality.

In general, factors that identify the degree of physiological derangement during the acute exacerbation predict higher in-hospital mortality following NIV. For example, higher APACHE II scores,[139, 144] lower conscious level [139, 150] and worse respiratory acidosis [282, 284] are all independently associated with increased mortality. Furthermore, complications during the hospital stay [147, 298] and comorbidity [142, 150] were also predictive of in-hospital mortality.

Interestingly, Levy et al [276] identified higher admission P_aCO_2 as protective against mortality and Anton et al [283] report that patients with lower FEV_1 had better outcomes following NIV than those with higher values. These two findings are at odds with other studies and also suggest that those with more severe underlying disease have better outcomes. However, it is difficult to apply the findings by Levy to individuals with AECOPD given that only 30% of the study population were receiving NIV for AECOPD. This surprising result of Anton et al may be because, in their study, patients with less severe COPD (i.e. a higher FEV_1) being treated on intensive care may have been experiencing a more severe acute illness and hence at a higher risk of treatment failure (i.e. patients with higher FEV_1 and milder exacerbations have been selected out because they did not require intensive care), whereas patients with lower FEV_1 may be pushed in to respiratory failure, and therefore require intensive care, by a relatively less severe acute illness and therefore be at a lower risk of death.

Few studies have examined predictors of long-term mortality in patients requiring assisted ventilation however they suggest that medical complications,[147, 298] severe stable-state dyspnoea,[264] older age,[266] and frequent prior health resource use [264, 266] are all predictive of mortality following discharge.

Table 2.8 summarises the key findings of the research investigating predictors of mortality in patients requiring NIV for AECOPD.

Table 2.8 Predictors of mortality following treatment of AECOPD with assisted ventilation (Italics indicate - Significance persists on multivariate analysis)

Study	Design[a]	Outcome[b]	Mortality rate	Factors associated with worse outcome
Confalonieri [139]	Prospective cohort. n=1,033	IHM or need for IPPV	13.7% IHM	Older age, *high APACHE II*, high P_aCO_2, *high RR*. *Low GCS*, low pH, low P_aO_2/FiO_2
Scarpazza [299]	Prospective cohort. AECOPD with ARF and DNACPR order. n=62	IHM	12.9% IHM	Older age, high APACHE II, low GCS, pH (after 1 hour)
Plant [284]	RCT. n=236	IHM or need for IPPV	10% IHM	*Low pH, high P_aCO_2*, reduced P_aO_2
Levy [276]	Prospective. Patients requiring NIV with DNACPR order. n=114†	IHM	57% IHM	*Weak cough, low P_aCO_2*
Schettino [277]	Prospective. Patients requiring NIV with DNACPR order. n=137†	IHM	64.9% IHM	*High SAPS*, high WBC, high HR. Low GCS, low haematocrit, low *albumin*
Ai Ping [248]	Retrospective. AECOPD requiring ICU. n=57	IHM	24% IHM	*Older age, previous IPPV, low albumin, high APACHE II*, low FEV_1, cardiac comorbidity
Baillard [290]	Prospective. AECOPD requiring ICU. n=71	IHM	25% IHM	*Elevated troponin, high SAPS,* low GCS
Rammaert [291]	Prospective. AECOPD requiring IPPV. n=116	Intensive care mortality	25%	High SAPS*, MODS,* low HCO_3^-, *elevated PCT,* elevated WBC
Ambrosini [282]	Retrospective. n=59†	IHM or need for IPPV	8.5% IHM	Reduced weight, impaired neurological status, high APACHE II, poor compliance with NIV, *low pH*
Anton [283]	Prospective. n=44†	IHM or need for IPPV	20% IHM	Impaired consciousness, high FEV_1
Soo Hoo [171]	Prospective. n=14	NIV failure or IHM	Not specified	Edentulous, radiological consolidation, poor compliance with therapy
Putinati [144]	Retrospective. n=75	IHM or need for IPPV	11.8% IHM	Low weight, *high APACHE II*, *low albumin*, low pH, high P_aCO_2

Study	Design[a]	Outcome[b]	Mortality rate	Factors associated with worse outcome
Ucgun [150]	Prospective. AECOPD requiring ICU with ARF. n=151	IHM	33% IHM	*Comorbidity*, *hypotension*, cardiac arrhythmia, *low GCS*, high APACHE II, *low haemoglobin*, elevated creatinine, high CRP, low pH, *low* HCO_3^-, *complication of ventilation,* pneumonia, low P_aCO_2
Mohan [142]	Prospective. AECOPD requiring ICU. n=116	IHM	16.7% IHM	*Comorbidity,* tachycardia, hypoalbuminaemia, acidaemia, pneumonia
Carratu [274]	Prospective. n=122	Failure of NIV or IHM	12%	Medical complication, pneumonia, CKD
Chakrabati [138]	Prospective. n=88	Failure of NIV or IHM	17%	Age, *high blood glucose*, *tachypnoea*, *high APACHE II score*, low pH
Jeffrey [287]	Prospective. AECOPD with ARF. n=139	IHM	12%	Low pH, high urea, low blood pressure
Roberts [146]	Retrospective. n=1077	IHM	25%	Increased time from admission to need for NIV, tachypnoea, Low HCO_3^-
Liu [259]	Retrospective. AECOPD requiring IPPV. n=138	IHM	39.9%	Comorbidity*, high APACHE II score, low pH*, sepsis, *MODS*
Scala [147]	Prospective. n=159	Failure of NIV or IHM and 6-month mortality	16% IHM. 35.3% 6-month	*Presence of acute comorbidity* , low* FEV_1*, non-cardiovascular comorbidity,‡ inability to perform ADL‡*
Fernandez [298]	Retrospective. ICU admissions requiring NIV. n=233†	IHM and 6-month mortality	33% IHM	*DNACPR order, Acute renal failure, need for vasoactive drugs*
Seneff [258]	Retrospective. AECOPD requiring ICU. n = 362	IHM and 6-month mortality	23.8% IHM	*Increased age, length of hospital stay (prior to ICU admission), abnormal non-respiratory physiology, abnormal respiratory physiology.*
Raurich [271]	Retrospective. AECOPD requiring ICU. n=101	IHM and 2-yr mortality	25.7% IHM	*Older age, cor pulmonale*, cardiac arrhythmia, *MODS*
Chu [264]	Prospective. n=110	Mortality after discharge	49% 1-year	*MRCD 4-5,* LTOT*,* low BMI, high prior health resource use

Study	Design[a]	Outcome[b]	Mortality rate	Factors associated with worse outcome
Echave-Sustaeta [266]	Prospective. n=120	Long-term mortality	52.7% 19-month	Prolonged length of stay, *older age*, low pH, *high* P_aCO_2, low FEV_1, *high prior health resource use*, domiciliary NIV
Wildman [246]	Prospective. AECOPD or asthma treated on ICU. n=832	180-day mortality	37.9%	*Older age, Male sex, length of hospital stay, reduced functional status, low mid arm muscle circumference, AF, GCS*

[a] Study involves unselected patients hospitalised with AECOPD requiring NIV unless otherwise stated; [b] IHM – in-hospital mortality; *acute comorbidity – e.g. shock, acute renal impairment, anaemia, hyponatraemia. †includes patients with and without AECOPD; ‡ only predictive of 6-month mortality

SAPS – simplified acute physiology score; RR – respiratory rate; GCS – Glasgow coma score; DNACPR – do not attempt cardiopulmonary resuscitation; WBC – white blood cell count; LTOT – long term oxygen therapy; BMI – body mass index; ADL – activities of daily living; ARF – acidaemic respiratory failure; IPPV – invasive ventilation; MODS – multiorgan dysfunction syndrome; PCT – procalcitonin; NIV – non invasive ventilation; AF – atrial fibrillation

2.2.7 CLINICAL PREDICTION TOOLS

In stable disease, clinical prediction tools, such as the BODE index (Table 2.2), have been shown to be valuable prognostic tools that help guide management, but their application to the population hospitalised with AECOPD is uncertain. Some investigators have attempted to develop clinical prediction instruments in AECOPD but most of the tools have not been validated outside the derivation cohort. Furthermore, many studies have investigated a highly selected group of patients (for example, patients requiring intensive care), and therefore their conclusions may not be relevant to practitioners working outside this environment. The relevant findings of this research are described below and summarised in Table 2.9.

Wildman et al developed two prognostic instruments to aid prediction of in-hospital [158] and six-month mortality [246] from two large cohorts of patients with acute exacerbations of COPD or asthma admitted to an ICU. The COPD and Asthma Physiology Score (CAPS) was developed for the prediction of in-hospital mortality and uses the following physiological indices: heart rate; mean arterial pressure; pH; sodium; urea; creatinine; albumin; WBC. Each variable is assigned a score resulting in a total score out of 100. Higher scores are associated with worse in-hospital mortality. The discriminating ability of CAPS (area under receiver operator characteristic curve (AUROC) = 0.72), with regard to in-hospital mortality, exceeded that of APACHE II (AUROC = 0.66). However, the retrospective methodology resulted in significant missing data with results for urea and albumin being absent for 14-32%. The authors assumed that missing values were within the normal range and therefore the final model may overestimate, or underestimate, the risk of mortality. The prognostic tool aimed at predicting six-month mortality included the following variables: CAPS; male sex; functional limitation; presence of atrial fibrillation; days spent in hospital; age; mid arm circumference; and GCS. The final model performed well (AUROC = 0.76) and both of the above tools showed good discrimination in their derivation cohorts and both underwent internal validation. However, their utility in a population of patients hospitalised with AECOPD not requiring intensive care is uncertain.

Roche et al [156] aimed to develop a clinical prediction tool in individuals presenting to the Emergency Department with AECOPD. The instrument that they developed was based upon: patient age; the number of 'clinical signs of severity' (defined by authors); and the level of dyspnoea. This model demonstrated good discrimination for mortality in both the derivation (AUROC = 0.79), and validation cohorts (AUROC = 0.83). The investigators were however hampered by slow recruitment which may have led to recruitment bias and the subjective nature of their pre-defined 'clinical signs of severity' means that application of such an instrument will vary from institution to institution, and from doctor to doctor.

Tabak et al [155] retrospectively identified almost 90,000 admissions with AECOPD from 191 hospitals and developed the BAP-65 (Blood urea nitrogen >25 mg/dL (≡ serum urea > 8.9 mmol/L), Altered mental status, Pulse rate >109/min, Age >65 years). On external validation in a second large retrospective cohort [300] this tool was found to be a good discriminator for in-hospital mortality (AUROC = 0.77). However, the accuracy of the diagnosis of AECOPD in this study is uncertain: patients were identified using admission coding data which is known to prone to error;[301] and no smoking history or spirometric confirmation of airflow obstruction was obtained from patients. Furthermore, the population studied were considerably less unwell than the population of patients hospitalised in the UK, according to the National COPD Audit: 2.1% of patients received ventilatory assistance compared to 12% in the UK National Audit.[12]

Ruiz-Gonzalez et al [221] 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.

The CURB-65 tool is a well validated, simple to use, instrument that accurately predicts morbidity and mortality in individuals presenting to hospital with community acquired pneumonia (section 1.2.4).[160] Chang and colleagues,[163] suggest that this instrument may be of prognostic value in AECOPD without complicating pneumonia. They showed that CURB-65 was independently predictive of 30-day mortality after

adjusting for other common prognostic indices, and that CURB-65 had good discrimination for 30-day mortality (AUROC = 0.73). External validation of these results is needed prior to their introduction to clinical practice.

Mohan et al [288] attempted to predict in-hospital mortality in a population of unselected admissions with AECOPD. In this prospective study, a simple instrument based upon serum creatinine and sodium levels on admission was produced. This equation produced showed good discriminating properties with AUROC = 0.73. However, no validation cohort was included and therefore it is unclear whether this prognostic tool is applicable outside of this study population.

Connors [102] analysed 1016 patients admitted with AECOPD and p_aCO_2 > 6.65 kPa. A formula aimed at predicting six-month mortality following discharge was developed. It was based upon: APACHE II score; age; p_aO_2 / F_iO_2; BMI; albumin; cor pulmonale; and comorbidity. The model demonstrated fair discrimination in the subsequent validation by the same authors (AUROC = 0.731) but there has been no external validation.

A small study [263] describing a prognostic tool aimed at predicting three-year mortality based on BMI and MRCD (Table 1.1) showed promise in its derivation cohort, but has not been externally validated.

A prediction score based on the following five variables: chronic renal failure; ECG evidence of RVH; FEV_1 < 590ml; ECG signs of IHD; and age was found to be predictive of five-year mortality following discharge for AECOPD (sensitivity 63%, specificity 77%).[244] This instrument has not been validated.

Anton and colleagues [283] attempted to develop a prediction equation to help predict failure of treatment in individuals requiring NIV. An equation based upon: change in p_a-CO_2 on NIV; initial pH; baseline FEV_1; and initial p_aCO_2 was shown to have an optimal sensitivity of 0.97 and a specificity of 0.9. However, there were only a small number of individuals in both the derivation cohort (n = 44) and the validation cohort (n = 15) and therefore this predictive tool should be used with caution. Confalonieri et al [139] developed a clinical prediction tool to help risk stratify patients with AECOPD requiring NIV. 1,033 individuals were prospectively identified and, on multivariate analysis, pH, respiratory rate, APACHE II score, and GCS were all significantly associated with

treatment failure and death and were therefore included in the prediction tool. The prognostic model had a high discriminative capability (AUROC = 0.88) and encouraging results from an external validation (AUROC = 0.83), but it is important to note that the outcome for both of the above studies was 'failure of NIV' and therefore it is not possible to use these tools to solely predict mortality in AECOPD.

Table 2.9 Summary of the clinical prediction tools developed for predicting mortality following hospitalisation for AECOPD

Study	Design‡	Outcome	Variables included in model	Discrimination	Validated?
Wildman [158]	Retrospective. ICU admissions.	IHM	Heart rate, blood pressure, pH, sodium, urea, creatinine, albumin, WBC	AUROC = 0.718	Yes. Internal validation
Tabak [155]	Retrospective	IHM	blood urea concentration, altered mental status, pulse rate >109/min, age >65 years	AUROC = 0.72	Yes. External validation
Roche [156]	Prospective ED attendances with AECOPD	IHM	Age, clinical signs of severity, dyspnoea grade	AUROC = 0.79	Yes. Internal validation
Mohan [288]	Prospective.	IHM	Serum creatinine, serum sodium	AUROC = 0.73	No
Wildman [246]	Prospective. AECOPD or asthma treated on ITU or HDU	Six-month mortality	CAPS, age, male sex, mid arm circumference, functional impairment, atrial fibrillation, length of stay, GCS	AUROC = 0.75	Yes. Internal validation
Connors [102]	Prospective admissions with severe AECOPD	Six-month mortality	APACHE III, age, PaO2/FiO2, BMI, level of disability*, albumin, CHF, cor pulmonale, comorbidity	AUROC = 0.731	Yes. Internal validation
Tsimogianni[263]	Prospective.	3-yr mortality	BMI, MRC Dyspnoea score	AUROC = 0.83	No
Antonelli-Incalzi [244]	Prospective discharges following AECOPD	Five-yr mortality	Age, ECG evidence of RVH, ECG evidence of IHD, chronic renal failure, FEV_1	Sensitivity 63%, specificity 77%†	No
Ruiz-Gonzalez [221]	Prospective.	Mortality or need for ICU	Confusion, CRP ≥ 50mg/L, ≥ 2 comorbidities, current smoking status	AUROC = 0.80	No
Anton [283]	Prospective. AECOPD requiring NIV	Failure of NIV	Change in P_aCO_2 on NIV, initial pH, baseline FEV_1, and initial P_aCO_2	Sensitivity 0.97, specificity 0.9†	Yes. Internal validation
Confalonieri [139]	Prospective. AECOPD requiring NIV	Failure of NIV	pH, respiratory rate, APACHE II score, GCS	AUROC = 0.88	Yes. External validation

* assessed by Katz ADL score; ‡ unselected admissions with AECOPD unless otherwise stated; † for optimum cut-off

IHM – in-hospital mortality; CAPS – COPD and asthma physiology score; ADL – activities of daily living; BMI – body mass index; WBC – white blood cell count; CHF – congestive heart failure; IHD – ischaemic heart disease; RVH – right ventricular hypertrophy; GCS – Glasgow Coma Score

2.2.8 SUMMARY OF PROGNOSTICATION FOLLOWING HOSPITALISATION FOR AECOPD

A vast array of prognostic indices associated with mortality following admission for AECOPD has been identified. However, some indices appear to be of value in predicting both in-hospital and post-discharge mortality: older age; previous admissions for AECOPD; and comorbidity (although acute comorbidity appears to predict in-hospital mortality, whereas the overall comorbidity burden appears to be a stronger predictor of mortality following discharge).

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 COPD. In general, the results from the studies discussed above support this approach. Although some well-established markers of disease severity such as low FEV_1 or hypercapnia have not routinely been found to predict in-hospital mortality, their discriminative value may be limited by the narrow range seen in the hospitalised population, most of whom have severe COPD. However, other variables reflecting severe underlying disease (i.e. the number of prior hospitalisations for AECOPD; the severity of dyspnoea; and low BMI) do have an important influence on in-hospital mortality, confirming the hypothesis that patients with more severe underlying disease are more likely to die in hospital.

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 acidaemia 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 (low FEV_1, severe dyspnoea, low BMI etc) becoming the more important factor. Functional disability and impairment of quality of life also independently predict long-term mortality.

Despite some agreement regarding prognostic indices, it has not been possible to combine the identifiable prognostic indices in to a clinical prediction tool that is both applicable outside of the study population and easy to use, and as a result, clinicians remain unable to risk-stratify patients according to their risk of death.

CHAPTER 3 PREDICTING HOSPITAL READMISSION FOLLOWING ADMISSION FOR ACUTE EXACERBATIONS OF COPD

Readmission following discharge from hospital for AECOPD is common and has been reported to occur in 34% of patients within three months,[254] and in up to 87% of patients within 1 year.[14, 15, 302, 303]

Several authors have investigated the risk of hospitalisation in stable COPD,[25, 57, 115, 199, 304] but few have studied variables associated with a high rate of readmission following hospitalisation for AECOPD. Clearly this is of importance to clinicians managing AECOPD in hospital and the available data are reviewed below. Table 3.1, Table 3.2 and Table 3.3 provide a summary of the important research in this area.

3.1 SOCIODEMOGRAPHIC FACTORS

Sociodemographic variables independently predictive of hospital readmission in patients admitted to hospital with AECOPD include: older age,[14, 305, 306] male sex,[14, 307] admission from a nursing home,[308] and being unmarried or widowed.[309] Cao et al [307] suggested that it is not age that independently predicts readmission, but prolonged disease duration (>5 years).

3.2 PREVIOUS ADMISSIONS AND SEVERITY OF UNDERLYING DISEASE

Consensus exists regarding the predictive value of some indices. The number of previous admissions (typically within the previous 12 months), for both respiratory and non-respiratory illnesses, has been repeatedly shown to independently predict readmission.[14, 254, 264, 303, 308, 310] The severity of underlying disease, measured by FEV_1,[306, 307, 311] or by the presence of cor pulmonale,[312] has also been shown to be independently predictive of readmission. Hypercapnia, another marker of the severity of underlying disease, was suggested by Almagro [310] to be independently predictive of readmissions, although Groenewegen [15] and Costello [285] could not identify an association. However, there was an important difference in the severity of hypercapnia between Almagro's study (mean $P_aCO_2 \approx 5.8$kPa) and

Groenewegen's and Costello's (mean P_aCO_2 = 6.74kPa and 6.79kPa respectively). The discriminative effects of hypercapnia in predicting readmission may therefore have been lost in these two negative studies because they involved a group of individuals who were, on average, already hypercapnic. It is not possible, therefore, to dismiss hypercapnia as not being predictive of readmission. The association between dyspnoea severity and readmission has been infrequently studied and no authors have identified an independent relationship, although five studies have shown a univariate association with readmission.[264, 307, 310, 313, 314]

3.3 HEALTH RELATED QUALITY OF LIFE, PSYCHOLOGICAL WELLBEING AND FUNCTIONAL IMPAIRMENT

Prospective cohort studies have identified that individuals with low health status (measured by SGRQ) are at significantly increased risk of readmission during the following year compared to patients with better quality of life. Stehr et al [315] showed that patients who had recently been bereaved were more likely to be rehospitalised. Osman [316] prospectively followed up 266 individuals discharged following AECOPD for 12 months. SGRQ was recorded for each individual during admission. No significant difference was found in the total SGRQ score in survivors and non-survivors but all components of the SGRQ (symptoms, activity and impacts) were independently associated with readmission within 12 months (high scores on SGRQ increased risk of readmission). Gudmundsson [305] undertook a similar prospective cohort study and identified the SGRQ activity and symptom subscores as being significantly associated with readmission within 1 year. It was also shown that in individuals with low health status, the presence of anxiety (Hospital Anxiety and Depression Scale (HADS) anxiety > 8) identified a subgroup with significantly increased rates of readmission. Depression, although frequently prevalent in individuals discharged from hospital following AECOPD, has not been shown to independently predict readmission [157, 309] even in those with underlying poor health status as measured by SGRQ.[305] This contrasts with data investigating mortality where depression has been shown to predict death. It has been hypothesised that a depressed individual's hopelessness and lack of motivation to change their

circumstances result in not seeking medical attention when unwell, thus reducing the readmission rates but increasing the risk of mortality following discharge.[262]

Functional impairment, as measured by an inability to manage ADLs or self care without assistance, has been shown to independently predict readmission.[254, 264, 308]

3.4 COMORBIDITY

Although a relationship between comorbidity and hospital readmission exists, it differs from that seen when mortality is the outcome of interest.

Coexistent asthma or cardiac comorbidities, including pulmonary hypertension, are independently predictive of readmission [14, 302] whereas, diabetes is apparently protective.[14] These findings contrast with those on mortality where the coexistence of diabetes is associated with a higher mortality [33] and asthma is protective.[14] Perhaps the extensive community support available for patients with diabetes ensures that episodes of AECOPD are recognised and treated promptly, with hospital admission thereby averted. Most studies have found no relationship between the comorbidity burden, measured using CCI (Table 17.1), and readmission,[15, 310] although a single study did identify a independent relationship.[306] However, alternative measures of the burden of comorbid conditions (the total number of comorbidities, and alternative comorbidity scoring tool, the Chronic Disease Score)[317] are stronger predictors of readmission.[309, 318] Possibly, the prognostic influence of individual comorbidities included in the CCI conflicts, in a similar way that asthma and diabetes conflict, and this may explain why the CCI does not appear to have a strong relationship with readmission.

3.5 OTHER ASSOCIATIONS WITH HOSPITAL 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.[15, 34, 264, 303, 307, 310, 312, 319] High respiratory muscle load (measured by the Pressure Time Index) at discharge independently predicts readmission,[312] and low fat free mass

and muscle mass are associated with rehospitalisation within 3 months, but not independent of other variables.[34]

At discharge, patients prescribed high dose inhaled corticosteroids;[308] oral theophylline;[185] and maintenance oral corticosteroids [15, 185, 303] are at an increased risk of hospital readmission, independent of other variables. LTOT independently predicts hospital readmission,[312, 320] and home nebulised bronchodilators [254, 305] and inhaled anticholinergics [303] have been shown to be associated with readmission, although the relationship is not independent of other variables and other studies have not confirmed these findings.[185, 305]

3.6 CLINICAL PREDICTION TOOLS FOR HOSPITAL READMISSION

Although risk factors for hospital readmission in patients admitted with AECOPD have been identified, no clinical prediction tools have been developed. This is in contrast to the population of hospitalised adult general medical patients where many attempts at developing clinical prediction tools for readmission have been made. In the hospitals where this study was conducted, two readmission prediction tools were commonly used to assist decisions regarding resource allocation: the LACE [321] and PARR [322] predictive tools. The LACE (Length of stay, emergent Admission, Comorbidity, visits to the Emergency department within the previous six months) tool was developed in Canada on a large, prospectively recruited cohort (n = 4812) of patients surviving a hospital admission. The tool is simple to use and underwent external validation although it was shown to only have moderate discrimination for 30-day readmission or death (AUROC = 0.684). The PARR (the Patients At Risk for Rehospitalisation) tool was developed in the United Kingdom on a retrospective sample of 24,276 patients discharged following hospitalisation due to a chronic medical condition (including COPD). The discrimination of this tool for 12-month readmission was moderate (AUROC = 0.685) and its clinical utility is limited by the complex risk calculation required and its reliance on data not routinely available during hospital admission.

3.7 SUMMARY OF THE LITERATURE PREDICTING READMISSIONS

A summary of the literature that identifies predictors of readmission is detailed in Table 3.1 to Table 3.3. In all tables, emphasis with italics indicates that the variable was a significant predictor of readmission on multivariate analysis.

Table 3.1 Factors associated with hospital readmission – Sociodemographic details, health related quality of life and functional status

Study	Design[a]	Readmission rate	Sociodemographic factors	Quality of life & psychological wellbeing	Functional status
McGhan [14]	Retrospective. n=51,353	25% 1-year	*Increasing age, male sex*		
Lusuardi [306]	Prospective. n=931	17.7% 6-month	*Increased age*		
Cao [307]	Retrospective. n=186	67% 1-year	Male sex, *prolonged disease duration*		
Groenewegen [15]	Prospective. n=171	55% 1-year	Younger age		
Wong [309]	Retrospective. n=109	Not specified	*Unmarried*		
Lau [308]	Retrospective. n=551	59% 1-year	NH residency		*Dependence in self care*
Gudmundsson [305]	Prospective. n=416	61% 1-year	*Increasing age*	*High SGRQº, high anxiety levels^*	
Vega Reyes [320]	Prospective. n=93	40% 1-year		*High SGRQº* (activity component)	
Osman [316]	Prospective. n=266	41% 1-year		*High SGRQº* (all components)	
Almagro [310]	Prospective. n=129	58% 1-year		*High SGRQº* (all components)	
Stehr [315]	Retrospective. n=33	Not specified		*Recent bereavement*	
Roberts [254]	Retrospective. n=1,221	34% 3-month			Dependence in self care
Chu [264]	Prospective. AECOPD requiring NIV	80% 1-year			*Reduced functional status**
Garcia-Aymerich [303]	Prospective. n=340	63% 1-year		*Low QoL*	*Low physical activity*

Italics indicate that variables is an independent predictor of readmission on multivariate analysis; [a] Study involves unselected patients with AECOPD surviving to discharge unless otherwise stated; * low Katz ADL score; ^ significant only in individuals with low health status (SGRQ>60); º High SGRQ = low health status; QoL – quality of life; NH – nursing home; SGRQ – St. George's Respiratory Questionnaire

Table 3.2 Factors associated with hospital readmission - clinical history, hospital admission, and investigations

Study	Design[a]	Readmission rate	Clinical history	Investigations
McGhan [14]	Retrospective. n=51,353	25% 1-year	*Previous hospitalisations*	
Chu [264]	Prospective. AECOPD requiring NIV. n=110	80% 1-year	*Previous hospitalisations*	
Lusuardi [306]	Prospective. n=931	17.7% 6-month		*Low FEV_1*
Bartolomeo [323]	Retrospective. n=123,162	34% 1-year	Discharge from ICU, admission with ARF	
Pouw [324]	Retrospective. n=28	Unspecified	Weight loss during initial admission	
Murata [325]	Retrospective. n=213	Unspecified	*Previous hospitalisations*	*Low FEV_1*, high FEV_1/FVC
Almagro [310]	Prospective. n=129	58% 1-year	*Previous hospitalisations*, severity of dyspnoea	*Hypercapnia*
Lau [308]	Retrospective. n=551	59% 1-year	*Previous hospitalisations*, hospital stay >5 days	*Rt heart strain†; high HCO_3^-*
Roberts [254]	Retrospective. n=1,221	34% 3-month	*Previous hospitalisations*	*Low FEV_1*
Garcia-Aymerich [326]	Case-control. n=172	Unspecified	*≥3 hospitalisations in previous year*	*Low FEV_1*
Cao	Retrospective. n=186	67% 1-year		*Low FEV_1*
Garcia-Aymerich [303]	Prospective. n=340	63% 1-year	*≥3 hospitalisations in previous year*	*Low FEV_1, Low P_aO_2*
Gudmundsson [305]	Prospective. n=416	61% 1-year	*Hospital stay >5 days*, current smoking	Low FEV_1, low FVC
Tsoumakidou [311]	Prospective. n=67	Not specified		COPD severity *
Wong [309]	Retrospective. n=109	Not specified		COPD severity*, *high WCC*
Bhatt [327]	Retrospective. n=100	87% 1-year		*Hypomagnesaemia*
Echave-Sustaeta [266]	Prospective. AECOPD requiring NIV. n=120	66% 1-year	*High hospital length of stay*	*Low FEV_1,* high P_aCO_2

Italics indicate that variables is an independent predictor of readmission on multivariate analysis; [a] Study involves unselected patients with AECOPD surviving to discharge unless otherwise stated; *when measured using GOLD or ERS criteria; *† assessed by ECG;* ARF – acidaemic respiratory failure; HCO_3^- - bicarbonate; ICU – intensive care unit; WCC – white blood cell count

Table 3.3 Factors associated with hospital readmission – comorbidity and medication

Study	Design[a]	Readmission rate	Comorbidities	Medications
McGhan [14]	Retrospective. n=51,353	25% 1-year	*Asthma, pulmonary hypertension*. (*Diabetes, hypertension protective*)	
Lusuardi [306]	Prospective. n=931	17.7% 6-month	*CCI*	
Groenewegen [15]	Prospective. n=171	55% 1-year		Maintenance corticosteroids
Roberts [254]	Retrospective. n=1,221	34% 3-month		*High total number of medications*, home nebuliser
Sin [185]	Retrospective. n=22,640	25% 1-year		Oral theophyllines, maintenance corticosteroids (ICS protective)
Almagro [310]	Prospective. n=129	58% 1-year	Cor pulmonale	
Gonzalez [312]	Prospective. n=112	32.1% 1-year	*Cor pulmonale*	*LTOT*
Vega Reyes [320]	Prospective. n=93	40% 1-year		*LTOT*
Wong [309]	Retrospective. n=109	Not specified	*Total number of comorbidities*, coronary artery disease, LVF	LTOT
Lau [308]	Retrospective. n=551	59% 1-year		*High dose ICS*
Gudmundsson [305]	Prospective. n=416	61% 1-year		LTOT, home nebuliser, theophylline. (Inhaled anticholinergics protective)
Garcia-Aymerich [326]	Prospective, case-control. n=172	n/a		*LTOT underprescription*
Garcia-Aymerich [303]	Prospective. n=340	63% 1-year		*Inhaled anticholinergics*

Italics indicate that variables is an independent predictor of readmission on multivariate analysis; [a] Study involves unselected patients with AECOPD surviving to discharge unless otherwise stated; ICS – inhaled corticosteroids; LTOT – long term oxygen therapy; LVF – left ventricular failure / dysfunction; CCI – Charlson comorbidity index

3.8 PREDICTING OUTCOMES IN AECOPD - SUMMARY

Summarising the research discussed above is difficult because of varied methodologies and populations studied. There does however appear to be an overlap between certain predictors of mortality and readmission as well as some key differences. The severity of physiological derangement is an important predictor of in-hospital and post-discharge mortality but has less influence on readmission rates. Similarly, along with other comorbidities discussed above, the link between coexistent cardiovascular disease and death does not appear to be as strong when predicting readmission. Anxiety, measured by the HADS, is a stronger predictor of readmission than mortality whereas depression, measured using the same scale, predicts mortality but not readmission. Nutritional depletion is an independent predictor of mortality in stable and acute COPD. However, many authors have been unable to identify an association with readmission, although many of these studies involved a population with relatively well preserved BMI (mean BMI >24 in all studies).

It is important, therefore, to consider the outcomes of readmission and mortality separately. The strength of the relationships between relevant variables and outcome in patients hospitalised with AECOPD is summarised in Table 3.4. Only articles showing an independent association with outcome have been included and the following criteria have been used to grade the strength of the association: strong evidence – at least 3 studies showing independent relationship; moderate evidence – 2 studies showing independent relationship; weak evidence – 1 study showing independent relationship.

Table 3.4 Relationships between different variables and outcomes following hospitalisation for AECOPD

	In-hospital mortality	Post-discharge mortality[†]	Hospital readmission
Strong evidence (listed in order of weight of supporting evidence)	Older age Elevated acute physiology scores Impaired consciousness Cardiac comorbidity Poor nutritional status‡ Prior hospitalisations Tachypnoea / respiratory distress Hypotension Acute comorbidity Acidaemia Hypoxaemia[n] Renal impairment Hypoalbuminaemia Positive sputum microbiology	Cardiac comorbidity Functional limitation Poor nutritional status‡ Low FEV_1 Older age Prior hospitalisations Cor pulmonale[Ω] Stable-state dyspnoea Diabetes Acute comorbidity Poor quality of life Depression Maintenance steroids Hypercapnia Elevated troponin Underlying malignancy	Prior hospitalisations Older age Low FEV_1 Functional limitation Poor quality of life Maintenance steroids Comorbidity burden[d]
Moderate evidence	Hypercapnia Hyponatraemia Comorbidity burden Male sex Low FEV_1[b] or low PEFR Tachycardia Hyperglycaemia Stable-state dyspnoea	Hypoalbuminaemia Male sex Anaemia	Cor pulmonale[Ω] LTOT Male sex
Weak evidence	Higher monthly income Current smoking LTOT Functional limitation Institutional care High BNP / troponin / PCT Abnormal WBC AECOPD severity^ Cerebrovascular disease Chronic liver disease Underlying malignancy Maintenance steroids Coexistent pneumonia Low serum bicarbonate Anaemia Cor pulmonale Weak cough	Disease duration Current smoking > 60 cigarette pack years Hypoxaemia[n] Unmarried Comorbidity burden Thromboembolic disease Chronic renal impairment Impaired consciousness Unintentional weight loss Tachycardia Length of hospital stay	Long duration of COPD Unmarried / widowed Institutional care Hypercapnia Anxiety Asthma Oral theophylline High dose ICS Inhaled anticholinergics Respiratory muscle overload[c] Cardiac comorbidity

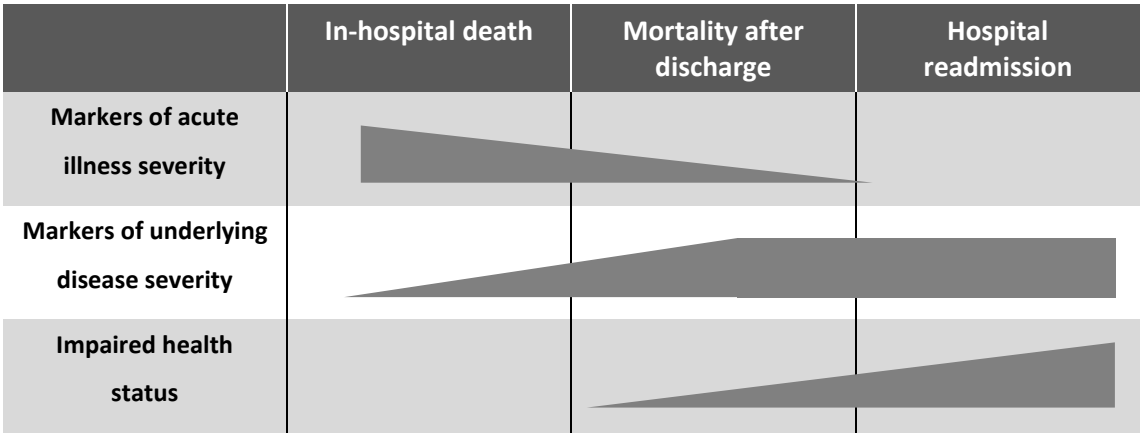
	In-hospital mortality	Post-discharge mortality[†]	Hospital readmission
	Inappropriate location of care[b]		

[†] Excluding studies investigating mortality within 30 days of discharge; ‡ low BMI or low % of ideal body weight; ⁿ hypoxaemia on ABG, low alveolar-arterial gradient, or low P_aO_2 / F_iO_2 ratio; ^ according to Anthonisen Criteria; [Ω]clinical diagnosis of cor pulmonale, pulmonary hypertension on echocardiogram, or presence of bilateral pedal oedema; [b] admitted to any ward except respiratory or intensive care; [c] measured non-invasively using pressure-time index; [d] high total number of comorbidities, high chronic disease score, or CCI >1.[318]

AECOPD – acute exacerbation of COPD; LTOT – long-term oxygen therapy; PEFR – peak expiratory flow rate; CCI – Charlson comorbidity index; FEV_1 – forced expiratory volume in 1 second; ICS – inhaled corticosteroids; WBC – white blood cell count; BNP - N-terminal pro-brain natriuretic peptide; PCT - procalcitonin

Potential prognostic variables (apart from the presence of chronic comorbid conditions and older 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. acidaemia, hypoxaemia, acute comorbidity); markers of underlying disease severity (e.g. low FEV_1, previous hospitalisation, 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 3.1.

Figure 3.1 Schematic representation of relative impact of 3 main groups of variables on different outcomes



Despite considerable research on patients hospitalised with AECOPD, we are still unable accurately to predict the important clinical outcomes in an individual patient. No single predictor variables have been shown to robustly predict outcome and prognostic models that have shown promise in their derivation cohort have frequently not been validated.

Hospitalisation for AECOPD becomes more frequent with advancing disease and places an enormous burden upon the patients and the healthcare system. Large prospective studies to develop tools which accurately predict readmission and mortality (both in-hospital and following discharge) would help to inform clinical decisions, such as the appropriate escalation of care and optimum utilisation 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.

CHAPTER 4 ASSESSING HEALTH AND QUALITY OF LIFE

4.1 DEFINITIONS

The wellbeing of an individual or individuals health status was traditionally defined biologically by survival rates and the absence of disease, but as healthcare quality and provision have improved, our expectations have risen and our view of health status is now best explained by a biopsychosocial model, incorporating the concepts of physical, mental, social and spiritual well-being in to the traditional biological viewpoint.

Reflecting the above changes, health status is currently defined by the WHO as "the state of health of a person or population assessed with reference to morbidity, impairments, anthropological measurements, mortality, and indicators of functional status and quality of life".[328] Quality of life is a broad multidimensional concept including evaluations of both positive and negative aspects of life,[329] whereas health-related quality of life (HRQoL) encompasses the aspects of quality of life that affect both physical and mental health. The definitions of health status, QoL and HRQoL vary in the literature resulting in terminological confusion. From this point forward I will use the term quality of life (QoL) when discussing health and quality of life assessment, although I accept that the instruments I refer to are limited and do not measure the full breadth of this concept.

It has been demonstrated that outcome measures traditionally used in COPD studies, such rate of FEV_1 decline, are only weakly correlated with an individual's symptoms, vitality, functional capabilities and feelings of personal well-being (i.e. their quality of life).[186, 330, 331] This has led to the development of a number of instruments aimed at assessing and estimating the impact disease has on an individual's QoL. The instruments can be divided into generic tools – to be used in a wide variety of conditions, and specific tools – designed for use in a specific condition and to assess the disease-specific impact on QoL. In addition, aspects of health status not assessed by generic or disease specific instruments, such as psychological wellbeing and functional status, can be reliably and accurately assessed using specific questionnaires.

4.2 GENERIC QOL INSTRUMENTS

Compared to disease-specific questionnaires, generic QoL instruments are broader in scope and allow comparisons to be made across different patient populations. However, they often include questions that are irrelevant to a particular condition and they are therefore limited in their ability to detect small changes in quality of life.

Examples of generic QoL instruments include the 36-item Short Form Health Survey (SF-36), the Sickness Impact Profile (SIP) and the Nottingham Health Profile (NHP). Generic instruments can also be used to screen for the presence of anxiety and depression, or to assess the degree of functional impairment that an individual experiences.

The SIP has been validated in COPD,[332] but its use is limited by its lack of discrimination in mild COPD and the time taken to administer. The SF-36 is quick and simple to administer and has been shown to predict hospitalisation in COPD,[333] but it has been found to be less responsive than disease specific questionnaires (section 4.3).[334] The NHP has also been shown to be reliable and responsive in COPD [333] although the minimally important clinical difference (MCID) is unknown and therefore its ability to detect clinically important changes in QoL is limited. Therefore, generic QoL instruments were not used in our study.

4.3 SPECIFIC QOL INSTRUMENTS

Disease-specific instruments attempt to define the effects of one condition on QoL. Although developed for use in a single condition, some of the instruments have been used in other related conditions thus extending their usage. Examples used in COPD include: the chronic respiratory disease questionnaire (CRQ); the St. George's Respiratory Questionnaire (SGRQ); the Breathing Problems Questionnaire (BPQ); and the Seattle Obstructive Lung Disease Questionnaire (SOLDQ). Disease specific questionnaires (CRQ and SGRQ) have been found to be substantially more responsive than generic measurements at assessing response to treatments in individuals with COPD.[334]

4.3.1 THE CHRONIC RESPIRATORY DISEASE QUESTIONNAIRE (CRQ)

The CRQ is a measure of QoL in patients with chronic airflow limitation. It was originally designed for use in patients with chronic airflow limitation of any cause and has been shown to be responsive, reliable and valid; changes in the CRQ correlate with changes in individuals lung function, exercise capacity and their physician's overall assessment of the individual's condition.[335] It has also been used to obtain responsive measures of acute changes in quality of life during AECOPD.[336]

The questionnaire contains 20 questions addressing four domains – dyspnoea, fatigue, emotional function and mastery. The questions regarding fatigue, emotional function and mastery are standardised requiring the patient to indicate the most appropriate answer on a seven point scale. The dyspnoea domain is personalised where the individual chooses five activities that make them breathless and then rates how breathless performing those activities has made them over the preceding two weeks. The CRQ is therefore able to assess the limitation that COPD has on patient-specific activities. This, however, makes it difficult to compare the dyspnoea domain results between individuals, and the scale is more useful for comparing results for the same individual. Lower scores in each domain reflect more severe impairment and the MCID for the CRQ has been accepted to be 0.5 in any one domain.[337]

The original questionnaire was designed to be interviewer-administered and was recommended to take approximately 25 minutes. Williams et al [338] developed a self-reported version of the CRQ and found it to be a reproducible and reliable measurement of health status in patients with COPD.

The CRQ has been found to be more sensitive to change than generic health status measurements [339, 340] and the BPQ.[341] On direct comparison in individuals with COPD, the CRQ has been shown to have similar reliability, responsiveness and validity to the SGRQ.[342]

4.3.2 THE ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

The SGRQ is a 50 item questionnaire which has been validated in both COPD and asthma.[343] It consists of three subscales: symptoms (eight questions), activity (16

questions) and impacts (26 questions). Responses are weighted and results are calculated by dividing the summed weights by the maximal possible weight and expressing the results as a percentage. The weights were originally derived from individuals with asthma but have been validated in patients with COPD.[333] The responses are aggregated into a total score and sub-domains for symptoms, activity and impacts. For each domain (symptoms, activity, impacts and total), scores range from 0 (no impairment) to 100 (maximum impairment or death).

The questionnaire has been demonstrated to be responsive, reliable and valid in individuals with both stable COPD and AECOPD.[332, 343, 344] Results from the SGRQ correlate with frequency of respiratory symptoms, exercise performance, breathlessness, mood state and annual frequency of exacerbations.[345] The questionnaire has been shown to outperform generic instruments at detecting impairments in QoL [346] and is effective at assessing the response to a variety of therapies.[333]

The SGRQ takes 15-20 minutes to complete and can be self-administered by patients without difficulty.[347] The MCID is 4 points [344] and Ferrer et al [348] established population normal values for the SGRQ so that individual results can be interpreted in context.

Due to the weight of literature supporting their use, and their advantage over both generic and other disease-specific QoL instruments, the SGRQ and CRQ were chosen for use in our study.

4.4 ASSESSMENT OF FUNCTIONAL STATUS

'Functional status' refers to the limitation that health problems place on an individual's ability to perform their usual behaviours and activities [349] and is an important part of an individual's assessment of health. Functional status usually worsens (i.e. limitation increases) as the severity of COPD increases. The term 'activities of daily living' (ADL) is defined as the basic physical, psychological, social or spiritual needs that fulfil usual roles and maintain health and well-being and is used in the assessment of functional status.[350] Activities of daily living can either be classed as basic (i.e.

concerned with primary biological functions – bathing, eating, toileting etc) or instrumental (i.e. enable individuals to live independently within a community – housework, shopping, managing money etc). Assessment of instrumental ADL is of more value in patients with chronic diseases living in the community. Instrumental ADLs require high energy exposure and therefore, compared to basic ADLs, are more likely to be restricted early on in the disease process, therefore providing a more sensitive assessment of functional status than basic ADL.[349]

The Nottingham Extended Activities of Daily Living (NEADL) scale [351] is a self-administered questionnaire assessing the impact of disease on functional status. It is divided into four categories (mobility – 6 activities, kitchen – 5 activities, domestic – 4 activities and leisure – 6 activities). The respondent is asked to score for each activity whether they: 0 - are unable to perform the activity; 1 - require help to perform the activity; 2 - perform it independently but with difficulty; or 3 - perform it independently with ease. Although originally designed as a 22-item questionnaire, one of the items has been dropped due to poor test-retest reliability.[351]

Originally a total score out of 21 was obtained by rating the individual as either dependent (score = 0) or independent (score = 1) for each activity. Higher scores reflect greater independence. The MCID between measurements is two points [352]. This method of applying the NEADL has been shown to be reliable and effective in assessing functional status in patients with COPD.[351, 353, 354] Alternatively, obtaining a total score out of 63 (MCID to detect clinically relevant change = 5)[355] has also been studied in COPD [356] and we choose to use this methodology because it may be more sensitive to small changes in functional status. The NEADL has also been shown to be a better discriminator of respiratory disability in elderly subjects than an alternative common measure of functional status (the Barthel Index).[353]

In addition to the NEADL, a simple yet useful measure of functional status is performance status (Table 4.1). This five-point scale was initially used in the oncology field but the National UK COPD audits [12, 254] have demonstrated its utility in predicting mortality in AECOPD following discharge. Subsequently, this tool has also been shown to be associated with in-hospital mortality in AECOPD.[260]

Table 4.1 Performance status [12]

Description	Performance status
Normal activity	0
Strenuous activity limited	1
Limited activity but able to self care	2
Limited self care	3
Bed or chair bound, no self care	4

4.5 ASSESSMENT OF PSYCHOLOGICAL WELLBEING

There is a high prevalence of psychiatric morbidity in non-psychiatric medical clinics and depression is common in COPD. Zigmund et al [357] developed the Hospital Anxiety and Depression Scale (HADS) to help clinicians screen patients for anxiety and depression. HADS is simple to administer and has been shown to be acceptable by the population for which it was designed.[358] It has been shown to be a reliable, valid and responsive instrument to assess the symptoms of mood disorders [358] and has previously been used effectively in assessing the prevalence and impact of mood disorders in individuals with COPD.[359] The instrument has two subscales – anxiety and depression, and the total value for each subscale is 21. A score less than 8 is regarded as normal, a score of 11 or greater indicates the probable presence of anxiety or depression, and score between 8 and 10 is suggestive of the presence of a mood disorder. Using a cut-off of 8 as diagnostic, HADS has been shown to have a sensitivity of 80% and a specificity of 90% in a population of depressed patients.[262] The MCID of the HADS in anxiety or depression is 1.5.[360]

4.6 PREDICTORS OF QUALITY OF LIFE RECOVERY FOLLOWING AECOPD

In stable COPD, it has been shown that quality of life decline is associated with: both single and frequent episodes of AECOPD;[112, 127, 361] hospitalisation for AECOPD;[111]; lower FEV_1;[60, 111] lower levels of physical activity;[362] male sex;[363] lower body weight;[363] more severe stable-state dyspnoea;[363, 364] frequent respiratory symptoms;[363] and greater comorbidity.[111]

Few studies have investigated indices associated with recovery (or decline) in quality of life following AECOPD. Tsai et al [365] showed in 330 patients attending the ED with AECOPD that, compared to patients whose quality of life fully recovered within two weeks, patients whose quality of life had not fully recovered: had a greater smoking burden; were less likely to have coexistent asthma; were more likely to have experienced AECOPD in the previous year; were more likely to be prescribed oxygen at home; were more likely to have coronary artery disease or congestive cardiac failure; and had higher oxygen saturations at the time of their ED attendance. However, the only factor found to independently predict quality of life recovery was a history of frequent (≥ 2) AECOPD.

Following hospitalisation for AECOPD, Wang et al [313] showed that low FEV_1 was associated with, and high levels of stable-state dyspnoea were independently predictive of, a subsequent decline in quality of life. These findings have not been confirmed by other authors and the only other study which attempted to identify predictors of quality of life decline following hospitalisation failed to identify any factors independently associated with outcome.[366]

Therefore, although an assessment of the likelihood of subsequent recovery of an individual's quality of life is important and recommended in many treatment decisions in AECOPD requiring hospitalisation,[174] there is little evidence of useful prognostic indices, aside from exacerbation frequency, to assist the treating clinician. Furthermore, all of the above studies used quality of life decline (or recovery) as the outcome variable. This is likely to have identified patients whose QoL declined from a well preserved baseline level rather than patients whose QoL deteriorated from an initially low level. However, the most clinically relevant group to identify is those who had an initially poor QoL which subsequently deteriorated because these patients may benefit from closer observation and more supportive care, or from early discussion of palliative care options. Different measures of subsequent QoL decline / recovery used in this study are outlined in section 12.4.1 and our definition of poor QoL following hospital discharge is described in section 13.6.1.

AIMS AND METHODS

CHAPTER 5 RESEARCH AIMS

Two distinct populations were studied and therefore the methods and results are included, for each population, under the relevant part (Part 1 - Predicting outcome following hospitalisation for AECOPD; and Part 2 - Longitudinal assessment of quality of life and health resource following hospitalisation for AECOPD). The following aims refer distinctly to either Part 1 (Aims 1a to g) or Part 2 (Aims 2a and 2b).

5.1 COEXISTENT PNEUMONIA IN AECOPD

Aim 1a: to compare the characteristics and outcomes of patients with and without coexistent pneumonia

Frequently, studies of AECOPD have excluded patients with pneumonia and therefore the impact of pneumonia in AECOPD remains uncertain. We wished to describe the characteristics of patients with pAECOPD and compare this to their non-pneumonic counterparts. We also wished to assess the impact of pneumonia on mortality and readmission in AECOPD and the prognostic strength of CURB-65 (Table 1.6) in both pAECOPD and npAECOPD.

5.2 EVALUATION OF THE EXTENDED MRC DYSPNOEA SCALE AND MALNUTRITION UNIVERSAL SCREENING TOOL

Aim 1b: evaluation of the extended MRC Dyspnoea Scale with specific reference to correlation with survival, quality of life, readmission rates length of stay and frequency of hospital readmission.

Aim 1c: evaluation of Malnutrition Universal Screening Tool with specific reference to correlation with survival, quality of life, readmission rates length of stay and frequency of hospital readmission.

The severity of dyspnoea during a stable state, measured by the traditional MRCD scale (Table 1.1) is a strong predictor of mortality in AECOPD. A previous study in our hospital [367] has suggested that subdividing individuals with traditional MRCD 5 in to two levels, depending on their ability to independently perform washing or dressing, more accurately predicted the risk of hospital admission following discharge than the

traditional scale. This novel modification of the MRCD is termed the Extended MRCD (eMRCD) and is detailed in Table 5.1:

Table 5.1 The Extended MRC Dyspnoea scale

Grade	Degree of breathlessness related to exercise
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying or walking up a slight hill
3	Walks slower than contemporaries on level ground because of breathlessness, or has to stop for breath when walking at own pace
4	Stops for breath when walking about 100m or after a few minutes on level ground
5a	Too breathless to leave the house unaided but independent in washing and / or dressing
5b	Too breathless to leave the house unaided and requires assistance in washing and dressing

The relationship between the extended MRCD scale (Table 5.1) and mortality has not previously been investigated, and the suggestion that eMRCD may be a better discriminator for hospital readmission [367] requires further investigation. We therefore wished to clarify the association between MRCD and outcome in AECOPD, and investigate whether eMRCD is a stronger predictor of mortality and readmission than MRCD.

Poor nutritional status is an important prognostic index in AECOPD (section 2.2.4.1), but malnutrition can be measured in a variety of ways and no single, easy to measure index has been found to accurately predict both short and long-term mortality, and readmission. The Malnutrition Universal Screening Tool (MUST) has been shown to be a useful prognostic tool in elderly acute general medical admissions [39, 41] but its utility in patients with AECOPD has not been investigated.

We therefore wished: to report the estimated risk of malnutrition in our population according to MUST; and to assess the prognostic strength of MUST compared to BMI and weight loss in AECOPD.

Table 5.2 The 'Malnutrition Universal Screening Tool' ('MUST')

Nutritional measurement	Score
Body mass index (BMI),	
>20	0
18.5-20	1
<18.5	2
Unplanned weight loss in past 6 months,	
<5%	0
5-10%	1
>10%	2
If patient acutely ill and there has been, or is likely to be, little nutritional intake for >5 days	2
Total MUST score	**/6**
Low risk of malnutrition	0
Moderate risk of malnutrition	1
High risk of malnutrition	≥ 2

MUST is reproduced here with the kind permission of BAPEN (British Association for Parenteral and Enteral Nutrition).[368]

5.3 PREDICTING OUTCOME FOLLOWING HOSPITALISATION FOR AECOPD

Aim 1d: identify independent predictors of in-hospital mortality following hospitalisation for AECOPD and develop a clinical prediction tool to accurately predict the risk of in-hospital mortality.

Aim 1e: identify independent predictors of in-hospital mortality in patients receiving assisted ventilation following hospitalisation for AECOPD.

Aim 1f: identify independent predictors of twelve-month mortality following hospitalisation for AECOPD.

Aim 1g: identify independent predictors of early and frequent readmission, and develop a clinical prediction tool, in patients surviving to discharge following hospitalisation with AECOPD.

Chapter 2 and Chapter 3 detail the current difficulties that clinicians face when attempting to predict outcome in AECOPD. Therefore, we aimed to identify, in a broad population of patients with AECOPD, independent predictors of mortality and readmission. Furthermore, we aimed to develop clinical prediction tools to assist clinicians in the prediction of in-hospital mortality and early readmission following discharge in a population hospitalised for AECOPD.

The planned prediction tools should be easily memorised and simple to use, and would therefore contain a limited number of variables, with predictor variables consisting of, ideally, two or three categories. The prediction tools would be internally validated during this study, but external validation would require subsequent studies.

Predicting short and long-term survival has been more extensively researched in patients with acidaemic respiratory failure requiring assisted ventilation than in general patients with AECOPD (Table 2.8) yet many of these studies have only been performed in the intensive care setting or have strict entry criteria. We aimed to identify independent predictors of short-term survival in this population. Comparisons with previously published data would be problematic and were therefore not undertaken. In most previous research, prognostic data (particularly APACHE and CAPS) were collected at the time of clinical deterioration, for example at the time of admission to ICU or commencement of ventilation. In the present study, most physiological data in patients requiring ventilation were collected at admission to hospital. Therefore, comparing our predictive model with the performance of APACHE and CAPS in our study is flawed because APACHE and CAPS were designed to be calculated at the time of clinical decline.

5.4 LONGITUDINAL ASSESSMENT OF QUALITY OF LIFE AND HEALTH RESOURCE USE

Aim 2a: Assess quality of life and subsequent health resource use among survivors of AECOPD.

The time course of recovery of symptoms and quality of life following hospitalisation for AECOPD has been infrequently studied. We wished to document health resource

use and the recovery, or decline, of quality of life and survival in a population of patients discharged from hospital following AECOPD, and in a subgroup of patients who received assisted ventilation during their hospital stay. We aimed to compare the baseline characteristics and subsequent quality of life following discharge of patients who received assisted ventilation with those who did not.

A central aim of this part of the study was to identify predictors to assist clinical decisions regarding escalation of care or timing of discussion of end-of-life care. We therefore aimed to identify patients at risk of death or at risk of survival with poor QoL following discharge. Consequently, we wished to characterise the population who experienced poor quality of life following discharge, and then identify independent predictors of poor quality of life or death.

CHAPTER 6 PATIENTS AND METHODS

6.1 ETHICAL APPROVAL

Ethical approval was sought and granted from NHS County Durham and Tees Valley Research Ethics Committee 2.

6.2 PARTICIPANT RECRUITMENT

All patients admitted to either North Tyneside General Hospital (NTGH) or Wansbeck General Hospital (WGH) (Northumbria Health NHS Foundation Trust) with a diagnosis of an acute exacerbation of COPD were eligible for inclusion in to the study. Participant recruitment began on 19th December 2008 and ended on 30th June 2010. Participants were identified through a variety of methods. In our trust, the Respiratory Specialist Nurses (RSpN) are informed of all patients admitted with an exacerbation of COPD. As well as obtaining participant details from the RSpN, close contact was maintained with the Medical Admissions Units, the Respiratory wards and the ICU in order to maximise patient recruitment and to include a comprehensive range of severity of AECOPD. Once participant details were obtained, the case notes were reviewed either whilst they were an in-patient, or post-discharge in a minority of cases. A small number of patients either rapidly died or were discharged from hospital prior to identification by the research team. In order to optimise participant recruitment (and minimise potential bias) hospital discharge records were screened and any not already included in the study were identified. The case notes were then reviewed individually and if eligible, the individual was recruited in to the study.

6.3 INSTITUTION BACKGROUND

Northumbria Health NHS Foundation Trust is situated in the North East of England and is geographically one of the largest NHS trusts in the UK, providing healthcare to over half a million people. The two main hospitals are: North Tyneside General Hospital, which has 534 in-patient beds and admits over 28,000 non-elective cases per year; and Wansbeck General Hospital, which has 396 in-patient beds and admits over 29,000 non-elective cases per year. NTGH is located in an urban area, 8 miles from Newcastle

City Centre, with an estimated COPD prevalence higher than the UK national average.[3] WGH is situated in Ashington, which is surrounded by a largely rural community and services a vast catchment area ranging from Tyneside to the Scottish Borders, and from North East coast to as far west as Haltwhistle. Wansbeck General Hospital is serviced by a number of smaller rural cottage hospitals where patients can be cared for, closer to their home, once their acute illness has recovered. The North East of England has the largest proportion of most deprived areas in the UK [369] and, in some areas of North Tyneside and Northumberland, measures of health deprivation and disability are amongst the highest in the country.[370]

6.4 INCLUSION CRITERIA

Inclusion criteria were: admission from the primary place of residence; age greater than 35 years; current or former smoker with a smoking history of greater than 10 cigarette-pack years; a clinician's diagnosis of COPD, supported by spirometry; and an acute exacerbation of COPD. COPD was defined as the presence of compatible symptoms coupled with airflow obstruction on spirometric measurement (FEV_1 / FVC < 70%). An acute exacerbation of COPD was defined as *"an acute worsening of the patient's condition from the stable-state, which is sustained and warrants the patient to seek additional treatment"*.[105] Both infective and non-infective exacerbations were included and radiographic consolidation did not preclude inclusion in the study. The participants' first admission to hospital during the period of the study was termed their index admission and data regarding readmissions and mortality was obtained from this point onwards. A participant could not be enrolled in the study more than once.

6.5 EXCLUSION CRITERIA

Patients were excluded if: they did not meet any of the above inclusion criteria; they had a life-threatening active malignancy (estimated survival < 1 year) or other serious life-threatening co-morbidity (i.e. If it was believed that the patient was unlikely to survive their admission because of an alternative diagnosis); or if they were in receipt of domiciliary ventilatory support prior to admission. Individuals were not included if it was felt by the treating clinician, or confirmed through subsequent investigations, that

the primary reason for admission was: pulmonary thromboembolic disease; pneumothorax; asthma; pulmonary fibrosis; bronchiectasis; cardiac failure; or pleural effusion.

6.6 DATA COLLECTED

In order to ensure that our prediction tool would be of clinical relevance we concentrated on data that were readily available to the admitting clinical team or to the RSpN who review patients on admission.

6.6.1 PRE-ADMISSION STATUS

Data were collected on: sociodemographic characteristics; residence prior to admission; need for social support (paid carers) prior to hospitalisation; smoking status (current smoker, former smoker – defined as self-reported abstinence of tobacco smoking for at least 3 months); smoking load (recorded as cigarette pack years (cpy): 20 cigarettes per day for 1 year = 1 cpy); self-reported annual frequency of exacerbations of COPD ("How many times have you received antibiotics or steroids for treatment of a chest infection in the past 12 months?"); the number of admissions (both respiratory and non-respiratory) in the preceding 12 months; independence in performing activities of daily living (washing, dressing, feeding, cooking, cleaning); number of previous exacerbations requiring NIV or invasive ventilation (including dates); previous participation in pulmonary rehabilitation course (including dates); details of the participants' maintenance therapies; their 'exercise tolerance' (defined as the estimated distance they can walk in metres unaided on the flat before having to stop for a rest); whether the participant can leave the house unaided; and their degree of breathlessness measured by both the MRCD (Table 1.1) and eMRCD (Table 5.1) scales. The patient was asked to estimate the amount of unintentional weight loss experienced in the three months prior to admission. If the patient was unable to report this, and weight measurements at the appropriate time points were available, it was calculated.

6.6.2 PREVIOUS SPIROMETRY AND SEVERITY OF COPD

Details of participants' most recent documented spirometric measurement were recorded. In participants presenting for the first time with suspected COPD, or those with no previous documented spirometry, spirometry was either performed at the time of hospital discharge or after six weeks post discharge in order to identify the presence or absence of airflow obstruction (FEV_1 / FVC < 0.70). Although spirometry performed at any time was used to satisfy inclusion criteria, only spirometry performed within two years of admission was used in data analysis.

6.6.3 COMORBIDITIES

Case notes were reviewed in order to obtain a detailed list of the participants' co-morbidities. Co-morbidities were deemed to be present if: they were mentioned in the admission clerking document, a hospital clinic letter or a primary care referral letter; or if an investigation demonstrated the condition to be present. Specifically, cor pulmonale was present if: 1) pedal oedema was present in the absence of an alternative cause; or 2) estimated pulmonary artery systolic pressure (PASP) > 30mmHg on transthoracic echocardiography.[371] Bronchiectasis required the presence of the typical symptoms of chronic cough and sputum production coupled with characteristic abnormalities on thoracic imaging. Left ventricular dysfunction was recorded if transthoracic echocardiography demonstrated left ventricular ejection fraction (LVEF) < 45%. Participants were listed as having depression if it was either included as an admission or discharge diagnosis in the hospital records, or if the participant was in the receipt of medication for treatment of depression. Abnormal bone densitometry results were required for the diagnosis of osteoporosis to be recorded. Charlson Comorbidity Index (Table 17.1) was calculated retrospectively.

6.6.4 ADMISSION DATA

A number of physiological indices obtained on arrival in hospital were recorded (pulse rate, blood pressure, respiratory rate, temperature, GCS and arterial oxygen saturation on stated level of inspired oxygen). Height and weight measurements, either from admission or from a recent clinic attendance (≤ 3 months, only if no recent weight loss

reported by patient), were used to calculate the body mass index (BMI – weight (kg)/height $(m)^2$), and combined with information regarding recent weight loss, the MUST score (Table 5.2) was obtained.

Furthermore, the following were recorded at hospital admission: self-reported expectoration of purulent sputum; the presence of pedal oedema; the presence of an acute confusional state; bedside assessment of cough effectiveness ('effective cough' - able to generate a forceful cough or if they were able to expectorate sputum; 'partially effective cough' - able to cough but could not generate sufficient force to mobilise secretions and fully expectorate sputum; 'ineffective cough' - unable to generate any significant force to their cough.) The participants' resuscitation status was recorded in one of the following three categories: for invasive ventilation if clinically indicated; for non-invasive ventilation if clinically indicated; for cardiopulmonary resuscitation if clinically indicated.

6.6.5 INVESTIGATIONS

The results from a number of investigations performed on admission were recorded, or calculated:

Table 6.1 Investigations performed on admission

	Investigation
Blood biochemistry	Sodium, Potassium, Urea, Creatinine, Glucose and C-Reactive Protein concentration
Blood haematology	Haemoglobin, Total White Cell Count, Neutrophil count Haematocrit, Eosinophil count
Arterial blood gas (ABG) analysis	FiO_2, pH, H^+ concentration, p_aCO_2, p_aO_2, actual HCO_3^-, Base excess
Chest X-ray	Presence or absence of radiographic consolidation

6.6.6 ACIDAEMIC EXACERBATIONS

All arterial blood gas results recorded during the participants' admission were scrutinised. The exacerbation was termed 'acidaemic' if at any point during admission the participant developed acidaemic respiratory failure (ARF) (pH < 7.35 and pCO_2 > 6kPa). In all acidaemic exacerbations, the arterial blood gas results that first demonstrated the presence of ARF were documented and the following were

recorded: the time between admission and recognition of acidaemia; whether the patient went on to receive assisted ventilation (NIV or IPPV); whether the patient improved on medical therapy and did not need ventilatory support; or whether there was a clinical decision not to institute ventilatory support. For participants who received assisted ventilation, the results of blood gas analysis and the participants' respiratory rate were recorded at 1-2 hours and 4-6 hours after the initiation of therapy. The total length of time ventilated was documented as well as the outcome.

6.6.7 DISCHARGE

At discharge, spirometry, if performed, was logged. Maintenance therapies were documented. The discharge destination was recorded and it was noted if the patient was being discharged with more social care than they were in receipt of on admission. Length of stay (days) was calculated based upon the time spent in the acute hospital (i.e. time spent in cottage hospitals following discharge was not included).

6.6.8 OUTCOME DATA

12 months after enrolment in the study, details of participants' mortality were collected from the Public Health Mortality File. Date of death, place of death (home, hospice or hospital) and cause of death was documented.

Hospital records were reviewed for details of hospital readmissions. The total number of hospital readmissions within 12 months of enrolment and the time to first readmission were noted. For this study, the readmission outcomes of interest were chosen to be: hospital readmission or death without readmission within 90 days of discharge (known as readmission or death from this point forward); and frequent (2 or more hospital admissions during the 12 months following discharge) readmission.

We selected the dependent variables for our subsequent analyses based upon what we believed to be the most clinically pertinent outcomes: in-hospital mortality; 12-month mortality; 90-day readmission or death; and frequent readmission.

6.7 STATISTICAL METHODS - GENERAL

Data were quantitative in nature and analysed using both SPSS-15 for Windows (IBM, NY, USA) and SigmaPlot-11 (Systat Software, CA, USA). Exact p values were used where appropriate, a two-sided p value < 0.05 was taken as statistically significant and 95% confidence intervals (CI) were reported for areas under the receiver operator characteristic curve (AUROC) and odds ratios (OR).

6.7.1 MISSING DATA

Great care was taken during data collection to minimise missing data. However, complete data capture was not possible and the amount of missing data for each variable is shown in Table 17.2. Variables not listed had complete (100%) data capture.

When considering missing data, it is important to decide whether the data was missing completely at random (MCAR), missing at random (MAR) or missing not at random (MNAR). Using the example of recording BMI on admission to hospital, Table 6.2 explains these terms:

Table 6.2 Missing data nomenclature

Reason for missing data	Definition [372]	Explanation
Missing completely at random (MCAR)	No systematic differences between the missing and observed values.	The measurement scales were broken and therefore BMI not recorded.
Missing at random (MAR)	Systematic difference between missing and observed values. Reason for 'missingness' is due to other independent variables and does not relate to missing data itself.	Missing BMI lower than observed BMI because older patients more likely to be bed-bound and therefore less likely to have BMI measured.
Missing not at random (MNAR)	Systematic difference between missing and observed values. Reason for 'missingness' is related to outcome.	BMI missing because patient died before measurement could be made

Potential bias can be introduced when dealing with missing data that is not MCAR however such biases can be overcome by using data imputation methods (such as Expectation-Maximisation (EM) analysis, section 6.7.1.1) which allows individuals with

incomplete data to be included.[373] Alternate options for dealing with missing variables, such as simple exclusion of missing values (using pairwise or listwise deletion) or mean imputation, introduce bias.[373] In a clinical observational study, it is unlikely that missing data will be MCAR, and it is not possible to distinguish between MAR and MNAR using the observed data. If data is MAR then data imputation methods, such as EM analysis, can be used. In our population, MAR was the most likely explanation for 'missingness' in the majority of cases and it has been recommended that, in "most realistic scenarios", even if data is not MAR, "departures from MAR are not large enough to invalidate MAR-based analysis."[373] Therefore, imputation using the EM algorithm was performed.

6.7.1.1 EXPECTATION-MAXIMISATION (EM) ALGORITHM

Traditional methods of data imputation include mean imputation (e.g. replacing missing BMI data with the mean BMI of the population) or regression substitution (e.g. predicting missing BMI data using other variables), however both of these methods result in a diminished standard error that may introduce bias.[373]

The EM algorithm is a process whereby missing data can be estimated and a smaller reduction in standard error results,[374] and can be used if data is MAR.[374, 375] The EM algorithm consists of a two-step iterative process where firstly (E step), missing variables are replaced by the predicted scores from a series of regression equations (where the remaining observed variables are used to estimate the regression coefficients). In the second M step, the complete dataset (including estimated data) is used to recalculate the regression coefficients. The regression coefficients are then used to recalculate the missing variables at the next E step, and the process begins again. The algorithm repeatedly cycles through these steps until the difference between estimations falls below a pre-specified criterion.[374]

For all missing variables in our study, EM imputation was performed and results are shown in Table 17.3. For continuous variables, the imputed data value replaced the missing value, and for categorical variables, the imputed data value was rounded to fit with possible values of the categorical variable, as recommended by Schafer.[376]

All subsequent univariate analyses were performed using both the complete and original (with missing data excluded pairwise) data set and the results for original, incomplete variables (Table 17.4 and Table 17.5) are unchanged from the complete dataset.

6.7.2 ASSESSMENT OF NORMALITY

Assessment of normality was performed for all continuous variables by visual inspection of the histogram (Appendix B), as well as analysing the mean, median, interquartile range, standard deviation, kurtosis and skewness. Specific statistical tests for normality (for example, the Kolmogrov-Smirnov test) can be used to check the assumption of normally distributed (parametric) data, however, a limitation of these tests is that the larger the sample size, the more likely it is to get significant results even with only very slight deviations from normality.[377] Therefore, in our large sample, the main method to assess normality was visual inspection of the histogram. Parametric tests were performed on variables assumed to come from a normal distribution and non-parametric tests were used on non-normally distributed variables.

6.7.3 POPULATION DESCRIPTION

Descriptive statistics were used to characterise the patient sample, using proportions for categorical variables, means with standard deviations (SD) for parametric variables, or medians with inter-quartile ranges (IQR) for non-parametric variables.

6.7.4 UNIVARIATE COMPARISONS

χ^2-test was used to compare categorical variables, Student's T-test to compare parametric data, and Mann-Whitney U to compare non-parametric variables. To examine for trends between multiple groups, ANOVA was used for parametric data and Kruskal-Wallis was used for non-parametric variables. Bonferroni's correction was applied to Student's T test or Mann-Whitney U respectively, to identify between group differences.[377]

6.8 STATISTICAL METHODS – PART 1

In addition to the statistical analyses described in section 6.7, variables associated with, and independently predictive of, outcome were identified. Logistic regression analysis was used to identify predictors of outcome (in-hospital mortality, 12-month mortality, 90-day readmission, and frequent readmission).

For the prediction of mortality, all patients included in the study were analysed, whereas, for the prediction of readmission, only the patients who survived the index admission were analysed.

6.8.1 VARIABLE SELECTION FOR REGRESSION ANALYSES

Univariate associations with outcome were assessed using Student's t-test, Mann-Whitney U test, and χ^2-test (for parametric, non-parametric, and categorical variables respectively). Variables with an association with outcome at the significance level of < 0.10 were carried forward to multivariate testing. Categorical variables with a markedly asymmetric split (< 10% of the population in one category) were excluded from multivariate testing. An assessment of face validity was also performed for all candidate prognostic indices. For example, if there was no biological plausible explanation for the relationship between the candidate variable and outcome, or if the direction of the relationship between the variable and outcome was in contrast to previous research and clinical reasoning, then the variable was excluded.[378]

Multicollinearity exists when two or more predictor variables are moderately or highly correlated. Multicollinearity, to some extent, is inevitable in observational studies but, if harmful, can lead to an unstable final regression model which generalises poorly outside the study population or can result in nonsensical results.[379] However, it is not possible to completely remove collinearity between predictor variables but 'harmful' collinearity can be identified using the following criteria:

1) Strong significant pairwise correlation between continuous variables (collinearity suggested if correlation coefficient > 0.70)[379]; or
2) High variance inflation factors (VIF): collinearity suggested if largest VIF > 3 or if mean VIF > 1.5.[377, 379]; or

3) Variables which share high (> 0.50) variance proportions for a corresponding low eigenvalue and condition index (i.e. condition index > 30);[377, 379] or
4) Two variables which measure very similar concepts.

If high levels of collinearity were detected, and conceptually, it was clear that the variables are measuring similar factors, one of the variables was excluded from the analysis.[379] For the purposes of this study, the variable with either the weakest statistical or conceptual association with outcome on univariate analysis was excluded.

The univariate relationships between maintenance medications and outcome were assessed however, with two exceptions, they were not included in multivariate analyses. Only medications which had set eligibility criteria or which might be related to underlying COPD disease severity (for example, LTOT or home nebuliser therapy) were included in multivariate testing. All other maintenance medications are likely to either be collinear with each other or with the participant's comorbidities. Furthermore, significant associations between medications and outcome are likely to be biased by 'confounding by indication'.[380]

Therefore, all eligible variables showing an association with outcome ($p < 0.10$) on univariate testing that did not show evidence of collinearity were included in the logistic regression analysis.

6.8.2 LOGISTIC REGRESSION ANALYSIS

Backward stepwise multivariable logistic regression analysis, including all variables selected using methods described in section 6.8.1, was performed separately for all of the above outcomes (dependent variables). At each step of the regression model, the likelihood ratio statistic was used to remove the variables with the weakest association with outcome ($p > 0.05$). Odds ratios were reported with 95% confidence intervals.

For multivariate models with variables in their original form (i.e. with variables on a continuous scale where appropriate), the odds of developing the relevant outcome were calculated using the equation below and are shown underneath the table summarising each regression model:

$$Odds\ of\ outcome = e^{-(\beta 0 + \beta 1 X 1 + \beta 2 X 2 + \beta 3 X 3 + \ldots + \beta n X n)}$$

Where β_0 is the Y intercept of the regression model and β_n is the regression coefficient of the corresponding variable X_n. Based upon this, the predicted probability of outcome can be calculated and used for the assessment of model accuracy (section 6.8.2.2):

$$Probability\ of\ outcome = {}^{1}/_{(1 + odds\ of\ outcome)}$$

6.8.2.1 CHECKING MODEL FIT AND ASSUMPTIONS

In order to assess whether the model was an accurate representation of the observed data, outliers were identified by screening studentised residuals. If more than 5% of cases are outliers (studentised residual > ±1.96) this implies an unacceptable level of error within the model.[377] To further investigate potential statistical outliers, Cook's distance (values greater than 1 suggest that the individual case may be distorting the regression model); and leverage values (scores 3 times greater than the expected mean leverage indicate cases that might be substantially influencing the model) were reported.[377] The expected mean leverage for the population can be calculated (expected mean leverage = k+1 / 920, where k = number of variables in the final regression model) and compared to the observed mean leverage. Outliers (residual > ± 1.96) which substantially influenced the model (Cook's distance > 1 or leverage > 3(k+1) / 920) were reported and investigated to identify reasons for their distance from, and influence on, the regression model.[377]

6.8.2.2 ASSESSING MODEL ACCURACY

The accuracy of a prognostic model (i.e. the degree to which predictions match outcomes) consists of two components: calibration and discrimination. Calibration refers to whether predicted probabilities agree with observed probabilities, and discrimination refers to the ability to distinguish between patients with different outcomes.[381] Although perfect discrimination and calibration are ideal, the relative importance of each varies with the intended application: good calibration would be important when trying to counsel patients regarding individual risk, whereas

discrimination is more important when trying to stratify patients according to severity of disease.[382] Fundamentally, if a model has poor discrimination then no adjustments can be made to improve the model, but if poor calibration is present, certain adjustments can be made without requiring more data.[381]

Calibration can be assessed using the Hosmer-Lemeshow goodness-of-fit test (HLGFT) which forms subgroups of patients and compares the observed proportion of outcomes with the predicted probabilities.[383] The statistic has a χ^2 distribution and a non-significant result ($p > 0.05$) implies that calibration is satisfactory. However, this statistic has limited power to detect poor calibration [384] and therefore, calibration can be further assessed by plotting the observed proportion of outcome against the predicted probability of outcome, for deciles of risk. Well-calibrated models having a line of best fit gradient of 1, while models providing over-optimistic predictions will have a gradient of less than 1.[382, 385] The distance from individual coordinates to the line of best fit provides information about whether the model is well calibrated across all deciles of risk.

Discrimination refers to the ability to distinguish high-risk patients from low-risk patients and is commonly quantified by a measure of concordance, the c-statistic. In logistic regression, with a binary dependent variable, the c-statistic is identical to the AUROC.

6.8.2.2.1 RECEIVER OPERATOR CHARACTERISTIC (ROC) CURVES

For a single binary predictor (or diagnostic test), a simple 2 x 2 contingency table can be used to assess how well the predictor (or diagnostic test) predicts outcome (or disease) (Table 6.3). The sensitivity (the proportion of true positive results) and specificity (the proportion of true negative results) can be calculated and it is preferable to have high values for both sensitivity and specificity.

Table 6.3 Calculating sensitivity and specificity

	Outcome positive	**Outcome negative**
Predictor positive	TP A	FP B
Predictor negative	C FN	D TN

$$Sensitivity = \frac{TP}{TP + FN} = \frac{A}{A + C}$$

$$Specificity = \frac{TN}{TN + FP} = \frac{D}{B + D}$$

TP – true positive; FP – false positive; FN – False negative; TN - true negative

The receiver operator characteristic (ROC) curve consists of a graphical plot of sensitivity against 1-specificity for different discrete cut off points for a diagnostic test or prognostic index. The AUROC summarises the discriminative ability of the test or predictor across a full range of cut offs. AUROC can take on any value between 0 and 1, with 1 being a perfect predictor of outcome, and 0.5 indicating that the test performs no better than pure chance. As a rule of thumb, it has been estimated that a diagnostic test with AUROC > 0.9 has high accuracy, while 0.7 to 0.9 indicates moderate accuracy and 0.5 to 0.7 low accuracy.[386] It is important to note, however, that the AUROC for prognostic models is usually lower than for diagnostic tests and 'good prognostic tools' typically have an AUROC between 0.75 and 0.85.[383, 387] Statistical comparisons of AUROC of different models (applied to the same population – paired comparison) can be made using the method of DeLong et al.[388]

ROC curves were drawn, and AUROC and differences between AUROC were calculated, using SigmaPlot-11.

6.8.2.3 ASSESSING MODEL VALIDITY

Compared to performance in another dataset, prognostic models will have better performance on the dataset from which they were derived.[389] The 'gold-standard' method to assess generalisability is to perform external validation where the model fit

and its predictive ability are reassessed on a similar population which differs from the derivation cohort in both time and geography.[390] However, although necessary prior to implementation in clinical practice, external validation requires a further study at a different time in a different population, to the original dataset, and is therefore time-consuming and expensive. In the absence of external validation, internal validation is often used to give further confidence to the prognostic model prior to future external validation.

The pseudo-R^2 (i.e. Nagelkerke's R^2) value provides an estimation of the amount of variance in the outcome variable that is explained by the model, and can be used to estimate model performance, with higher values implying better generalisability. An alternative option is to split the cohort so that a proportion of patients are used to derive the prognostic tool and a second distinct proportion used to validate it (split-sample validation). However, this: does not replace the need for external validation; limits the power of the derivation cohort therefore weakening the developed prognostic tool; and requires a very large sample size to provide a reliable approximation to external validation.[389] A method which can be used to assess internal validation which uses the entire study population to both derive and internally validate the prognostic tool is bootstrapping.

Bootstrapping is a well known method to assess variability in test statistics and, in a predictive logistic regression model, is recommended as a better method to assess internal validity than split-sample validation.[389] The bootstrap is a resampling procedure where a dataset is randomly sampled with replacement (i.e. when an item is sampled it is immediately replaced) multiple times.[391] From the resampled dataset, conclusions can be drawn regarding the internal consistency of the data and tests of model performance (e.g. AUROC) can be bootstrapped to check internal validity. To assess internal validity of the prognostic models developed here, bootstrap estimates (using 10,000 bootstrap samples) of the AUROC were performed and reported with 95% confidence intervals.

6.8.3 DEVELOPING A PREDICTIVE TOOL

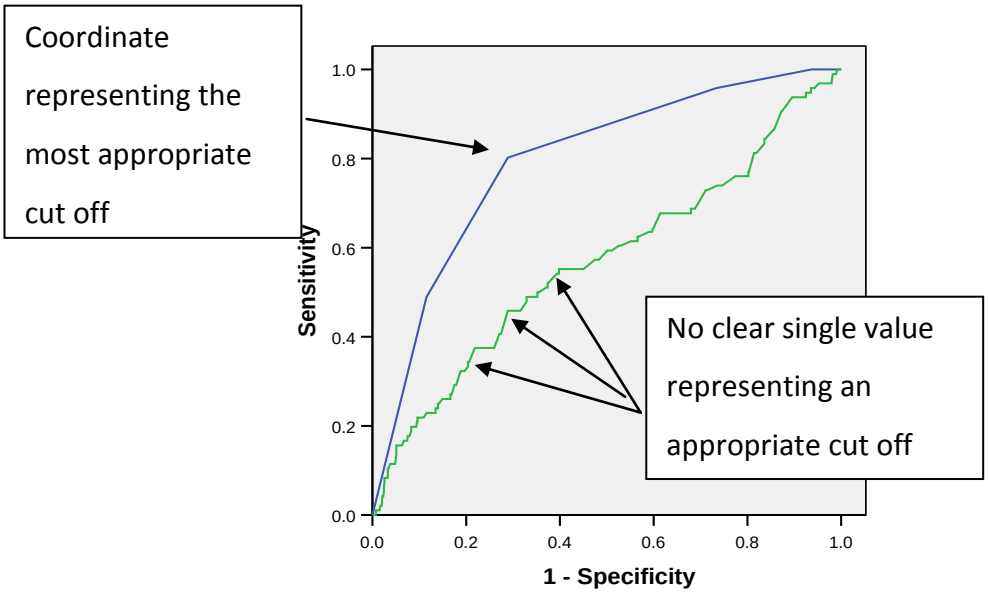
6.8.3.1 TOOL OUTLINE

We wished to develop a prognostic tool that would both accurately predict outcome and be simple to remember and to use in clinical practice. Therefore, the predictive instrument would ideally contain a limited number of variables and the predictor variables should be categorical, with only 2 or 3 categories. Therefore, prior to selecting variables for our predictive tool, all continuous variables were dichotomised or categorised. Categorical variables with a markedly asymmetric split (< 10% of the population in one category) were excluded from further analyses.

6.8.3.2 SELECTING APPROPRIATE CUT OFFS

Visual inspection of the ROC curve can be used to identify which cut off value optimises both sensitivity and specificity. The coordinate of the ROC curve which lies closest to either the upper left-hand corner of the graph (y = 1, x = 0) when predicting mortality, or closest to the bottom right-hand corner (y = 0, x = 1) when predicting survival, corresponds to the 'best' cut off value (Figure 6.1).

Figure 6.1 Using ROC curve to select most appropriate cut offs for variables that are independently predictive of outcome



A single cut off point may not always be obvious from ROC curve analysis (Figure 6.1) and therefore, in such situations we used further methods to confirm appropriate cut-

offs. We therefore used the following hierarchy of decisions to assign categories to continuous variables: 1. ROC curve analysis; 2. Results from previous relevant research; 3. A clinically appropriate cut off; 4. Using a median split.

6.8.3.3 IDENTIFYING PREDICTOR VARIABLES AND ASSIGNING WEIGHTS

All variables associated with outcome on univariate analysis were, following categorisation, entered into a backward stepwise logistic regression analysis, as outlined in sections 6.8.2 and 6.8.2.1. The β coefficient was then used to select variables with the strongest association with outcome to be retained in the predictive tool. For pragmatic reasons, between 5 and 7 predictive indices were included in the clinical prediction tool. The β coefficient was also used to assign relative weights to the predictor variables so that particularly strong predictors scored more highly than less strong predictors.[392]

6.8.3.4 ASSESSING PREDICTIVE TOOL PERFORMANCE

Discrimination of the predictive tool for in-hospital mortality was assessed via AUROC. Comparison between AUROC of the predictive tool and other prognostic scores (i.e. APACHE, CAPS and CURB-65 prognostic scores) was made using the method described by Delong.[388] Internal validation of the predictive tool was performed by bootstrapping the AUROC and obtaining 95% confidence intervals. Calibration of the tool was assessed by comparing the predicted probability of outcome (according to the regression model including all uncategorised variables, described in section 6.8.2.2) against the observed probability of outcome, for each grade of the predictive tool.

PART 1: PREDICTING OUTCOME FOLLOWING HOSPITALISATION FOR AECOPD

CHAPTER 7 DATA SCREENING AND POPULATION DESCRIPTION

7.1 MISSING VALUES AND DATA IMPUTATION

Data on 920 patients were collected. Prior to further analysis, pH was converted to hydrogen ion concentration ($[H^+] = 10^{-pH}$) and results converted back to pH where appropriate to assist interpretation. Details of missing data for the remaining 920 patients were collected and the characteristics of patients with missing data values are shown in Table 17.2. Variables with < 1% missing values (respiratory rate, temperature, sodium, haemoglobin, white cell count, haematocrit, urea, creatinine, CRP, and eosinophil count) are not shown. Most variables had few (< 10%) missing values although serum glucose, the number of exacerbations in the previous year, and spirometry within 2 years of admission had frequent missing values (> 10%). There were no differences between patients with and without serum glucose values, although patients with missing spirometry and exacerbation frequency data were: older; had a higher comorbidity burden; were more likely to be male (for exacerbation frequency only); experienced more severe stable-state dyspnoea; and had a lower BMI.

Data for missing values were imputed using EM algorithm (section 6.7.1.1), the results of which are shown in Appendix C (Table 17.3). Comparisons between the imputed and original dataset for variables with < 1% missing values were virtually identical, with no significant differences, and are therefore not shown. Mean, standard deviation and standard error are shown for all variables (including non-parametric data) in order to assist more detailed comparison between the original and imputed dataset.

All subsequent analyses are reported using the complete dataset. All univariate analyses were repeated using the original dataset and there are no significant differences in results between the two datasets (Appendix D, Table 17.4 and Table 17.5).

The distribution of individual variables was assessed as detailed in section 6.7.2. Histograms, descriptive statistics, and the assessment of distribution (parametric or non-parametric) are shown in section Appendix B.

7.2 POPULATION DESCRIPTION

7.2.1 SUMMARY OF STUDY POPULATION

Summary characteristics of the 920 patients recruited are listed in Table 7.1. Mean patient age was 73.1 and most: had a significant smoking history; were markedly limited by dyspnoea during their stable state; and reported frequent episodes of AECOPD in the year preceding admission. Most also had severe airflow obstruction, multiple medical comorbidities, and although mean BMI was within the normal range, 16.7% were underweight (BMI < 18.5 kgm^{-2}).

Table 7.1 Population summary

Variable	Value*
Sociodemographic details,	
Admission hospital (NTGH), %	54.9
Age (years)	73.1 (10.0)
Female, %	53.9
Smoking load (CPY), median (IQR)	45 (32 to 60)
Institutional care, %	6.5
Markers of disease severity,	
Number of hospital admissions in previous year, median (IQR)	0 (0 to 1)
Number of AECOPD in previous year, median (IQR)	3 (1 to 4)
FEV_1 % predicted	43.6 (17.2)
MRCD, median (IQR)	4 (4 to 5)
Comorbidity & nutritional status,	
CCI, median (IQR)	2 (1 to 3)
BMI, kgm^{-2}	24.6 (6.3)

* values quoted are mean (SD) unless otherwise stated; CPY – cigarette pack years; CCI - Charlson comorbidity index

A more detailed description of the population follows in Chapter 9.

7.2.2 COMPARISON BETWEEN HOSPITAL SITES

There was no difference in sociodemographic details, between patients admitted to each of the two institutions involved in this study. There were also similar average values for: markers of health resource use in the previous year; severity of stable-state dyspnoea; comorbidity burden; and nutritional status. There was however, a clinically

small but statistically significant difference in FEV_1 % predicted, with lower mean values in the WGH cohort (Table 7.2).

Table 7.2 Comparison of population description between institutions

Variable	NTGH* (n=505)	WGH* (n=415)
Sociodemographic details,		
Age (years)	73.1 (10.4)	73.1 (9.7)
Female, %	54.5	53.3
Smoking load (CPY), median (IQR)	45 (32 to 60)	45 (32 to 60)
Institutional care prior to admission, %	6.5	6.5
Markers of disease severity,		
Number of hospital admissions in previous year, median (IQR)	0 (0 to 1)	0 (0 to 1)
Number of AECOPD in previous year, median (IQR)	3 (1 to 4)	3 (2 to 4)
FEV_1 % predicted	44.8 (16.7)†	42.1 (17.6)†
MRCD, median (IQR)	4 (3 to 5)	4 (4 to 5)
Comorbidity & nutritional status,		
CCI, median (IQR)	2 (1 to 3)	2 (1 to 3)
BMI, kgm^{-2}	24.4 (6.2)	24.7 (6.4)

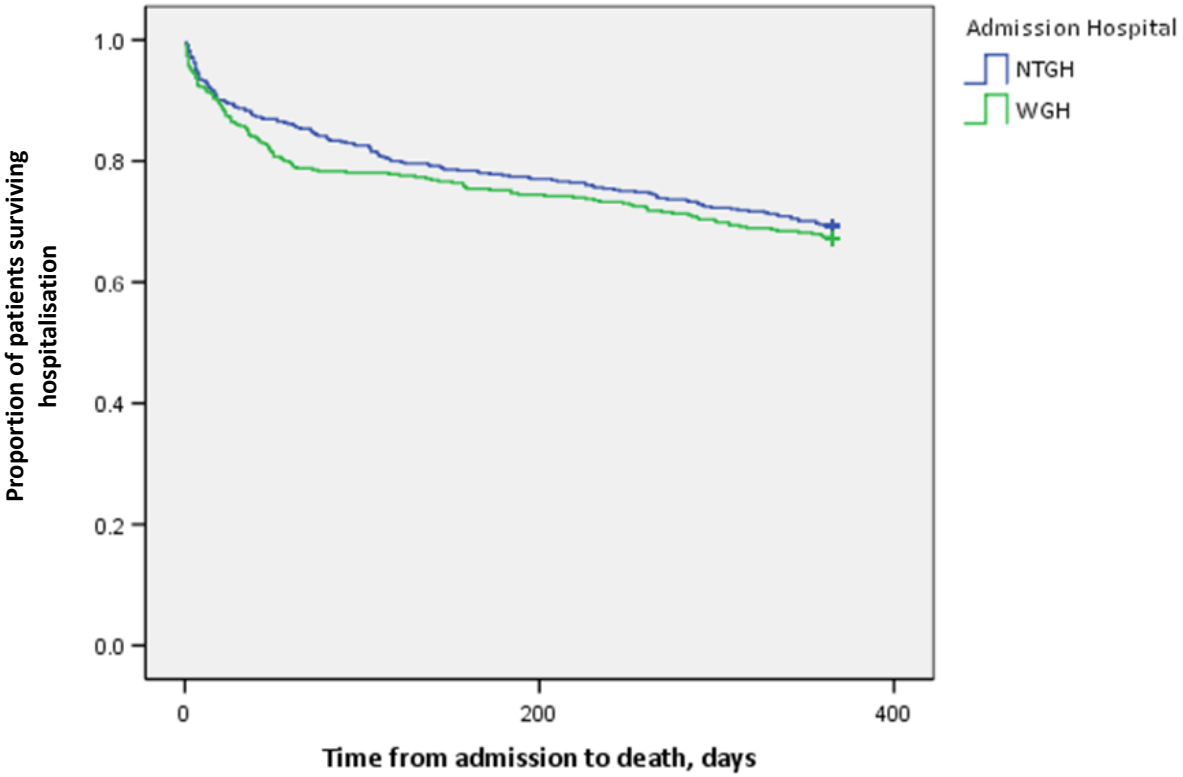
* values quoted are mean (SD) unless otherwise stated; † significant difference between NTGH and WGH, p=0.016; CPY – cigarette pack years; CCI – Charlson comorbidity index

7.2.3 MORTALITY FOLLOWING HOSPITALISATION FOR AECOPD

96 (10.4%) died during the index admission and 115 (12.5%) died within 30 days of admission. The mortality rates from admission were: 19.0% at 90 days; 23.5% at 180 days; and 31.6% at 1 year (Figure 7.1). For those who died within 12 months of admission, median time to mortality following admission was 50 (IQR 13 to 184) days.

In-hospital mortality was similar at both institutions (10.3% at NTGH, 10.6% WGH, p = 0.88), and there was no significant difference between institutions in 12-month survival following admission (Log-rank p = 0.41).

Figure 7.1 Proportion of patients surviving following hospitalisation for AECOPD, stratified according to site of hospital admission



Most of the 291 deaths (78.4%) during the follow-up period were due to respiratory causes although the relative proportion of deaths due to non-respiratory causes increased as the time to death increased (Table 7.3).

Table 7.3 Cause of death stratified according to time from admission to death

	Respiratory cause, n (%)	Cardiovascular cause, n (%)	Other cause, n (%)
In-hospital mortality	86 (89.6)	3 (3.1)	7 (7.3)
30-day mortality	100 (87)	9 (7.8)	6 (5.2)
12-month mortality	227 (78.3)	29 (10)	35 (12.0)

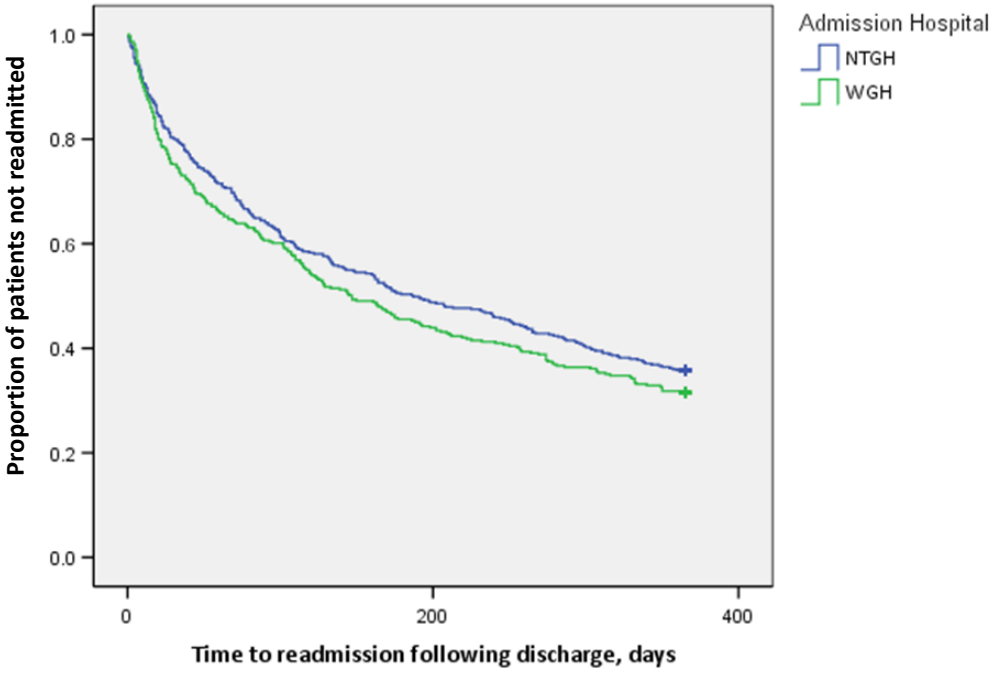
7.2.4 READMISSION

Of the 824 patients surviving the index admission, the proportions of patients who were readmitted, or who died without being readmitted, to hospital were: 21.0% within 28 days of discharge; 37.3% within 90 days; 51.8% within 180 days; and 66.3% within 1 year (Figure 7.2). Median admission-free survival time was 168 (IQR 136 to 200) days. There was no significant difference in readmission rates between institutions (Log rank p = 0.14). There was no difference in the 90-day readmission rate

(not including deaths without readmission) in this study compared to the UK National COPD Audit (33.4% v. 33% respectively).[12]

The median annual number of readmissions following hospital discharge was 1 (IQR 0 to 2, range 0 to 15) and 287 (34.7%) patients experienced frequent (≥ 2) readmissions during the year following discharge. There was no difference between the number of patients experiencing frequent readmissions between institution (p = 0.64).

Figure 7.2 Survival curve for readmission following discharge, stratified according to admission hospital site



For all patients surviving to discharge, whether they were readmitted or not, the median total length of stay during the follow-up period was 2 (IQR 0 to 14, range 0 to 228) days, and, of those patients who experienced at least 1 readmission (n = 546), medial total length of stay was 9 (IQR 2 to 23) days.

7.2.5 DEVELOPMENTS DURING ADMISSION

7.2.5.1 ASSISTED VENTILATION

At the time of, or shortly after, hospital admission, 18.8% (173) of patients had acidaemic respiratory failure (pH < 7.35 and p_aCO_2 > 6kPa) and were therefore potential candidates for assisted ventilation. Of these, 33 (19.1%) improved with

medical therapy and did not require assisted ventilation and in 10 (5.8%) assisted ventilation was deemed not clinically appropriate. Therefore, 130 (75.1%) patients were ventilated (127 treated with NIV and 3 intubated and ventilated) shortly after admission to hospital.

A further 84 (9.1%) patients developed acidaemic respiratory failure during their hospital stay and of these: 11 (13.1%) improved with medical therapy; 4 (4.8%) were deemed not suitable for assisted ventilation; and 69 (82.1%) were ventilated (68 treated with NIV, 1 intubated and ventilated) (Appendix F, Figure 17.1).

7.2.5.2 SPECIALIST CARE, LENGTH OF STAY AND DISCHARGE LOCATION

Overall, 67.4% of patients were under the care of a respiratory consultant during at least part of their hospital stay. Significantly more patients at the larger institute in our study (NTGH) were cared for by a respiratory consultant for some period of their hospital stay (72.1% at NTGH v. 61.7% at WGH, p = 0.0009).

Median length of stay was 6 (IQR 8 days) and there was no significant difference in length of stay between NTGH and WGH (median (IQR) 6 (8) v. 6 (7) respectively, p = 0.0600). The apparent trend to a shorter length of stay at WGH is likely to be due to different geographical locations and catchment areas. In comparison to NTGH, WGH is located in a rural setting with a number of satellite, rural cottage hospitals available to facilitate early discharge of patients to a location close to their home, particularly in patients thought likely to require institutional care in the medium to long-term. The discharge destinations of patients surviving the index admission highlight the larger proportion of patients discharged from WGH to a community or rehabilitation hospital (Table 7.4):

Table 7.4 Discharge destination and admission institution

Discharge destination	NTGH, n (%)	WGH, n (%)
Home	376 (83.0)	316 (85.2)
Sheltered accommodation	37 (8.2)	10 (2.7)
Residential care	12 (2.6)	6 (1.6)
Nursing home	18 (4)	2 (0.5)
Community / rehabilitation hospital	10 (2.2)	37 (10)

CHAPTER 8 CONSOLIDATION, DYSPNOEA AND NUTRITION

8.1 COEXISTENT CONSOLIDATION AND THE EXTENDED MRC DYSPNOEA SCORE

Aim 1a: to compare the characteristics and outcomes of patients with and without coexistent pneumonia

Aim 1b: evaluation of the extended MRC Dyspnoea Scale with specific reference to correlation with survival, readmission rates length of stay and frequency of hospital readmission.

8.1.1 COEXISTENT PNEUMONIA IN AECOPD

299 (32.5%) patients had evidence of consolidation on the admission chest radiograph (pAECOPD). Compared to npAECOPD, patients with coexistent consolidation were: older; had more severe lung function impairment; and had a greater comorbidity burden (Table 8.1). Furthermore, pAECOPD was also associated with more markers of exacerbation severity: more frequent acute confusion; lower blood pressure; lower serum albumin; higher p_aCO_2; higher urea; and higher neutrophil count. pAECOPD was associated with increased risks of adverse outcome: need for ventilation; length of hospital stay; and in-hospital mortality, although there was no difference in 28-day readmission rates amongst survivors of the initial admission (Table 8.1).

Table 8.1 Characteristics of pneumonic and non-pneumonic exacerbations

Variable	pAECOPD*, n = 299	npAECOPD*, n = 621	p value
Sociodemographic details,			
Age (years)	75.8 (9.1)	71.7 (10.2)	<0.0001
Female, %	49.5	56.0	0.0665
Smoking load (CPY), median (IQR)	43 (30 to 60)	45 (32 to 60)	0.42
Institutional care, %	9.4	5.2	0.0217
Markers of disease severity,			
Number of hospital admissions in previous year, median (IQR)	1 (0 to 1)	0 (0 to 1)	0.18
Number of AECOPD in previous year, median (IQR)	3 (1 to 4)	3 (1 to 4)	0.87

Variable	pAECOPD*, n = 299	npAECOPD*, n = 621	p value
FEV_1 % predicted	45.4 (16.6)	42.7 (17.4)	0.0261
MRCD, median (IQR)	4 (4 to 5)	4 (3 to 5)	0.0520
Housebound, %	38.8	32.2	0.0540
Comorbidity & nutritional status,			
CCI, median (IQR)	2 (1 to 3) ‡	2 (1 to 3) ‡	0.0150
BMI, kgm^{-2}	24.4 (6.0)	24.7 (6.4)	0.52
Severity of acute exacerbation,			
Purulent sputum, %	56.2	47.8	0.0201
Acute confusion, %	18.4	9.8	0.0004
Pedal oedema, %	29.8	24.6	0.11
Heart rate, min^{-1}	103.9 (22.3)	102.1 (20.0)	0.23
Respiratory rate, min^{-1}	26.2 (6.9)	25.9 (6.0)	0.44
Diastolic blood pressure, mmHg	72.2 (17.9)	78.1 (16.2)	<0.0001
Albumin, g/L	36.2 (4.8)	39.4 (4.4)	<0.0001
pH (median, IQR)	7.42 (7.35 to 7.46)	7.41 (7.36 to 7.45)	0.64
p_aCO_2, kPa (median, IQR)	5.6 (4.7 to 7.3)	6.0 (5.1 to 7.5)	0.0190
Urea, mmol/L (median, IQR)	7.9 (5.7 to 11.2)	6.0 (4.4 to 8.4)	<0.0001
Glucose, mmol/L (median, IQR)	7.1 (6.0 to 8.2)	6.8 (6.0 to 8.0)	0.18
Neutrophil count, $x10^9$/L (median, IQR)	11.7 (8.3 to 15.5)	8.3 (6.2 to 11.7)	<0.0001
Developments during hospital admission,			
Assisted ventilation, %	27.1	19.0	0.0062
Length of stay, days (median, IQR)	7 (4 to 13)	6 (3 to 10)	<0.0001
In-hospital mortality, %	20.1	5.8	<0.0001
28-day readmission, %†	20.1	21.4	0.68

* values quoted are mean (SD) unless otherwise stated; † in patients surviving to discharge, n=824; ‡ pAECOPD greater than npAECOPD; CPY – cigarette pack years; CCI – Charlson comorbidity index (Table 17.1)

8.1.2 THE EXTENDED MRC DYSPNOEA SCALE

The distribution of patients within each dyspnoea grade and the frequency of outcomes for the total population and the pAECOPD and npAECOPD subgroups are shown in Table 8.2 and Table 8.3. Pre-admission, during a period of clinical stability, 315 (34.2%) patients were too breathless to leave the house (MRCD 5). Of these, 173 (54.9%) were independent in washing and / or dressing (eMRCD 5a) and 142 (45.1%) were dependent in washing and dressing (eMRCD 5b) (Table 5.1).

Of the 96 patients who died in hospital, 30 were eMRCD 5a (17.3% mortality) and 47 eMRCD 5b (33.1% mortality) (p = 0.0015). The higher in-hospital mortality rate in eMRCD 5b is not explainable by clinicians limiting the level of care or introducing early

palliative care in this group: of the 51 patients with eMRCD 5b who met the criteria for assisted ventilation, 44 received it. In both the pAECOPD and npAECOPD subgroups, patients with eMRCD 5b had a higher in-hospital mortality rate than 5a ($p = 0.0533$ and $p = 0.0846$ respectively) (Table 8.2). For the total population, eMRCD 5b had a significantly higher 30-day ($p = 0.0313$) and 12-month ($p = 0.0002$) mortality rate.

The 28-day readmission or death rate was significantly higher for eMRCD 5b than eMRCD 5a in the case of npAECOPD ($p = 0.0017$). It was absolutely, but non-significantly, higher in the total population ($p = 0.0858$). In pAECOPD, the rate was non-significantly lower with eMRCD 5b than 5a ($p=0.21$); this is likely to be due to a survivor effect given the high in-hospital mortality in the former group. The 90-day readmission or death rate for both the total population and the subgroup without coexistent consolidation was higher with eMRCD 5b than 5a ($p = 0.0008$ and $p = 0.0003$ respectively). In pAECOPD, the 90-day readmission or death rate increased as dyspnoea severity increased, although there was no difference between 5b and 5a ($p = 0.81$). There was a significant difference in the number of patients who experienced frequent readmission across both the traditional and extended MRCD scales ($p = 0.0002$ for MRCD and $p = 0.0005$ for eMRCD), although there was no significant difference between 5b and 5a.

Table 8.2 Relation of dyspnoea grade and presence or absence of consolidation to mortality

Dyspnoea grade	n	In-hospital mortality, n (%)			30-day mortality, %*	12-month mortality, %*
		Total	npAECOPD	pAECOPD	Total	Total
1	6	0	0	0	0	0
2	46	0	0	0	0	2 (4.3)
3	171	4 (2.3)	2 (1.6)	2 (4.4)	5 (2.9)	19 (11.1)
4	382	15 (3.9)	1 (0.4)	14 (11.8)	23 (6.0)	82 (21.5)
5	315	77 (24.4)	33 (16.6)	44 (37.9)	87 (27.6)	188 (59.7)
5a	173	30 (17.3)†	15 (12.4)	15 (28.8)	39 (22.5)‡	87 (50.3)†
5b	142	47 (33.1)†	18 (23.1)	29 (45.3)	48 (33.8)‡	101 (71.1)†

* from time of hospital admission; † significant difference between 5a and 5b, p<0.01; ‡ significant difference between 5b and 5a, p<0.05

Table 8.3 Relation of dyspnoea grade and presence or absence of consolidation to readmission

Dyspnoea grade	n	28-day readmission or death, %*			90-day readmission or death, %*			Frequent readmission, %
		Total	npAECOPD	pAECOPD	Total	npAECOPD	pAECOPD	Total
1	6	0	0	0	1 (16.7)	1 (20.0)	0	1 (16.7)
2	46	3 (6.5)	3 (10.7)	0	5 (10.9)	5 (17.9)	0	11 (23.9)
3	167	21 (12.6)	15 (12.1)	6 (14.0)	34 (20.4)	28 (22.6)	6 (14.0)	35 (21.0)
4	367	75 (20.4)	55 (21.0)	20 (19.0)	129 (35.1)	91 (34.7)	38 (36.2)	145 (39.5)
5	238	74 (31.1)	52 (31.3)	22 (30.6)	138 (58.0)	90 (54.2)	48 (66.7)	94 (39.5)
5a	143	38 (26.6)	24 (22.6)†	14 (37.8)	70 (49.0)†	46 (43.4)†	24 (64.9)	55 (38.5)
5b	95	36 (37.9)	28 (46.7)†	8 (22.9)	68 (71.6)†	44 (73.3)†	24 (68.6)	39 (41.1)

* Of those surviving to discharge (n=824), the number of patients readmitted or who died without being readmitted, within the stated time period; † significant difference between 5a and 5b, p<0.005

8.1.3 PNEUMONIA, DYSPNOEA AND CURB-65

Of the 299 patients with pAECOPD, median CURB-65 score was 2 (IQR 1 to 3) and 109 (36.5%) had CURB-65 scores of 3 to 5 and therefore a high risk of mortality (Table 8.4). Mortality rates for each CURB-65 score were higher in pAECOPD than npAECOPD. For comparison, the expected mortality in community acquired pneumonia is shown in the last column.

Table 8.4 Distribution of patients, and rates of mortality, according to CURB-65 score

CURB-65 Score	Total population		npAECOPD		pAECOPD		
	n (%)	Mortality, %	n	Mortality, %	n	Mortality, %	Expected mortality in CAP, %*
0	135 (14.7)	4.4	115	2.6	20	15	0.6
1	278 (30.2)	4.0	208	1.9	70	10.0	3.0
2	295 (32.1)	9.5	195	6.2	100	16.0	6.1
3	169 (18.4)	20.1	87	16.1	82	24.4	16.1
4	36 (3.9)	36.1	15	20	21	47.6	36.9
5	7 (0.8)	57.1	1	n/a	6	66.7	43

*for community acquired pneumonia (from Aujesky et al)[393]

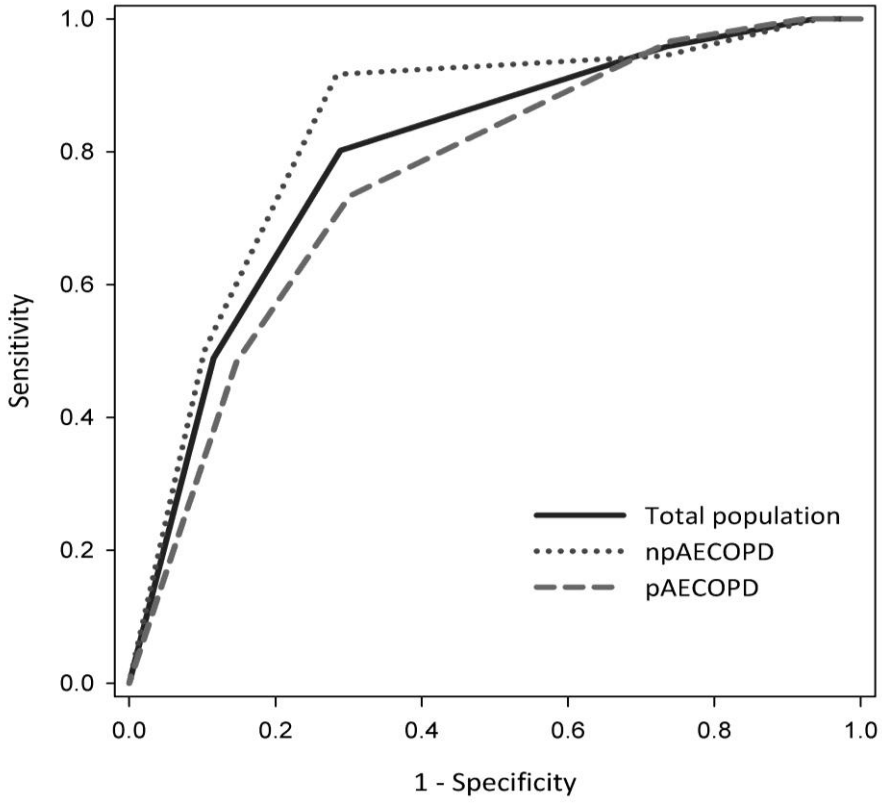
The discriminatory ability, of MRCD, eMRCD and CURB-65 to predict in-hospital mortality were assessed and compared using AUROC (Table 8.5). In the population as a whole, eMRCD had significantly better discrimination for mortality than either MRCD ($p = 0.0012$) or CURB-65 ($p = 0.0193$), and in npAECOPD there was a non-significant trend to better discrimination for eMRCD compared to both CURB-65 ($p = 0.0528$) and MRCD ($p = 0.0571$). In pAECOPD, eMRCD performed significantly better than CURB-65 ($p = 0.0168$), and there were also non-significant trends favouring both eMRCD over MRCD ($p = 0.0714$) and MRCD over CURB-65 ($p = 0.0630$). The discriminative strength of eMRCD for in-hospital mortality is shown in Figure 8.1.

Table 8.5 Area under ROC curve for prediction of in-hospital mortality

	MRCD	eMRCD	CURB-65
Total	0.769 (0.73 to 0.81)	0.794 (0.75 to 0.84)†‡	0.717 (0.66 to 0.77)
npAECOPD	0.809 (0.75 to 0.87)	0.833 (0.77 to 0.90)	0.719 (0.63 to 0.81)
pAECOPD	0.740 (0.68 to 0.80)	0.759 (0.70 to 0.82)‡	0.661 (0.58 to 0.74)

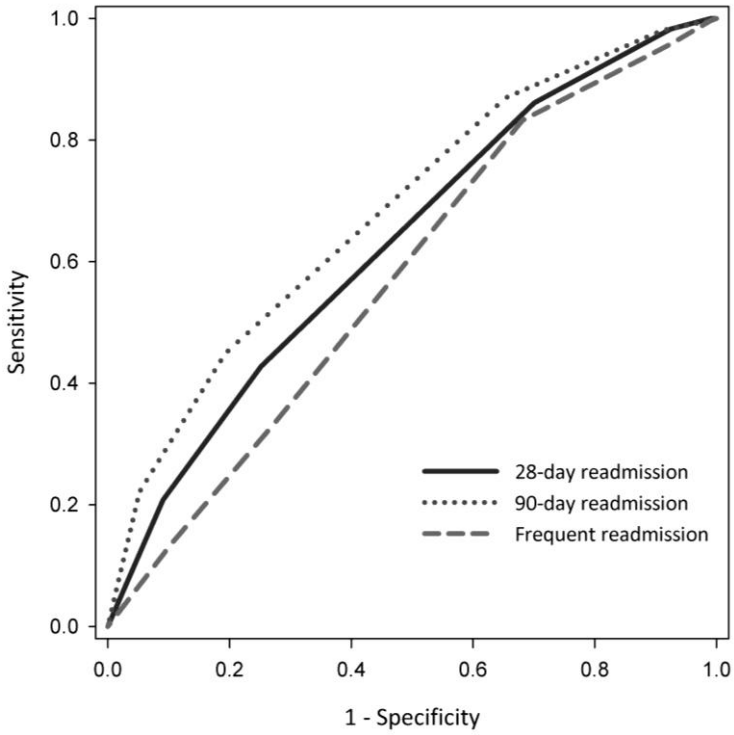
† significant difference compared to MRCD, p<0.01; ‡ significant difference compared to CURB-65, p<0.05

Figure 8.1 The discrimination of eMRCD for in-hospital mortality for the total population, non-pneumonic and pneumonic exacerbations of COPD



Compared to the discrimination of mortality, among the total population of patients surviving to discharge, eMRCD was a less strong predictor of single and frequent readmission: $AUROC_{28\text{-}day}$ = 0.631, 0.588 to 0.675; $AUROC_{90\text{-}day}$ = 0.683, 0.648 to 0.718; $AUROC_{frequent}$ = 0.576, 0.539 to 0.614 (Figure 8.2).

Figure 8.2 The discrimination of eMRCD for readmission for the total population

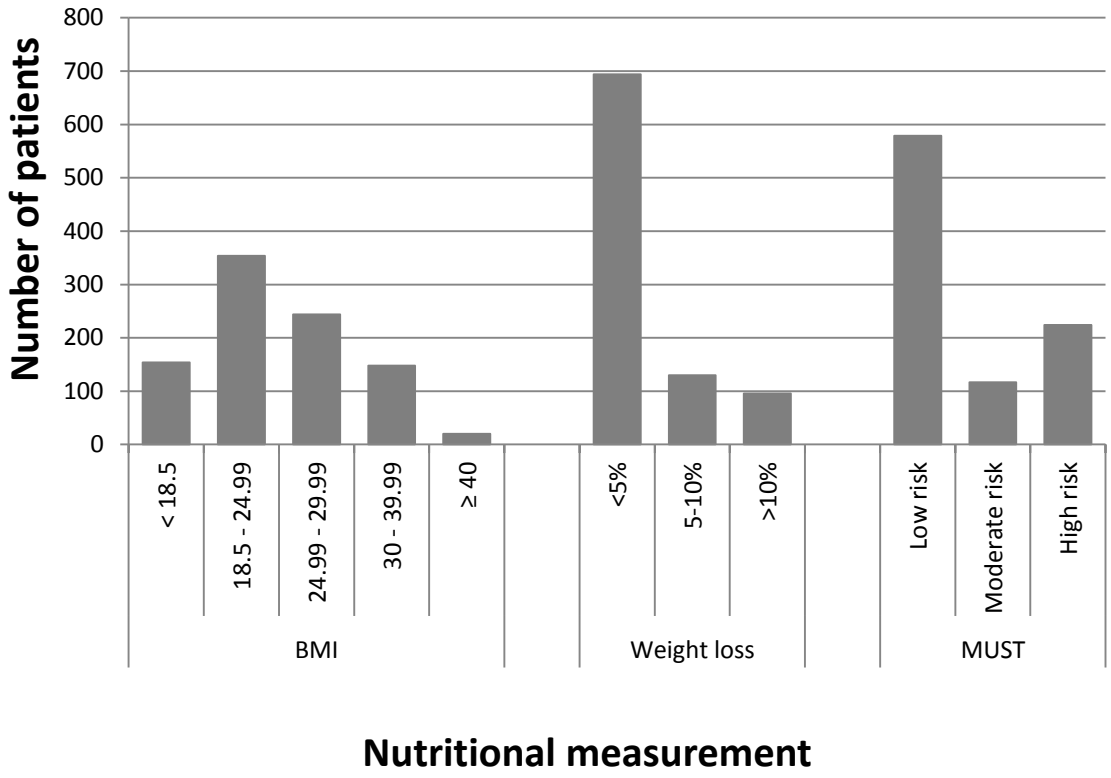


8.2 NUTRITIONAL STATUS, MORTALITY AND READMISSION

Aim 1c: evaluation of the Malnutrition Universal Screening Tool with specific reference to correlation with survival, readmission rates length of stay and frequency of hospital readmission.

Mean BMI (SD) within our population was 24.6 (6.3) kgm^{-2}: 16.3% were underweight (< 18.5 kgm^{-2}); 18.3% were obese (≥ 30 kgm^{-2}) and 2.2% were morbidly obese (≥ 40 kgm^{-2}). 226 (24.6%) reported at least 5% of unintentional weight loss in the previous six months, and 341 (37.1%) were at least at a moderate risk of malnutrition (MUST ≥ 1). The distribution of nutritional parameters within our population is shown in Figure 8.3.

Figure 8.3 Distribution of nutritional parameters within the population



Low BMI (< 18.5 kgm^{-2}) was associated with the highest risk of in-hospital mortality compared to other BMI categories. Our data showed evidence of the 'obesity paradox' (lower mortality risk in overweight individuals with COPD, section 1.1.3.1.2) with the lowest mortality rate in obese patients (30 – 39.99 kgm^{-2}). There was a non-linear relationship between BMI and both in-hospital and 12-month mortality (Figure 8.4): the risk of death increased in the morbidly obese (≥ 40 kgm^{-2}). More self-reported weight loss and a high risk of malnutrition were both strongly associated with in-hospital and 12-month mortality.

Hospital readmission was strongly and linearly associated with unintentional weight loss and malnutrition risk, whereas there was a U-shaped relationship with BMI (Figure 8.4). In agreement with the data on mortality, the highest rates of readmission were in the underweight and morbidly obese individuals. No relationship was found between nutritional status and frequent readmissions, perhaps due to the association between nutritional parameters and mortality.

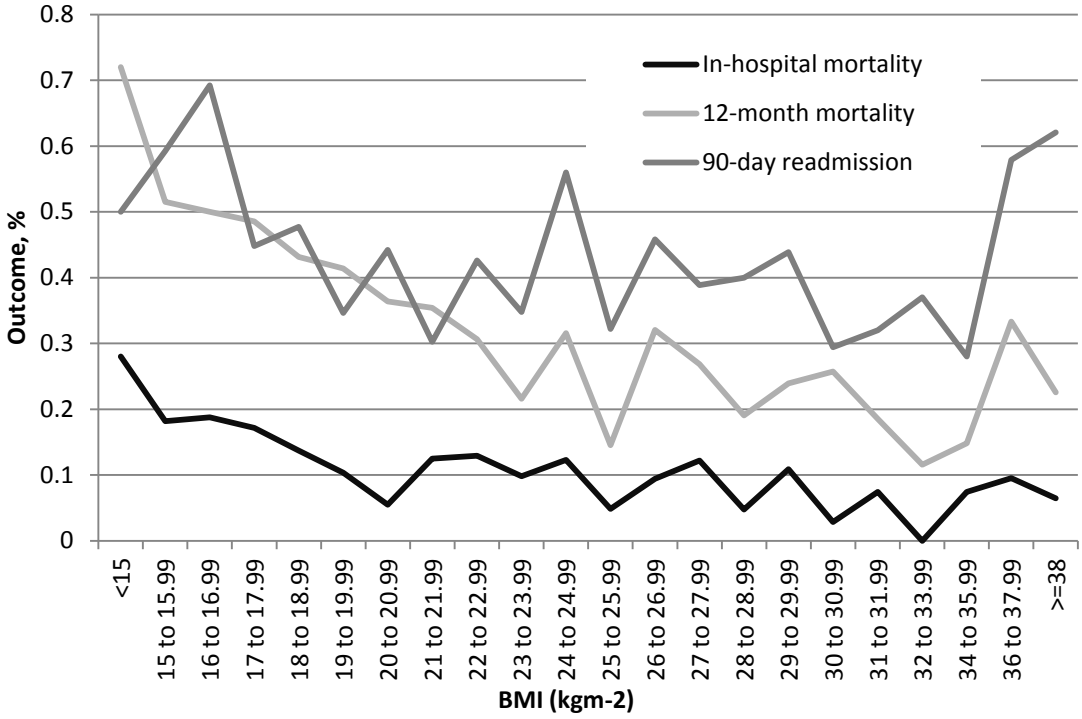
Table 8.6 Distribution of nutritional measurements within our population and their association with in-hospital mortality and readmission following discharge

Nutritional parameter	n*	In-hospital mortality, %		12-month mortality, %		n†	90-day readmission, %†		Frequent readmission, %‡	
BMI, kgm^{-2}										
< 18.5	154	18.8	p = 0.0012	53.2	p < 0.0001	125	50.4	p = 0.013	36.0	p = 0.44
18.5 - 24.99	354	10.7		35.0		316	34.2		34.5	
25 – 29.99	244	8.2		23.8		224	34.8		37.9	
30 – 39.99	148	4.7		19.6		141	34.8		28.4	
≥ 40	20	10.0		35.0		18	50.0		38.9	
Weight loss,										
< 5%	694	7.9	p = 0.0001	26.5	p < 0.0001	639	33.3	p = 0.0001	33.6	p = 0.43
5 - 10%	130	18.5		43.8		106	47.2		36.8	
> 10%	96	17.7		61.5		79	55.7		40.5	
MUST,										
0	579	6.9	p < 0.0001	23.1	p < 0.0001	539	32.8	p = 0.0001	34.3	p = 0.63
1	117	12		35.9		103	35.9		32.0	
≥ 2	224	18.8		55.4		182	51.1		37.4	

* at admission to hospital, n=920; † of patients surviving to discharge, n=824, and including patients who died without being readmitted; ‡ ≥ 2 hospital readmissions within 12 months of discharge

To further investigate the increase in risk of mortality and readmission at very high BMI values, a plot of in-hospital and 12-month mortality rates, and 90-day readmission rates, against BMI (split into categories with n > 20) is shown in Figure 8.4. This suggests that BMI has a non-linear relationship with 12-month mortality and 90-day readmission or death. It is difficult to comment on the shape of the in-hospital mortality line because of the small number of deaths in patients with a very high BMI (2 deaths in BMI ≥ 40 kgm^{-2}).

Figure 8.4 Graph showing risk of mortality and readmission according to BMI



In our population, underweight patients were older and had greater impairment of lung function compared to obese and morbidly obese individuals (Table 8.7). Therefore the relationship between low BMI and outcome may be explained by the effects of age and lung function. However, when comparing morbidly obese patients to obese patients, there was no difference in age or the severity of underlying disease to explain the higher 12-month mortality and 90-day readmission in morbidly obese individuals (Table 8.7). This suggests that the effect of very high BMI on outcome is mediated through other mechanisms: increased prevalence of cardiovascular comorbidity and diabetes; or limitation in respiratory function due to the restrictive effects of central adiposity.

Table 8.7 Age and FEV_1 stratified by BMI

Variable	BMI (kgm^{-2})				
	< 18.5	18.5 to 24.99	25 to 29.99	30 to 39.99	≥ 40
Age, years (mean, SD)	75.1 (9.9)	73.5 (10.3)	73.2 (9.7)	70.6 (9.5)*†	66.1 (8.9)*†‡
FEV_1 % predicted (mean, SD)	38.9 (16.5)	42.1 (17.3)	44.8 (17.1)*	49.3 (16.0)*†	47.7 (15.8)

* significant difference compared to BMI <18.5; † significant difference compared to BMI 18.5 to 24.99; ‡ significant difference compared to BMI 25 to 29.99.

CHAPTER 9 PREDICTING MORTALITY IN PATIENTS HOSPITALISED WITH AECOPD

9.1 PREDICTING IN-HOSPITAL MORTALITY

Aim 1d: identify independent predictors of in-hospital mortality following hospitalisation for AECOPD and develop a clinical prediction tool to accurately predict the risk of in-hospital mortality.

9.1.1 UNIVARIATE ASSOCIATIONS WITH IN-HOSPITAL MORTALITY

9.1.1.1 SOCIODEMOGRAPHIC DETAILS

There was no association between in-hospital mortality and patient sex, admission institution and overall smoking load. However, older age, residence in institutional care prior to admission, abstinence from cigarette smoking, and need for assistance with activities of daily living were all associated with in-hospital mortality (Table 9.1).

Table 9.1 Sociodemographic details and their relationship with in-hospital mortality

Variable	Total population, n=920	Survived to discharge, n=824	Died in hospital, n=96	p value
Age	73.1 (10.0)	72.3 (10.0)	79.2 (8.0)	<0.0001
Female, %	53.9	54.2	51.0	0.59
Admission hospital (NTGH), %	54.9	55	54.2	0.91
Institutional care, %	6.5	5.2	17.7	<0.0001
Social care prior to admission, %	22.9	20.1	46.9	<0.0001
Current smoker, %	44.3	45.9	31.3	0.0069
Smoking load (CPY), median (IQR)	45 (32 to 60)	45 (32 to 60)	42.5 (30 to 60)	0.69

NTGH – North Tyneside General Hospital; CPY – cigarette pack years

9.1.1.1.1 SMOKING STATUS

The direction of the relationship between smoking status and mortality is at first sight surprising, with ex-smokers at increased risk of in-hospital mortality. This is in contrast to previous research and clinical reasoning. It was acknowledged that smoking status was inconsistently reported by patients, and was biased by both a survivor effect

(ongoing smokers at increased risk of premature death prior to potential entry in to study) and by confounding effects of age and COPD severity (i.e. older patients and those with severe disease are more likely to have been successfully treated with smoking cessation therapies). Comparing current smokers with ex-smokers confirmed this hypothesis: ex-smokers were older (mean (SD) age = 76 (9.2) v. 69 (9.9) years, $p < 0.0001$), had worse lung function (mean (SD) FEV_1 = 0.93 (0.45) L v. 1.01 (0.42) L, $p = 0.0057$), had a greater comorbidity burden (median (IQR) CCI = 2 (2) v. 2 (2), $p = 0.0024$), and were more breathless during stable state (median (IQR) eMRCD = 4 (1) v. 4 (2), $p < 0.0001$). The association with mortality is in spite of current smoking status being associated with more markers of severe AECOPD compared to ex-smokers: median (IQR) pH = 7.39 (0.10) in current smokers v. 7.40 (0.09) in ex-smokers, p=0.007; and median (IQR) p_aO_2 = 8.3 (3.4) v. 8.8 (3.2), $p = 0.030$. Therefore, the relationship between smoking status and mortality is likely to be a surrogate for other prognostic variables and, due also to concerns over the validity of the information, current smoking status was removed from further analyses.

9.1.1.2 HEALTH RESOURCE USE AND DISEASE SEVERITY

Many patients had been hospitalised during the year prior to admission: 37.8% had experienced at least 1 respiratory admission (range 0 to 12), and 48.2% had experienced at least 1 admission for any cause (range 0 to 14). Most patients included in the study had experienced frequent episodes of AECOPD during the previous year (median AECOPD = 3, range 0 to 18).

Patients who died in-hospital had: lower FEV_1, FEV_1 % predicted and FVC values; higher scores on the traditional and extended MRCD scales (higher score indicated more severe dyspnoea); and lower exercise tolerance. There was a trend to increased mortality in patients who had experienced more frequent hospitalisation (for any cause) in the year preceding admission (Table 9.2).

Table 9.2 Prior health resource use, markers of disease severity and in-hospital mortality

Variable	Total population, n=920	Survived to discharge, n=824	Died in hospital, n=96	p value
Health resource use,				
Number of respiratory admissions in previous year, median (IQR)	0 (0 to 1)	0 (0 to 1)	0 (0 to 1)	0.58
Total number of admissions in previous year, median (IQR)	0 (0 to 1)	0 (0 to 1)	1 (0 to 2)	0.0946
Number of AECOPD in previous year, median (IQR)	3 (1 to 4)	3 (1 to 4)	3 (2 to 4)	0.57
Previous assisted ventilation, %	11.7	11.3	15.6	0.23
Previous pulmonary rehabilitation, %	9.5	9.8	6.3	0.28
Spirometry,				
FEV_1 (litres)	0.97 (0.4)	0.99 (0.4)	0.83 (0.3)	<0.0001
FEV_1 % predicted	43.6 (17.2)	44.0 (17.4)	39.9 (14.2)	0.0099
FVC (litres)	2.15 (0.8)	2.18 (0.8)	1.86 (0.6)	<0.0001
FEV_1/ FVC, median (IQR)	0.45 (0.37 to 0.53)	0.45 (0.37 to 0.53)	0.44 (0.39 to 0.53)	0.91
Exercise capacity and disease complications,				
MRCD, median (IQR)	4 (4 to 5)	4 (3 to 5)	5 (5 to 5)	<0.0001
eMRCD, median (IQR)	4 (4 to 5a)	4 (3 to 5a)	5a (5a to 5b)	<0.0001
Exercise tolerance (metres), median (IQR)	25 (10 to 80)	30 (15 to 100)	10 (5 to 20)	<0.0001
Cor pulmonale, %	10.0	9.8	11.5	0.72

9.1.1.3 COMORBIDITY

Comorbidity, particularly cardiovascular comorbidity, was common in our population. For example, hypertension was present in approximately 40% of patients, and ischaemic heart disease in just under 30%. Significant associations with mortality were found with atrial fibrillation, cerebrovascular disease, chronic kidney disease, chronic cognitive impairment and the overall comorbidity burden (CCI, Table 17.1). There was a trend to an increased risk of mortality in patients with coexistent pulmonary fibrosis and valvular heart disease, although both of these conditions were rare in our cohort (prevalence of 1.7% and 3.3% respectively) (Table 9.3).

The low prevalence rate of certain comorbid conditions in our population is surprising. For example, obstructive sleep apnoea (OSA) is estimated to have a population prevalence of approximately 10% [394] but was only recorded in 1.6% of our population: this may be explained by the difficulties in diagnosing OSA in patients with coexistent COPD.[394]

Table 9.3 Comorbidity and in-hospital mortality

Variable	Total population, n=920	Survived to discharge, n=824	Died in hospital, n=96	p value
Respiratory,				
Bronchiectasis, %	6	5.6	9.4	0.17
Asthma, %	4.9	5.1	3.1	0.47
Pulmonary fibrosis, %	1.7	1.5	4.2	0.0759
Obstructive sleep apnoea, %	1.6	1.6	2.1	1.0
Cardiovascular,				
Hypertension, %	39.6	39.2	42.7	0.51
Cerebrovascular disease, %	14	12.6	26	0.0007
Ischaemic heart disease, %	29.3	29.5	28.1	0.81
Atrial fibrillation, %	12.5	10.9	26	<0.0001
LV dysfunction, %	7.3	7.4	6.3	0.84
Thromboembolic disease, %	3.8	3.9	3.1	0.79
Valvular heart disease, %	3.3	2.9	6.3	0.12
Peripheral vascular disease, %	7.9	7.8	9.4	0.69
General,				
Diabetes mellitus, %	14.8	14.7	15.6	0.88
Osteoporosis, %	12.6	12.0	17.7	0.14
Rheumatoid arthritis, %	4.0	4.0	4.2	1.0
Cognitive impairment, %	5.4	4.6	12.5	0.0035
Chronic kidney disease, %	6.7	5.7	15.6	0.0010
Anxiety / depression, %	24.2	24.8	19.8	0.32
Chronic liver disease, %	0.7	0.6	1.0	1.0
Peptic ulcer disease, %	6.5	6.3	8.3	0.51
Past history of cancer, %	7.7	7.4	10.4	0.31
History of active cancer, %	3.8	3.8	4.2	0.78
Comorbidity burden,				
Charlson Comorbidity Index, median (IQR)	2 (1 to 3)	2 (1 to 3)	2 (1 to 3)	0.0028

9.1.1.4 PRESCRIBED MEDICATION ON ADMISSION

Approximately 1 in 8 patients had severe resting hypoxaemia necessitating treatment with LTOT and 21% were in receipt of some form of home oxygen therapy. This reflects the severity of COPD within this population and is consistent with our data on

spirometry and stable-state dyspnoea (section 7.2). Most patients were being treated with both ICS and inhaled long-acting beta agonist, and the majority received these drugs via a combination inhaler. In keeping with national guidelines, most patients were also prescribed an inhaled anticholinergic agent. In total, 9.1% of patients were receiving long-term treatment with oral corticosteroids (for any indication), and despite evidence of potential harm [15] 70% of these (59 patients) were receiving long-term oral corticosteroids for the treatment of COPD.

Individuals in receipt of either LTOT or any form of home oxygen therapy were at a significantly higher risk of in-hospital mortality compared to those not receiving oxygen. There were no other significant associations with death for any other medications (Table 9.4).

Table 9.4 Maintenance medications at admission and in-hospital mortality

Variable	Total population, n=920	Survived to discharge, n=824	Died in hospital, n=96	p value
Respiratory,				
LTOT, %	12.4	11.3	21.9	0.0042
Ambulatory oxygen, %	3.4	3.4	3.1	1.0
Short burst oxygen, %	7.8	7.6	9.4	0.69
Home oxygen therapy,* %	21.1	19.8	32.3	0.0057
Home nebuliser, %	16.6	16.6	16.7	1.0
Inhaled corticosteroid (ICS), %	81.6	81.3	84.4	0.49
ICS dose (BDP equivalent), median (IQR)	2000 (1000 to 2000)	2000 (1000 to 2000)	2000 (2000 to 2000)	0.69
Inhaled long-acting beta agonist, %	77.7	77.5	79.2	0.80
Combination inhaler, %	72.1	71.8	74	0.72
Inhaled anticholinergic, %	70.8	70.3	75	0.35
Long-term oral corticosteroid, %	9.1	8.7	12.5	0.26
Carbocysteine, %	16.1	15.8	18.8	0.46
Theophylline, %	8	7.9	9.4	0.69
Cardiovascular,				
Statin, %	44.9	45.3	41.7	0.52
Beta-blocker, %	10.8	10.8	10.4	1.0
ACE inhibitor, %	24.2	24.4	22.9	0.80
Angiotensin receptor blocker, %	5.7	5.6	6.3	0.81
Diuretic, %	35.4	34.6	42.7	0.14
Other,				
Benzodiazepine,† %	5.8	5.6	7.3	0.64
Opiate,† %	0.9	0.8	1	1.0

* either LTOT, ambulatory O_2 or short burst O_2; † prescribed for the symptomatic relief of dyspnoea / anxiety; ICS – inhaled corticosteroid; BDP – beclomethasone diproprionate; ACE – Angiotensin converting enzyme

9.1.1.5 ADMISSION CLINICAL DATA

Purulent sputum was reported to have been expectorated during the exacerbation by 51.3% of patients, although a further 25.1% were recorded as having a non-effective cough which may have resulted in an inability to clear purulent secretions from the lungs. One in eight patients were acutely confused at hospital admission and most patients were tachycardic and tachypnoeic. Although most patients were

normotensive, 17.7% were hypotensive (systolic blood pressure (BP) < 90 mmHg or diastolic BP ≤ 60 mmHg) on admission. Almost a third of patients had evidence of coexistent radiographic consolidation at admission to hospital.

Significant associations with mortality are shown in Table 9.5 and the strongest associations were with: cough effectiveness; acute confusion; high respiratory rate; low temperature; low BMI; weight loss; high MUST score; and radiographic consolidation.

Table 9.5 Clinical information on admission and in-hospital mortality

Variable	Total population, n=920	Survived to discharge, n=824	Died in hospital, n=96	p value
History and examination findings,				
Purulent sputum, %	51.3	52.6	39.6	0.0202
Ineffective cough, %	11.8	9.3	33.3	<0.0001
Pedal oedema, %	27.7	26.9	34.5	0.16
Acute confusion, %	12.6	10.0	35.4	<0.0001
Heart rate (min^{-1})	102.7 (20.8)	102.7 (20.5)	102.7 (23.3)	0.98
Initial non-invasive investigations,				
Systolic BP (mmHg)	139.3 (28.4)	139.7 (28.1)	135.4 (30.6)	0.16
Diastolic BP (mmHg)	76.2 (17.0)	76.6 (16.7)	72.8 (19.1)	0.0384
Respiratory rate (min^{-1})	26.0 (6.3)	25.8 (6.1)	27.8 (7.6)	0.0038
Temperature (°C), median (IQR)	36.9 (36.4 to 37.5)	36.9 (36.4 to 37.6)	36.8 (36.2 to 37.3)	0.0914
S_pO_2 (%), median (IQR)	92 (87 to 96)	92 (87 to 96)	92 (86 to 96)	0.99
BMI (kgm^{-2})	24.6 (6.3)	24.8 (6.3)	22.5 (6.1)	0.0007
Weight loss > 5%, %$^{+}$	24.6	22.5	42.7	<0.0001
CXR consolidation, %	32.5	29.0	62.5	<0.0001

BP – blood pressure

9.1.1.6 BLOOD RESULTS ON ADMISSION

Abnormal blood gas values were common: 18.3% were in type 1 respiratory failure (p_aO_2 < 8kPa) at admission, and 20.3% were in type 2 respiratory failure (p_aO_2 < 8kPa and p_aCO_2 > 6kPa). 184 (20%) were acidaemic on hospital admission (pH < 7.35 or H^+ > 45 nmol/L). Of these, 173 had a predominant respiratory acidaemia (pH <7.35 and p_aCO_2 > 6kPa), and 11 had a metabolic acidaemia.

Individual associations with mortality are shown in Table 9.6: low pH (high H^+); high p_aCO_2; high potassium; high urea; low albumin; high CRP; low haemoglobin; high neutrophil count; and low eosinophil count were all strongly associated with mortality.

Table 9.6 Blood results on admission and in-hospital mortality

Variable	Total population, n=920	Survived to discharge, n=824	Died in hospital, n=96	p value
Arterial blood gas values,				
H^+ (nmol/L), median (IQR)	38.9 (35.5 to 43.7)	38.0 (7.2)	41.7 (16.8)	0.0008
pH, median (IQR)	7.41 (7.36 to 7.45)	7.42 (7.37 to 7.45)	7.38 (7.28 to 7.45)	0.0008
p_aO_2 (kPa), median (IQR)	8.7 (7.3 to 10.7)	8.7 (7.3 to 10.5)	8.4 (7.1 to 12.7)	0.82
p_aCO_2 (kPa), median (IQR)	5.9 (4.9 to 7.5)	5.8 (4.9 to 7.3)	6.4 (5.2 to 9.2	0.0044
Bicarbonate (mmol/L)	29.1 (6.5)	29.0 (6.3)	30.0 (8.0)	0.22
Acidaemic exacerbation, %‡	19.3	18.1	30.2	0.0062
Biochemistry,				
Sodium (mmol/L)	136.3 (4.6)	136.3 (4.5)	136.7 (5.0)	0.39
Potassium (mmol/L)	4.32 (0.6)	4.3 (0.5)	4.5 (0.7)	0.0016
Urea (mmol/L), median (IQR)	6.5 (4.7 to 9.3)	6.3 (4.6 to 8.8)	9.5 (6.0 to 14.2)	<0.0001
Creatinine (μmol/L), median (IQR)	93 (77 to 114)	92 (77 to 112)	100 (75 to 148)	0.0428
Albumin (g/L)	38.3 (5.1)	38.6 (4.9)	35.4 (5.3)	<0.0001
Glucose (mmol/L), median (IQR)	6.9 (6.0 to 8.1)	6.9 (6.0 to 8.0)	7.4 (6.0 to 8.9)	0.0301
CRP (mg/L), median (IQR)	42 (11 to 117)	36 (10 to 111)	89 (30 to 145)	0.0001
Haematology,				
Hb (g/dL)	13.6 (1.9)	13.6 (1.9)	13.0 (2.2)	0.0043
Haematocrit	0.411 (0.058)	0.412 (0.57)	0.399 (0.064)	0.0425
White cell count ($x10^9$/L), median (IQR)	12.0 (9.1 to 15.5)	11.8 (9.1 to 15.3)	12.7 (9.5 to 17.1)	0.0682
Neutrophil count ($x10^9$/L), median (IQR)	9.2 (6.9 to 12.8)	9.1 (6.8 to 12.6)	10.5 (7.7 to 15.2)	0.0081
Eosinophil count ($x10^9$/L), median (IQR)	0.1 (0 to 0.2)	0.1 (0 to 0.2)	0 (0 to 0.1)	<0.0001

‡ pH < 7.35 (H^+ > 45) and pCO_2 > 6kPa

9.1.2 IDENTIFYING INDEPENDENT PREDICTORS OF MORTALITY

All variables which were potentially prognostically significant had been identified by the univariate analysis and therefore, those associated with outcome at a p-value < 0.10 were considered eligible for multivariate analysis. Categorical variables with a markedly asymmetric split (< 10% in one category) were excluded from further analysis.

9.1.2.1 VARIABLE SELECTION

To assess multicollinearity (section 6.8.1), variables with clear potential for collinearity were screened first and consequently: FEV_1 % predicted was retained over FEV_1 (Pearson's r = 0.74, p < 0.0001); eMRCD was retained over both MRCD (Spearman's ρ = 0.984, p < 0.0001) and exercise tolerance (ρ = -0.85, p < 0.0001); neutrophil count was retained over total WCC (ρ = 0.90, p < 0.0001); and haemoglobin was retained over haematocrit (r = 0.95, p < 0.0001). H^+ and p_aCO_2 were strongly correlated (r = 0.69, p < 0.0001) and more detailed collinearity testing suggested they were collinear (VIF > 3 for both variables): p_aCO_2 was therefore excluded from further analysis. Zero-order correlations between the remaining potential continuous predictor variables are shown in Appendix E (Table 17.6). Due to the suggestion of a non-linear relationship between BMI and mortality (Table 8.6), BMI was entered as < 18.5 or ≥ 18.5 kgm^{-2}.

Repeating the collinearity diagnostics after obvious collinearity had been removed confirmed no significant multicollinearity between our potential independent variables: no absolute VIF > 3, mean VIF = 1.39, and no evidence of multicollinearity from analysis of eigenvalues, condition indices and variance proportions.

9.1.2.2 MULTIVARIABLE REGRESSION MODELLING

A prognostic model was developed using the following variables: age; number of admissions in the previous year; FEV_1 % predicted; FVC; eMRCD; diastolic blood pressure; respiratory rate; temperature; body mass index; H^+; p_aO_2; potassium; urea; creatinine; albumin; glucose; CRP; haemoglobin; neutrophil count; eosinophil count; social care prior to admission; cerebrovascular disease; atrial fibrillation; LTOT; acute

confusion; ineffective cough; purulent sputum production; CXR consolidation; and recent weight loss greater than 5%.

Backward stepwise logistic regression analysis identified the following variables as independent predictors of in-hospital mortality (Table 9.7)

Table 9.7 Independent predictors of in-hospital mortality – Model 1

Variable	B	S.E.	OR (95% CI)	p value
eMRCD	0.89	0.14	2.43 (1.83 – 3.22)	<0.0001
CXR consolidation	1.16	0.28	3.18 (1.86 – 5.47)	<0.0001
Eosinophil count, $x10^9$/L	-4.89	1.41	0.0075 (0.0005 – 0.12)	0.0005
Temperature, °C	-0.51	0.15	0.60 (0.45 – 0.80)	0.0006
Atrial fibrillation	1.01	0.33	2.74 (1.43 – 5.28)	0.0025
Ineffective cough	0.97	0.33	2.64 (1.39 – 5.01)	0.0031
Age, years	0.036	0.016	1.04 (1.00 – 1.07)	0.0256
Cerebrovascular disease	0.68	0.33	1.98 (1.05 – 3.75)	0.0353
Albumin, g/L	-0.055	0.028	0.95 (0.90 – 1.00)	0.0485
H^+, nmol/L	0.021	0.01	1.02 (1.00 – 1.04)	0.0492
Glucose, mmol/L	0.074	0.038	1.08 (1.00 – 1.16)	0.0513
Intercept	9.725	5.656		

S.E. – standard error; OR – odds ratio; CI – confidence interval
Odds of in-hospital death = e^ - [9.725 + (0.89 × *eMRCD*) - (0.51 × *temperature*) + (0.021 × *Hydrogen ions*) + (0.036 × *age*) - (4.89 × *eosinophil count*) + (0.68 if *cerebrovascular disease*) + (1.01 if *Atrial Fibrillation*) + (1.16 if *CXR consolidation*) + (0.97 if *cough ineffective*) + (0.074 × *glucose*) - (0.055 × *albumin*)]

The regression model explained 43% of the variance in outcome (Nagelkerke's R^2 = 0.428) and the HLGFT suggested that the model is well calibrated and a good fit of the data (p = 0.379).

28 (3.0%) cases were identified as statistical outliers (studentised residuals > ±1.96) and the mean leverage value of the population = 0.0130 (expected mean leverage = (11+1)/920 = 0.0130). Of those cases with a residual > ±1.96, none had a Cook's distance > 1 and although one case was identified as having a significant influence on the regression analysis (leverage > 0.0391), this individual died suddenly and unpredictably from a stroke (i.e. the cause of death was not directly related to the cause of admission). This case was not excluded from the analysis because its distance from the regression model was both explainable and reflected 'real-life' clinical practice.

Based on the regression analysis, observed probabilities were plotted against predicted probabilities for patients grouped according to deciles of risk (Figure 9.1). The slope of this calibration plot was 1.04 (perfect calibration = 1.0) and all data points are closely clustered around the line of best fit, suggesting that calibration is good across all deciles of risk. Furthermore, discrimination of the regression model was excellent: AUROC = 0.896 (0.868 to 0.925) (Figure 9.2).

Figure 9.1 Calibration plot of predicted versus observed probability for in-hospital mortality

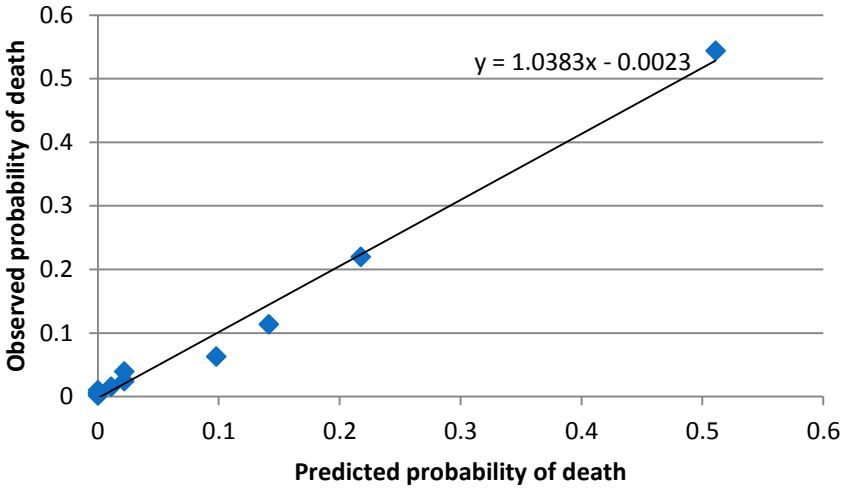
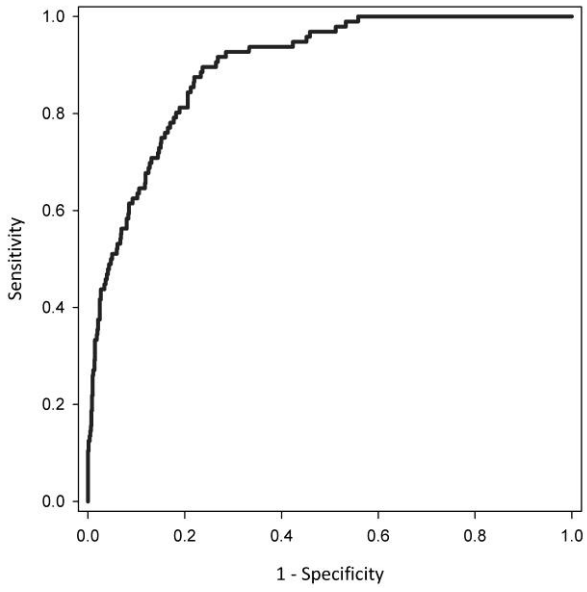


Figure 9.2 ROC curve showing discrimination of regression model for in-hospital mortality



9.1.3 DEVELOPING A CLINICAL PREDICTION TOOL

All continuous variables associated with mortality on univariate analysis (section 9.1.1) were categorised according to methods described in section 6.8.3.2. Categorical variables were entered in to a backward stepwise logistic regression model to identify the strongest independent predictors of mortality. Categorical variables with < 10% of the population in one category were excluded from subsequent analyses. Variables which showed evidence of collinearity (section 9.1.2.1) were also excluded. There was no evidence of multicollinearity between the remaining categorical variables: mean VIF = 1.24, no absolute VIF > 1.52, and no evidence of multicollinearity on analysing eigenvalues, condition indices or variance proportions.

Therefore, the following dichotomous variables were entered in to a backward stepwise logistic regression analysis:

Table 9.8 Categorical variables entered in to multivariate regression analysis

Variable	Categories		
	0†	1	2
Age (years)	< 80	≥ 80	
Total number of admissions in the previous year	< 3	≥ 3	
Social care prior to admission	No	Yes	
eMRCD	1 to 4	5a	5b
FEV_1 (% predicted)	< 50	≥ 50	
FVC (L)	< 2	≥ 2	
Diastolic blood pressure (mmHg)*	< 60	≥ 60	
Respiratory rate (min^{-1})*	< 30	≥ 30	
Temperature (°C)*	< 37	≥ 37	
BMI (kgm^{-2})	≥ 18.5	< 18.5	
Recent weight loss (%)	< 5	≥ 5	
pH*	≥ 7.3	< 7.3	
Potassium (mmol/L)*	< 5	≥ 5	
Urea (mmol/L)*	< 7	≥ 7	
Creatinine (µmol/L)*	< 120	≥ 120	
Albumin (g/L)*	≥ 36	< 36	
Glucose (mmol/L)*	< 8	≥ 8	
Haemoglobin (g/dL)*	≥ 12	< 12	
Neutrophil count ($x10^9$/L)*	< 9	≥ 9	
Eosinophil count ($x10^9$/L)*	≥ 0.05	< 0.05	
CRP (mg/L)*	< 50	≥ 50	
LTOT	No	Yes	

Variable	Categories		
	0†	1	2
Atrial fibrillation (AF)	No	Yes	
Cerebrovascular disease	No	Yes	
Acute confusion*	No	Yes	
Ineffective cough*	No	Yes	
Radiographic consolidation*	No	Yes	

† reference category for regression analysis; * at the time of hospital admission

The regression model (Table 9.9) accounted for 42% of the variance in the outcome variable (Nagelkerke's $R^2 = 0.423$) and was a good fit of our data (HLGFT, p = 0.385). No regression assumptions were violated by our model and none of the small number of statistical outliers (2.8% of cases) significantly influenced the regression model (acceptable leverage values and Cook's distance <1).

Table 9.9 Independent categorical predictors of in-hospital mortality – Model 2

Variable	B	Odds Ratio (95% CI)	Significance
eMRCD 1 – 4		1	
eMRCD 5a	1.63	5.11 (2.62 – 9.97)	<0.0001
eMRCD 5b	1.99	7.30 (3.77 – 14.2)	<0.0001
Consolidation	1.06	2.88 (1.69 – 4.90)	<0.0001
Eosinophil count < 0.05 $x10^9$/L	1.02	2.76 (1.58 – 4.83)	0.0001
pH < 7.3	0.99	2.68 (1.41 – 5.09)	0.0026
AF	0.98	2.66 (1.39 – 5.09)	0.0032
Ineffective cough	0.94	2.57 (1.37 – 4.84)	0.0033
Albumin < 36 g/L	0.84	2.32 (1.36 – 3.96)	0.0020
Cerebrovascular disease	0.70	2.02 (1.18 – 3.42)	0.0369
Age > 80	0.70	2.01 (1.18 – 3.42)	0.0106
BMI < 18.5kgm^{-2}	0.60	1.83 (1.00 – 3.33)	0.0486
Intercept	-4.30		

For pragmatic reasons, the strongest five variables were chosen to comprise our prognostic tool (eMRCD, eosinophils, consolidation, AF and pH) and relative weights were assigned according to the regression coefficient (B). Table 9.10 shows how to calculate the resulting DECAF (**D**yspnoea, **E**osinopenia, **C**onsolidation, **A**cidaemia, atrial **F**ibrillation) score:

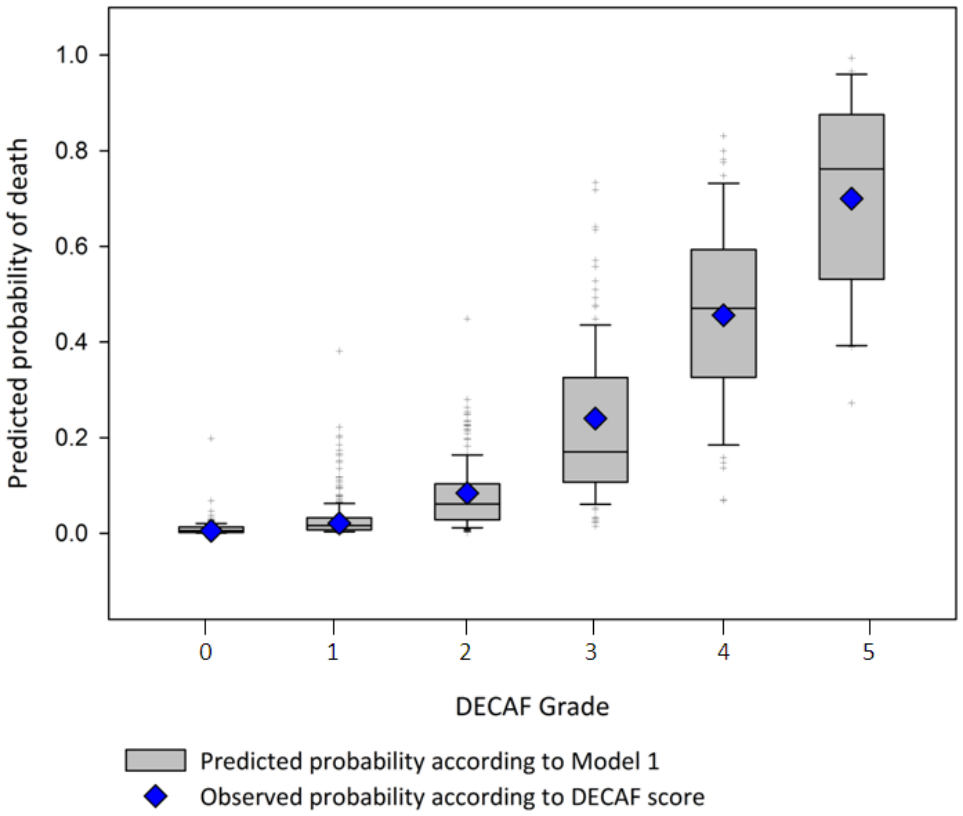
Table 9.10 The DECAF Score

Variable	Score
Dyspnoea:	
eMRCD 5a	1
eMRCD 5b	2
Eosinopenia (< 0.05 $x10^9$/L)	1
Consolidation	1
Acidaemia (pH < 7.3)	1
atrial Fibrillation	1
Maximum DECAF score	**/6**

9.1.3.1 ASSESSING PREDICTIVE TOOL ACCURACY

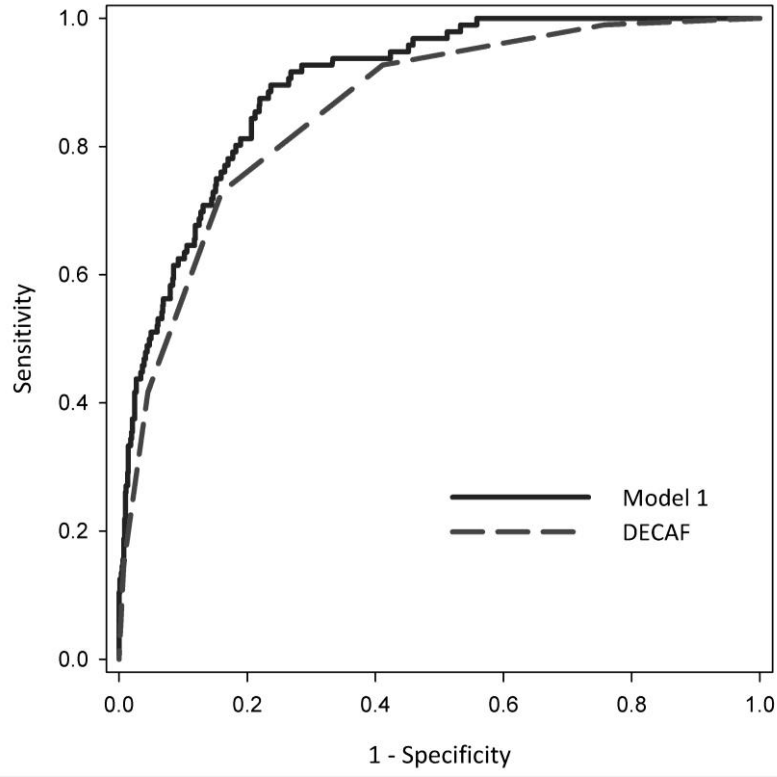
To ensure that the methodology for developing the DECAF tool had not significantly weakened its performance, when compared to the regression model described in section 9.1.2.2 (termed 'Model 1'), the calibration between DECAF and Model 1 was assessed by plotting the predicted probability of mortality (according to Model 1) and the observed probability of death, for each DECAF grade (Figure 9.3). The observed proportion of patients dying for each DECAF grade can be seen to be well calibrated with the predicted probability according to Model 1. It can also be seen that as DECAF grade increases, both the observed and predicted probabilities of dying increase.

Figure 9.3 Observed and predicted probabilities of death stratified by DECAF score



Performance of the tool for discrimination of in-hospital mortality was assessed using ROC curve analysis. The AUROC for the DECAF score was 0.858 (95% CI 0.822 – 0.895). Internal validation was performed and the mean (95% CI) AUROC of 10,000 bootstrapped samples was 0.858 (0.819 – 0.894). Comparing the discrimination of DECAF and Model 1 identified a small but significant difference ($p < 0.0001$) in discrimination for in-hospital mortality ($AUROC_{model\ 1}$ = 0.896, 0.867 to 0.925, and $AUROC_{DECAF}$ = 0.858, 0.822 to 0.895).

Figure 9.4 ROC curves showing discrimination of model 1 and DECAF score



In-hospital mortality rates, and sensitivity and specificity, for the DECAF score are shown in Table 9.11:

Table 9.11 DECAF score and in-hospital mortality

DECAF Score	n	In-hospital mortality, %	Sensitivity*	Specificity*
0	201	0.5	1	0
1	291	2.1	0.99	0.24
2	226	8.4	0.93	0.59
3	125	24	0.73	0.84
4	57	45.6	0.42	0.96
5	20	70	0.15	0.99
6	0	n/a	n/a	n/a

* Positive test result = score ≥ corresponding DECAF score

In our cohort, the DECAF score performed significantly better for the prediction of in-hospital mortality than: the Acute Physiology and Chronic Health Evaluation (APACHE) II prognostic index [395] (AUROC = 0.73, DECAF v. APACHE II p <0.0001); the COPD and Asthma Physiology Score (CAPS) [158] (AUROC = 0.71, p <0.0001); and the BAP-65 score [155] (AUROC = 0.68, p<0.0001) which have all been proposed as useful predictive instruments in AECOPD (Figure 9.5).[139, 158, 300]

In patients with AECOPD, DECAF was a significantly stronger predictor of in-hospital mortality than CURB-65 for both patients with (AUROC = 0.77 v. 0.66, p = 0.003, n = 299) (Figure 9.6, panel A) and without (AUROC = 0.87 v. 0.72, p = 0.002, n = 621) (Figure 9.6, panel B) coexistent consolidation. Although derived for in-hospital mortality, the utility of the DECAF score to predict 30-day mortality was also assessed. The AUROC of DECAF for the prediction of 30-day mortality was 0.82 (0.78 to 0.86) and, in the subgroup with coexistent consolidation, it was a stronger predictor than CURB-65 (AUROC = 0.75 v. 0.64, p=0.0026).

Figure 9.5 ROC curve showing discrimination of DECAF score for in-hospital mortality in the total population, n = 920

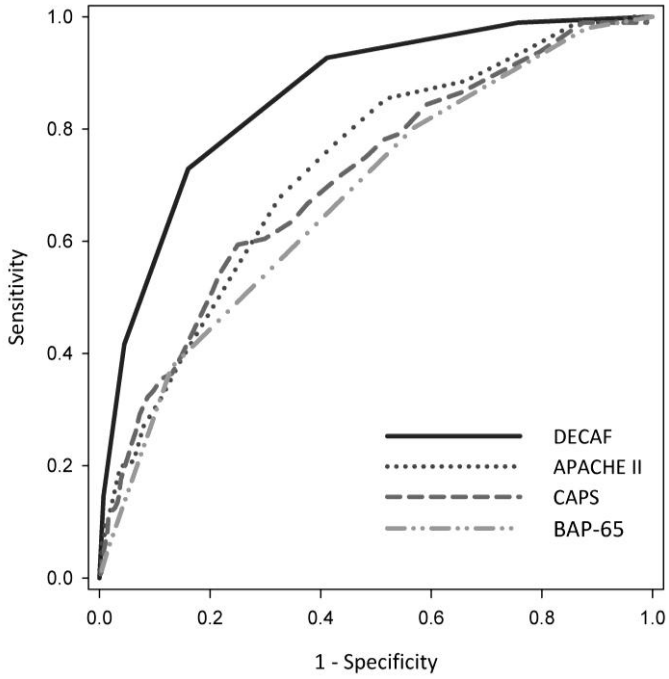
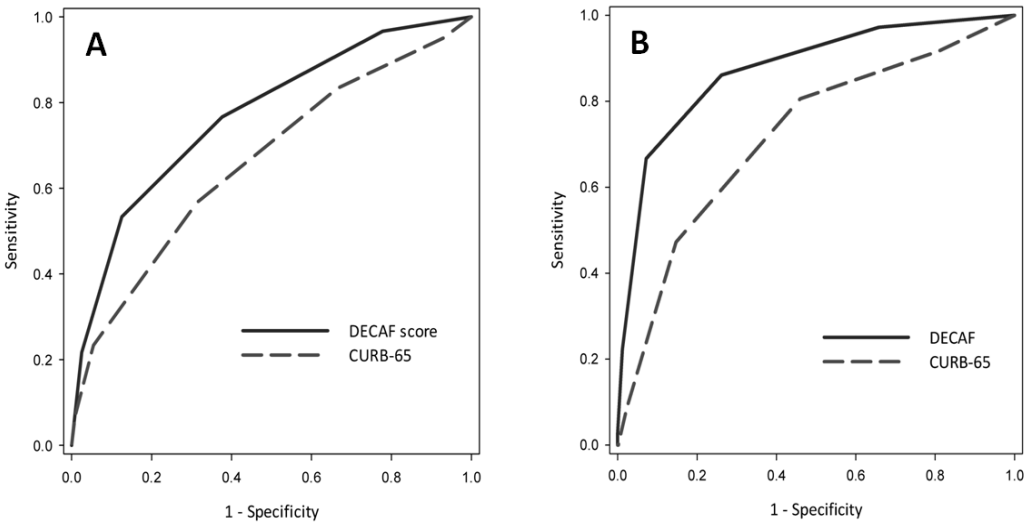


Figure 9.6 ROC curve showing discrimination of DECAF score and CURB-65 for in-hospital mortality for patients with (n=299, panel A) and without (n=621, panel B) complicating pneumonia



9.2 PREDICTING LONG-TERM MORTALITY

Aim 1f: identify independent predictors of twelve-month mortality following hospitalisation for AECOPD.

9.2.1 UNIVARIATE ASSOCIATIONS WITH 12-MONTH MORTALITY

Similarly to in-hospital mortality (section 9.1.1), older age, institutional care and an inability to live at home independently were all associated with 12-month mortality. Males had a higher risk of death, although this was not statistically significant (Table 9.12).

Table 9.12 The relationship between sociodemographic details and 12-month mortality

Variable	Total population, n=920	Survived 12-months, n=621	Died within 12-months, n=291	p value
Age	73.1 (10.0)	70.9 (9.8)	77.8 (8.7)	<0.0001
Female, %	53.9	56	49.5	0.0754
Admission hospital (NTGH), %	54.9	55.6	53.3	0.52
Institutional care, %	6.5	3.0	14.1	<0.0001
Social care prior to admission, %	22.9	14.5	41.2	<0.0001
Smoking load (cpy), median (IQR)	45 (32 to 60)	45 (32 to 60)	45 (30 to 60)	0.63

Individuals with more severe underlying disease were at an increased risk of 12-month mortality: more frequent hospitalisation (for any cause), a previous episode of AECOPD treated with assisted ventilation, greater lung function (FEV_1 and FVC) impairment, worse stable-state breathlessness and exercise capacity, and presence of cor pulmonale were all associated with an increased risk of death (Table 9.13).

Table 9.13 Prior health resource use and markers of disease severity, and the association with 12-month mortality

Variable	Total population, n=920	Survived 12-months, n=621	Died within 12-months, n=291	p value
Health resource use,				
Number of respiratory admissions in previous year, median (IQR)	0 (0 to 1)	0 (0 to 1)	0 (0 to 1)	0.26
Number of non-respiratory admissions in the previous year, median (IQR)	0 (0 to 0)	0 (0 to 0)	0 (0 to 1)	<0.0001
Total number of admissions in previous year, median (IQR)	0 (0 to 1)	0 (0 to 1)	1 (0 to 2)	0.0016
Number of AECOPD in previous year, median (IQR)	3 (1 to 4)	3 (1 to 4)	3 (2 to 4)	0.46
Previous assisted ventilation, %	11.7	9.9	15.8	0.0061
Previous pulmonary rehabilitation, %	9.5	9.5	9.3	0.90
Spirometry,				
FEV_1 (litres)	0.97 (0.44)	1.02 (0.44)	0.86 (0.41)	<0.0001
FEV_1 % predicted	43.6 (17.2)	45.2 (17.6)	40.0 (15.5)	<0.0001
FVC (litres)	2.15 (0.78)	2.25 (0.79)	1.93 (0.72)	<0.0001
FEV_1 / FVC, median (IQR)	0.45 (0.37 to 0.53)	0.45 (0.37 to 0.53)	0.44 (0.38 to 0.52)	0.54
Exercise capacity and disease complications,				
MRCD, median (IQR)	4 (4 to 5)	4 (3 to 4)	5 (4 to 5)	<0.0001
eMRCD, median (IQR)	4 (4 to 5a)	4 (3 to 4)	5a (4 to 5b)	<0.0001
Exercise tolerance (metres), median (IQR)	25 (10 to 80)	50 (20 to 150)	15 (10 to 30)	<0.0001
Housebound, %	34.3	20.3	64.6	<0.0001
Cor pulmonale, %	10.0	7.8	14.8	0.0010

No respiratory comorbidities were associated with higher 12-month mortality although coexistent asthma was protective. Several cardiovascular (cerebrovascular disease, atrial fibrillation, left ventricular (LV) dysfunction and valvular heart disease) and general (chronic cognitive impairment, chronic kidney disease, and a history of malignancy) comorbidities were associated with long-term mortality. The contrast between the prognostic importance of respiratory and non-respiratory comorbidities is consistent with the data on prior health resource use (Table 9.13) which showed that a marker of non-respiratory comorbidity (i.e. hospital admission due to non-respiratory cause) was associated with mortality, whereas an admission for a respiratory cause (which reflects respiratory comorbidity) was not.

Table 9.14 Comorbidity and long-term mortality

Variable	Total population, n=920	Survived 12-months, n=621	Died within 12-months, n=291	p value
Respiratory,				
Bronchiectasis, %	6	5.6	6.9	0.46
Asthma, %	4.9	5.9	2.7	0.0476
Pulmonary fibrosis, %	1.7	1.3	2.7	0.17
Obstructive sleep apnoea, %	1.6	1.4	2.1	0.58
Cardiovascular,				
Hypertension, %	39.6	39.4	39.9	0.94
Cerebrovascular disease, %	14	11.8	18.9	0.0056
Ischaemic heart disease, %	29.3	28.1	32.0	0.24
Atrial fibrillation, %	12.5	9.9	18.2	0.0006
LV dysfunction, %	7.3	5.6	11.0	0.0041
Thromboembolic disease, %	3.8	3.7	4.1	0.71
Valvular heart disease, %	3.3	2.5	4.8	0.0758
Peripheral vascular disease, %	7.9	7.0	10.0	0.15
General,				
Diabetes mellitus, %	14.8	14.9	14.4	0.92
Osteoporosis, %	12.6	11.6	14.8	0.20
Rheumatoid arthritis, %	4.0	3.5	5.2	0.28
Cognitive impairment, %	5.4	2.4	12.0	<0.0001
Chronic kidney disease, %	6.7	4.3	12.0	<0.0001
Anxiety/depression, %	24.2	23.5	25.8	0.46

Variable	Total population, n=920	Survived 12-months, n=621	Died within 12-months, n=291	p value
Chronic liver disease, %	0.7	0.6	0.7	1
Peptic ulcer disease, %	6.5	5.6	8.6	0.0867
Past history of cancer, %	7.7	6.8	9.6	0.15
History of active cancer, %	3.8	2.5	6.5	0.0050
Comorbidity burden,				
Charlson Comorbidity Index, median (IQR)	2 (1 to 3)	2 (1 to 2)	2 (1 to 3)	<0.0001

Maintenance home oxygen therapy, long-term oral corticosteroid therapy, and diuretic therapy were associated with 12-month mortality (Table 9.15). Our finding that maintenance systemic corticosteroids are associated with an increased risk of death is in agreement with previous studies (section 2.2.2.6) but may be confounded by underlying disease severity. Previous studies have shown statin [245] and beta-blocker [114] therapy to be protective against mortality, but in the present study, no relationships with mortality were identified.

Table 9.15 Medications on admission to hospital and long-term mortality

Variable	Total population, n=920	Survived 12-months, n=621	Died within 12-months, n=291	p value
Respiratory,				
LTOT, %	12.4	8.6	20.6	<0.0001
Ambulatory oxygen, %	3.4	2.4	5.5	0.0186
Short burst oxygen, %	7.8	7.3	8.9	0.43
Home oxygen therapy,* %	21.1	16.5	30.9	<0.0001
Home nebuliser, %	16.6	15.6	18.9	0.22
Inhaled corticosteroid (ICS), %	81.6	81.6	81.8	1
ICS dose (BDP equivalent), median (IQR)	2000 (1000 to 2000)	2000 (1000 to 2000)	2000 (1000 to 2000)	0.92
Inhaled long-acting beta agonist, %	77.7	78.2	76.6	0.61
Inhaled anticholinergic, %	70.8	69.8	72.9	0.35
Long-term oral corticosteroid, %	9.1	7.8	12.0	0.0483
Carbocysteine, %	16.1	15.9	16.5	0.85
Theophylline, %	8	7.9	8.2	0.90
Cardiovascular,				

Variable	Total population, n=920	Survived 12-months, n=621	Died within 12-months, n=291	p value
Statin, %	44.9	44.5	45.7	0.78
Beta-blocker, %	10.8	10.3	11.7	0.57
ACE inhibitor, %	24.2	25.1	22.3	0.41
Angiotensin receptor blocker, %	5.7	5.7	5.5	1
Diuretic, %	35.4	32.9	40.9	0.0215
Other,				
Benzodiazepine,† %	5.8	5.1	7.2	0.22
Opiate,† %	0.9	0.8	1.0	0.71

* either LTOT, ambulatory O_2 or short burst O_2; † prescribed for the symptomatic relief of dyspnoea / anxiety; ICS – inhaled corticosteroid; BDP – beclomethasone diproprionate; ACE – Angiotensin converting enzyme

Similarly to in-hospital mortality (Table 9.5), patients were at an increased risk of death if: they were confused; or had an ineffective cough; or did not expectorate purulent sputum. Furthermore, similar markers of acute physiological derangement (hypotension, tachypnoea etc) and nutritional depletion were associated with in-hospital and 12-month mortality. It is of interest that diastolic hypotension (< 60mmHg) was associated with both in-hospital and 12-month mortality whereas systolic hypotension (< 90mmHg) was only associated with 12-month mortality, suggesting that diastolic hypotension is the more useful prognostic marker. Low oxygen saturation had no discriminative value for in-hospital mortality but was significantly associated with long-term mortality (Table 9.16).

Table 9.16 Findings at admission and long-term mortality

Variable	Total population, n=920	Survived 12-months, n=621	Died within 12-months, n=291	p value
History and examination findings,				
Purulent sputum, %	51.3	54.6	44.0	0.0033
Ineffective cough, %	11.8	8.1	19.9	<0.0001
Pedal oedema, %	26.3	24.6	29.9	0.11
Acute confusion, %	12.6	7.8	23.0	<0.0001
Heart rate (min^{-1})	102.7 (20.8)	103.1 (20.6)	101.7 (21.1)	0.34
Initial non-invasive investigations,				
Systolic BP (mmHg)	139.3 (28.4)	140.9 (28.0)	135.8 (29.0)	0.0122
Diastolic BP (mmHg)	76.2 (17.0)	77.2 (16.7)	74.1 (17.5)	0.0094

Variable	Total population, n=920	Survived 12-months, n=621	Died within 12-months, n=291	p value
Respiratory rate (min^{-1})	26.0 (6.3)	25.5 (5.98)	27.1 (6.87)	0.0002
Temperature (°C), median (IQR)	36.9 (36.4 to 37.5)	36.9 (36.4 to 37.6)	36.8 (36.3 to 37.3)	0.0048
S_pO_2 (%), median (IQR)	92 (87 to 96)	90.8 (7.41)	89.6 (8.43)	0.0533
BMI (kgm^{-2})	24.6 (6.3)	25.4 (6.16)	22.7 (6.23)	<0.0001
Weight loss >5%, %+	24.6	17.6	39.5	<0.0001
MUST score, median (IQR)	0 (0 to 1)	0 (0 to 1)	1 (0 to 2)	<0.0001
CXR consolidation, %	32.5	27.2	44.0	<0.0001

BP – blood pressure

Individuals with severe exacerbations (low pH, high p_aCO_2) were at a greater risk of long-term mortality. Consistent with the data on renal comorbidity (Table 9.14), patients with evidence of higher serum creatinine were also at a higher risk of death. Eosinopenia, which was shown to be a strong independent predictor of in-hospital mortality (section 9.1.2), did not discriminate for mortality 12-months following admission.

Table 9.17 Laboratory investigations at admission and 12-month mortality

Variable	Total population, n=920	Survived 12-months, n=621	Died within 12-months, n=291	p value
Arterial blood gas values,				
H^+ (nmol/L), median (IQR)	38.9 (35.5 to 43.7)	38.0 (34.7 to 42.7)	39.8 (35.5 to 45.7)	<0.0001
pH, median (IQR)	7.41 (7.36 to 7.45)	7.42 (7.37 to 7.46)	7.40 (7.34 to 7.45)	<0.0001
p_aO_2 (kPa), median (IQR)	8.7 (7.3 to 10.7)	8.7 (7.3 to 10.4)	8.5 (7.1 to 11.4)	0.81
p_aCO_2 (kPa), median (IQR)	5.90 (4.9 to 7.5)	5.70 (4.9 to 7.1)	6.19 (5.1 to 8.4)	0.0002
Bicarbonate (mmol/L)	29.1 (6.5)	28.8 (6.06)	29.7 (7.38)	0.0514
Acidaemic exacerbation, %‡	19.5	16.9	25.1	0.0041
Biochemistry,				
Sodium (mmol/L)	136.3 (4.6)	136.2 (4.41)	136.6 (4.95)	0.29
Potassium (mmol/L)	4.32 (0.56)	4.26 (0.52)	4.44 (0.61)	<0.0001
Urea (mmol/L), median (IQR)	6.50 (4.7 to 9.3)	6.0 (4.4 to 8.2)	8.10 (5.7 to 11.9)	<0.0001

Variable	Total population, n=920	Survived 12-months, n=621	Died within 12-months, n=291	p value
Creatinine (µmol/L), median (IQR)	93.0 (77 to 114)	91.0 (77 to 110)	98.0 (75 to 139)	0.0039
Albumin (g/L)	38.4 (4.79)	39.3 (4.46)	36.4 (4.86)	<0.0001
Glucose (mmol/L), median (IQR)	6.90 (6.0 to 8.1)	6.90 (6.1 to 8.0)	6.90 (5.8 to 8.2)	0.41
CRP (mg/L), median (IQR)	41.5 (11 to 117)	31 (9 to 108)	63 (19 to 132)	0.0001
Haematology,				
Haemoglobin (g/dL)	13.6 (1.95)	13.8 (1.82)	13.1 (2.11)	<0.0001
Haematocrit	0.410 (0.058)	0.416 (0.054)	0.399 (0.064)	0.0002
White cell count ($x10^9$/L), median (IQR)	11.9 (9.1 to 15.5)	11.9 (9.1 to 15.3)	11.9 (9.4 to 16.2)	0.37
Neutrophil count ($x10^9$/L), median (IQR)	9.2 (6.9 to 12.8)	9.0 (6.8 to 12.6)	9.5 (7.1 to 13.0)	0.13
Eosinophil count ($x10^9$/L), median (IQR)	0.1 (0 to 0.2)	0.1 (0 to 0.2)	0 (0 to 0.1)	0.32

9.2.2 INDEPENDENT PREDICTORS OF 12-MONTH MORTALITY

All variables associated with 12-month mortality ($p < 0.10$) were selected as potential covariates for logistic regression analysis (categorical variables with < 10% of the population in one category excluded). No additional variables, which on clinical grounds were thought to be prognostically important, were identified by the above univariate analysis. Prior to multivariate analysis, all candidate variables were screened for multicollinearity (section 6.8.1): FEV_1 % predicted was therefore retained over FEV_1 (Pearson's r = 0.770); haemoglobin was retained over haematocrit (r = 0.95, p <0.0001); diastolic BP was included instead of systolic BP (r = 0.636 and eigenvalues suggest collinearity); eMRCD was retained over exercise tolerance (ρ =-0.845); CRP was retained over temperature at admission (ρ = 0.238 and eigenvalues suggest collinearity); and hydrogen ion concentration was retained over p_aCO_2 (Spearman's-ρ = -0.616 and eigenvalues suggest collinearity). Furthermore, cough effectiveness was included instead of purulent sputum at admission, and BMI was included as a dichotomous variable (BMI < 18.5 kgm^{-2}) due to its non-linear relationship with 12-month mortality (Table 8.6). Following exclusion of these variables, there were no strong zero order correlations between potential predictors (Appendix E, Table 17.6),

but more detailed collinearity testing suggested that there might be persistent collinearity between predictor variables (mean VIF = 1.53, no absolute VIF >3). However, no specific interaction between variables could be identified through further collinearity screening, and no variables could be excluded because collinearity was suspected on clinical grounds. Furthermore, given the suggestion of only minor collinearity (mean VIF ≈ 1.50) no further variables were excluded.

Table 9.18 details the independent predictors of 12-month mortality following hospitalisation for AECOPD (termed 'Model 3'). Further tests of model performance showed that: 2.7% of cases were statistical outliers (no outliers were significantly influential on the model i.e. acceptable Cook's distances and leverage values); model calibration was satisfactory (HLGFT, p = 0.559, and a calibration plot shows the model to be well calibrated across all deciles of risk (Figure 9.7)). Model 3 accounted for 42.5% of the variance in 12-month mortality (Nagelkerke's R^2 = 0.425).

Figure 9.7 Calibration plot of predicted against observed probability of 12-month mortality for Model 3

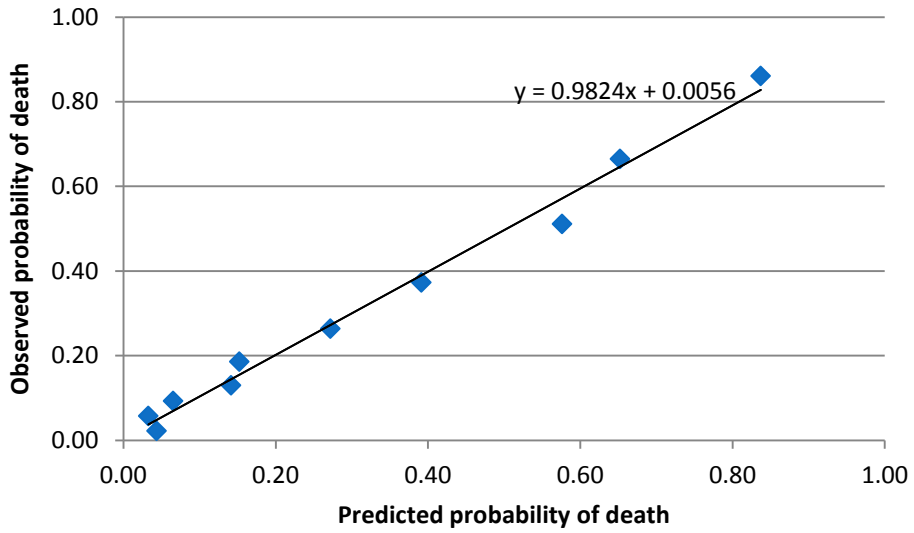


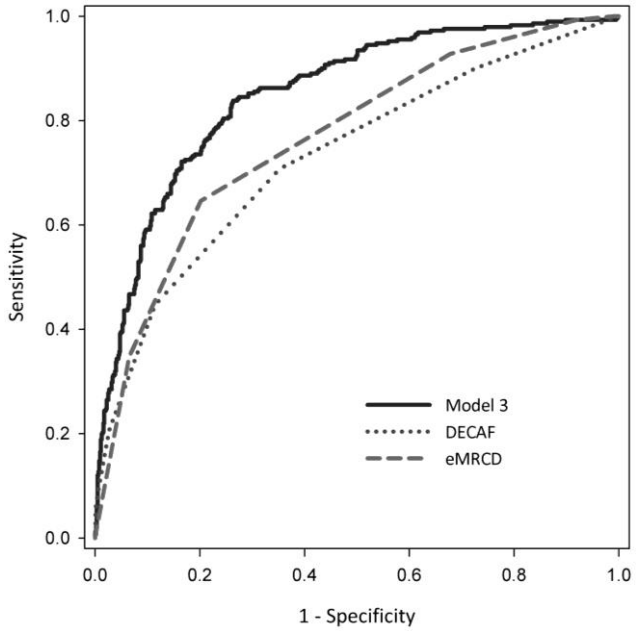
Table 9.18 Independent predictors of 12-month mortality – Model 3

Variable	B	S.E.	OR (95% CI)	p value
eMRCD	0.71	0.10	2.04 (1.68 to 2.48)	<0.0001
Age (years)	0.05	0.01	1.05 (1.03 to 1.07)	<0.0001
Albumin, g/L	-0.07	0.02	0.930 (0.891 to 0.970)	0.0007
Urea, mmol/L	0.06	0.02	1.06 (1.02 to 1.10)	0.0038
Unexplained weight loss > 5%	0.57	0.20	1.77 (1.19 to 2.64)	0.0047
CXR consolidation	0.55	0.20	1.73 (1.18 to 2.54)	0.0053
BMI < 18.5 kgm^{-2}	0.62	0.23	1.86 (1.19 to 2.92)	0.0064
Ineffective cough	0.63	0.27	1.88 (1.11 to 3.18)	0.0187
FEV_1 (% predicted)	-0.01	0.01	0.987 (0.975 to 0.998)	0.0239
LTOT	0.56	0.25	1.74 (1.06 to 2.86)	0.0283
Male sex	0.35	0.18	1.42 (0.997 to 2.02)	0.0522
CRP	-0.001	0.00	0.998 (0.996 to 1.00)	0.0624
Respiratory rate	0.03	0.01	1.03 (0.998 to 1.05)	0.0642
Intercept	-5.88	1.34		

Odds of 12-month mortality = e ^ - [-5.88 + (0.71 x *eMRCD*) + (0.05 x *age*) - (0.07 x *albumin*) + (0.06 x *urea*) + (0.57 if *unexplained weight loss >5%*) + (0.55 if *CXR consolidation*) + (0.62 if *BMI < 18.5kgm*$^{-2}$) + (0.63 if *ineffective cough*) – (0.01 x *FEV_1 % predicted*) + (0.56 if *LTOT*) + (0.35 if *male*) – (0.001 x *CRP*) + (0.03 x *respiratory rate*)]

Model 3 showed good discrimination for 12-month mortality: AUROC = 0.850 (95% CI 0.824 to 0.877) (Figure 9.8) and the result was internally valid (bootstrapped AUROC = 0.849, 95% CI 0.823 to 0.876). The DECAF score was a good predictor of 12-month mortality (AUROC = 0.730, 95% CI 0.695 to 0.765), but was weaker ($p < 0.0001$) than both Model 3 and the eMRCD scale (AUROC = 0.766, $p = 0.0170$) (Figure 9.8).

Figure 9.8 ROC curve showing discrimination of Model 3 and the DECAF score for 12-month mortality



CHAPTER 10 PREDICTING READMISSION IN PATIENTS SURVIVING TO DISCHARGE FOLLOWING HOSPITALISATION WITH AECOPD

Aim 1g: identify independent predictors of early and frequent readmission, and develop a clinical prediction tool, in patients surviving to discharge following hospitalisation with AECOPD.

10.1 UNIVARIATE ASSOCIATIONS WITH READMISSION OR DEATH

The association between indices and (a) 90-day readmission or death and (b) frequent (≥ 2 within 12 months of discharge) readmission are shown in Table 10.1 to Table 10.6.

Older age, male sex and an inability to manage independently at home were all associated ($p < 0.10$) with an increased risk of 90-day readmission or death. A greater smoking burden was significantly associated with increased risk of frequent readmissions (Table 10.1).

Table 10.1 Sociodemographic details and their association with readmission following discharge

Variable	Total population, n=824	90-day readmission or death		Frequent readmission	
		No, n=517	Yes, n=307	No, n=537	Yes, n=287
Age (years)	72.3 (10.0)	71.1 (9.7)‡	74.5 (10.2)‡	72.3 (10.3)	72.5 (9.5)
Female, %	54.2	56.5$^{\Delta}$	50.5$^{\Delta}$	55.5	51.9
Institutional care, %	5.2	3.3†	8.5†	5.0	5.6
Social care prior to admission, %	20.1	13.3‡	31.6‡	18.4$^{\Delta}$	23.3$^{\Delta}$
Smoking load (cpy), median (IQR)	45 (32 to 60)	45 (32 to 60)	48 (32 to 60)	42 (30 to 58)†	50 (35 to 62)†

Values shown are mean (SD) unless stated otherwise. Significant differences between presence and absence of stated outcome: *p<0.05; †p<0.01; ‡p<0.001; $^{\Delta}$ p<0.10; cpy – cigarette pack years

Individuals who experienced frequent episodes of health resource use (hospital admissions or episodes of AECOPD in the preceding year, or previous AECOPD requiring treatment with NIV), or had more severe underlying disease (lower FEV_1 % predicted, worse stable-state dyspnoea, or cor pulmonale), were at a higher risk of both single and frequent readmission following discharge (Table 10.2).

Table 10.2 Prior health resource use, markers of disease severity and their association with readmission

Variable	Total population, n=824	90-day readmission or death		Frequent readmission	
		No, n=517	Yes, n=307	No, n=537	Yes, n=287
Health resource use,					
Number of respiratory admissions in previous year, median (IQR)	0 (0 to 1)	0 (0 to 1)‡	0 (0 to 1)‡	0 (0 to 1)‡	1 (0 to 2)‡
Total number of admissions in previous year, median (IQR)	0 (0 to 1)	0 (0 to 1)‡	1 (0 to 2)‡	0 (0 to 1)‡	1 (0 to 2)‡
Number of AECOPD in previous year, median (IQR)	3 (1 to 4)	2 (1 to 4)‡	3 (2 to 5)‡	2 (1 to 4)‡	3 (2 to 5)‡
Previous NIV, %	10.4	8.7*	13.4*	7.4‡	16.0‡
Previous pulmonary rehabilitation, %	9.8	9.7	10.1	8.8	11.8
Spirometry,					
FEV_1 (litres)	0.99 (0.4)	1.02 (0.4)†	0.93 (0.4)†	1.01 (0.5)*	0.94 (0.4)*
FEV_1 % predicted	44.0 (17.4)	45.5 (17.6)†	41.5 (16.8)†	45.4 (17.5)†	41.4 (17.1)†
FVC (litres)	2.18 (0.8)	2.25 (0.8)†	2.07 (0.8)†	2.21 (0.8)	2.13 (0.8)
Exercise capacity and disease complications,					
MRCD, median (IQR)	4 (3 to 5)	4 (3 to 4)‡	4 (4 to 5)‡	4 (3 to 5)‡	4 (4 to 5)‡
eMRCD, median (IQR)	4 (3 to 5a)	4 (3 to 4)‡	4 (4 to 5a)‡	4 (3 to 5a)‡	4 (4 to 5a)‡
Exercise tolerance (metres), median (IQR)	30 (15 to 100)	50 (20 to 180)‡	20 (10 to 50)‡	40 (15 to 150)‡	20 (10 to 60)‡
Housebound, %	29.0	19.5‡	45.0‡	27.0^{Δ}	32.8^{Δ}
Cor pulmonale, %	9.8	6.8‡	15.0‡	9.1	11.1

Values shown are mean (SD) unless stated otherwise. NIV – non-invasive ventilation. Significant differences between presence and absence of stated outcome: *p<0.05; †p<0.01; ‡p<0.001; $^{\Delta}$p<0.1

Histories of anxiety or depression, or cerebrovascular disease, were associated with an increased rate of both measures of readmission. Coexistent ischaemic heart disease was associated with a significantly higher rate of frequent readmission although was non-significantly associated with a lower rate of 90-day readmission. This discrepancy is difficult to explain and the latter non-significant association (p = 0.07) may not be a true finding. Furthermore, a history of obstructive sleep apnoea, chronic kidney

disease, and the presence of an active malignancy were all associated with 90-day readmission. However, these findings should be interpreted with caution given the small number of patients with these three diagnoses in our cohort. Lastly, the overall comorbidity burden (CCI) was strongly associated with both outcomes (Table 10.3).

Table 10.3 Comorbidity and its association with readmission

Variable	Total population, n=824	90-day readmission or death		Frequent readmission	
		No, n=517	Yes, n=307	No, n=537	Yes, n=287
Respiratory,					
Bronchiectasis, %	5.6	6.2	4.6	5.0	6.6
Asthma, %	5.1	5.4	4.6	5.2	4.9
Pulmonary fibrosis, %	1.5	1.4	1.6	1.1	2.1
Obstructive sleep apnoea, %	1.6	0.8*	2.9*	1.1	2.4
Cardiovascular,					
Hypertension, %	39.2	38.9	39.7	41.3$^{\Delta}$	35.2$^{\Delta}$
Cerebrovascular disease, %	12.6	10.3†	16.6†	9.9†	17.8†
Ischaemic heart disease, %	29.5	37.3$^{\Delta}$	33.2$^{\Delta}$	27.2*	33.8*
Atrial fibrillation, %	10.9	8.9*	14.3*	10.8	11.1
LV dysfunction, %	7.4	5.2†	11.1†	7.4	7.3
Valvular heart disease, %	2.9	2.3	3.9	2.6	3.5
Peripheral vascular disease, %	7.8	6.8	9.4	8.2	7.0
General,					
Diabetes mellitus, %	14.7	14.9	14.3	14.0	16.0
Osteoporosis, %	12	12.0	12.1	11.4	13.2
Rheumatoid arthritis, %	4.0	3.9	4.2	3.9	4.2
Thromboembolic disease, %	3.9	3.3	4.9	3.9	3.8
Cognitive impairment, %	4.6	3.1†	7.2†	4.3	5.2
Chronic kidney disease, %	5.7	4.3*	8.1*	5.4	6.3
Anxiety/depression, %	24.8	22.2*	29.0*	21.6†	30.7†
Chronic liver disease, %	0.6	0.4	1.0	0.6	0.7
Peptic ulcer disease, %	6.3	5.6	7.5	6.3	6.3
Past history of cancer, %	7.4	6.2	9.4	8.0	6.3
History of active cancer, %	3.8	2.5*	5.9*	3.5	4.2
Composite score,					
Charlson Comorbidity Index, median (IQR)	2 (1 to 3)	2 (1 to 2)‡	2 (1 to 3)‡	2 (1 to 3)*	2 (1 to 3)*

Significant differences between presence and absence of stated outcome: *p<0.05; †p<0.01; ‡p<0.001; $^{\Delta}$p<0.1

In agreement with the results reported in Table 10.2, individuals with more severe disease, who required treatment with home oxygen therapy (LTOT or short burst oxygen), were at an increased risk of readmission (Table 10.4). Patients in receipt of

nebulised bronchodilators or carbocysteine were also more likely to be readmitted, however the clinical significance of these relationships are uncertain because commonly, nebulised bronchodilators and maintenance carbocysteine are provided to those patients most at risk of admission and exacerbation. Long-term oral corticosteroids were associated with an increased risk of both 90-day and frequent readmission, and patients receiving a higher dose of inhaled corticosteroid also had more frequent readmission. In addition, patients who experienced frequent readmissions were more likely to be prescribed long-acting beta-agonists and inhaled anticholinergic agents.

Table 10.4 Maintenance medications at hospital discharge and their association with readmission

Variable	Total population, n=824	90-day readmission or death		Frequent readmission	
		No, n=517	Yes, n=307	No, n=537	Yes, n=287
Respiratory,					
LTOT, %	13.3	10.8†	17.6†	11.5*	16.7*
Ambulatory oxygen, %	3.8	3.3	4.6	3.5	4.2
Short burst oxygen, %	8.9	7.5$^{\Delta}$	11.1$^{\Delta}$	6.7†	12.9†
Home oxygen therapy$^{\Phi}$, %	22.9	19.3‡	29.0‡	19.2‡	30.0‡
Home nebuliser, %	16.6	13.0‡	22.8‡	13.2‡	23.0‡
Inhaled corticosteroid (ICS), %	88.3	87.6	89.6	87.2	90.6
ICS dose (BDP equivalent), median (IQR)	2000 (1000 to 2000)	2000 (1000 to 2000)	2000 (1000 to 2000)	2000 (1000 to 2000)*	2000 (2000 to 2000)*
Inhaled long-acting beta agonist, %	86.5	85.9	87.6	84.5*	90.2*
Combination inhaler, %	83.1	82.2	84.7	80.6†	87.8†
Inhaled anticholinergic, %	80.6	82.2	77.9	78.6*	84.3*
Long-term oral corticosteroid, %	8.0	6.8$^{\Delta}$	10.1$^{\Delta}$	6.3*	11.1*
Carbocysteine, %	19.4	18.4	21.2	14.9‡	27.9‡
Theophylline, %	7.4	7.2	7.8	7.6	7.0
Cardiovascular,					
Statin, %	44.4	42.7	47.2	43.4	46.3
Beta-blocker, %	11.0	10.1	12.7	10.6	11.8
ACE inhibitor, %	22.9	21.9	24.8	21.8	25.1

Variable	Total population, n=824	90-day readmission or death		Frequent readmission	
		No, n=517	Yes, n=307	No, n=537	Yes, n=287
Angiotensin receptor blocker, %	5.2	5.2	5.2	5.0	5.6
Diuretic, %	34.7	30.0‡	42.7‡	26.8	30.3
Other,					
Benzodiazepine,[i] %	6.4	5.6	7.8	5.4$^{\Delta}$	8.4$^{\Delta}$
Opiate,[i] %	0.7	0.2$^{\Delta}$	1.6$^{\Delta}$	0.7	0.7

Significant differences between presence and absence of stated outcome: *p<0.05; †p<0.01; ‡p<0.001; $^{\Delta}$p<0.1; [i] prescribed for the symptomatic relief of dyspnoea / anxiety; $^{\phi}$ either LTOT, ambulatory O_2 or short burst O_2; ICS – inhaled corticosteroid; BDP – beclomethasone diproprionate; ACE – Angiotensin converting enzyme

Few clinical or laboratory measurements available at admission or during the hospital stay were shown to predict readmission following discharge. Of interest, we found no relationship between low BMI and readmission rates although high self-reported weight loss and malnutrition risk (MUST score) were strongly associated with readmission or death within 90 days of discharge. We found no relationship between high p_aCO_2 and outcome and the only laboratory measurement significantly associated with both single and frequent readmissions was a high eosinophil count. Low albumin was strongly associated with 90-day readmission or death whereas, conversely, higher albumin scores were associated with frequent readmission (Table 10.5). This is because of the strong relationship between lower albumin values and mortality, i.e. patients with lower albumin scores have a shorter survival time and are therefore less likely to be frequently readmitted to hospital.

Table 10.5 Clinical and laboratory findings at admission and their association with readmission

Variable	Total population, n=824	90-day readmission or death		Frequent readmission	
		No, n=517	Yes, n=307	No, n=537	Yes, n=287
History and examination findings,					
Purulent sputum, %	52.6	52.3	53.0	51.7	54.3
Ineffective cough, %	9.3	7.5*	12.4*	9.1	9.8
Pedal oedema, %	26.9	23.2†	33.2†	25.1	30.3
Acute confusion, %	10.0	7.7†	13.7†	10.1	9.8

Variable	Total population, n=824	90-day readmission or death		Frequent readmission	
		No, n=517	Yes, n=307	No, n=537	Yes, n=287
Initial non-invasive investigations,					
Heart rate (min^{-1})	102.7 (20.5)	102.9 (19.8)	102.4 (21.6)	102.3 (20.5)	103.4 (20.5)
Systolic BP (mmHg)	139.7 (28.1)	140.6 (27.9)	138.2 (28.4)	138.9 (28.7)	141.3 (26.9)
Diastolic BP (mmHg)	76.6 (16.7)	77.3 (16.5)	75.4 (17.0)	76.2 (16.8)	77.3 (16.5)
Respiratory rate (min^{-1})	25.8 (6.1)	25.8 (6.0)	25.7 (6.3)	25.8 (5.9)	25.8 (8.5)
Temperature (°C), median (IQR)	36.9 (36.4 to 37.6)	36.9 (36.4 to 37.6)	36.9 (36.4 to 37.5)	36.9 (36.4 to 37.6)	36.8 (36.4 to 37.4)
S_pO_2 (%), median (IQR)	92.0 (87.3 to 96.0)	92.0 (88.0 to 96.0)	92.0 (87.0 to 96.0)	92.0 (88.0 to 96.0)	93.0 (87.0 to 98.0)
BMI (kgm^{-2})	24.8 (6.3)	25.1 (6.0)	24.4 (6.7)	24.9 (6.3)	24.7 (6.4)
Weight loss >5%, %	22.5	17.6‡	30.6‡	21.2	24.7
MUST score, median (IQR)	0 (0 to 1)	0 (0 to 1)‡	0 (0 to 2)‡	0 (0 to 1)	0 (0 to 1)
CXR consolidation, %	29	28.4	30.0	31.1$^{\Delta}$	25.1$^{\Delta}$
Arterial blood gas values,					
H^+ (nmol/L), median (IQR)	38.0 (35.5 to 42.7)	38.0 (35.5 to 42.7)	38.9 (35.5 to 43.7)	38.0 (34.7 to 42.7)	38.9 (35.5 to 42.7)
pH, median (IQR)	7.42 (7.37 to 7.45)	7.42 (7.37 to 7.45)	7.41 (7.36 to 7.45)	7.42 (7.37 to 7.46)	7.41 (7.37 to 7.45)
p_aO_2 (kPa), median (IQR)	8.7 (7.3 to 10.5)	8.7 (7.3 to 10.5)	8.7 (7.2 to 10.7)	8.7 (7.3 to 10.5)	8.7 (7.3 to 10.7)
p_aCO_2 (kPa), median (IQR)	5.8 (4.9 to 7.3)	5.7 (4.9 to 7.2)	6.0 (4.9 to 7.6)	5.7 (4.8 to 7.2)	5.9 (4.9 to 7.5)
Bicarbonate (mmol/L)	27.7 (5.2)	27.6 (5.0)	27.9 (5.5)	27.6 (5.1)	28.0 (5.3)
Acidaemic exacerbation, %‡	23.7	23.2	24.4	23.6	23.7
Biochemistry,					
Sodium (mmol/L)	136.3 (4.5)	136.1 (4.5)$^{\Delta}$	136.6 (4.6)$^{\Delta}$	136.2 (4.5)	136.4 (4.6)
Potassium (mmol/L)	4.3 (0.5)	4.3 (0.5)	4.3 (0.5)	4.3 (0.5)	4.3 (0.5)
Urea (mmol/L), median (IQR)	6.3 (4.6 to 8.8)	6.0 (4.4 to 8.5)*	6.7 (4.9 to 9.3)*	6.4 (4.7 to 9.1)	6.2 (4.5 to 8.2)
Creatinine (µmol/L), median (IQR)	92 (77 to 112)	93 (77 to 112)	91 (76 to 112)	92 (77 to 115)	92 (77 to 109)
Albumin (g/L)	38.7 (4.6)	39.2 (4.6)‡	38.0 (4.6)‡	38.4 (4.8)*	39.2 (4.1)*
Glucose (mmol/L), median (IQR)	6.9 (6.0 to 8.0)	7.0 (6.1 to 8.0)$^{\Delta}$	6.7 (5.8 to 8.0)$^{\Delta}$	6.9 (6.0 to 8.0)	6.8 (6.0 to 7.8)

Variable	Total population, n=824	90-day readmission or death		Frequent readmission	
		No, n=517	Yes, n=307	No, n=537	Yes, n=287
CRP (mg/L), median (IQR)	36 (10 to 111)	34 (9 to 116)	39 (11 to 104)	42 (10 to 118)$^{\Delta}$	27 (9 to 91)$^{\Delta}$
Haematology,					
Hb (g/dL)	13.6 (1.9)	13.8 (1.8)†	13.4 (2.1)†	13.7 (1.9)	13.6 (1.8)
Haematocrit	0.43 (0.06)	0.42 (0.05)*	0.40 (0.06)*	0.41 (0.06)	0.41 (0.06)
White cell count ($x10^9$/L), median (IQR)	11.8 (9.1 to 15.3)	11.8 (9.1 to 15.1)	12 (9.1 to 16.1)	12.0 (9.1 to 15.5)	11.6 (9.1 to 15.2)
Neutrophil count ($x10^9$/L), median (IQR)	9.1 (6.8 to 12.6)	9.1 (6.8 to 12.6)	9.1 (6.8 to 12.8)	9.2 (6.9 to 12.7)	8.8 (6.5 to 12.4)
Eosinophil count ($x10^9$/L), median (IQR)	0.1 (0 to 0.2)	0.1 (0 to 0.1)*	0.1 (0 to 0.2)*	0 (0 to 0.1)†	0.1 (0 to 0.2)†

Values shown are mean (SD) unless stated otherwise. Significant differences between presence and absence of stated outcome: *p<0.05; †p<0.01; ‡p<0.001; $^{\Delta}$p<0.1; BP – blood pressure

Length of the index hospital stay was positively correlated with risk of 90-day readmission or death, and patients who required increased social care immediately following hospital discharge had a higher risk of readmission or death compared to those who did not require increased care. There was no relationship between need for assisted ventilation during the index admission and subsequent readmission risk (Table 10.6).

Table 10.6 Developments during hospital admission and their association with readmission

Variable	Total population, n=824	90-day readmission or death		Frequent readmission	
		No, n=517	Yes, n=307	No, n=537	Yes, n=287
Received assisted ventilation, %	18.2	17.2	19.9	17.1	20.2
Length of stay (days), median (IQR)	6 (4 to 11)	6 (3 to 10)‡	8 (4 to 12)‡	6 (4 to 11)	7 (3 to 11)
Increased care package at discharge, %	11.3	9.5*	14.3*	12.3	9.4
Specialist respiratory care, %	68.2	68.5	67.8	68.0	68.6

10.2 INDEPENDENT PREDICTORS OF 90-DAY READMISSION OR DEATH

After screening for collinearity (section 6.8.1): FEV_1 % predicted was retained over FEV_1 (Pearson's r = 0.748); albumin was retained over both haemoglobin and haematocrit (r = 0.377 and 0.313 respectively, and eigenvalues suggest collinearity); the total number of admissions in the previous year was retained over the number of respiratory admissions (Spearman's-ρ = 0.852); and eMRCD was retained over exercise tolerance (ρ = -0.845) and MRCD (ρ = 0.990). Zero-order correlations between the remaining potential continuous prognostic variables are shown in Appendix E (Table 17.8). Pedal oedema at admission and a past history of cor pulmonale were thought likely to be collinear and they were therefore combined into a single variable: cor pulmonale or pedal oedema at admission. Individual comorbidities were entered instead of the CCI and the level of dependency prior to admission was assessed by the need for social care rather than residence in institutional care. Following exclusion of these variables, there was no significant collinearity between potential independent predictors (mean VIF = 1.36; highest individual VIF = 2.59).

The remaining variables underwent backward stepwise logistic regression analysis which identified the following independent predictors of outcome (Table 10.7):

Table 10.7 Independent predictors of 90-day readmission or death – 'Model 4'

Variable	B	S.E.	OR (95% CI)	p value
eMRCD	0.53	0.09	1.69 (1.42 to 2.02)	<0.0001
Number of hospitalisations in the previous year	0.28	0.06	1.32 (1.18 to 1.48)	<0.0001
Recent unexplained weight loss > 5%	0.51	0.19	1.66 (1.15 to 2.40)	0.0067
Cor pulmonale or pedal oedema	0.44	0.17	1.56 (1.11 to 2.18)	0.0097
Social care prior to admission	0.48	0.21	1.62 (1.07 to 2.44)	0.0213
Serum glucose	-0.07	0.03	0.933 (0.873 to 0.997)	0.0402
Male sex	0.31	0.16	1.36 (0.988 to 1.87)	0.0595
Atrial fibrillation	0.42	0.25	1.52 (0.934 to 2.48)	0.0916
Intercept	-3.04	0.45		

S.E. – standard error; OR – odds ratio; CI – confidence interval
Odds of readmission or death = e ^ - [-3.04 + (0.53 x *eMRCD*) + (0.28 x *number of hospitalisations in the previous year*) + (0.51 if *recent unexplained weight loss >5%*) + (0.44 if *cor pulmonale or pedal oedema*) + (0.48 if *social care prior to admission*) - (0.07 x *serum glucose*) + (0.31 if *male sex*) + (0.42 if *atrial fibrillation*)]

Severe stable-state dyspnoea; recent unexplained weight loss; and frequent hospital admissions in the preceding year were all strong independent predictors of 90-day outcome. Our results suggest that a high glucose on admission is weakly protective against poor outcome in those surviving to discharge. This is, perhaps, at odds with clinical reasoning as well as our results (Table 9.6) and previous research on in-hospital mortality (section 2.2.4.4). Although McGhan et al [14] showed a comorbid history of diabetes was protective against readmission, which is in keeping with the association we have shown between glucose and readmission, the lack of association between diabetes and readmission in our study suggests that this is not a true result and may not generalise beyond the study population.

The regression model was estimated to predict 23.3% of the variance of the dependent variable (Nagelkerke's $R^2 = 0.233$) and was a satisfactory fit of the overall dataset (HLGFT, $p = 0.72$). Plotting the observed probability of readmission against predicted probability, per decile of risk, confirms a well calibrated model, with data points closely aligned to the line of best fit (Figure 10.1). 11 cases were statistical outliers although none of these cases significantly influenced the regression model (satisfactory leverage values and Cook's distances). The regression model has good discrimination for 90-day readmission or death: AUROC = 0.752, 95% CI 0.718 to 0.785, and bootstrap estimation of the AUROC confirmed that our results were internally consistent (AUROC = 0.751, 95% CI 0.717 to 0.783).

Figure 10.1 Calibration plot for regression model of 90-day readmission

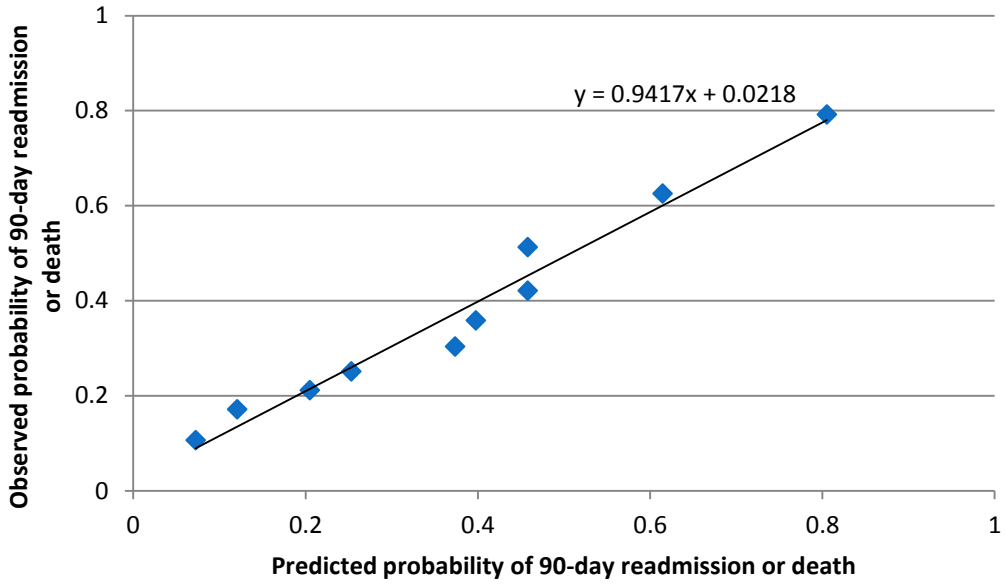
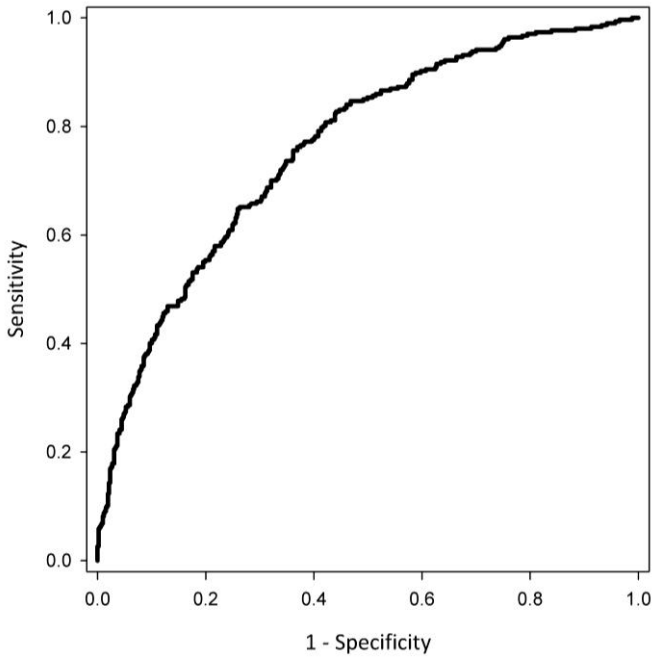


Figure 10.2 Discrimination of Model 4 (Table 10.7) for the prediction of 90-day readmission



10.2.1 DEVELOPING A CLINICAL PREDICTION TOOL FOR 90-DAY READMISSION

Using the same methods described in section 6.8.3.2, variables associated with 90-day readmission or death were categorised (Table 10.8) and independent categorical predictors of 90-day readmission were identified using backwards stepwise logistic

regression analysis (Table 10.9). Due to concerns over validity and generalisability, serum glucose was excluded from the analysis.

Table 10.8 Categorical variables entered in to logistic regression analysis

Variable	Categories			
	0†	1	2	3
Age, years	< 75	≥ 75		
Number of hospitalisations in the previous year	< 2	≥ 2		
Number of episodes of AECOPD in the previous year	< 3	≥ 3		
FEV_1 % predicted	≥ 30	< 30		
FVC, litres	≥ 1.9	< 1.9		
eMRCD	1 to 3	4	5a	5b
Serum sodium, mmol/L*	≥ 135	< 135		
Eosinophil count, $x10^9$/L*	< 0.05	≥ 0.05		
Urea, mmol/L*	< 6.5	≥ 6.5		
Albumin, g/L*	≥ 38	< 38		
Length of hospital stay, days	< 7	≥ 7		
Acute confusion*	No	Yes		
Recent unexplained weight loss	< 5%	≥ 5%		
Sex	Female	Male		
Social care prior to admission	No	Yes		
Stroke disease	No	Yes		
Ischaemic heart disease	No	Yes		
Atrial fibrillation	No	Yes		
Cor pulmonale or pedal oedema	No	Yes		
Anxiety or depression	No	Yes		
LTOT	No	Yes		
Home nebuliser	No	Yes		
Previous AECOPD requiring NIV	No	Yes		

† reference category for regression analysis; * at the time of hospital admission

The regression model (Table 10.9) explained 22.9% of the variance in the outcome variable (Nagelkerke's $R^2 = 0.229$) and was a good fit of the overall dataset (HLGFT, p = 0.31). There were few (1.2%) statistical outliers, and no outliers had a significant influence on the regression model (all leverage values < 0.036 and Cook's distances < 1).

Table 10.9 Independent categorical predictors of 90-day readmission or death

Variable	B	S.E.	OR (95% CI)	p value
eMRCD				
1 to 3			1	
4	0.62	0.22	1.86 (1.22 to 2.84)	0.0038
5a	0.94	0.26	2.56 (1.53 to 4.28)	0.0003
5b	1.72	0.32	5.58 (2.98 to 10.4)	<0.0001
≥ 2 hospitalisations in previous 12 months	1.02	0.19	2.76 (1.92 to 3.99)	<0.0001
Recent unexplained weight loss > 5%	0.57	0.19	1.76 (1.22 to 2.55)	0.0025
Social care prior to admission	0.47	0.21	1.59 (1.05 to 2.41)	0.0270
Cor pulmonale or pedal oedema	0.43	0.17	1.54 (1.10 to 2.16)	0.0121
Urea ≥ 6.5 mmol/L	0.32	0.16	1.38 (1.00 to 1.90)	0.0469
Eosinophil count ≥ $0.05x10^9$/L*	0.31	0.16	1.36 (0.993 to 1.87)	0.0555
Intercept	-1.32	0.20		

S.E. – standard error; OR – odds ratio; CI – confidence interval. *at hospital admission

Based on the above findings, scores were assigned to all categorical independent predictors that remained significant in the final model, and the CRUSHED (**C**or pulmonale (or pedal oedema); **R**ecent unexplained weight loss; elevated **U**rea; **S**ocial care; previous **H**ospitalisations; **e**xtended **D**yspnoea score) predictive tool was developed (Table 10.10).

Table 10.10 The CRUSHED prognostic score

Variable	Score
Cor pulmonale or pedal oedema	1
Recent unexplained weight loss > 5%	1
Urea ≥ 6.5 mmol/L	1
Social care prior to admission	1
≥ 2 hospitalisations in previous 12 months	2
extended MRC Dyspnoea score	
1 to 3	0
4	1
5a	2
5b	3
Maximum CRUSHED score	9

The distribution of patients across the CRUSHED score, and the associated readmission rate, sensitivity and specificity are shown in Table 10.11. The discrimination of CRUSHED score was good for 90-day readmission or death (AUROC = 0.735, 95% CI

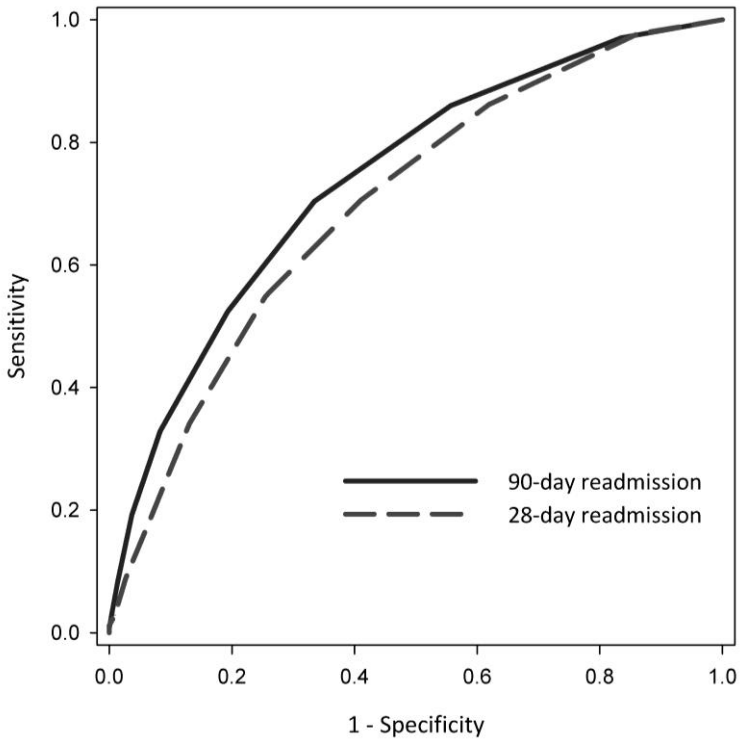
0.701 to 0.770), and moderate for 28-day readmission or death (AUROC = 0.691, 95% CI 0.647 to 0.734) (Figure 10.3). Internal validation confirmed the performance of the tool to be good for 90-day readmission (bootstrapped AUROC = 0.735, 95% CI 0.700 to 0.769).

Table 10.11 The CRUSHED score and 90-day readmission or death

CRUSHED Score	n	90-day readmission, n (%)	Sensitivity*	Specificity*
0	69	11.6	1	0
1	175	16.0	0.97	0.10
2	173	30.1	0.88	0.34
3	127	40.9	0.71	0.56
4	118	48.3	0.58	0.72
5	81	56.8	0.36	0.85
6	44	70.5	0.19	0.93
7	24	91.7	0.11	0.97
8	10	80.0	0.05	0.99
9	3	100	0.012	1

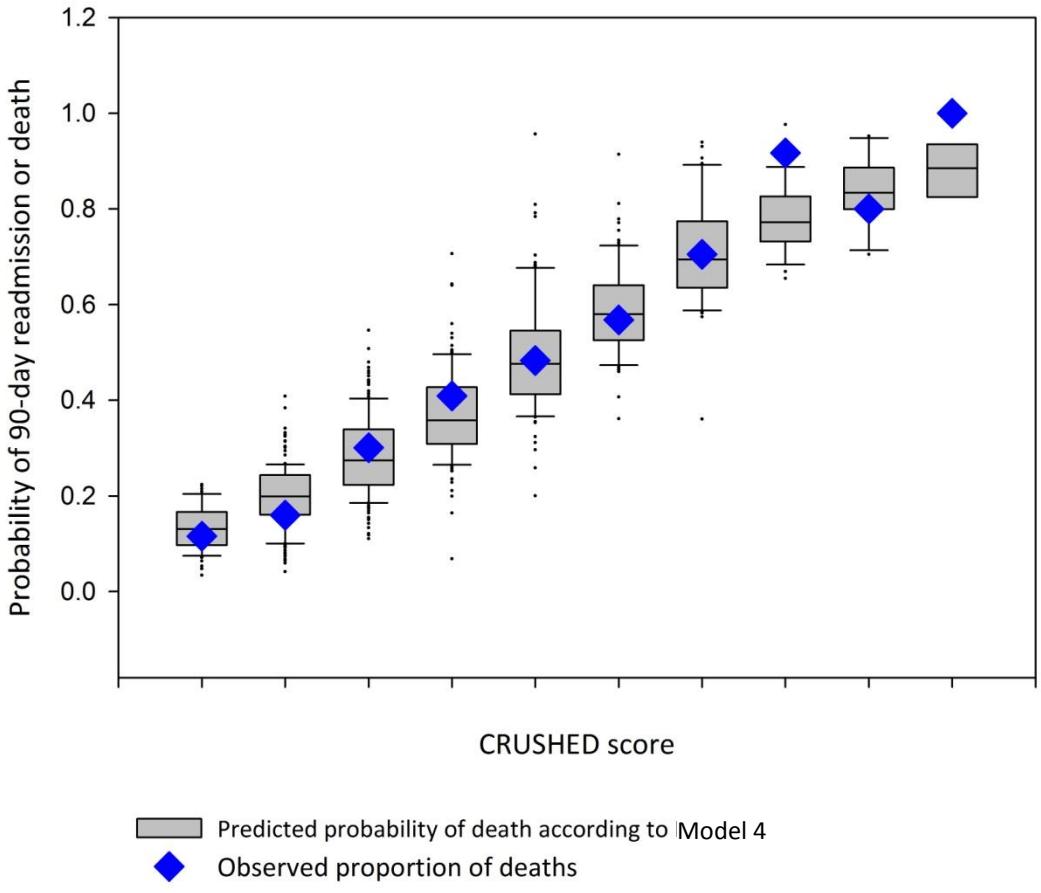
* Positive test result = score ≥ corresponding CRUSHED score

Figure 10.3 ROC curve showing discrimination of CRUSHED score for 90-day and 28-day readmission or death



There was no significant difference in discrimination between Model 4 and the CRUSHED score (p = 0.059). The calibration between the CRUSHED score and the predicted probabilities according to Model 4 (Table 10.7) is shown in Figure 10.4. This shows a stepwise increase in the predicted probability of readmission for each CRUSHED grade, and the CRUSHED score is well calibrated to Regression Model 4 across most risk categories (CRUSHED grade 0 to 6). There is suboptimal calibration for patients at a very high risk of outcome (CRUSHED grades 7, 8, 9) where the observed proportion of outcome lies outside the predicted probability however, this may be due to the small numbers of patients within these grades.

Figure 10.4 Calibration between the observed probability according to CRUSHED score and the predicted probability of readmission according to Model 4



10.3 INDEPENDENT PREDICTORS OF FREQUENT READMISSION

Variables which were not collinear, but were associated with frequent readmission ($p < 0.10$) on univariate analysis were entered in to backward stepwise logistic regression analysis (Table 10.12).

Table 10.12 Independent predictors of frequent hospital readmission ('Model 5')

Variable	B	S.E.	OR (95% CI)	p value
Total number of hospitalisations in previous year	0.42	0.06	1.52 (1.35 to 1.71)	<0.0001
Previous NIV for AECOPD	0.72	0.24	2.06 (1.28 to 3.32)	0.0030
Serum albumin, g/L	0.04	0.02	1.05 (1.01 to 1.08)	0.0107
Cerebrovascular disease	0.60	0.23	1.82 (1.15 to 2.86)	0.0101
Hypertension	-0.35	0.16	0.708 (0.513 to 0.977)	0.0355
Intercept	-2.80	0.69		

S.E. – standard error; OR – odds ratio; CI – confidence interval

Nagelkerke's R^2 for the regression model was 0.153 and the model was a satisfactory fit of the data (HLGFT, $p = 0.271$). Only 4 cases were statistical outliers and none had a significant influence on the regression model. Plotting predicted against observed probabilities of frequent readmission (Figure 10.5) shows that the regression model has good calibration overall although it slightly overestimates the risk of frequent readmission (line of best fit gradient = 0.846). The discrimination of Model 5 for frequent readmission was satisfactory (AUROC = 0.701, 0.662 to 0.739) and was internally valid (bootstrapped AUROC = 0.700, 0.661 to 0.738) (Figure 10.6).

Figure 10.5 Calibration plot for Model 5 for the prediction of frequent readmission

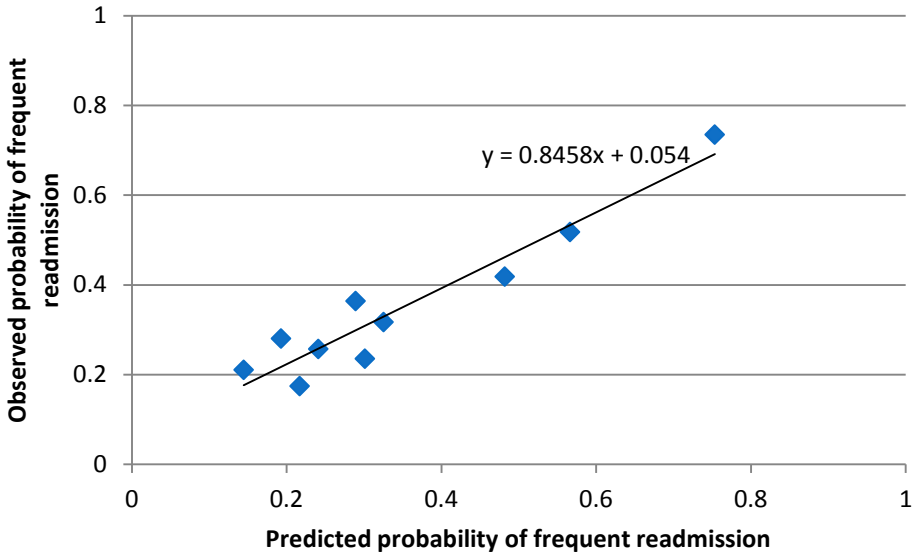
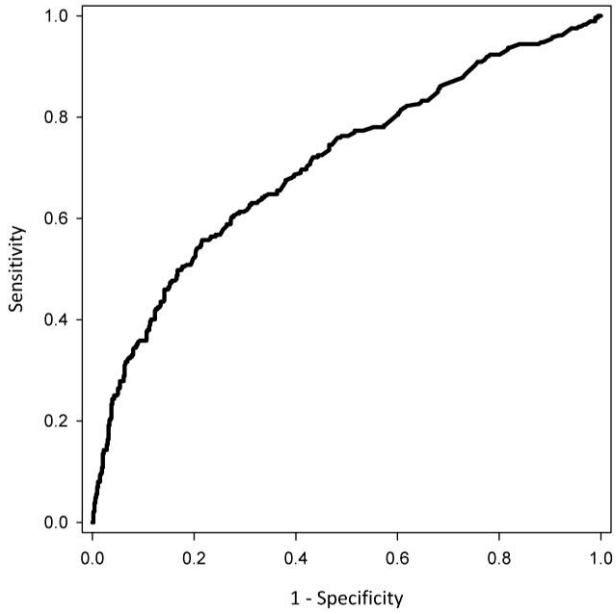


Figure 10.6 Discrimination of Model 5 for frequent readmission following hospital discharge



CHAPTER 11 PREDICTING IN-HOSPITAL MORTALITY IN PATIENTS RECEIVING ASSISTED VENTILATION

Aim 1e: identify independent predictors of in-hospital mortality in patients receiving assisted ventilation following hospitalisation for AECOPD.

199 (21.6%) patients required assisted ventilation during their hospital stay due to development of ARF; commenced at the time of admission in 130. Compared to the remainder of the population (n = 721), patients treated with assisted ventilation: were more likely to be female; had more severe lung function impairment; had more severe stable-state dyspnoea; had less comorbidity; and had markers suggesting they were experiencing a more severe acute exacerbation (more frequent coexistent consolidation and acute confusion) (Table 11.1). Patients receiving assisted ventilation were more likely to die in hospital (24.6% v. 6.5%, $p < 0.0001$) and had a longer median length of stay (10 v. 6 days, $p < 0.0001$). There were no differences between the two groups in rates of readmission or death following discharge.

Table 11.1 Characteristics of patients receiving assisted ventilation, and comparisons with patients not ventilated

Variable	Patients receiving assisted ventilation, n=199	Patients not receiving assisted ventilation, n=721
Sociodemographic details,		
Admission hospital (NTGH), %	54.3	55.1
Age (years)	73.6 (9.8)	72.9 (10.1)
Female, %	61.3†	51.9†
Smoking load (cigarette pack years), median (IQR)	46 (35 to 60)	45 (31 to 60)
Institutional care, %	6.5	6.5
Markers of disease severity,		
Number of hospital admissions in previous year, median (IQR)	0 (0 to 1)	0 (0 to 1)
Number of AECOPD in previous year, median (IQR)	3 (1 to 4)	3 (1 to 4)
FEV_1 % predicted	38.1 (16.1)†	45.1 (17.1)†
MRCD, median (IQR)	4 (4 to 5)†	4 (3 to 5)†
Cor pulmonale, %	18.1†	7.8†
LTOT, %	23.1†	9.4†
Comorbidity & nutritional status,		
CCI, median (IQR)	2 (1 to 3)†	2 (1 to 3)†*
BMI, kgm^{-2}	25.1 (7.0)	24.4 (6.1)

Variable	Patients receiving assisted ventilation, n=199	Patients not receiving assisted ventilation, n=721
Admission information and hospital outcomes,		
Coexistent consolidation, %	40.7†	30.2†
Acute confusion, %	26.6†	8.7†
In-hospital mortality, %	24.6†	6.5†
30-day mortality, %	26.6†	8.6†
Length of stay (days), median (IQR)	10 (6 to 16)†	6 (3 to 10)†
Readmission or death‡		
28-day	22.0	20.8
90-day	40.7	36.5

† significant difference between patients receiving and not receiving assisted ventilation; * CCI significantly higher in patients not receiving assisted ventilation; ‡ in patients surviving to discharge; CCI – Charlson comorbidity index

To assist comparisons with the published randomised controlled trials in the use of NIV in patients hospitalised with NIV,[170, 396] which included patients with mild to moderate acidaemia (7.25 ≤ pH < 7.35) and reported an in-hospital mortality rate of ~10%, Table 11.2 shows the mortality rates in patients receiving ventilation in this study, stratified according to the severity of acidaemia.

Table 11.2 In-hospital mortality rates in ventilated patients, stratified according to severity of acidaemia

pH	Acidaemic at hospital admission, n = 130		Acidaemic at any time, n = 199	
	n	In-hospital mortality, n (%)	n	In-hospital mortality, n (%)
< 7.25	54	11 (20.4)	80	27 (33.8)
7.25 to 7.35	76	9 (11.8)	119	22 (18.5)

11.1.1 UNIVARIATE ASSOCIATIONS WITH IN-HOSPITAL MORTALITY IN PATIENTS RECEIVING ASSISTED VENTILATION

As with the total population (section 9.1.1), patients who died in hospital after being treated with assisted ventilation were older and less likely to be living independently (Table 11.3). Although associated with in-hospital death in the total population (Table 9.2), spirometric measures of disease severity (FEV_1 and FVC) had no relationship with mortality in patients ventilated (Table 11.4). It is worth noting, however, that patients receiving assisted ventilation had lower mean FEV_1 values than those not ventilated and therefore the narrow range of FEV_1 values in ventilated patients may have limited its discriminative strength. As with the total population of 920 patients studied, among the 199 who were treated with assisted ventilation, the severity of stable-state

dyspnoea (MRCD, eMRCD) and exercise capacity were strongly associated with in-hospital mortality.

There was a similar overall burden, and distribution, of comorbidity in the total population (n = 920) (Table 9.3) and the subgroup receiving assisted ventilation (Table 11.5). Also, similarly to the total population, cerebrovascular disease, chronic kidney disease and the overall comorbidity burden (CCI) were associated with in-hospital death, but no respiratory comorbidities were associated with mortality. Osteoporosis was also associated with mortality in those ventilated and interestingly, coexistent anxiety or depression may have been protective against death (p = 0.0578). No pre-admission maintenance medications were associated with in-hospital mortality (Table 11.6), and in particular, patients in receipt of LTOT were not at a greater risk of death. It should, however, be noted that a larger proportion of patients treated with assisted ventilation were in receipt of LTOT compared to the total population (23.1% v. 12.4% respectively).

Patients with an ineffective cough on admission, who received assisted ventilation during their hospital stay, had a higher mortality. Similarly to the total population, coexistent pneumonia and poor nutritional status (low BMI or recent weight loss) were associated with mortality (Table 11.7). Interestingly, low oxygen saturation appeared to be protective against mortality, however this is likely to be because the most unwell patients received high-flow oxygen treatment in the pre-hospital setting and therefore had higher oxygen saturations compared to less unwell patients who did not receive (high-flow) oxygen prior to admission. Furthermore, patients with well preserved oxygen saturation at admission to hospital are unlikely to have had ARF at admission, and therefore well preserved oxygen saturation at admission is likely to be associated with a longer time to recognition of ARF.

Similar biochemical and haematological markers were associated with mortality in patients receiving assisted ventilation as in the total population (high urea, low albumin, high CRP, low haemoglobin, high neutrophil count and low eosinophil count), although in the former, creatinine, potassium and glucose were not associated with mortality (Table 11.8).

Table 11.3 Sociodemographic details of ventilated patients and in-hospital mortality

Variable	Population ventilated, n=199	Survived admission, n=150	Died in-hospital, n=49	p value*
Age	73.6 (9.8)	71.8 (9.7)	79.2 (8.2)	<0.0001
Female, %	61.3	60.0	65.3	0.61
Admission hospital (NTGH), %	54.3	52.7	59.2	0.51
Institutional care, %	6.5	6.0	8.2	0.74
Social care prior to admission, %	27.6	24.0	38.8	0.0647
Smoking load (cpy), median (IQR)	46 (35 to 60)	53 (35 to 60)	40 (32.5 to 60)	0.24

* comparison between patients surviving admission and those who died during admission in patients treated with assisted ventilation

Table 11.4 Health resource use, disease severity and mortality in ventilated patients

Variable	Population ventilated, n=199	Survived admission, n=150	Died in-hospital, n=49	p value*
Health resource use,				
Number of respiratory admissions in previous year, median (IQR)	0 (0 to 1)	0 (0 to 1)	0 (0 to 1)	0.31
Total number of admissions in previous year, median (IQR)	0 (0 to 1)	0 (0 to 1)	1 (0 to 2)	0.22
Number of AECOPD in previous year, median (IQR)	3 (1 to 4)	3 (1 to 4)	3 (2 to 4)	0.81
Previous NIV for AECOPD, %	26.1	28.7	18.4	0.19
Previous pulmonary rehabilitation, %	9.5	10.0	8.2	1.0
Spirometry,				
FEV_1 (litres)	0.788 (0.36)	0.807 (0.38)	0.732 (0.28)	0.21
FEV_1 % predicted	38.1 (16.1)	37.9 (16.5)	38.7 (14.7)	0.75
FVC (litres)	1.83 (0.70)	1.87 (0.72)	1.73 (0.62)	0.21
FEV_1 / FVC, median (IQR)	43 (36 to 50)	43 (35 to 50)	43 (37.5 to 51.5)	0.78
Exercise capacity and disease complications,				
MRCD, median (IQR)	4 (4 to 5)	4 (4 to 5)	5 (5 to 5)	<0.0001
eMRCD, median (IQR)	4 (4 to 5a)	4 (4 to 5a)	5a (5a to 5b)	<0.0001
Exercise tolerance (metres), median (IQR)	20 (10 to 50)	20 (10 to 50)	10 (6 to 20)	<0.0001
Housebound, %	50.3	41.3	77.6	<0.0001
Cor pulmonale, %	18.1	18.7	16.3	0.83

* comparison between patients surviving admission and those who died during admission in patients treated with assisted ventilation

Table 11.5 Comorbidity and mortality in patients treated with assisted ventilation

Variable	Population ventilated, n=199	Survived admission, n=150	Died in-hospital, n=49	p value*
Respiratory,				
Bronchiectasis, %	6.0	4.7	10.2	0.17
Asthma, %	3.0	3.3	2.0	1.0
Pulmonary fibrosis, %	1.5	0.7	4.1	0.15
Obstructive sleep apnoea, %	2.0	1.3	4.1	0.25
Cardiovascular,				
Hypertension, %	43.2	43.3	42.9	1
Cerebrovascular disease, %	10.6	6.7	22.4	0.0053
Ischaemic heart disease, %	23.1	22.0	26.5	0.56
Atrial fibrillation, %	12.6	10.7	18.4	0.21
LV dysfunction, %	7.0	6.0	10.2	0.34
Thromboembolic disease, %	5.0	5.3	4.1	1.0
Valvular heart disease, %	3.0	2.7	4.1	0.64
Peripheral vascular disease, %	5.0	4.0	8.2	0.27
General,				
Diabetes mellitus, %	17.6	19.3	12.2	0.29
Osteoporosis, %	12.6	9.3	22.4	0.0242
Rheumatoid arthritis, %	2.5	2.0	4.1	0.60
Cognitive impairment, %	4.5	4.7	4.1	1.0
Chronic kidney disease, %	7.0	4.0	16.3	0.0072
Anxiety / depression, %	24.6	28.0	14.3	0.0578
Chronic liver disease, %	1.0	1.3	0	1.0
Peptic ulcer disease, %	5.0	4.7	6.1	0.71
Past history of cancer, %	5.5	3.3	12.2	0.0281
History of active cancer, %	2.5	2.0	4.1	0.60
Comorbidity burden,				
Charlson Comorbidity Index, median (IQR)	2 (1 to 3)	2 (1 to 2)	2 (1 to 3)	0.0132

* comparison between patients surviving admission and those who died during admission in patients treated with assisted ventilation

Table 11.6 Medications at admission and mortality in ventilated patients

Variable	Population ventilated, n=199	Survived admission, n=150	Died in-hospital, n=49	p value*
Respiratory,				
LTOT, %	23.1	21.3	28.6	0.33
Ambulatory oxygen, %	4.5	4.7	4.1	1.0
Short burst oxygen, %	13.1	13.3	12.2	1
Home oxygen therapy,$^{\phi}$ %	37.2	35.3	42.9	0.40
Home nebuliser, %	16.1	15.3	18.4	0.66
Inhaled corticosteroid (ICS), %	77.9	77.3	79.6	0.84
ICS dose (BDP equivalent), median (IQR)	2000 (1000 to 2000)	2000 (1000 to 2000)	2000 (2000 to 2000)	0.38
Inhaled long-acting beta agonist, %	75.9	75.3	77.6	0.85
Inhaled anticholinergic, %	68.8	66.0	77.6	0.16
Long-term oral corticosteroid, %	8.0	7.3	10.2	0.55
Carbocysteine, %	12.6	10.0	20.4	0.0797
Theophylline, %	9.0	7.3	14.3	0.16
Cardiovascular,				
Statin, %	42.7	43.3	40.8	0.87
Beta-blocker, %	8.0	7.3	10.2	0.55
ACE inhibitor, %	27.6	27.3	28.6	0.86
Angiotensin receptor blocker, %	5.0	4.0	8.2	0.27
Diuretic, %	43.2	42.0	46.9	0.62
Other,				
Benzodiazepine,† %	8.0	9.3	4.1	0.37
Opiate,† %	0.5	0	2.0	0.25

* comparison between patients surviving admission and those who died during admission in patients treated with assisted ventilation; $^{\phi}$ either LTOT, ambulatory O_2 or short burst O_2; ICS – inhaled corticosteroid; BDP – beclomethasone diproprionate; ACE – Angiotensin converting enzyme

Table 11.7 Clinical findings at admission to hospital and mortality in patients treated with assisted ventilation

Variable	Population ventilated, n=199	Survived admission, n=150	Died in-hospital, n=49	p value*
History and examination findings,				
Purulent sputum, %	48.2	48.6	46.7	0.87
Ineffective cough, %	23.6	20.0	34.7	0.0515

Variable	Population ventilated, n=199	Survived admission, n=150	Died in-hospital, n=49	p value*
Pedal oedema, %	41.5	43.4	34.9	0.38
Acute confusion, %	26.6	24.7	32.7	0.27
Heart rate (min^{-1})	107.3 (20.6)	108.0 (20.7)	105.0 (20.2)	0.37
Initial non-invasive investigations,				
Systolic BP (mmHg)	141.8 (27.6)	142.0 (26.9)	141.1 (30.0)	0.84
Diastolic BP (mmHg)	77.6 (18.5)	78.3 (18.4)	75.4 (18.8)	0.34
Respiratory rate (min^{-1})	27.1 (7.4)	26.9 (6.9)	27.9 (8.8)	0.43
Temperature (°C), median (IQR)	36.9 (0.91)	36.9 (0.89)	36.7 (0.95)	0.21
S_pO_2 (%), median (IQR)	89 (80 to 96)	88 (79 to 96)	93 (85 to 96.5)	0.0228
BMI (kgm^{-2})	25.1 (6.96)	25.7 (6.90)	23.3 (6.90)	0.0363
Weight loss >5%, %+	23.1	18.7	36.7	0.0117
CXR consolidation, %	40.7	36.0	55.1	0.0200

* comparison between patients surviving admission and those who died during admission in patients treated with assisted ventilation

Table 11.8 Laboratory results at admission and in-hospital mortality in patients treated with assisted ventilation

Variable	Population ventilated, n=199	Survived admission, n=150	Died in-hospital, n=49	p value*
Biochemistry,				
Sodium (mmol/L)	136.5 (5.11)	136.4 (5.34)	136.8 (4.37)	0.65
Potassium (mmol/L)	4.60 (0.59)	4.59 (0.57)	4.65 (0.67)	0.57
Urea (mmol/L), median (IQR)	7.1 (5.1 to 10.8)	6.8 (5.0 to 10.6)	8.8 (6.1 to 12.0)	0.0374
Creatinine (µmol/L), median (IQR)	92 (74 to 120)	93 (78 to 119)	90 (73 to 136)	0.83
Albumin (g/L)	38.1 (5.07)	38.6 (4.96)	36.4 (5.09)	0.0085
Glucose (mmol/L), median (IQR)	7.5 (6.6 to 9.3)	7.5 (6.6 to 9.3)	7.6 (6.2 to 8.8)	0.71
CRP (mg/L), median (IQR)	49 (14 to 112)	43 (11 to 98)	77 (28.5 to 130.5)	0.0084
Haematology,				
Hb (g/dL)	13.7 (2.17)	13.9 (2.16)	13.2 (2.15)	0.0337
Haematocrit	0.425 (0.068)	0.431 (0.068)	0.406 (0.063)	0.0242
White cell count ($x10^9$/L), median (IQR)	12.2 (9.5 to 15.2)	12.2 (9.1 to 15.0)	12.6 (9.7 to 18.2)	0.26

Variable	Population ventilated, n=199	Survived admission, n=150	Died in-hospital, n=49	p value*
Neutrophil count (x10^9/L), median (IQR)	9.3 (7.0 to 12.8)	9.1 (6.8 to 12.5)	10.6 (7.7 to 16.9)	0.0488
Eosinophil count (x10^9/L), median (IQR)	0 (0 to 0.1)	0 (0 to 0.2)	0 (0 to 0.1)	0.0037

* comparison between patients surviving admission and those who died during admission in patients treated with assisted ventilation

Of the 199 patients who received assisted ventilation, 4 patients were immediately invasively ventilated and 195 were initially treated with NIV: of these, 4 patients progressed to invasive ventilation due to failure of NIV. At hospital admission, patients with a lower pH, and higher p_aCO_2 appeared to, counterintuitively, be at a lower risk of mortality. However this is due to the strong effect that the time from admission to the development of ARF has on mortality. Therefore, the patients at the highest risk of death were those who had no evidence of respiratory failure (i.e. higher pH and lower p_aCO_2) at admission, but then deteriorated and developed ARF later during their hospital stay.

At the time of commencement of assisted ventilation, median (IQR) pH was 7.26 (7.19 to 7.30) and most patients had severe hypercapnia (median (IQR) = 9.9 (8.4 to 11.7) kPa) (Table 11.9). Of the 186 patients who had ABG data recorded 1 to 2 hours after commencing assisted ventilation, 136 (73.1%) showed evidence of improvement (increase in pH), compared to ABG at ventilation commencement, and 50 (26.9%) had not improved. 4 to 6 hours after ventilation commencement, acidaemia had improved to some extent in 114 (76.5%) and worsened or not improved in 35 (23.5%). The relationships between subsequent ABG results and mortality are shown in Table 11.9.

Table 11.9 Blood gas results during initiation of assisted ventilation and mortality

Variable	Population ventilated, n=199	Survived admission, n=150	Died in-hospital, n=49	p value*
ABG results at hospital admission, n = 199				
Hydrogen ion concentration (nmol/L), median (IQR)	51.3 (42.7 to 58.9)	51.3 (45.4 to 58.9)	43.7 (36.3 to 56.2)	0.0039
pH, median (IQR)	7.29 (7.23 to 7.37)	7.29 (7.23 to 7.34)	7.36 (7.25 to 7.44)	0.0039

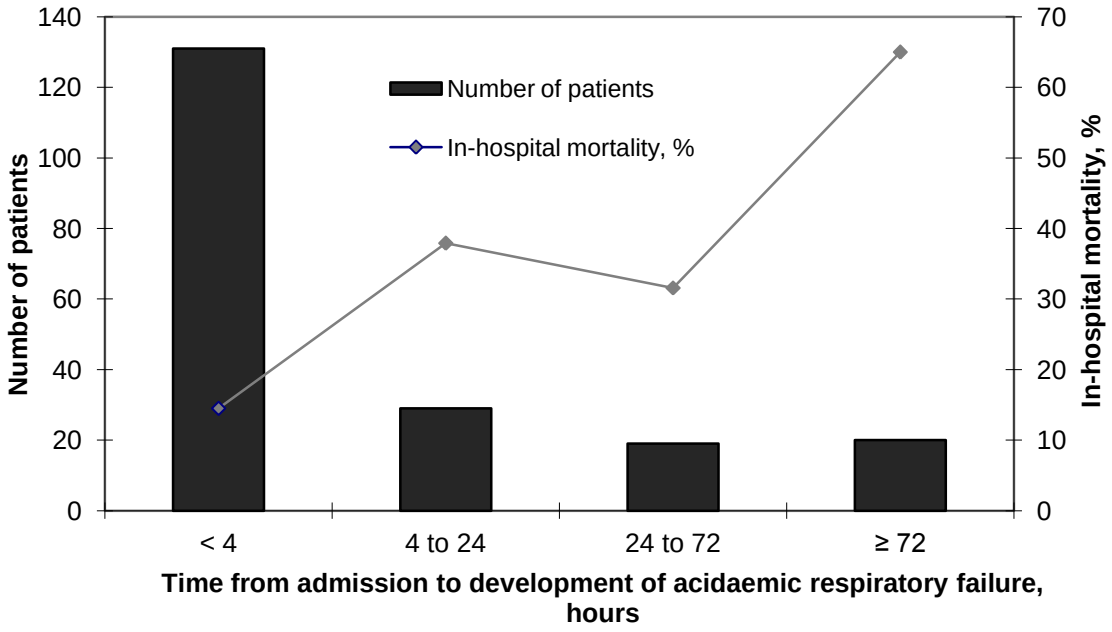
Variable	Population ventilated, n=199	Survived admission, n=150	Died in-hospital, n=49	p value*
p_aCO_2 (kPa), median (IQR)	9.20 (7.20 to 11.3)	9.50 (7.58 to 11.5)	7.60 (5.55 to 10.1)	0.0017
p_aO_2 (kPa), median (IQR)	8.40 (6.80 to 12.0)	8.60 (6.70 to 12.4)	7.90 (6.80 to 11.0)	0.39
Bicarbonate (mmol/L)	33.6 (7.30)	34.1 (7.20)	31.9 (7.43)	0.0631
Time from admission to first recognition of ARF (hours), median (IQR)	1.51 (0.50 to 14.8)	1.24 (0.41 to 4.16)	10.7 (1.32 to 99.6)	<0.0001
ABG at commencement of assisted ventilation, n=199				
Hydrogen ion concentration (nmol/L), median (IQR)	59.9 (50.1 to 64.6)	53.7 (49.8 to 62.0)	58.9 (50.7 to 72.4)	0.0309
pH, median (IQR)	7.26 (7.19 to 7.30)	7.28 (7.21 to 7.30)	7.23 (7.13 to 7.31)	0.0309
p_aO_2 (kPa), median (IQR)	8.1 (6.9 to 10.1)	8.1 (6.9 to 9.8)	7.7 (6.8 to 10.5)	0.30
p_aCO_2 (kPa), median (IQR)	9.9 (8.4 to 11.7)	10.0 (8.5 to 11.6)	10.1 (9.1 to 12.7)	0.75
Bicarbonate (mmol/L)	33.2 (8.44)	34.3 (7.19)	30.8 (8.36)	0.0055
RR, min^{-1}	27.8 (8.12)	26.8 (8.13)	30.8 (7.36)	0.0022
ABG 1-2 hours post ventilation commencement, n=186				
Hydrogen ion concentration (nmol/L), median (IQR)	49.5 (44.7 to 57.5)	49.0 (44.7 to 56.2)	51.3 (45.2 to 59.6)	0.17
pH, median (IQR)	7.31 (7.24 to 7.35)	7.31 (7.25 to 7.35)	7.29 (7.22 to 7.34)	0.17
pH improved, %¤	73.1	73.4	72.1	0.98
p_aO_2 (kPa), median (IQR)	8.7 (7.6 to 10.5)	8.7 (7.6 to 10.5)	8.9 (7.7 to 11.2)	0.63
p_aCO_2 (kPa), median (IQR)	9.0 (7.3 to 10.7)	9.2 (7.5 to 10.8)	8.4 (7.1 to 10.5)	0.38
Bicarbonate (mmol/L)	32.9 (7.8)	33.8 (7.3)	30.1 (8.8)	0.0067
RR, min^{-1}	22.3 (7.3)	21.1 (6.4)	26.2 (9.0)	0.0018
ABG 4-6 hours post ventilation commencement, n=149				
Hydrogen ion concentration (nmol/L), median (IQR)	47.9 (41.7 to 53.7)	47.9 (41.7 to 53.7)	51.3 (45.2 to 59.6)	0.0438
pH, median (IQR)	7.32 (7.27 to 7.38)	7.32 (7.27 to 7.38)	7.29 (7.23 to 7.35)	0.0438
pH improved, %†	76.5	75.9	78.8	0.50
p_aO_2 (kPa), median (IQR)	9.2 (8.1 to 10.6)	9.2 (8.0 to 10.5)	9.3 (7.9 to 10.7)	0.92
p_aCO_2 (kPa), median (IQR)	8.8 (7.2 to 10.4)	8.8 (7.2 to 10.4)	8.9 (7.4 to 10.2)	0.88
Bicarbonate (mmol/L)	33.3 (7.4)	33.8 (7.6)	31.7 (6.5)	0.15

Variable	Population ventilated, n=199	Survived admission, n=150	Died in-hospital, n=49	p value*
RR, min^{-1}	20.7 (6.1)	19.9 (5.2)	23.4 (8.1)	0.0288
Progress of assisted ventilation,				
Invasively ventilated, %‡	2.0	2.0	2.1	1.0
Length of assisted ventilation (days), median (IQR)	4 (1 to 5)	4 (2 to 6)	3 (1 to 6)	0.0023

ARF – acidaemic respiratory failure; * comparison between patients surviving admission and those who died during admission in patients treated with assisted ventilation; † compared to pH at ventilation commencement; ‡ progressed to invasive ventilation following failure of NIV

The time between admission and the first recognition of ARF was strongly positively correlated with in-hospital mortality (Table 11.9) and a detailed breakdown of time to respiratory acidosis and mortality in patients treated with assisted ventilation is shown in Figure 11.1. The risk of mortality increased significantly if acidaemia developed after 4 hours, and further increased in patients developing acidaemia after 72 hours (65% in-hospital mortality).

Figure 11.1 Time between admission and treatment with assisted ventilation, and the respective in-hospital mortality



11.1.2 INDEPENDENT PREDICTORS OF MORTALITY IN PATIENTS RECEIVING ASSISTED VENTILATION

Categorical variables with a markedly asymmetric split were excluded and all variables associated with in-hospital mortality ($p < 0.10$) were assessed for evidence of multicollinearity (section 6.8.1). Where appropriate, physiological measurements at the time of ventilation commencement were included instead of those recorded at the time of admission. Individual comorbidities were chosen over the CCI. Zero-order correlations between the remaining potential predictors are shown in Appendix E (Table 17.7). The remaining variables showed no evidence of significant collinearity (mean VIF = 1.37; maximum VIF = 1.79).

The final regression model is shown in Table 11.10. The model was estimated to account for 55% of the variance in the dependent variable (Nagelkerke's $R^2 = 0.55$) and was a satisfactory fit of the dataset (HLGFT, $p = 0.658$; 7 (3.5%) statistical outliers; and acceptable leverage values and Cook's distances).

Table 11.10 Independent predictors of in-hospital mortality in patients treated with assisted ventilation – 'Model 6'

Variable	B	S.E.	OR (95% CI)	p value
eMRCD	0.87	0.26	2.38 (1.44 to 3.95)	0.0007
Age (years)	0.09	0.03	1.09 (1.03 to 1.15)	0.0029
HCO_3^- concentration (mmol/L)*	-0.09	0.03	0.912 (0.856 to 0.971)	0.0038
Ineffective cough†	1.53	0.55	4.61 (1.57 to 13.5)	0.0055
Time to recognition of ARF (hours)	0.01	0.00	1.01 (1.00 to 1.02)	0.0076
Neutrophil count ($x10^9$/L)†	0.11	0.04	1.12 (1.03 to 1.22)	0.0105
Unintentional weight loss >5%	1.35	0.56	3.85 (1.29 to 11.5)	0.0156
History of anxiety or depression	-1.45	0.61	0.235 (0.071 to 0.774)	0.0173
Cerebrovascular disease	1.54	0.67	4.68 (1.26 to 17.4)	0.0215
Eosinophil count ($x10^9$/L)†	-5.63	2.86	0.004 (0.000 to 0.979)	0.0491
Intercept	-10.7	2.79		

* at the time of commencement of assisted ventilation; † at the time of hospital admission

Odds of in-hospital mortality = e^ - [-10.7 + (0.87 x *eMRCD*) + (0.09 x *age*) – (0.09 x *HCO_3^- concentration**) + (1.53 if *ineffective cough*†) + (0.01 x *time to recognition of ARF*) + (0.11 x *neutrophil count*) + (1.35 if *unintentional weight loss >5%*) – (1.45 if *history of anxiety or depression*) + (1.54 if *cerebrovascular disease*) - (5.63 x *eosinophil count*†)]

Discrimination for in-hospital mortality for the model was excellent (AUROC = 0.913, 0.869 to 0.956) (Figure 11.2) and internally valid (bootstrapped AUROC = 0.911, 0.863

to 0.950). A calibration plot of observed versus predicted probability of death, per decile of risk, showed the model to be well calibrated (gradient = 0.98) and the coordinates were clustered close to the line of best fit (Figure 11.3).

Figure 11.2 ROC curve showing discrimination of Model 6

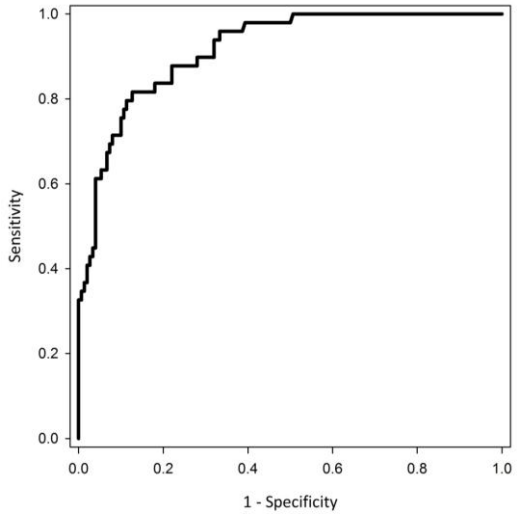
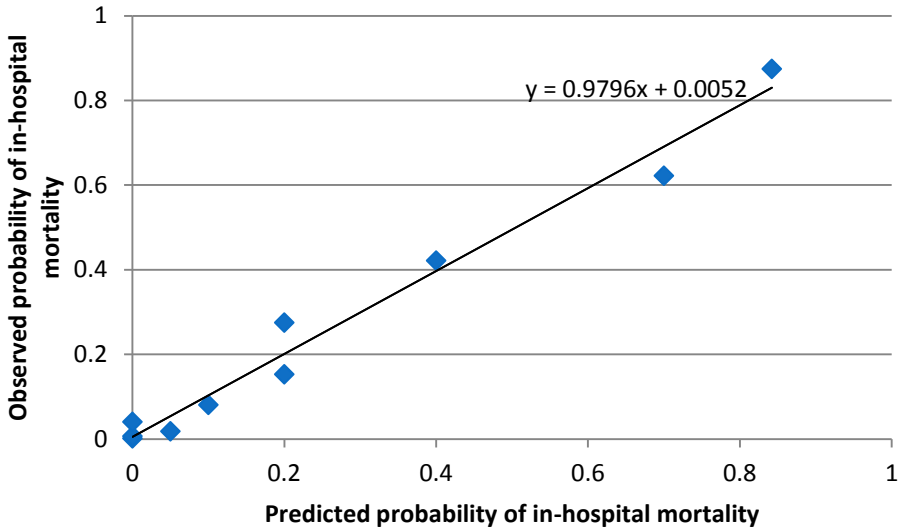


Figure 11.3 Calibration of the regression Model 6 for patients receiving assisted ventilation



PART 2 - LONGITUDINAL ASSESSMENT OF QUALITY OF LIFE AND HEALTH RESOURCE USE FOLLOWING HOSPITALISATION FOR AECOPD

CHAPTER 12 PATIENTS AND METHODS

12.1 PARTICIPANT RECRUITMENT

Patients admitted to either NTGH or WGH between 19th December 2008 and 19th September 2010 with an acute exacerbation of COPD, who survive to discharge, were eligible for entry in to the study. We aimed to prospectively recruit 100 patients with an exacerbation of COPD who were treated with assisted ventilation and 100 patients with an exacerbation of COPD who did not receive ventilation and then perform regular follow up for 1 year post discharge. Participants were approached during their hospital stay and written consent was obtained. No randomisation of patients occurred. It was expected that individuals with AECOPD receiving ventilation would be admitted less frequently than those with AECOPD not receiving assisted ventilation. All patients hospitalised with AECOPD receiving assisted ventilation were approached for consent. In order to avoid differential recruitment bias, the number of individuals hospitalised with AECOPD not receiving ventilation who were approached for consent was matched, over a two week period, to the number receiving ventilation.

12.2 INCLUSION AND EXCLUSION CRITERIA

In addition to the criteria used for Part 1 ("Predicting mortality and readmissions following hospital admission for AECOPD") detailed in section 6.4 and 6.5, participants were excluded if they had significant cognitive or sensory impairment (resulting in their inability to provide informed consent or to complete the questionnaires independently). Participants could be enrolled in both Part 1 and Part 2, but no participant could be enrolled more than once.

12.3 DATA COLLECTED

All of the data listed above in the generic methods (section 6.6) were collected for the participants involved in this part of the study. Following informed written patient consent, assessments were made once clinical stability had been reached close to discharge, and then six weeks, three months, six months and twelve months post-discharge. Post-discharge assessments were performed by me in the out-patient

department or, in a minority of cases, in the participants' home. Data were collected through a combination of case note review and direct participant interview.

At each assessment: the number of exacerbations experienced since the last assessment, and time elapsed (in days) since resolution (defined as the completion of acute antibiotic and steroid therapy) of the most recent exacerbation, were documented. The number of hospital admissions since the last assessment, the number of hospital readmissions requiring treatment with assisted ventilation, and the length of hospital stay for each admission, were recorded. Any significant medical developments since the last assessment were also documented. If a patient died: date of death; place of death; and cause of death were collected from the Public Health Mortality File.

Transcutaneous arterial oxygen saturation (recorded with Nonin Onyx 9500: fingertip pulse oximeter), body mass index (weight (kg)/height (m^2)), MRCD (Table 1.1) and eMRCD (Table 5.1), and spirometry (pre-bronchodilator FEV_1 and FVC, using a MicroLab portable digital volume transducer spirometer) were recorded at each visit.

12.3.1 HEALTH STATUS MEASURES

The St. Georges' Respiratory Questionnaire (SGRQ), Chronic Respiratory Disease Questionnaire (CRQ), Nottingham Extended Activities of Daily Living Scale (NEADL) and Hospital Anxiety and Depression Scale (HADS) were self-administered by the participant. The questionnaires were randomly ordered and supervision was available if difficulties arose. In all of the graphical examples below, a higher score on the QoL measure (i.e. a higher score on the y-axis) represents a better QoL. It is important to note that, for the questionnaires used in this study, this is not always applicable. Table 12.1 summarises the measurement of each of the QoL questionnaires used.

Table 12.1 Summary of the QoL questionnaires used

Questionnaire	Range of possible scores	Score assigned to death	Interpretation	Minimally clinically important difference (MCID)
St Georges' Respiratory Questionnaire (SGRQ)	0 – 100	100	Higher scores indicate worse QoL	+/- 4
Chronic Respiratory Disease Questionnaire (CRQ)	1 – 7	1	Lower scores indicate worse QoL	+/- 0.5
Hospital Anxiety and Depression Scale (HADS)	0 – 21 (for each domain)	n/a	Higher scores indicate worse anxiety or depression	+/- 1.5
Nottingham Extended Activity of Daily Living Score (NEADL)	0 – 63	0	Lower scores indicate lower levels of activity	+/- 5

12.4 STATISTICAL METHODS

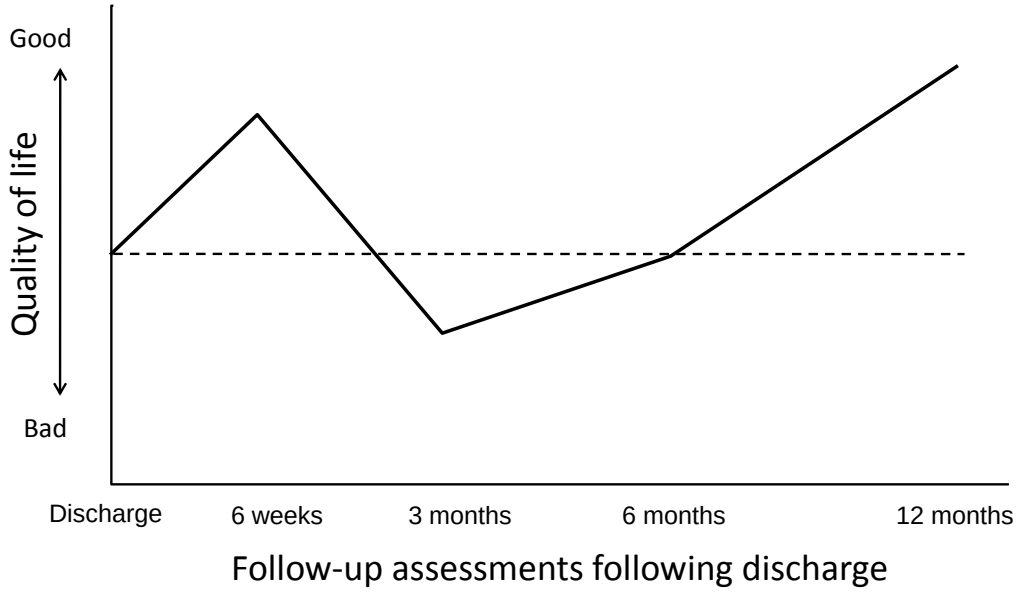
12.4.1 QUALITY OF LIFE MEASURES

A simple method to analyse the longitudinal quality of life measures would be to consider each time point separately and compare QoL scores at each time point between ventilated and non-ventilated patients. However, this approach has major problems: the analysis ignores the longitudinal nature of the data; follow-up QoL assessment needs to be performed at fixed time points; and multiple analyses are performed which is more likely to lead to a type 1 statistical error.[397] We therefore chose to use summary measures to analyse longitudinal quality of life data. It is important that the choice of summary measures is clinically meaningful [397] and consequently, we choose to use the following summary QoL measures:

1) QoL at baseline (time of hospital discharge);
2) mean change in QoL during the follow-up period;
3) time taken to achieve best QoL; and
4) time spent with a QoL better than the baseline level.

Figure 12.1 shows a hypothetical patient's quality of life during the year following discharge, as recorded in Part 2 of this study. In this example, a higher questionnaire score indicates a better QoL. The hashed line represents the quality of life recorded at discharge and the solid line indicates the individual's quality of life measured, using questionnaires described in section 12.3.1, at the following times after hospital discharge: six weeks; three months; six months; and 12 months. The follow-up period ended when either: a patient completed the 12-month assessment; the patient died; or the patient withdrew their consent to participate. If an individual missed a follow-up assessment and did not attend any subsequent scheduled visits, it was assumed that this patient withdrew their consent at the time of the last attended follow-up appointment.

Figure 12.1 Longitudinal change in quality of life following discharge – example patient

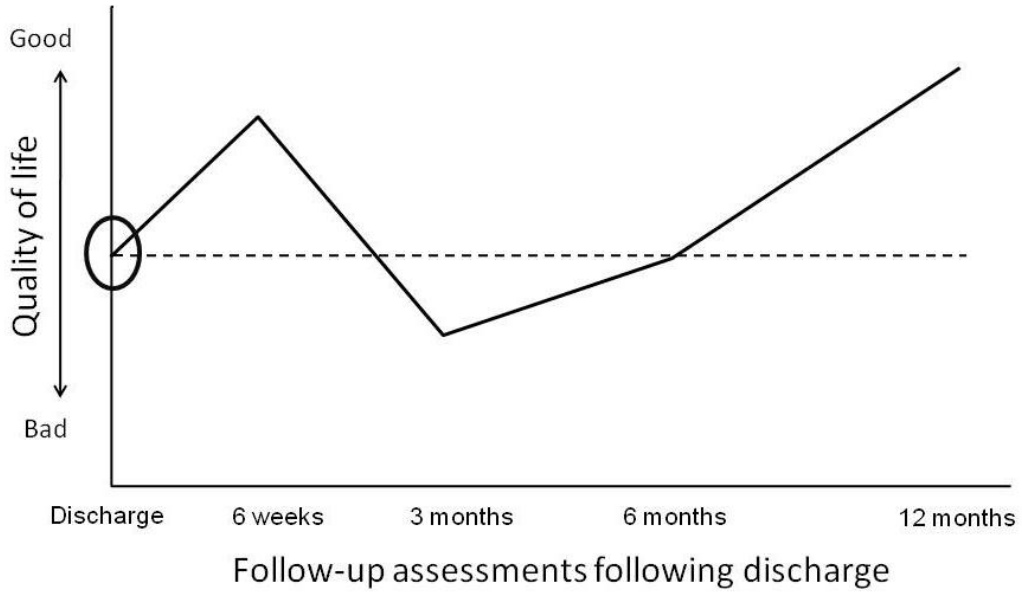


1) Quality of life at baseline

This represents the quality of life recorded at a time of clinical stability close to hospital discharge (represented by the circle, Figure 12.2). This enables the identification and stratification of patients who entered the study with either a very good, or very poor, quality of life. This is a clinically important measure because patients whose QoL is very well maintained at baseline are more likely to show a 'ceiling effect' and experience a decline in QoL than patients whose QoL is initially less

good, simply because of the constraints of the QoL measurement scale. Therefore, any subsequent information regarding longitudinal change in QoL needs to be referenced against the individual's baseline measurement.

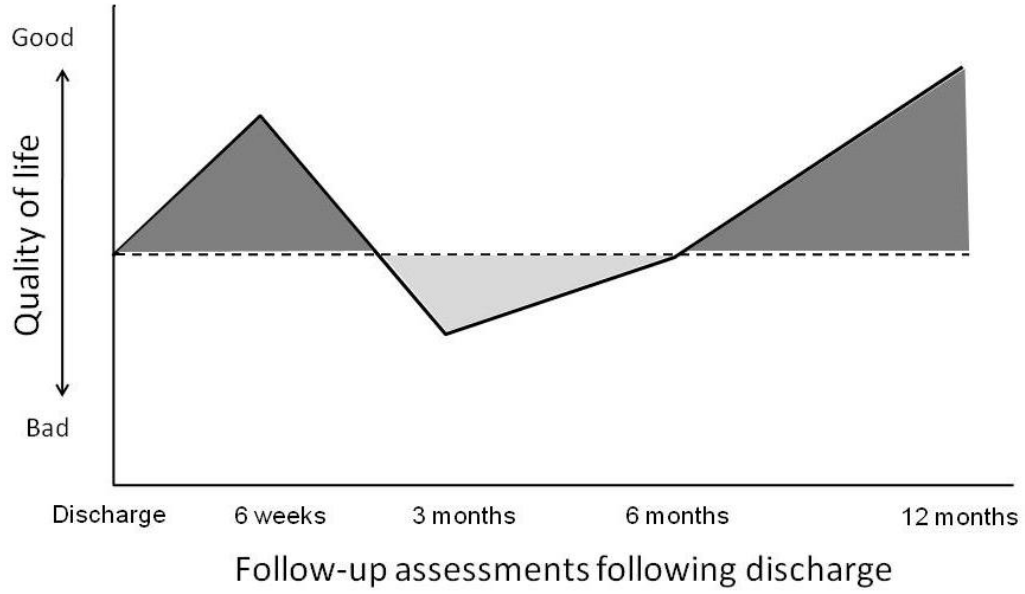
Figure 12.2 Graph to illustrate quality of life at baseline measure



2) (Time-adjusted) mean change in quality of life

This metric provides an overall assessment of whether an individual's quality of life has improved or deteriorated during the period of follow-up. Its calculation, for an individual, is illustrated in Figure 12.3: mean change in quality of life = [area above the patient's baseline value (dark grey shading)] – [area below the patient's baseline value (light grey shading)] divided by the follow-up time to provide a time-adjusted value. This can be compared to the MCID for the questionnaire to estimate whether, on average, an individual's QoL improved (or declined) by a pre-defined clinically significant amount during follow-up.

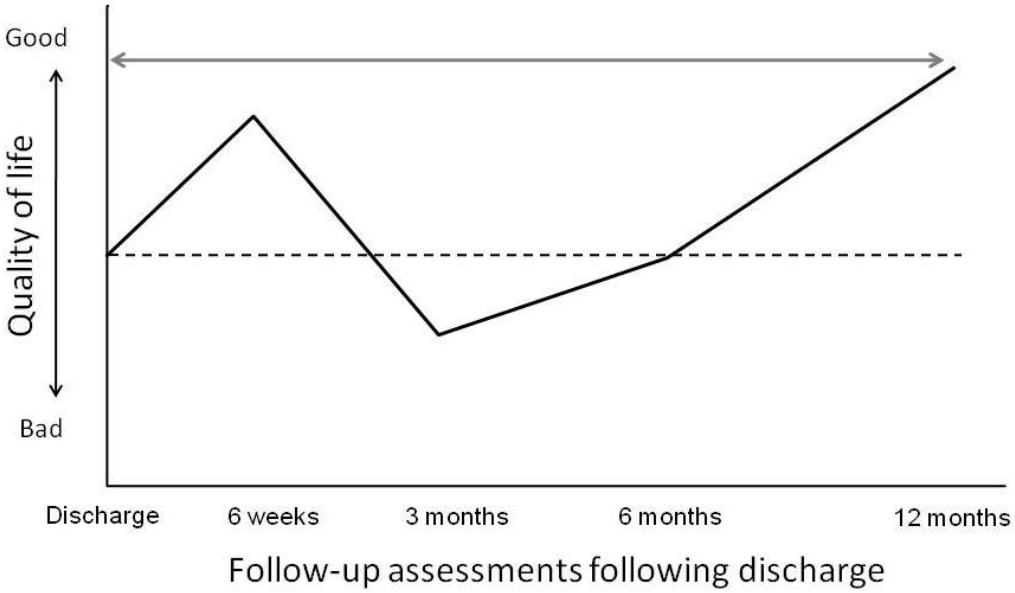
Figure 12.3 Graph illustrating calculation and clinical implication of mean change in quality of life during follow-up period



3) Time taken to achieve best quality of life

The time taken to achieve the best quality of life (grey arrow, Figure 12.4) was, for the purposes of this study, used as an indicator of the time taken for the patient's quality of life to recover following discharge. This measure helps identify patients who have a prolonged recovery following hospital discharge.

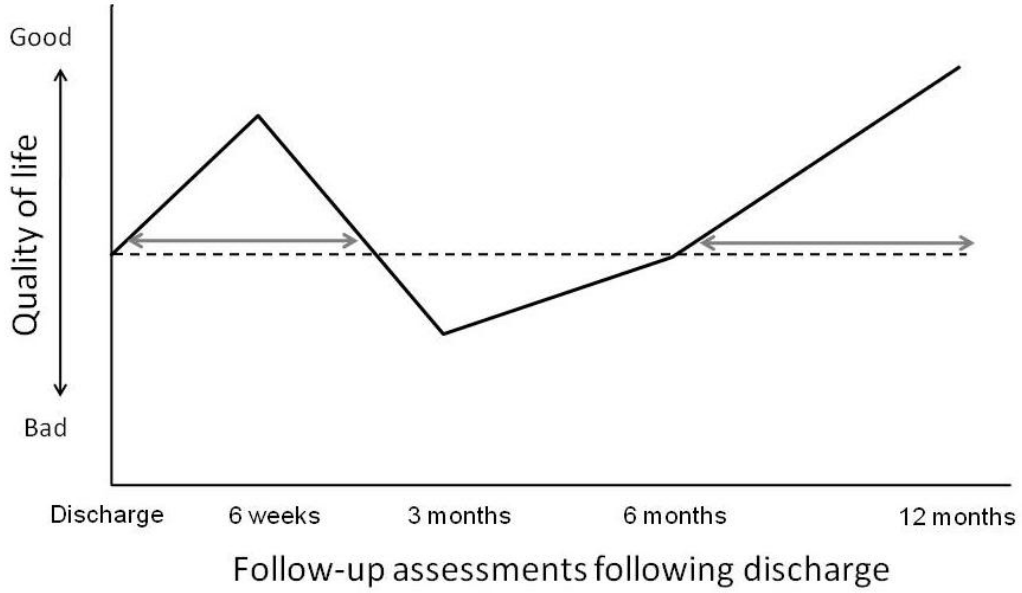
Figure 12.4 Graph illustrating the time taken to achieve best quality of life



4) Time spent with QoL better than baseline level

For patients with a very poor quality of life at baseline, it is often a clinical concern that their quality of life will never significantly improve, and may even continue to deteriorate, and this assumption often influences clinical decisions. The length of time spent with a quality of life above the baseline level (grey arrows, Figure 12.5) provides a useful quantification of subsequent quality of life that can be easily explained and understood by patients and clinicians alike. Expressing the time spent above baseline quality of life as a percentage of the total follow-up time will also assist interpretation and explanation (for example, "following hospital discharge, patient X spent 75% of time with a quality of life better than their baseline level").

Figure 12.5 Graph illustrating time spent with QoL better than baseline



12.4.2 POPULATION DESCRIPTION, MISSING DATA AND DATA ANALYSIS

The population description, univariate analyses and multivariate analyses were performed using the methodologies outlined in section 6.7. Missing values for admission clinical data were imputed as described in sections 6.7.1 and 7.1. It was assumed that there was a linear change in QoL between assessments and therefore if a participant failed to attend a follow-up appointment but their quality of life was recorded at the next scheduled visit, a time-adjusted average was imputed for the missing value by assuming a linear change between the two data points either side of

the missing assessment (Figure 12.6). Furthermore, similar to previous longitudinal QoL studies,[398, 399] for each questionnaire (except HADS) the score representing the worst QoL was assigned to represent death and, if a patient died during follow up, a linear decrease in QoL was assumed from the value of the last assessment to the value at the time of patient death (Figure 12.7).

Figure 12.6 Longitudinal quality of life measurement in a patient who failed to attend a follow-up appointment

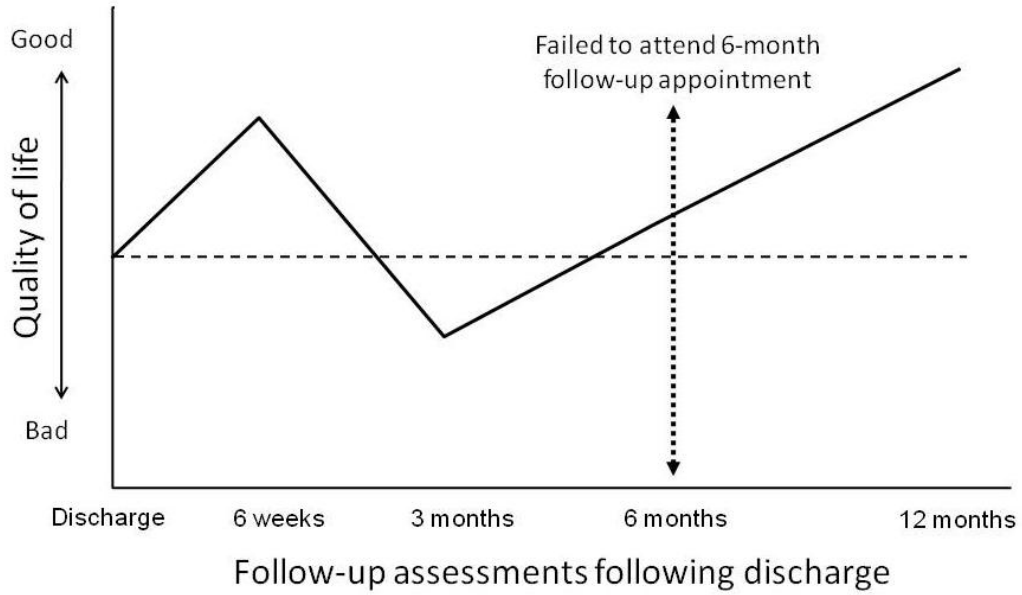
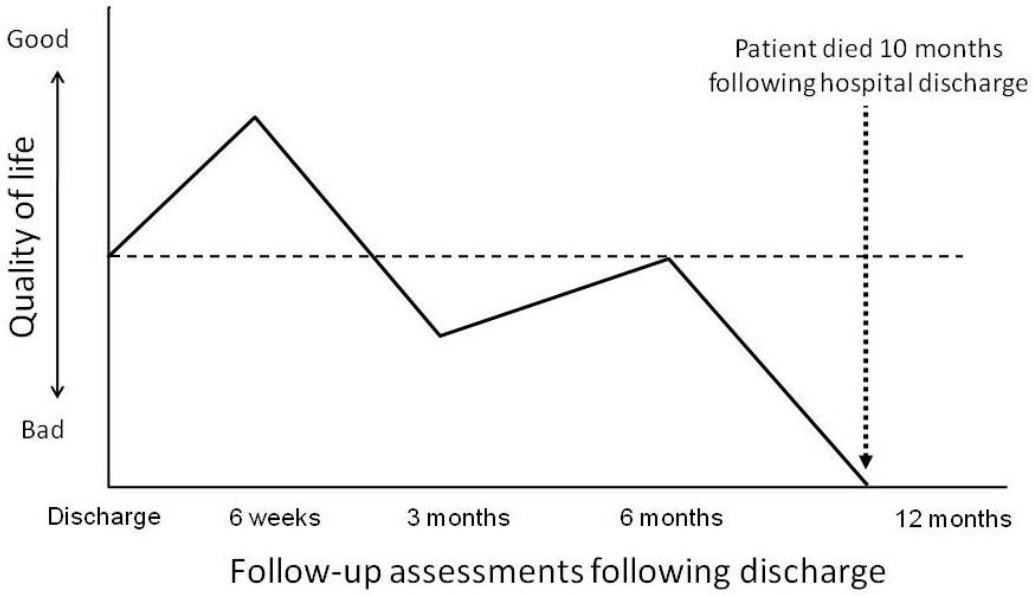


Figure 12.7 Longitudinal QoL measurement in a patient who died prior to completing 12-months follow-up



CHAPTER 13 RESULTS

13.1 MISSING DATA AND VARIABLE DISTRIBUTION

The dataset was virtually complete and the small number of missing values (serum glucose (30 missing); serum albumin (13 missing); ABG results, respiratory rate, temperature, potassium concentration, venous bicarbonate concentration and neutrophil count (≤ 5 missing)) were imputed using the analysis described in sections 6.7.1 and 7.1.

The distributions of the quality of life metrics described in section 12.4.1 are shown in Appendix B.2. All variables were treated as non-parametric except for the mean change in all QoL indices.

13.2 POPULATION DESCRIPTION

183 patients consented to participate in the longitudinal assessment of quality of life and health resource use following their discharge from hospital: 82 had received assisted ventilation during their hospital stay and 101 had not. In the total population, most patients (58.5%) were female and the majority (61.7%) were recruited from NTGH. The characteristics of the total population, and of those who received, and did not receive, ventilatory assistance, are shown in Table 13.1.

Both the ventilated and non-ventilated patients in Part 2 of the study were broadly similar to the larger population included in Part 1. However, compared to the equivalent Part 1 patients, Part 2 patients who did not receive assisted ventilation were: younger; more likely to have completed a course of pulmonary rehabilitation in the past; slightly less breathless during stable-state; had slightly higher BMI; and had a longer length of stay. The longer length of stay is probably, in part, due to the difficulties in consenting and performing the discharge assessments on patients with a very short hospital stay. For patients receiving assisted ventilation, there were trends to Part 2 patients being slightly younger ($p = 0.0616$) and more likely to have been previously treated with NIV ($p = 0.0581$) (Table 13.1). Therefore, compared to all

patients hospitalised with AECOPD, patients who consented to participate in Part 2 were younger and had slightly milder disease severity.

As expected, however, there were more obvious differences between the two populations included in Part 2 of the study. Compared to patients who did not receive ventilation, those who received assisted ventilation: were more likely to be female; were more likely to have experienced a previous admission requiring NIV; had lower FEV_1 % predicted; had worse stable-state dyspnoea; were more likely to have cor pulmonale; were more likely to be receiving LTOT; and (almost inevitably) had a higher P_aCO_2 and a lower pH the time of hospital admission and a longer length of stay. The absence of a similar difference in P_aO_2 values between the two populations is likely to be a result of more of the ventilated group being treated with oxygen (78% of ventilated patients had the ABG measured whilst receiving supplementary oxygen versus 51.5% of the non-ventilated group, $p = 0.0008$). In summary, ventilated patients had evidence of more severe underlying COPD and were experiencing a more severe exacerbation at the time of hospital admission. Subsequent comparisons of quality of life data between these two cohorts needs to be interpreted in the light of these differences.

Table 13.1 Characteristics of patients enrolled in Part 2, with comparison to Part 1 patients and between Part 2 patients

Variable	Patients not receiving assisted ventilation			Patients receiving assisted ventilation			
	Part 1 population* (n=674)	Part 2 population (n=101)	p value	Part 1 population* (n=150)	Part 2 population (n=82)	p value	p value†
Sociodemographic details & prior health resource use,							
Age, years	72.5 (10.1)	68.7 (8.8)	<0.0001	71.8 (9.7)	69.3 (9.2)	0.0616	0.63
Female, %	53.0	51.5	0.831	60	67.1	0.32	0.0360
No of hospital admissions in previous year (median, IQR)	0 (0 to 1)	0 (0 to 1)	0.963	0 (0 to 1)	0 (0 to 2)	0.15	0.52
Previous episode of assisted ventilation for AECOPD, %	6.4	9.9	0.203	28.7	41.5	0.0581	<0.0001
Previous pulmonary rehabilitation, %	9.8	18.8	0.0102	10	14.6	0.39	0.55
Severity of underlying disease & comorbidity,							
FEV_1 % predicted	46.4 (18.1)	42.9 (16.1)	0.0666	38.1 (16.6)	36.8 (18.3)	0.60	0.0184
eMRCD (median, IQR)	4 (3 to 5a)	4 (3 to 4)	0.0486	4 (4 to 5a)	4 (4 to 5a)	0.63	<0.0001
Cor pulmonale, %	8.0	6.9	0.843	16.3	18.3	0.84	0.0227
LTOT, %	9.1	5.9	0.348	21.3	30.5	0.15	<0.0001
Charlson Comorbidity Index (median, IQR)	2 (1 to 3)	2 (1 to 2)	0.120	1 (1 to 2)	1 (1 to 2)	0.42	0.14
BMI, kgm^{-2}	24.6 (6.2)	25.9 (6.8)	0.0479	25.8 (7.0)	26.4 (7.2)	0.48	0.62
MUST score (median, IQR)	0 (0 to 1)	0 (0 to 1)	0.895	0 (0 to 1)	0 (0 to 1)	0.90	0.52
Clinical information on admission to hospital,							
CXR consolidation, %	27.4	28.7	0.812	36.0	28.0	0.25	1
pH (median, IQR)	7.43 (7.40 to 7.46)	7.43 (7.39 to 7.47)	0.544	7.29 (7.23 to 7.34)	7.29 (7.24 to 7.34)	0.92	<0.0001
p_aO_2, kPa (median, IQR)	8.4 (7.3 to 10.1)	8.3 (7.2 to 10.0)	0.459	8.5 (6.7 to 12.4)	8.4 (6.6 to 12.2)	0.76	0.98

Variable	Patients not receiving assisted ventilation			Patients receiving assisted ventilation			
	Part 1 population* (n=674)	Part 2 population (n=101)	p value	Part 1 population* (n=150)	Part 2 population (n=82)	p value	p value†
p_aCO_2, kPa (median, IQR)	5.5 (4.8 to 6.4)	5.3 (4.9 to 6.5)	0.967	9.5 (7.6 to 11.6)	9.3 (7.6 to 11.6)	0.93	<0.0001
Developments during admission,							
Length of stay, days	6 (3 to 9)	7 (4 to 11)	0.0059	10 (7 to 16)	10 (7 to 15)	0.79	<0.0001

Values quoted are mean (SD) unless otherwise stated; *of those patients surviving to discharge; †comparison between Part 2 patients treated with assisted ventilation (n=82) and those not treated with assisted ventilation (n=102)

At the time of hospital discharge, patients who had received assisted ventilation during their hospital stay reported that, prior to hospitalisation, they had less severe respiratory symptoms (lower SGRQ symptom domain, p=0.021), but their respiratory symptoms had a greater impact on their emotional function (lower CRQ emotional function domain, p=0.0612) and levels of activity (lower NEADL, p = 0.0008). There were, however, no other differences in quality of life (measured using either SGRQ or CRQ) or symptoms of anxiety or depression between the two patient groups.

Table 13.2 Comparison of health related quality of life measures recorded at hospital discharge between patients treated with and not treated with assisted ventilation

Variable	Ventilated (n=82)*	Not ventilated (n=101)*	p value
SGRQ†,			
Symptoms	65.2 (49.3 to 80.9)	71.5 (60.7 to 83.0)	0.0260
Activity	82.9 (72.7 to 92.5)	85.8 (66.8 to 92.5)	0.969
Impacts	50.3 (38.1 to 68.8)	51.1 (36.0 to 62.9)	0.643
Total	62.5 (51.9 to 73.6)	63.1 (52.3 to 73.5)	0.943
CRQ‡,			
Dyspnoea	2.8 (2.2 to 3.8)	2.8 (2 to 4)	0.571
Emotional function	2 (1.3 to 3)	3.7 (2.7 to 4.8)	0.0612
Fatigue	3.3 (2.1 to 4.9)	2.5 (1.8 to 3.2)	0.172
Mastery	2.8 (2 to 4.1)	3.3 (2.3 to 4.5)	0.138
HADS†,			
Anxiety	8.5 (4 to 14)	8 (4.5 to 12.5)	0.347
Depression	6 (3 to 10)	6 (3 to 8)	0.500
NEADL‡,	31 (19 to 41)	38 (32 to 47.5)	0.0006

*Values shown are median (IQR); †Lower scores indicate better quality of life; ‡Higher scores indicate better quality of life; SGRQ – St George's Respiratory Questionnaire; CRQ – Chronic Respiratory Disease Questionnaire; HADS – Hospital Anxiety and Depression Scale; NEADL – Nottingham Extended Activity of Daily Living Scale.

13.3 HEALTH RESOURCE USE AND MORTALITY FOLLOWING HOSPITAL DISCHARGE

Of the total population (n = 183), most patients (n = 130, 71%) were rehospitalised at least once during the 12-month follow up period and the median number of readmissions was 1 (IQR 0 to 3; range 0 to 15). 35 (19.1%) patients required assisted ventilation during a hospital admission for the treatment of ARF. The majority of patients (n = 157, 86%) reported that they had experienced at least one episode of AECOPD during the follow up period and the median number of AECOPD was 3 (IQR 1

to 6; range 0 to 15). Overall, 33 (18.0%) patients died during the 12-month follow-up period. Of these patients, 12 (6.6%) died with 3 months of discharge and 19 (10.4%) died within 6 months of discharge.

There was no significant difference in the risk of all-cause rehospitalisation between the ventilated and non-ventilated groups (p = 0.14) although patients who were originally treated with assisted ventilation experienced more frequent respiratory readmissions (p = 0.0339) and spent a longer period in hospital (p = 0.0393) during the subsequent year than those who were not treated with ventilation. Furthermore, patients who received assisted ventilation during their index admission were significantly more likely to require assisted ventilation during a subsequent hospital admission. There were no significant differences in the number of episodes of AECOPD or in the total number of readmissions (i.e. both respiratory causes and non-respiratory causes) (Table 13.3).

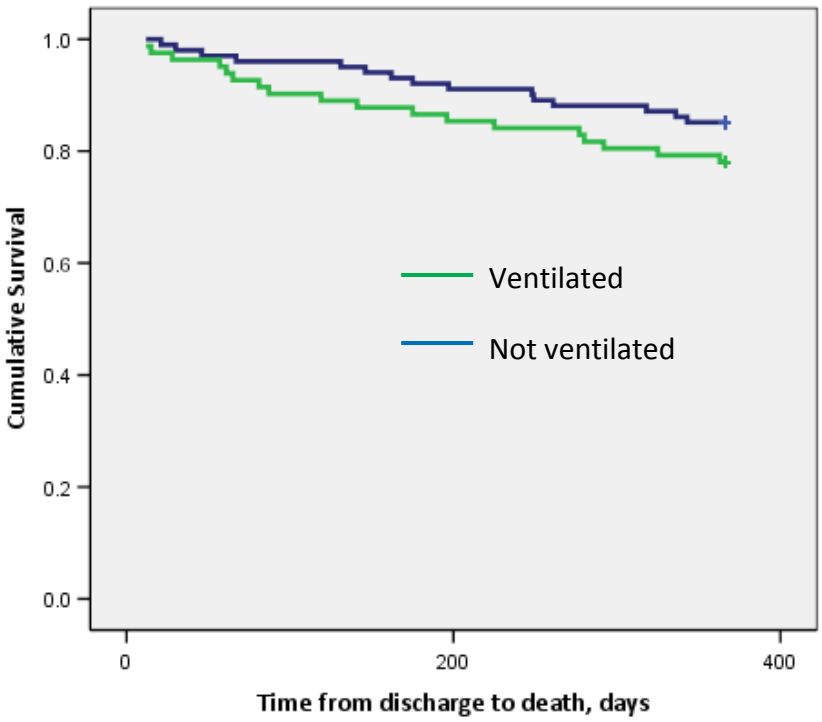
Table 13.3 Health resource use and mortality during follow-up

Outcome	Assisted ventilation, n=82	Not ventilated, n=101	p value
Health resource use following discharge,			
Readmitted within 12-months, %	76.8	66.3	0.14
Episodes of AECOPD, median (IQR)	3 (1 to 6)	3 (1 to 6)	0.94
Total no. of readmissions, median (IQR)	2 (1 to 3)	1 (0 to 2)	0.0877
No. of respiratory readmissions, median (IQR)	1 (0 to 3)	1 (0 to 2)	0.0339
Total length of hospital stay (days), median (IQR)	11 (1 to 28)	4 (0 to 18)	0.0393
Readmission requiring assisted ventilation for ARF, %	29.3	10.9	0.0023
Mortality following discharge,			
3-month, %	9.8	4.0	0.14
6-month, %	13.4	7.9	0.24
12-month, %	22.0	14.9	0.25

Patients treated with assisted ventilation were at a non-significantly higher risk of mortality compared to patients not ventilated (Table 13.3). The Kaplan-Meier survival curve showing the cumulative survival, stratified according to whether the patient received assisted ventilation, is shown in Figure 13.1. Although the lines diverge and

more ventilated patients died, there is no significant difference in cumulative survival between the two groups (Log-rank p = 0.20).

Figure 13.1 12-month survival of ventilated and non-ventilated patients



Most patients died from a respiratory cause (81.8%) and cardiovascular disease was the second commonest cause of 12-month mortality (12.1%). There was no clear relationship between time to death and the cause of death (Table 13.4). Four patients died with, or from, an advanced cancer (three with lung cancer) and malignancy was not implicated in any patients who died within six months of discharge.

Table 13.4 Cause of death during follow-up in Part 2 patients

	Respiratory cause, n (%)	Cardiovascular cause, n (%)	Other cause, n (%)
3-month mortality	10 (83.3)	0	2 (16.7)
6-month mortality	15 (78.9)	2 (10.5)	2 (10.5)
12-month mortality	27 (81.8)	4 (12.1)	2 (6.1)

13.4 QUALITY OF LIFE AT DISCHARGE AND SUBSEQUENT OUTCOME

Compared to survivors, patients who died during follow up (n = 33) were less active with higher baseline (discharge) SGRQ Activity and lower NEADL scores (Table 13.5). There was also a trend to higher 12-month mortality in patients: whose COPD had a greater impact on their day-to-day life (SGRQ Impacts, p = 0.0714); who reported more depressive symptoms (HADS Depression, p = 0.0825); and who had a worse overall QoL (SGRQ Total, p = 0.13).

Table 13.5 QoL at discharge and mortality within 12 months

Quality of life measurement	Died, n =33	Survived, n = 150	p value*
SGRQ Symptoms, mean (SD)†	63.3 (20.8)	66.7 (19.7)	0.38
SGRQ Activity, mean (SD)†	85.0 (12.8)	77.9 (16.3)	0.0209
SGRQ Impacts, mean (SD)†	55.7 (19.1)	48.9 (19.8)	0.0714
SGRQ Total, mean (SD)†	65.6 (15.2)	60.7 (17.1)	0.13
CRQ Dyspnoea, median (IQR)‡	2.8 (1.7 to 4.1)	2.8 (2.15 to 3.8)	0.56
CRQ Emotional, median (IQR)‡	2.3 (1.5 to 3)	2.4 (1.5 to 3.3)	0.83
CRQ Fatigue, median (IQR)‡	3.7 (2.65 to 4.4)	3.4 (2.38 to 4.9)	0.69
CRQ Mastery, median (IQR)‡	3 (2.15 to 4.15)	3.3 (2.2 to 4.5)	0.60
HADS anxiety, median (IQR)†	8 (5 to 12.5)	8 (4 to 14)	0.93
HADS depression, median (IQR)†	8 (5 to 10.5)	6 (3 to 9)	0.0825
NEADL, median (IQR)‡	28 (14 to 37)	38 (28 to 45)	<0.0001

†Lower values indicate improved quality of life; ‡Higher values indicate improved quality of life. SGRQ – St George's Respiratory Questionnaire; CRQ – Chronic Respiratory Disease Questionnaire; HADS – Hospital Anxiety and Depression Scale; NEADL – Nottingham Extended Activity of Daily Living Scale.

Patients who were readmitted during the follow up period reported lower baseline levels of activity (i.e. higher SGRQ Activity score and lower NEADL score) than non-readmitted patients, but there were no significant differences in any other QoL measure (Table 13.6).

Table 13.6 QoL at discharge and readmission during follow-up

Mean change in quality of life	Readmitted, n =130	Not readmitted, n = 53	p value*
SGRQ Symptoms, mean (SD)†	66.3 (19.5)	65.6 (20.8)	0.85
SGRQ Activity, mean (SD)†	81.1 (14.8)	74.6 (17.8)	0.0119
SGRQ Impacts, mean (SD)†	51.4 (20.5)	47.1 (17.6)	0.19
SGRQ Total, mean (SD)†	62.6 (17.6)	59.1 (14.9)	0.21
CRQ Dyspnoea, median (IQR)‡	2.8 (2 to 4)	2.8 (2 to 3.6)	0.46
CRQ Emotional, median (IQR)‡	3.4 (2.4 to 4.9)	3.6 (2.4 to 4.8)	0.90
CRQ Fatigue, median (IQR)‡	2.3 (1.5 to 3)	2 (1.3 to 3.2)	0.56
CRQ Mastery, median (IQR)‡	3 (2.3 to 4.3)	3.3 (1.8 to 4.9)	0.92

Mean change in quality of life	Readmitted, n =130	Not readmitted, n = 53	p value*
HADS anxiety, median (IQR)†	8 (4 to 14)	9 (4.5 to 13)	0.83
HADS depression, median (IQR)†	6 (3 to 10)	6 (3 to 8)	0.37
NEADL, median (IQR)‡	34 (24 to 42)	42 (33 to 51)	0.0001

†Lower values indicate improved quality of life; ‡Higher values indicate improved quality of life. SGRQ – St George's Respiratory Questionnaire; CRQ – Chronic Respiratory Disease Questionnaire; HADS – Hospital Anxiety and Depression Scale; NEADL – Nottingham Extended Activity of Daily Living Scale.

13.5 QUALITY OF LIFE FOLLOWING HOSPITAL DISCHARGE

13.5.1 TOTAL POPULATION, N = 183

Overall, 781 assessments were performed on 183 patients. Seven patients did not attend any follow-up appointments following hospital discharge and were therefore not included in the analysis of longitudinal QoL data. Eight patients died prior to attending their first assessment following discharge. Full details of the attendance at each scheduled assessment are shown in Appendix G (Figure 17.2).

In the total population, compared to their reported status at discharge, most patients experienced: improved respiratory symptoms during the year of follow up (mean change in SGRQ symptoms = -8.65 (MCID = ±4)) and improved mastery of their condition; (mean change in CRQ mastery = 0.77 (MCID = ±0.5)); and less anxiety (mean change in HADS anxiety = -1.52 (MCID = ±1.5)). Although, on average, patients activity levels worsened during the 12 month follow-up (mean change in SGRQ activity = 1.79 and mean change in NEADL = -3.44) neither of these changes were greater than the MCID for each instrument. The overall quality of life measured using the SGRQ (SGRQ total), the levels of depressive symptoms and the patients' ability to undertake activities of daily living were stable during the follow-up period (Table 13.7).

Most QoL measures peaked at 3 months following discharge, with the exception of activity levels (measured using NEADL and SGRQ activity) which peaked after 6 weeks. For all measures of QoL except those measuring patient activity (SGRQ Activity and NEADL), a quarter of patients took six months or longer to fully recover (i.e. reach their peak QoL). For all QoL measures, except those assessing activity, patients experienced a QoL better than their baseline for more than 50% of the subsequent year of follow-up.

13.5.2 COMPARISON OF VENTILATED AND NON-VENTILATED PATIENTS

There was a significant difference ($p = 0.0193$) in the mean change in QoL, measured using SGRQ total, between ventilated and non-ventilated patients: ventilated patients' QoL was stable during follow up (mean change = 0.05); whereas non-ventilated patients experienced a clinically important improvement in their QoL (mean change = -4.55). Both ventilated and non-ventilated patients experienced a clinically important improvement in their respiratory symptoms (measured using SGRQ symptoms) although the improvement was greater in the non-ventilated patients ($p = 0.0172$). Furthermore, the impact of their respiratory disease on an individual's QoL (SGRQ impacts) improved significantly more ($p = 0.0239$) in patients not ventilated compared to those who required assisted ventilation (Table 13.7). No other QoL measure except the SGRQ highlighted any difference in QoL during follow-up between the two patient groups although there was a trend towards worse respiratory symptoms, measured using the CRQ Dyspnoea, during the follow-up period ($p = 0.11$).

Compared to ventilated patients, patients who did not receive assisted ventilation spent a greater proportion of the total follow-up time with a quality of life (measured using all domains of the SGRQ) better than their baseline (discharge) level, although these results did not achieve statistical significance ($0.05 < p \leq 0.10$ for all SGRQ domains). For all other measures of health status there were no differences in the length of time spent with a quality of life better than the baseline level between the two populations, and there were no differences in the time taken to achieve the best recorded QoL (for any QoL measure) between the populations (Table 13.7).

Table 13.7 Quality of life during the follow up period

QoL measure	Total population, n=176	Ventilated, n = 80	Not ventilated, n = 96	p value*
Mean change in QoL (mean (SD)),				
SGRQ Symptoms†	-8.65 (19.5)	-4.80 (19.4)	-11.8 (19.2)	0.0172
SGRQ Activity†	1.79 (12.0)	3.22 (10.2)	0.60 (13.3)	0.15
SGRQ Impacts†	-2.98 (15.4)	-0.09 (15.5)	-5.36 (14.9)	0.0239
SGRQ Total†	-2.47 (13.0)	0.05 (12.5)	-4.55 (13.2)	0.0193
CRQ Dyspnoea‡	0.34 (1.28)	0.17 (1.16)	0.48 (1.37)	0.11
CRQ Emotional‡	0.42 (1.13)	0.42 (1.10)	0.42 (1.16)	0.98
CRQ Fatigue‡	0.38 (1.16)	0.40 (1.12)	0.36 (1.20)	0.82
CRQ Mastery‡	0.77 (1.33)	0.66 (1.41)	0.87 (1.27)	0.30
HADS anxiety†	-1.52 (3.34)	-1.30 (2.73)	-1.70 (3.76)	0.45
HADS depression†	-0.44 (2.95)	-0.43 (2.65)	-0.45 (3.18)	0.43
NEADL‡	-3.44 (7.98)	-4.35 (8.32)	-2.69 (7.64)	0.17
Time taken to achieve best QoL, days (median (IQR)),				
SGRQ Symptoms	91 (44 to 185)	92 (43 to 180)	91 (45 to 189)	0.27
SGRQ Activity	48 (0 to 111)	46 (0 to 102)	49 (0 to 179)	0.23
SGRQ Impacts	88 (40 to 188)	91 (9 to 189)	87 (42 to 188)	0.72
SGRQ Total	92 (46 to 188)	91 (40 to 186)	96 (48 to 190)	0.40
CRQ Dyspnoea	87 (42 to 183)	96 (46 to 186)	79 (41 to 181)	0.28
CRQ Emotional	93 (46 to 192)	98 (49 to 190)	88 (42 to 193)	0.19
CRQ Fatigue	87 (43 to 180)	90 (46 to 123)	86 (40 to 184)	0.77
CRQ Mastery	94 (48 to 190)	98 (46 to 192)	92 (49 to 189)	0.84
HADS anxiety	90 (43 to 190)	96 (49 to 190)	87 (37 to 191)	0.21
HADS depression	83 (0 to 184)	92 (0 to 187)	64 (26 to 112)	0.59
NEADL	46 (0 to 109)	44 (0 to 104)	46 (0 to 174)	0.82
Time spent better than baseline QoL, % of total follow-up time (median (IQR)),				
SGRQ Symptoms	79 (37 to 100)	67 (25 to 100)	83 (48 to 100)	0.0678
SGRQ Activity	26 (0 to 84)	13 (0 to 70)	35 (0 to 84)	0.10
SGRQ Impacts	67 (22 to 100)	59 (4 to 98)	71 (36 to 100)	0.0615
SGRQ Total	70 (27 to 100)	57 (6 to 100)	83 (36 to 100)	0.0543
CRQ Dyspnoea	71 (20 to 100)	59 (14 to 100)	84 (27 to 100)	0.12
CRQ Emotional	83 (32 to 100)	84 (30 to 100)	83 (34 to 100)	0.78
CRQ Fatigue	83 (25 to 100)	83 (35 to 100)	83 (20 to 100)	0.98
CRQ Mastery	88 (46 to 100)	86 (25 to 100)	98 (59 to 100)	0.18
HADS anxiety	78 (31 to 100)	76 (32 to 100)	79 (29 to 100)	0.77
HADS depression	59 (0 to 100)	53 (0 to 100)	71 (12 to 100)	0.44
NEADL	31 (0 to 77)	16 (0 to 65)	36 (0 to 84)	0.14

* comparison between ventilated and not ventilated groups; †Lower values indicate improved quality of life; ‡Higher values indicate improved quality of life. SGRQ – St George's Respiratory Questionnaire; CRQ – Chronic Respiratory Disease Questionnaire; HADS – Hospital Anxiety and Depression Scale; NEADL – Nottingham Extended Activity of Daily Living Scale.

13.5.3 LONGITUDINAL CHANGE IN QOL AND HOSPITAL READMISSION

Table 13.8 explores the relationship between hospital readmission and subsequent QoL. This analysis shows that, compared to patients who were not readmitted during follow-up, readmitted patients had significantly less improvement in QoL for all measures except those assessing depressive symptoms (mean change in HADS depression, p = 0.50).

Table 13.8 Mean change in QoL and hospital readmission

Mean change in quality of life	Readmitted, n =126	Not readmitted, n = 50	p value*
SGRQ Symptoms†	-4.95 (17.6)	-17.9 (21.2)	<0.0001
SGRQ Activity†	3.06 (8.70)	-1.42 (17.6)	0.0907
SGRQ Impacts†	0.75 (13.8)	-12.2 (15.3)	<0.0001
SGRQ Total†	0.46 (11.4)	-9.79 (14.1)	<0.0001
CRQ Dyspnoea‡	-0.16 (1.20)	0.80 (1.37)	0.0028
CRQ Emotional‡	0.25 (1.05)	0.86 (1.22)	0.0010
CRQ Fatigue‡	0.20 (1.06)	0.84 (1.28)	0.0008
CRQ Mastery‡	0.48 (1.19)	1.53 (1.38)	<0.0001
HADS anxiety†	-1.16 (3.31)	-2.39 (3.28)	0.0287
HADS depression†	-0.34 (2.94)	-0.68 (2.99)	0.50
NEADL‡	-4.39 (7.73)	-1.05 (8.17)	0.0119

†Lower values indicate improved quality of life; ‡Higher values indicate improved quality of life. SGRQ – St George's Respiratory Questionnaire; CRQ – Chronic Respiratory Disease Questionnaire; HADS – Hospital Anxiety and Depression Scale; NEADL – Nottingham Extended Activity of Daily Living Scale.

13.6 IDENTIFYING INDIVIDUALS WITH POOR QUALITY OF LIFE FOLLOWING HOSPITAL DISCHARGE

13.6.1 DEFINING "POOR QUALITY OF LIFE"

The SGRQ was the most responsive measure for identifying change in quality of life in our population (Table 13.7). We therefore chose this instrument to help define "poor quality of life" and we combined the two populations described above (treated with assisted ventilation and not treated with assisted ventilation). An individual was said to have experienced a poor quality of life following hospital discharge if either:

1) Their quality of life (SGRQ total) at discharge was within the worst (i.e. highest) 50% of scores **and** their average quality of life over the follow up period

declined by a value greater than the MCID (i.e. mean change in quality of life <-4); or

2) They died within six months of hospital discharge.

The remaining patients were regarded as having an acceptable QoL. Using these criteria, 29 patients experienced a poor quality of life (15 of whom required assisted ventilation) and their characteristics, and comparisons with patients with acceptable QoL, are shown in Table 13.9 to Table 13.11. Markedly asymmetric categorical variables (< 5% of the population in one category) are not shown.

Compared to those with an acceptable QoL, patients who experienced a poor QoL: were more likely to be housebound; were more likely to be receiving social care support; had worse lung function; were more breathless during their stable-state; were more likely to have recently lost weight; and had a higher risk of malnutrition. Furthermore, those with a poor QoL: had a greater comorbidity burden and, specifically, were more likely to suffer from vascular disease (Table 13.9). At their index admission, patients who experienced a poor quality of life following discharge had: lower blood pressure; lower serum sodium, potassium and albumin concentrations; and lower blood haemoglobin concentrations (Table 13.10). There was no difference in subsequent QoL between patients who received assisted ventilation and those not ventilated. At the time of hospital discharge, only the SGRQ (which is used in the definition of poor QoL) and the reported activity levels (measured using the NEADL) differed between those who subsequently experienced a poor QoL and those who did not (Table 13.11).

Table 13.9 Univariate associations between features prior to index admission and subsequent poor quality of life

Variable*	Acceptable QoL, n = 147	Poor QoL, n = 29	p value
Sociodemographic details & prior health resource use,			
Age, years	68.8 (9.2)	71.0 (8.3)	0.24
Female, %	59.9	62.1	1
Cigarette pack years (median, IQR)	49 (36 to 64)	48 (38 to 62)	0.86
Housebound, %	19.0	44.8	0.0067
Social care prior to admission, %	12.9	31.0	0.0241
No. of hospital admissions in previous year (median, IQR)	0 (0 to 1)	1 (0 to 2)	0.0817

Variable*	Acceptable QoL, n = 147	Poor QoL, n = 29	p value
No. of AECOPD in previous year (median, IQR)	3 (1 to 5)	3 (1 to 5)	0.41
Previous episode of NIV for AECOPD, %	23.8	24.1	1
Previous pulmonary rehabilitation, %	17.0	17.2	1
Severity of underlying disease,			
Home nebuliser, %	17.0	27.6	0.20
LTOT, %	17.0	24.1	0.43
Long-term prednisolone	9.5	17.2	0.32
FEV_1 % predicted	41.8 (17.8)	32.0 (13.0)	0.0052
FVC, litres	2.12 (0.75)	1.74 (0.73)	0.0146
eMRCD (median, IQR)	4 (3 to 4)	4 (4 to 5a)	0.0004
Cor pulmonale, %	12.2	10.3	1
BMI, kgm^{-2}	26.5 (6.7)	24.3 (8.2)	0.13
Recent weight loss >5%, %	22.4	44.8	0.0194
MUST score	0 (0 to 1)	1 (0 to 2)	0.0010
Comorbidity,			
Charlson comorbidity index (median, IQR)	1 (1 to 2)	2 (1 to 3)	0.0379
Bronchiectasis, %	6.1	0	0.36
Diabetes, %	16.3	10.3	0.58
Hypertension, %	40.8	44.8	0.69
Stroke disease, %	9.5	6.9	1
IHD, %	23.1	41.4	0.0621
AF, %	10.2	6.9	0.74
Anxiety / depression, %	29.3	20.7	0.50
History of cancer, %	8.8	10.3	0.73
Osteoporosis, %	12.2	17.2	0.55
Peripheral vascular disease, %	4.8	20.7	0.0090
Rheumatoid arthritis, %	4.8	6.9	0.64
Peptic ulcer disease, %	5.4	6.9	0.67

* values shown are mean (SD) unless otherwise stated

Table 13.10 Univariate associations between clinical information at the time of index hospital admission and subsequent poor quality of life

Variable*	Acceptable QoL, n = 147	Poor QoL, n = 29	p value
Clinical information on admission to hospital,			
Pedal oedema, %	32.7	27.6	0.67
Purulent sputum, %	53.1	44.8	0.43
Acute confusion, %	10.9	6.9	0.74
CXR consolidation, %	29.3	31.0	0.83
Ineffective cough, %	10.2	13.8	0.52
Pulse rate	109.3 (20.1)	110.4 (21.9)	0.79
Diastolic blood pressure, mmHg	80.9 (19.0)	74.2 (15.8)	0.0793

Variable*	Acceptable QoL, n = 147	Poor QoL, n = 29	p value
Respiratory rate	26.2 (6.1)	26.5 (6.5)	0.81
DECAF Score	1 (0 to 2)	2 (1 to 2)	0.14
Laboratory investigations on admission to hospital,			
H^+ concentration, nmol/L (median, IQR)	39.7 (35.3 to 47.5)	41.7 (36.9 to 52.3)	0.26
p_aO_2, kPa (median, IQR)	8.4 (7.1 to 11.3)	7.7 (6.7 to 9.2)	0.20
p_aCO_2, kPa (median, IQR)	6.7 (5.2 to 9.2)	7.7 (5.6 to 9.4)	0.35
Arterial bicarbonate, mmol/L	30.6 (7.0)	31.0 (6.7)	0.78
Sodium, mmol/L	136.4 (4.7)	134.4 (4.6)	0.0372
Potassium, mmol/L	4.35 (0.56)	4.61 (0.49)	0.0228
Chloride	97.8 (6.2)	96.5 (6.2)	0.30
Urea, mmol/L (median, IQR)	6.0 (4.4 to 8.1)	6.4 (4.3 to 11.1)	0.26
Creatinine, µmol/L (median, IQR)	87.0 (74.0 to 111.5)	92.5 (71.5 to 119.3)	0.77
Albumin, g/L	39.6 (4.4)	37.3 (4.8)	0.0144
Glucose, mmol/L (median, IQR)	7.1 (6.3 to 9.0)	7.1 (6.0 to 7.8)	0.67
CRP, mg/L (median, IQR)	46.5 (11.3 to 109.0)	51.0 (12.0 to 115.0	0.76
Hb, g/dL	14.1 (1.8)	13.4 (2.3)	0.0899
Neutrophil count, $x10^9$/L (median, IQR)	8.65 (6.48 to 12.1)	10.1 (6.20 to 11.8)	0.56
Eosinophil count, $x10^9$/L (median, IQR)	0.10 (0 to 0.20)	0.10 (0 to 0.20)	0.88

* values shown are mean (SD) unless otherwise stated; H^+ - hydrogen

Table 13.11 Univariate associations between developments during the index admission, discharge quality of life and subsequent poor quality of life

Variable*	Acceptable QoL, n = 147	Poor QoL, n = 29	p value
Developments during the index hospital admission,			
Treated with assisted ventilation, %	44.2	51.7	0.54
Increased care package at discharge, %	8.2	10.3	0.72
Specialist care, %	92.9	92.0	1
Length of stay, days	8 (5 to 13)	10 (6 to 14)	0.28
QoL recorded at discharge,			
SGRQ Symptoms, median (IQR)‡	68.3 (52.0 to 81.7)	71.6 (55.2 to 82.4)	0.67
SGRQ Activity, median (IQR)‡	79.7 (66.6 to 92.5)	92.5 (79.4 to 92.5)	0.0165
SGRQ Impacts, median (IQR)‡	47.5 (34.1 to 63.0)	58.4 (46.3 to 64.5)	0.0603
SGRQ Total, median (IQR)‡	61.1 (48.7 to 72.4)	68.5 (63.0 to 73.7)	0.0339
CRQ Dyspnoea, median (IQR)†	2.9 (2.2 to 3.8)	2.8 (1.7 to 4.2)	0.60
CRQ Emotional, median (IQR)†	3.6 (2.4 to 5.0)	3.8 (2.6 to 4.4)	0.94
CRQ Fatigue, median (IQR)†	2.3 (1.5 to 3.3)	2.3 (1.6 to 3.0)	0.96
CRQ Mastery, median (IQR)†	3.3 (2.3 to 4.5)	2.7 (2.1 to 4.2)	0.32
HADS anxiety, median (IQR)‡	8 (4 to 14)	8 (6 to 11)	0.79
HADS depression, median (IQR)‡	6 (3 to 9)	6 (5 to 9)	0.24
NEADL, median (IQR)†	38 (27 to 47)	30 (15 to 39)	0.0008

* values shown are mean (SD) unless otherwise stated; †higher scores indicate better QoL; ‡lower scores indicate better QoL

During the period of follow-up, patients who experienced a poor QoL following discharge were significantly more likely to have: been readmitted to hospital (p = 0.0034); experienced more frequent readmissions for respiratory causes (p = 0.0321); and spent longer in hospital (p = 0.0236) than patients with an acceptable QoL. There were no significant differences in either the number of AECOPD experienced, or the risk of rehospitalisation requiring assisted ventilation, between patients with a poor and acceptable QoL (Table 13.12).

Table 13.12 Comparison of health resource use following discharge in patients with an acceptable and poor QoL

Health resource use following discharge	Acceptable QoL	Poor QoL	p value
Total number of AECOPD, median (IQR)	3 (1 to 6)	2 (1 to 5)	0.18
Hospital readmission, %	67.3	93.1	0.0034
Total number of hospital readmissions, median (IQR)	1 (0 to 3)	2 (1 to 2)	0.39
Number of respiratory readmissions, median (IQR)	1 (0 to 2)	2 (1 to 3)	0.0321
Total length of stay during follow up (days), median (IQR)	4 (0 to 20)	15 (3 to 37)	0.0236
Readmission requiring assisted ventilation, %	20.4	17.2	0.80

13.7 INDEPENDENT PREDICTORS OF POOR QUALITY OF LIFE

All variables associated with poor quality of life ($p < 0.10$) were entered in to a backward stepwise logistic regression analysis. In addition, important descriptive and prognostic variables (i.e. requirement for ventilation during index admission, sex, age, BMI, AF, coexistent radiographic consolidation, hydrogen ion concentration, P_aCO_2, and the length of stay of the index admission) were forced in to the regression analysis. Individual comorbidities were included instead of the CCI and IHD and peripheral vascular disease (PVD) were combined in to a single variable. BMI and recent weight loss were included instead of the MUST score. SGRQ scores at discharge were not entered because of their relationship with the dependent variable. There was evidence of some collinearity between the remaining potential predictor variables (mean VIF 1.75, largest absolute VIF = 3.69) although the correlation matrix of potential predictors did not identify any sources of collinearity (Table 17.9). Although it was likely that eMRCD and NEADL at discharge were collinear to some extent, the

statistical measures of collinearity did not suggest that either variable should be excluded from the analyses.

Therefore, the following variables were entered in to the multivariate analysis: age; male sex; social care input prior to index admission; total number of hospital admissions in the preceding year; FEV_1 % predicted; FVC; eMRCD; BMI; recent unexplained weight loss; AF; IHD or PVD; pH and p_aCO_2 at admission; serum sodium, potassium and albumin at admission; haemoglobin concentration at admission; coexistent radiographic consolidation at admission to hospital; diastolic blood pressure at admission; length of hospital stay; NEADL score at hospital discharge; requirement for assisted ventilation during the index admission.

Independent predictors of poor quality of life are shown in Table 13.13. The regression model ('Model 7') was estimated to predict 31% of the variance in the dependent variable (Nagelkerke's R^2 = 0.313) and was a satisfactory fit of the data (HLGFT, p = 0.757).

Table 13.13 Independent predictors of poor quality of life during follow-up – 'Model 7', (n = 176)

Variable	B	S.E.	OR (95% CI)	p value
IHD or PVD	1.30	0.51	3.67 (1.34 to 10.0)	0.0112
Serum sodium (mmol/L)*	-0.11	0.05	0.893 (0.814 to 0.978)	0.0151
NEADL†	-0.05	0.02	0.954 (0.919 to 0.992)	0.0167
Serum potassium (mmol/L)*	0.99	0.45	2.69 (1.11 to 6.49)	0.0278
Serum albumin (g/L)*	-0.11	0.05	0.898 (0.809 to 0.997)	0.0434
FEV_1 % predicted	-0.03	0.02	0.968 (0.938 to 1.00)	0.0523
Intercept	15.6	7.0		

* measured at admission to hospital; † measured at hospital discharge; IHD – ischaemic heart disease; PVD – peripheral vascular disease

6 (3.4%) cases were statistical outliers from the regression model although none had a significant impact on the regression model (acceptable leverage values and Cook's distances). Further assessment confirmed that across deciles of risk, the model was well calibrated (gradient = 0.92) (Figure 13.2), and the discrimination was excellent (AUROC = 0.829, 0.756 to 0.902) (Figure 13.3) and internally valid (bootstrapped AUROC = 0.828, 0.750 to 0.895).

Figure 13.2 Calibration plot for Model 7 against the observed probability of poor quality of life

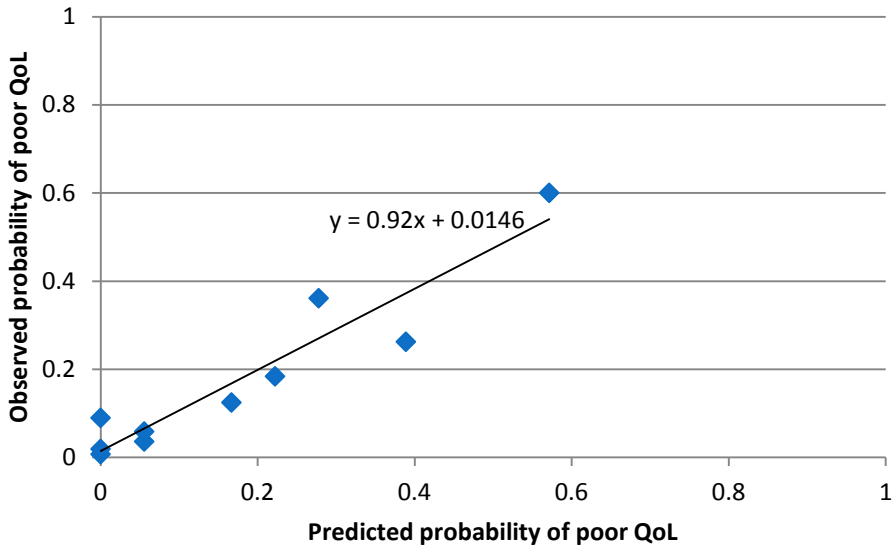
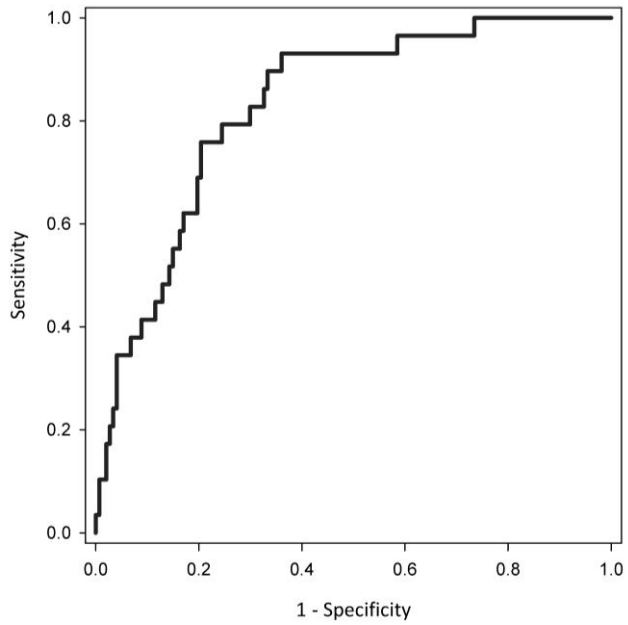


Figure 13.3 ROC curve showing the discrimination of Model 7 for poor quality of life



The severity of stable-state dyspnoea (eMRCD) is strongly associated with poor QoL but is not retained in the final multivariate analysis. This is likely to be due to the inclusion of the NEADL which measures, in detail, patients self-reported activity levels encompassing much of the information included in the eMRCD. Although no tests of collinearity between NEADL and eMRCD were met, leaving NEADL out of the analysis resulted in eMRCD being retained (OR 1.85, 1.05 to 3.28, p = 0.0336) without any change in the remaining predictor variables (Table 13.14). The discrimination of this

model was good (AUROC = 0.836, 0.759 to 0.913) and was not significantly different from Model 7 (p = 0.73). Therefore, for ease of clinical application, eMRCD could be used instead of the more cumbersome NEADL.

Table 13.14 Independent predictors of poor QoL using easy to measure indices

Variable	B	S.E.	OR (95% CI)	p value
IHD or PVD	1.32	0.51	3.73 (1.39 to 10.0)	0.0092
Serum potassium (mmol/L)*	1.00	0.44	2.71 (1.14 to 6.41)	0.0235
eMRCD	0.62	0.29	1.85 (1.05 to 3.28)	0.0336
Serum sodium (mmol/L)*	-0.10	0.05	0.905 (0.824 to 0.996)	0.0401
Serum albumin (g/L)*	-0.10	0.05	0.903 (0.817 to 0.998)	0.0449
FEV_1 % predicted	-0.03	0.02	0.971 (0.939 to 1.00)	0.0809
Intercept	9.27	7.2		

Nagelkerke's R^2 = 0.302; HLGFT = 0.391

CHAPTER 14 DISCUSSION – PART 1

14.1 SUMMARY OF MAIN FINDINGS

We have shown that, in patients hospitalised with acute exacerbations of COPD, important patient outcomes can be predicted accurately using clinical indices routinely available at the time of, or during, hospital admission. We have also described the extended MRC Dyspnoea Score which identifies a particular subgroup of patients (i.e. those with the most disabling stable-state dyspnoea) who are at an extremely high risk of in-hospital mortality. Furthermore, the eMRCD was found to be a strong discriminator for 12-month mortality.

Table 14.1 summarises the key independent prognostic variables (i.e. $p < 0.05$ on multivariate analysis), in descending order of prognostic strength, for our three main measures of patient outcome. For all three outcomes, the severity of stable-state dyspnoea is the strongest predictor of outcome. eMRCD aside, similar to our summary of previous prognostic research (Figure 3.1), the risk of in-hospital mortality is mostly explained by markers indicating a severe acute illness (for example, coexistent consolidation, ineffective cough, worse acidaemia etc), whereas long-term mortality is associated with a combination of underlying markers of disease severity (for example, low BMI, low FEV_1 % predicted, need for LTOT etc) and markers of a severe acute illness. Our study shows an overlap in predictors of in-hospital and 12-month mortality which is typically not present in previous research. However, we predicted 12-month mortality from the time of hospital admission (i.e. including in-hospital deaths) whereas most previous studies predicted long-term mortality from the time of hospital discharge (i.e. excluding in-hospital deaths). For the prediction of hospital readmission, prior health resource use and a broad assessment of functional impairment (need for formal social care prior to admission) are strong predictors and although we did not record individual QoL in this part of the study, these findings are consistent with previous research (Figure 3.1).

Table 14.1 Summary of the key independent prognostic indices (including continuous variables where applicable) for our three main outcomes

In-hospital mortality	12-month mortality	90-day readmission or death
eMRCD	eMRCD	eMRCD
Coexistent consolidation	Older age	Greater total number of admissions in the previous year
Lower eosinophil count	Lower serum albumin	Recent unexplained weight loss
Lower temperature	Higher urea	Cor pulmonale or pedal oedema
Atrial fibrillation	Unexplained weight loss	Social care prior to admission
Ineffective cough	Coexistent consolidation	Lower serum glucose
Older age	Lower BMI	
Cerebrovascular disease	Ineffective cough	
Lower serum albumin	Lower FEV_1 (% predicted)	
Worse acidaemia	LTOT	

The DECAF score accurately stratifies patients hospitalised with AECOPD according to their risk of in-hospital mortality and is a stronger discriminator of mortality than other well-established prognostic scores. Over 50% of our patients had a low risk DECAF score (DECAF 0 to 1) and a corresponding in-hospital mortality rate of 1.4%, and almost a quarter had a high risk DECAF score (DECAF 3 to 6) and a 34.6% risk of in-hospital mortality. This information can be used at the time of hospital admission to help inform clinical decision making.

We have identified robust independent predictors of both in-hospital mortality in patients requiring treatment with assisted ventilation and 12-month mortality in all hospitalised patients, and, in particular, have shown the time between admission and the development of acidaemic respiratory failure is a strong independent predictor of mortality in ventilated patients.

In patients surviving to discharge, the CRUSHED score is a good discriminator of 90-day readmission or death and we report strong independent predictors of frequent readmission that could be used to assist in the early identification of patients at risk of poor outcome.

14.2 STRENGTHS AND WEAKNESSES

Our study conclusions are strengthened by the recruitment of a large number of sequential patients. Furthermore, although external validation is necessary, our

findings support the generalisability of the conclusions, in particular: the two institutions reflect different catchment areas (urban and rural) with different structures of care and a wide range of socio-economic status represented; our inclusion criteria ensured that a broad spectrum of patients with AECOPD were recruited; mortality (allowing for the difference in proportions with consolidation) and readmission rates were in line with UK national audit data; and performance of the prognostic tools on internal validation were strong.

We are aware that comparisons between other prognostic tools and tools derived in this study (for example, the DECAF) will introduce bias in favour of our tools: prognostic performance is invariably stronger in derivation cohorts rather than in an external population. However, the large number of patients included, the generalisability of our methodology, and the size of the differences in prognostic performance, suggest that the stronger performance our tools (particularly the DECAF tool) compared to the other tools assessed is likely to be valid.

In patients not acidaemic at admission but who deteriorated and required ventilatory assistance during the hospital stay (n = 68), only certain physiological measurements (arterial blood gas data and respiratory rate) were collected at the time of deterioration. Therefore, the analysis to identify predictors of in-hospital mortality in all (n = 199) ventilated patients (section 11.1.2) could potentially be improved by including a more detailed assessment of other important physiological variables at the time of deterioration in the 68 patients. However, a clinician faced with an acutely unwell patient who has developed acute respiratory failure is unlikely to be able to wait for collection and analysis of biochemical and haematological parameters. Furthermore, the regression model had a good R^2 (0.584) suggesting that it explains a large proportion of the likely variance in the outcome variable (i.e. mortality). Therefore, not including variables at the time of clinical deterioration does not, in my opinion, weaken the clinical or statistical strength of this model.

We acknowledge certain limitations in the way the data were obtained, but the study was designed to reflect the “real life” clinical situation. Thus, clinical information was gathered by medical, nursing and research staff using standard protocols, and the presence or absence of consolidation was recorded by the admitting medical team.

Although missing data were relatively few, data had to be imputed for a small number of variables. To ensure that imputation using EM analysis did not bias our results, univariate analyses were repeated using the original dataset and the conclusions were unchanged.

14.3 STUDY FINDINGS AND COMPARISON TO PREVIOUS RESEARCH

14.3.1 STUDY POPULATION

Our study population is comparable to that reported in the UK National COPD Audit,[12] with similar: mean age; sex split; and admission clinical information (Table 14.2). However, it is noteworthy that our study had: more current smokers; greater levels of dependency prior to hospitalisation (higher proportion of patients living in institutions or requiring paid social care); a higher proportion of patients in whom cardiopulmonary resuscitation was not deemed to be an appropriate treatment option if required; higher median blood creatinine concentrations; more frequent coexistent consolidation; and more frequent treatment with assisted ventilation. Therefore, there is evidence that our population are more dependent and more unwell than the 2008 National Audit and both this observation and the higher proportion of patients with coexistent radiographic consolidation are likely to explain the differences in observed in-hospital mortality (10.4% in our study v. 7.7% in the National Audit). It is also important to note that the National Audit contained a large amount of missing data with over 50% missing values for some variables and this may further explain some of the differences.

The higher rate of coexistent consolidation in our study is likely to be due to a number of factors. Firstly, there is varying practice regarding whether patients with coexistent consolidation should be included in the diagnosis of AECOPD (Section 1.2.4) and although consolidation was not an exclusion criterion for the National Audit, we believe that the stated rate of consolidation (16%) underestimates the true prevalence due to varying reporting among participating hospitals. Furthermore, the National Audit reported that a further 20% of radiographs had an abnormality not thought to be due to pneumonia, cancer or COPD. Due to the diagnostic confusion surrounding coexistent consolidation in AECOPD, a number of patients with consolidation may have

been included in this category. Lastly, 10% of radiographs in the National Audit were either not commented on, or of poor quality.

The higher rates of assisted ventilation in our study may also partly explain the higher mortality. This reflects upon a more unwell population of patients in our study compared to the National Audit. In addition to the differences in disease and exacerbation severity highlighted in Table 14.2, more patients in the National Audit appeared to have ARF which was reversible with medical therapy and did not require NIV: despite similar rates of ARF (27.9% of our patients developed ARF at any time during their hospital stay compared to 26% in the National Audit) a greater proportion of our patients with ARF received ventilatory assistance (77.4% in our study compared v. 54.5% in the National Audit). A small proportion of this gap is due to differences in service provision: 3% of patients who required ventilation in the National Audit did not receive it because appropriate facilities were not available. However, it is likely that much of the difference is due to more patients in the National Audit having ARF reversible with medical therapy (and hence a milder exacerbation) with a consequent lower mortality rate.

Therefore, although minor differences exist, our study population is comparable to that reported in the UK National COPD Audit and where differences exist, they are likely to be explained by a combination of: a more unwell population in our study; differences in the provision of care (particularly assisted ventilation) between the hospitals involved in our study and those participating in the National Audit; and a high rate of missing data in the National Audit.

Table 14.2 Comparisons between our study and the UK National COPD Audit [12]

Variable*	Our study	UK National COPD Audit
Study population, n	920	9716
Sociodemographic details,		
Age, mean (SD)	73.1 (10.0)	73 (10)
Female, %	53.9	49.5
Institutional care, %	6.5	5
Social care prior to admission, %	22.9	17
Current smoker, %	44.3	33
Smoking load (cpy), median (IQR)	45 (32 to 60)	40 (30 to 60)
Disease severity & comorbidity,		

FEV_1 % predicted, median (IQR)	41 (31.7 to 54)	38 (28 to 52)
Respiratory rate (min^{-1}), median (IQR)	25 (22 to 29)	24 (20 to 28)
BMI (kgm^{-2}), median (IQR)	24 (19.9 to 28.5)	24 (20 to 29)
MRCD Grade 5, %	34.2	31
1 or more significant medical comorbidities, %	80.5	77
Admission clinical information,		
Purulent sputum, %	51.3	61
Pedal oedema, %	27.7	32
Coexistent pneumonia on admission CXR, %	32.5	16
Serum albumin (g/L), median (IQR)	39 (36 to 42)	39 (35 to 42)
Blood urea (mmol/L), median (IQR)	6.5 (4.7 to 9.3)	6.2 (4.6 to 8.7)
Blood creatinine (µmol/L), median (IQR)	93 (77 to 114)	83 (68 to 105)
pH, median (IQR)	7.41 (7.36 to 7.45)	7.41 (7.36 to 7.45)
pH < 7.35, %	20.5	20
DNACPR decision at admission, %	25.8	11
Outcomes,		
Treated with assisted ventilation,† %	21.6	12
In-hospital mortality, %	10.4	7.7
Length of stay (days), median (IQR)	6 (3 to 11)	5 (3 to 10)
Readmitted within 90-days,‡ %	33.4	33

DNACPR – do not attempt cardiopulmonary resuscitation; * values are quoted according to their distribution in the National Audit to assist comparisons; † at any time during the hospital admission; ‡ excluding deaths without readmission

14.3.2 CONSOLIDATION, DYSPNOEA AND MALNUTRITION

In our study, compared to patients with npAECOPD, patients with pAECOPD were: older, more likely to be female; and had slightly better preserved spirometry (Table 8.1). This is in contrast to the study by Lieberman et al [141] where no significant differences were found between npAECOPD and pAECOPD in these parameters. The difference in reported spirometry values is small and may be because our population were notably older (mean age 73.1 v. ~67 years) and the Lieberman study had less power: pAECOPD had better preserved spirometry than npAECOPD (FEV_1 % predicted = 41.6 v. 40.7 respectively) but small numbers (n = 23 with pAECOPD) may explain a non-significant result. Lieberman et al [141] found no differences in the prevalence of diabetes and cardiovascular comorbidity between pAECOPD and npAECOPD and although our study showed that patients with pAECOPD had a greater total comorbidity burden (measured by CCI) than npAECOPD (Table 8.1), there were no significant differences in the prevalence of diabetes or cardiovascular comorbidities (results not shown). Therefore, although our population was older than that reported

by Lieberman et al, the level of comorbidities and the severity of underlying COPD in patients with pAECOPD is comparable between the two studies. The generalisability of our results is further supported by comparable findings in the two studies of a longer length of hospital stay and higher rates of in-hospital mortality in pAECOPD.

We have shown that patients with coexistent consolidation have significantly higher rates of in-hospital mortality compared to those with simple exacerbations. The relationship between coexistent consolidation and outcome in patients hospitalised with AECOPD has been infrequently studied and although it is has been established that coexistent COPD is a predictor of poor outcome in patients with community acquired pneumonia,[161, 295, 296] only two studies [135, 141] have shown, in an unselected population of patients hospitalised with AECOPD, that coexistent consolidation is associated with increased mortality, and neither study adjusted for the effect of confounders. We have confirmed that, after adjusting for the effects of important confounders, coexistent consolidation independently predicts mortality.

We have also shown that a routinely used clinical prediction tool in patients with pneumonia, the CURB-65 score, has suboptimal performance in patients hospitalised with pAECOPD (AUROC = 0.661). It has recently been suggested that the CURB-65 may be a useful clinical prediction tool in npAECOPD [163] and although our study confirms a similar predictive strength (AUROC for in-hospital mortality = 0.719) to a recent publication by Chang et al [163] (AUROC for 30-day mortality = 0.733), both the eMRCD and DECAF score outperformed CURB-65 for the prediction of in-hospital mortality in npAECOPD (Table 8.5).

The severity of stable-state dyspnoea in patients hospitalised with AECOPD has rarely been reported. Similarly to our finding, the 2008 UK National COPD Audit [12] suggested that approximately 30% of admitted patients were too breathless to leave the house (MRCD 5), but the conclusion was limited by missing data in more than half of the subjects audited. Other studies [58, 263, 264] have recorded dyspnoea severity only in patients surviving to discharge which underestimates its importance due to its strong association with mortality. Higher MRCD scores have previously been shown to be associated with greater in-hospital mortality in patients attending the emergency department with AECOPD,[156] an association we have confirmed for all patients

hospitalised with AECOPD. A recent study [314] showed an association between the traditional MRCD score and hospital readmission in patients enrolled in an early supported discharge scheme, but to our knowledge a similar association between MRCD and hospital readmission in all patients hospitalised with AECOPD has not been reported.

Greater functional dependence has been shown to independently predict hospital readmission,[264, 308] and performance status, which includes an assessment of an individual's ability to self care, has been shown to be predictive of 3-month mortality following admission.[254] Also, in patients surviving to discharge, a high level of functional dependence is associated with long-term mortality.[58, 102, 249] Most of the in-hospital deaths (80%) in our study occurred in patients with severe stable-state dyspnoea (MRCD 5). We have shown that combining a measure of functional dependence with the assessment of dyspnoea severity (eMRCD) improves the predictive ability of the traditional MRCD scale, with a significantly higher risk of mortality in patients housebound and dependent in washing and dressing (eMRCD 5b) than in those housebound but independent in washing and / or dressing (eMRCD 5a).

Clinical decisions were in the hands of the admitting medical teams and uninfluenced by our study; however, we recognise that severe disability is likely to have been an important consideration in determining the management of individual patients. However, our finding does not appear to be explained by early introduction of palliative care, or limiting the level of care, in this population because, even among patients with the most severe limitation (eMRCD 5b), most of those potentially eligible for assisted ventilation received it, and there was no difference in this regard between eMRCD 5a and 5b.

Using the extended scale, each increase in dyspnoea severity was accompanied by a significantly higher mortality, and the prediction of in-hospital mortality was significantly better using eMRCD than MRCD (AUROC = 0.794 v. 0.769; p=0.0012). Furthermore, eMRCD outperformed CURB-65 for the prediction of in-hospital mortality in both pAECOPD and npAECOPD (Table 8.5) and, in the total population, was a stronger predictor of 12-month mortality than the DECAF score (Figure 9.8).

In our study population, average BMI (mean BMI = 24.6 kgm^{-2}) was similar to that reported in the National UK COPD Audit (median BMI = 24 kgm^{-2}) [12] and many patients (16.3%) were underweight (BMI < 18.5 kgm^{-2}). In agreement with previous research, low BMI was predictive of in-hospital [157, 247, 279] and long-term [33, 102, 250, 263] mortality, and although associated with hospital readmission in our population, similarly to previous studies [15, 264, 307, 310] it was not independently predictive. Our results also suggest that BMI has a non-linear relationship with mortality (Figure 8.4), with the lowest rate of death in overweight patients (BMI 25 to 29.99 kgm^{-2}), which is consistent with data from both AECOPD [33] and stable disease [35]. Our suggestion that BMI has a non-linear relationship with readmission has not previously been reported.

In single studies, recent unexplained weight loss has been shown to be predictive of long-term mortality [14] and early readmission [324] following hospitalization for AECOPD, as well as long-term mortality in stable disease [219]. Although Giron et al [34] failed to identify an association between weight loss and readmission, it is important to note that the generalisability of their results is uncertain due to the exhaustive patient selection undertaken. We have therefore confirmed the association between weight loss, mortality and readmission, and have also shown that recent unexplained weight loss is a strong independent predictor of both 12-month mortality and 90-day readmission or death.

Lastly, our study is the first to show the MUST score to be a useful clinical and prognostic measure in patients hospitalised with AECOPD. The prevalence of high malnutrition risk (MUST ≥ 2) reported in our population (24.3%) is similar to a general population of elderly hospitalised patients (28.6%) [41] although lower than a hospitalised population of elderly care-home residents (41.3%).[39] In AECOPD, a high MUST score is associated with an increased risk of in-hospital death in agreement with the study of elderly hospitalised, general medical patients by Stratton et al,[39] however our study identified an association with hospital readmission which had not been shown by Stratton et al. The higher in-hospital mortality rate (20.7%) in the study of elderly patients, and the lower readmission rate (26.0%) compared to our study may explain differing relationships between MUST and readmission.

14.3.3 PREDICTING MORTALITY IN PATIENTS HOSPITALISED WITH AECOPD

Our results show that in-hospital and 12-month mortality can be accurately predicted in AECOPD using indices routinely available at the time of hospital admission.

Reasons for the slight discrepancy in the in-hospital mortality rate between our population and the UK National COPD Audit have been discussed (section 14.3.1) but it is important to note the similarities between our long-term mortality rates and those reported in other studies. In our population, 31.6% of all patients (n = 920) died within 12 months of admission and 23.7% of patients who survived the index admission (n = 824) died within 1 year. These figures are comparable to studies investigating similar unselected populations in similar health care settings where the quoted 1-year mortality rates from the time of hospital admission range from 23% to 33%,[15, 242, 247] and 1-year mortality rates for patients surviving the index admission range from 16% to 36%.[14, 58, 249, 251, 269] This further emphasises the generalisability of our study population.

14.3.3.1 IN-HOSPITAL MORTALITY

Many of the independent prognostic indices for in-hospital mortality (Table 9.7) are consistent with previously published research in AECOPD: increasing age;[156, 239] dyspnoea severity;[156] low BMI;[157] low pH;[135, 157] low serum albumin;[158, 248, 288] cough effectiveness;[276] and coexistent consolidation.[141] Both cardiovascular and non-cardiovascular chronic comorbidity have been found to be associated with in-hospital mortality,[147] but, to our knowledge this is the first study to report, in an unselected population of AECOPD requiring hospitalisation, that both atrial fibrillation and cerebrovascular disease are independently predictive of in-hospital mortality.

Holland et al [289] previously reported that eosinopenia ($< 0.04x10^9/L$) was associated with higher in-hospital mortality in AECOPD, but the study population was small (n = 65) and the role of confounders was not evaluated. Our results show that eosinopenia is a strong independent predictor of in-hospital mortality. Of note, this finding is not due to better prognosis among patients with eosinophilia, as patients with confirmed

or suspected asthma were excluded, and only a small proportion had an eosinophil count above the usually quoted normal range (> $0.4x10^9$/L, n = 55) at admission; if the latter are excluded from analysis, our conclusions remain unchanged (results not shown). It is noteworthy that Holland et al [289] excluded individuals who had recently received oral corticosteroids, and in our study, there was no significant difference in eosinophil count between patients receiving either long-term inhaled (p = 0.38) or oral (p = 0.51) corticosteroids and those not in receipt of these therapies. In murine models, eosinopenia has been shown to be induced by infection [400] and inflammation.[401] This response was independent of endogenous corticosteroids and persisted for longer than the neutrophilic response to the same stimuli. Furthermore, eosinopenia has been shown to be a useful marker of sepsis in patients who are receiving intensive care.[402, 403] Therefore, although infrequently reported and recognised, previous research supports our finding that eosinopenia is of prognostic importance.

The DECAF score shows promise for the risk stratification of patients hospitalised with AECOPD. ROC analysis suggests that it has excellent performance and is a stronger prognostic score than the CURB-65, APACHE or CAPS predictive tools. Roche et al [156] derived a predictive tool from 794 patients attending an emergency department with AECOPD. Their prognostic score showed good discrimination for in-hospital mortality (AUROC = 0.79) but may be less generalisable as it included subjectively assessed signs of clinical severity. The DECAF Score performed more strongly in our population than the tool described by Roche et al, and furthermore, the prognostic indices included in the DECAF score are objective with little potential for varying interpretation.

The mortality rates for each grade of the DECAF score (Table 9.11) suggest the following risk categories: DECAF 0-1 (‘low risk’; in-hospital mortality = 1.4%); DECAF 2 (‘moderate risk’; mortality = 8.4%); and DECAF 3-6 (‘high risk’; mortality = 34.6%). Consequently, more than half of patients hospitalised with AECOPD can be classified as ‘low-risk’ for both in-hospital and 30-day mortality and might therefore potentially be suitable for early supported discharge schemes. In addition, the DECAF score identifies a group of patients at a particularly high risk of mortality (DECAF ≥ 3 = 34.6% in-

hospital mortality) in whom early escalation of care, or early discussion of end-of-life care may be appropriate.

In its derivation cohort, for the prediction of in-hospital mortality, DECAF outperforms the CURB-65, CAPS and APACHE prognostic scores and is also a good predictor of 12-month mortality (AUROC = 0.730). The DECAF score is well calibrated to a dummy prognostic model including all independent predictors in their original form, 'model 1' (Figure 9.3). Although 'model 1' had a small but statistically significant improvement in discrimination compared to DECAF (Figure 9.4), this is outweighed by the ease with which DECAF can be clinically applied.

14.3.3.2 LONG-TERM MORTALITY

We have identified strong, easily measured predictors of long-term mortality in patients hospitalised with AECOPD. Of these, severe stable-state dyspnoea,[58, 263, 264] older age,[15, 255] lower serum albumin,[102, 247] low BMI,[102, 247, 250] lower FEV_1,[31, 242, 244, 270] unplanned weight loss [14] and LTOT prescription [58] have all been previously shown to be independently predictive of mortality following hospital discharge. Coexistent radiographic consolidation, although a recognised marker for in-hospital mortality in AECOPD (section 14.3.2), has not previously been shown to independently predict long-term mortality.

Previous studies have shown that tachypnoea is independently predictive of the in-hospital mortality of patients receiving assisted ventilation,[138, 139] and although Seneff et al [258] showed that more abnormal respiratory physiology (abnormal respiratory rate, P_aCO_2, pH or A-a gradient) was predictive of 180-day mortality in patients surviving intensive care admission, our results are the first to suggest that a high respiratory rate may be of long-term prognostic importance in unselected patients with AECOPD. However, the non-significant p value for this result on multivariate analysis (p = 0.0642) may suggest that this association is not generalisable outside of this study population. Furthermore, our results suggest that a low CRP is predictive of long-term mortality. This is contrary both to clinical reasoning and to the univariate association we found with in-hospital mortality (Table 9.6) (i.e. higher CRP associated with greater mortality) and is therefore difficult to explain. However, its

borderline significance on multivariate analysis (p = 0.0624) indicates that this is not a strong independent predictor and this unexpected result may also be limited to our dataset and not generalisable to clinical practice.

It is noteworthy that no measure of comorbidity was independently predictive of 1-year mortality despite strong univariate relationships between specific comorbidities and mortality following discharge (Table 9.14). This is likely to be, in part, due to the variable selection techniques employed in our analyses. We choose to exclude the Charlson comorbidity index and categorical variables where any category included < 10% of the population. This was done to optimise the clinical utility and generalisability of our results by avoiding including measures that were both cumbersome and difficult to measure (i.e. the Charlson index), or that were prognostically useful only in a small proportion of the population. For this reason, both chronic kidney disease and LV dysfunction were excluded from the multivariate analysis despite strong univariate associations with outcome.

14.3.3.3 PREDICTING IN-HOSPITAL MORTALITY IN PATIENTS RECEIVING ASSISTED VENTILATION

In agreement with Roberts et al,[146] we have confirmed that, compared to patients not receiving assisted ventilation, ventilated patients had more severe underlying COPD. We have also shown that they have more markers to suggest a severe exacerbation than patients not receiving ventilation. The in-hospital mortality rate in our study (24.6%) is higher than the rates reported in the trials on which the use of NIV in AECOPD is based (typically ~10%),[170, 396] but comparable with both the 2008 National COPD Audit (25%) and a 'real-life' perspective on ward-based treatment with NIV (32.9%).[176] The lower mortality rates in the large NIV trials are likely to be due to different selection methods: for example, the YONIV study [170] only recruited patients with mild to moderate acidaemia (7.25 ≤ pH < 7.35) and reported a median pH of 7.32, compared to 7.26 in our study. The subgroup of ventilated patients in our study most closely matched to the YONIV cohort (respiratory acidaemia at admission, with 7.25 ≤ pH < 7.35; Table 11.2) showed a similar mortality (11.8%) to the YONIV study (10.2%) emphasising that it is patient selection and not differences in the

provision or standard of care which explains the mortality difference. We did not identify any association between requirement for assisted ventilation and readmission following discharge (Table 11.1).

Roberts et al [146], reporting the findings of the 2008 UK National COPD Audit, showed that patients who were initially non-acidaemic on admission but later developed ARF during their hospital stay were at a high risk of mortality. Our more detailed investigation of the relationship between the time to recognition of ARF and mortality has confirmed that patients with 'late-acidaemia' (i.e. not acidaemic on admission but developing acidaemia during the hospital stay) have a particularly high mortality risk, independent of confounders: in-hospital mortality = 14.5% if ARF develops within 4 hours of admission, but 65% if ARF develops more than 72 hours after admission (Figure 11.1). This has not been previously reported in the AECOPD literature but patients who initially improve on NIV and then deteriorate after 48 hours of admission have a particularly high in-hospital mortality rate.[172, 274] Based on these studies, it is suggested that patients who deteriorate in spite of NIV therapy should be considered for invasive ventilation; our study, in agreement with other studies of NIV use in the UK,[146, 176] shows that despite this evidence and the recommendation in the National UK NIV Guideline that IPPV should be considered in patients with very severe ARF (pH < 7.26) or in those who deteriorate after 48 hours on NIV,[174] very few (4/195, 2.1%) received invasive ventilation after initial treatment with NIV.

We have shown that, in this population, a low eosinophil count is independently predictive of mortality which has not been investigated or reported previously. Furthermore, although several authors have shown that a high comorbidity burden [150, 259] or chronic non-respiratory comorbidity [147] are associated on univariate analysis with in-hospital mortality in patients requiring ventilation, to our knowledge, this is the first study to report that a past history of cerebrovascular disease is independently predictive of death. In addition, many authors have shown that low body weight or low BMI are associated with in-hospital mortality,[144, 282] but this is the first study to report that recent unexplained weight loss is independently predictive of death.

Other independent predictors of mortality in our population treated with assisted ventilation (Table 11.10) are consistent with previous research: time between admission and the development of ARF;[146] cough effectiveness;[276] and low arterial bicarbonate concentration.[146, 150] We identified older age as an independent predictor of mortality and, although many other studies [138, 139, 299] have shown a strong univariate relationship between age and mortality, none have shown this to be independent of confounders. This discrepancy may be because many of the studies of NIV in AECOPD have been undertaken in ICU and are likely to include a younger population than our study, and furthermore, much of the data collected in these studies is taken from the time of admission to ICU (i.e. the time of clinical deterioration). It may be that physiological measures at the time of clinical deterioration (which we did not collect in detail in this study) are stronger predictors of outcome than age and therefore, in these studies, age is not an independent prognostic marker.

Only a single study has investigated the relationship between stable-state dyspnoea and mortality: Chu et al [264] showed that high MRCD scores were independently predictive of long-term mortality following treatment with NIV, and we have confirmed that this relationship exists for in-hospital mortality. Our finding that a high neutrophil count predicts mortality is consistent with previous research which has shown that a high total WBC [277, 291] and a high CRP [150] are associated with mortality.

Our finding that a history of anxiety or depression is protective against in-hospital mortality has not been reported previously. On the contrary, in all patients hospitalised with AECOPD, depression (measured using the HADS) is associated with increased long-term mortality.[359] The relationship between a history of anxiety or depression and short-term mortality has not previously been reported in AECOPD and our finding is difficult to explain and consequently requires external validation before application to clinical practice.

A low pH has frequently been found to independently predict mortality in patients requiring assisted ventilation,[259, 282, 284] but was not independently predictive of mortality in our study. However, in the three studies referenced above, arterial

bicarbonate was not included as a covariate in the multivariate analysis. In the only study of patients requiring ventilation to include both pH and arterial bicarbonate concentration in the multivariate analysis,[150] low bicarbonate was a strong independent predictor of death whereas low pH was only associated on univariate analysis. This is consistent with our results and it is likely that, in our study, arterial bicarbonate is included in the regression model ahead of pH because it relates to other important prognostic factors, such as the duration of respiratory failure (i.e. a normal bicarbonate concentration in the setting of ARF is likely to indicate a rapid clinical deterioration whereas an elevated bicarbonate level indicates underlying chronic respiratory failure), or the presence of a mixed respiratory and metabolic acidosis, a known adverse prognostic marker.[146]

The model including all of the independent predictors (Table 11.10) was an excellent discriminator for in-hospital mortality (AUROC = 0.913) and the results are likely to be generalisable beyond the study population (excellent performance on bootstrapping and relatively high R^2 value).

14.3.4 PREDICTING READMISSION IN PATIENTS SURVIVING TO DISCHARGE FOLLOWING HOSPITALISATION FOR AECOPD

In our population, 60.3% of patients surviving to discharge were readmitted within 12 months, and 66.3% were readmitted, or died without being readmitted, within 12 months. The reported annual readmission rates after AECOPD vary greatly from 25% to 87% although most of these studies do not include death without readmission in their outcome definition. The 90-day readmission rate in our study (33.4% for readmission only; 37.3% for readmission or death without readmission) is very similar to the figure of 33% reported in the 2008 National UK COPD Audit,[12] suggesting that our results are representative of the UK as a whole. During the year following discharge, 34.8% of our cohort experienced frequent (≥ 2) readmissions. The definition of 'frequent readmissions' varies and has rarely been studied although: Bhatt et al [327] reported that 23% of patients surviving hospitalisation for AECOPD experienced ≥ 3 readmissions in the subsequent 12 months; Garcia-Aymerich et al [303] reported that, during a median follow up period of 410 days, 40% of patients experienced ≥ 2

hospitalisations; and in a retrospective study, Cao et al [307] suggested that almost half (45.7%) of patients had ≥ 2 hospitalisations in the year prior to admission.

We identified a number of simple to measure strong independent predictors of 90-day readmission or death (Table 10.7). Of these, severe stable-state dyspnoea,[264, 308] previous hospitalisations,[14, 264, 325] unexplained weight loss,[324] lower ability to self-care,[264, 308], cor pulmonale,[312] and male sex [14] have all been shown to be predictive of hospital readmission in previous research. As discussed above (section 11.1.1) the finding that high glucose is protective against readmission is difficult to explain and requires further investigation.

The clinical prediction tool for 90-day readmission, the CRUSHED score, is simple to measure and shows good discrimination for the prediction of readmission (AUROC = 0.735). Furthermore, CRUSHED also shows moderate discrimination (AUROC = 0.691) for the identification of patients at risk of 28-day readmission or death. There was no significant difference between the CRUSHED score and Model 4 suggesting that CRUSHED is a good approximation of our most robust prediction tool for 90-day readmission. The CRUSHED tool was not directly compared with other readmission predictive tools however, when comparing performance in each tool's derivation cohort, CRUSHED performed favourably compared to the LACE (AUROC for 30-day readmission or death = 0.684) and PARR (AUROC for 12-month readmission = 0.685) predictive tools.

Therefore, the CRUSHED score provides a potential framework to risk-stratify patients hospitalised with AECOPD and consequently direct resources to patients most at risk of poor outcome.

Bhatt et al [327] suggested that: a preserved FEV_1; previous pneumococcal and influenza vaccination; a low BNP value; and low serum magnesium were associated with frequent (≥ 3 per annum) readmissions and the only independent predictor was low magnesium. However, many important well-known predictors of readmission were not evaluated in this study: dyspnoea severity; dependency in self-care; prior health resource use; and other blood tests apart from BNP and magnesium. Therefore it is uncertain whether the relationship between low magnesium and frequent

readmission would persist after inclusion of these potentially important confounders. A retrospective, but more extensive examination of potential predictors of readmission, [307] showed that: FEV_1 < 50% predicted; a long duration of COPD; and consumption of psychotropic drugs (e.g. antidepressants, tranquilizers etc) were independently predictive of frequent readmission. However, it is uncertain whether these findings are comparable to our study because the outcome was readmission frequency during the year prior to admission and not readmission frequency following hospital discharge.

We identified many variables strongly associated with frequent readmission on univariate analysis (Table 10.1 to Table 10.6) and the independent predictors of frequent readmission were: prior health resource use (assessed by either the frequency of hospitalisation in the past year or a previous hospital admission requiring NIV); high serum albumin at admission; a history of cerebrovascular disease; and no coexistent hypertension (Table 10.12). It is likely that the relationship between a preserved serum albumin concentration at admission and an increase risk of frequent readmission is likely to be partly explained by the strong relationship between low albumin and mortality following discharge (Table 9.18). Therefore patients with a higher albumin concentration were more likely to survive and therefore at a relatively higher risk of frequent readmission. Our finding that the strongest predictor of frequent readmission is prior health resource use is consistent with the data in stable disease investigating predictors of frequent exacerbations.[123]

The regression model including all of the independent predictors showed satisfactory discrimination (AUROC = 0.701) and although bootstrapped internal validation implies that our results are likely to be generalisable, the relatively low Nagelkerke's R^2 value (R^2 = 0.153) suggests that there are likely to be other important predictors of frequent readmission (for example, quality of life measures) which, if included, might produce a better predictive model. Although some of the individual prognostic indices identified in Model 5 may be of clinical utility to assist the identification of patients at risk of poor outcome, as a whole it lacks both prognostic strength and generalisability and hence further predictive tools for frequent readmission should be sought.

14.4 CLINICAL APPLICATION

In 2010, the National UK COPD Guideline [44] identified the following research question as a high priority in COPD: *"Could a simple multidimensional assessment be used to give a better indication of COPD outcomes than either FEV1 or other components measured alone in a wide range of COPD patients…?"* The extensive review of the literature (Chapter 2 to Chapter 3) recognises that this question has been addressed in stable disease (Table 2.9), but there has been little research in patients hospitalised with AECOPD. Within the published literature, there is some agreement regarding important predictors of mortality and readmission (Table 3.4 and Figure 3.1) but robust, simple to use clinical prediction tools have not previously been developed.

This study describes the DECAF tool which is simple to measure at the time of hospital admission and accurately stratifies patients according to their risk of in-hospital mortality. Therefore, at the time of hospital admission, patients at the highest risk of mortality can either be: managed in the most appropriate clinical setting (i.e. critical care or high dependency unit); monitored closely to ensure prompt action if evidence of clinical deterioration develops; and / or engaged in an early and well-informed discussion of prognosis and end-of-life care. It is perhaps the latter point which may have greatest clinical impact: an ability to provide accurate and informed prognostic information to patients, relatives and carers. In addition, application of the knowledge of the strong independent predictors of mortality in patients receiving assisted ventilation for ARF may help improve further the access to timely end-of-life care and improve communication with patients and relatives at this critical stage of a patient's illness.

Furthermore, although currently there are no firm recommendations regarding suitability criteria for entry in to Early Supported Discharge Schemes (ESD) following hospitalisation for AECOPD, it is advised that patient selection should depend on an assessment of prognosis.[44] Therefore, the DECAF score may provide a framework for selection for ESD and may increase the proportion of patients accepted on to such schemes. For example, if a low-risk DECAF score (DECAF = 0 – 1) were used to indicate suitability for ESD, approximately 50% of admitted patients might be considered,

compared to enrolment rates of approximately 25% of patients in most of the studies investigating ESD in AECOPD.[404]

Hospital readmission places a large financial burden upon the health service, is associated with a decline in QoL [405] and an increased risk of mortality,[242] and is the outcome most feared by patients with COPD.[406] Clinical application of the CRUSHED score would enable the early identification of patients most at risk of readmission and actions could be taken to try and help reduce the risk of readmission (for example, early clinical review post-discharge, better integration between primary and secondary care, respiratory specialist nurse involvement, or early referral for pulmonary rehabilitation).

14.5 FURTHER RESEARCH QUESTIONS

The development of clinical prediction models in clinical practice has four stages: development; validation; impact analysis; and implementation.[407] All prognostic models or clinical prediction tools that we have developed were internally validated and we believe that the results are generalisable to all patients hospitalised with AECOPD in the UK. However, formal external validation is optimal prior to clinical application. In addition to further validation work, it needs to be shown that utilising the tool in clinical practice can improve important clinical outcomes.

Options for further research include:

- ★ Can risk stratification of patients hospitalised with AECOPD, in terms of their DECAF score, be used to help guide in-hospital management and improve patient outcomes? In particular, do patients at a suspected high risk of death benefit from earlier and more intensive medical management?
- ★ Can a low DECAF score allow patients at a low-risk of in-hospital mortality be enrolled on to Early Supported Discharge Schemes and safely managed in the community?
- ★ Is it possible to reduce the risk of malnutrition, according to MUST, and consequent risk of mortality and readmission in patients hospitalised with AECOPD at a high malnutrition risk?

- ★ Does eosinopenia independently predict mortality in conditions similar to AECOPD, for example: community acquired pneumonia; or exacerbations of bronchiectasis?
- ★ Given the pressure on pulmonary rehabilitation services, does the CRUSHED score provide a feasible mechanism to select the patients at risk of early hospital readmission following discharge who may benefit most from early rehabilitation following discharge?

CHAPTER 15 DISCUSSION – PART 2

15.1 SUMMARY OF MAIN FINDINGS

Our results detail the longitudinal changes in QoL experienced by a large cohort of patients surviving hospitalisation for AECOPD. We have shown that, for the majority of patients, QoL takes approximately three months to recover following discharge although measures of patient activity peaked after six weeks of follow-up. In stable COPD, individuals who are hospitalised experience a greater decline in longitudinal QoL compared to stable patients who do not require hospitalisation.[111] In the present study of longitudinal QoL changes following hospitalisation for AECOPD, most patients did not experience an overall decline in QoL during follow-up and, for certain QoL domains (disease-specific symptoms, mastery of their condition and anxiety levels), it improved by a clinically important amount. For patients who were readmitted within 12 months of discharge, QoL was significantly lower than patients who were not readmitted, however, even for readmitted patients, QoL did not decline on average.

We have also shown that the QoL of patients treated with assisted ventilation was stable during follow-up although, when measured using the SGRQ, there was a significantly larger improvement in non-ventilated patients. Therefore, in spite of frequent poor outcomes (mortality and readmission) in patients discharged following hospitalisation for AECOPD, especially those who require assisted ventilation, the majority of patients did not experience a declining QoL and hence our results suggest that treatment decisions cannot be influenced by an assumption that following discharge, an inevitable decline in QoL will ensue.

Patients with advanced COPD report the most important element of end-of-life care to be *"not to be kept alive on life support when there is little hope of meaningful recovery"*.[89] We therefore attempted to identify individuals who experienced a poor QoL (section 13.6.1) following discharge in order to assist decisions surrounding level of care and end-of-life care. In our study, 29 patients experienced a poor QoL following discharge and, compared to those with an acceptable QoL, patients with a poor

subsequent QoL: were less active; had greater lung function impairment; had been more breathless during the stable-state prior to admission; were more likely to have lost weight and were at a higher malnutrition risk; had greater comorbidity; and at admission to hospital had lower serum sodium, potassium and albumin concentrations. Of these, a history of vascular disease, lower serum sodium, lower activity levels, higher serum potassium, and lower serum albumin on admission independently predicted poor QoL. Clinical application of these prognostic indices may improve discussions around end-of-life care and address the unmet palliative care needs of patients with severe COPD.

15.2 STRENGTHS AND WEAKNESSES

This is the largest study to date investigating QoL following hospital admission for AECOPD and is the only study to measure the longitudinal change in QoL over the year following discharge. As a consequence, one of its main strengths is that it addresses an important clinical question never previously answered: *"how does individuals' quality of life vary after discharge following hospitalisation for AECOPD?"* Similar to the points outlined in the Part 1 discussion (section 14.2), we believe that because of the size of this study and broad recruitment methodology, our results are generalisable beyond the study population.

Although a chronic condition with a typically progressive course, COPD can be associated with frequent exacerbation and short-term fluctuations in an individual's symptoms and QoL. Therefore, studies investigating QoL change between only two time points, or intervals widely spaced in time, will not reflect the short-term variation which individual patients experience. Our study, due to multiple longitudinal QoL measurements, will better take account of this subtle variation.

When considering longitudinal changes in QoL we opted to take account of patient death in a similar way to that used in the measurement of preference-based QoL (i.e. utility), whereby the lowest possible score on the measurement scale is assigned to indicate patient death.[408] Of the few longitudinal QoL studies in patients surviving hospitalisation for AECOPD, none included death as an important component of an individual's QoL. In similar fashion, death is not included in studies of QoL change in

stable COPD although in the non-COPD literature, some authors have used similar methodology to ours.[397, 399] We chose to include death in the assessment because of its clear clinical relevance when considering long-term change in QoL. In any population of patients similar to ours (i.e. severe underlying COPD surviving hospitalisation for AECOPD) it is likely that most deaths following discharge will be the result of either progressive organ (i.e. respiratory or cardiac) failure, malignancy, or an acute exacerbation of COPD: all of which are likely to be associated with a declining QoL leading up to the point of death. It is much less likely that the cause of death will be a sudden cardiac event with no preceding decline in QoL. This assumption is supported by a longitudinal QoL study in individuals with severe COPD which showed that, in the patients who died during follow up, QoL (measured using the SGRQ) deteriorated linearly prior to death.[409] Therefore, ignoring death will not accurately represent the QoL experienced by the patient. The time-course of QoL decline prior to death is uncertain and, whilst we are aware that assuming a linear decline prior to death will not reflect the short-term variation in QoL that an individual is likely to experience, this is a well-established method of analysing sequential QoL data [60, 119, 409] and is consistent with the findings of the longitudinal QoL study in severe COPD described above.[409] Furthermore, if the trajectory of QoL change is non-linear, area under the curve (AUC) is a better approximation of true QoL change than direct comparisons at each time point,[119] and therefore our use of AUC further improves the accuracy of our assessment.

We have attempted to define quantitatively whether an individual experienced a poor QoL following discharge from hospital. National guidelines recommend that, in patients hospitalised with AECOPD, clinical decision making should be influenced by an assessment of the "*potential for recovery to a quality of life acceptable to the patient*".[174] Our study is the first to identify prognostic markers which could help clinicians more accurately predict the likelihood of QoL recovery or decline in an individual patient. We are aware that all QoL measurement scales are limited by floor and ceiling effects: individuals with well preserved baseline QoL (i.e. at the top of the measurement scale) are more likely to report a decline in QoL during follow-up than patients with a very low baseline score (i.e. at the bottom of the measurement scale) whose QoL cannot worsen due to the confines of the measurement scale. In our

definition of poor QoL (section 13.6.1), we therefore included only patients who had an initially poorer than average baseline QoL and who also experienced a clinically important decline during follow-up. This definition may result in some patients who, despite a well preserved baseline value, experienced very poor QoL following discharge not being included. However, our definition will identify patients who have the greatest clinical need for either increased medical and supportive care, and / or for early discussion of end-of-life care. Furthermore, we chose death within six months of discharge in our definition of poor QoL. Although some individuals may have been defined as having a poor QoL solely because they died within six months of discharge, rather than because of a clinically important measured decline in QoL, we chose this methodology because: firstly, in this population, the likely decline in QoL prior to death is important and not ignorable; and secondly, we believe that when trying to identify patients with "*little hope of meaningful recovery*",[89] death is an important outcome.

15.3 STUDY FINDINGS AND COMPARISON WITH PREVIOUS RESEARCH

15.3.1 STUDY POPULATION AND BASELINE QOL

In our subgroup of patients surviving hospitalisation for AECOPD undergoing longitudinal follow-up, we found the expected differences between patients who received assisted ventilation and those who did not: greater lung function impairment; a higher proportion receiving LTOT; worse stable-state dyspnoea; lower pH and higher p_aCO_2 at admission; and longer length of stay (Table 13.1). This is similar to the findings of Roberts et al [146] who showed that, despite frequent missing data, compared to patients without ARF, those with respiratory acidaemia had: greater functional dependency; worse stable-state dyspnoea; and worse lung function impairment.

Despite these important differences between our ventilated and non-ventilated patients, those who were ventilated reported better COPD symptoms at baseline (i.e. time of hospital discharge) compared to those not ventilated (Table 13.2). This finding is, at first, difficult to explain but ventilated patients may report less symptoms because they are less active (significant difference in NEADL scores and eMRCD). Also, ventilated patients had a longer hospital stay than non-ventilated patients and their QoL may have recovered in-hospital to a higher level than that of non-ventilated

patients. Furthermore, the effect of a recent life-threatening illness on individuals' self-reported quality of life is uncertain. Therefore, although the SGRQ asks patients about their symptoms during the preceding four weeks, the recent survival after a life-threatening illness and the possibility of a greater in-hospital recovery in QoL may have skewed the ventilated patients' towards reporting less COPD-related symptoms. It is important to note that apart from the SGRQ Symptoms domain there were no other significant differences in QoL according to the SGRQ, the CRQ, or the HADS.

Our patients required frequent health resource use during the follow-up period (Table 13.3). Most patients (71.0%) were readmitted within 12 months of discharge and those treated with assisted ventilation during their index admission were more likely to be readmitted for both a respiratory cause ($p = 0.0339$) and an episode of AECOPD requiring assisted ventilation ($p = 0.0023$) than those not initially ventilated. The overall 12-month mortality rate for patients recruited to Part 2 of the study was slightly lower than comparable Part 1 patients (i.e. those who survived their index admission): 18.0% versus 23.7% respectively. The entry criteria for Part 2 will have excluded some patients at a high risk of post-discharge mortality (for example, chronic confusional states or significant comorbidity causing the patient to be unable to complete the longitudinal assessments, such as a severe stroke) and Table 13.1 highlights that patients enrolled in Part 2 were slightly younger than Part 1 patients which may further have influenced the mortality rate. In this subgroup of 183 patients, there was a non-significantly higher mortality rate in ventilated patients compared to non-ventilated patients although, given the relatively large absolute differences in mortality (22.0% v. 14.9% 12-month mortality), this may represent a true finding with a lack of statistical power explaining the non-significant result.

15.3.2 ASSOCIATIONS BETWEEN BASELINE QOL AND SUBSEQUENT OUTCOME

In this study, the baseline QoL measures associated with subsequent readmission and mortality were those assessing patients' activity levels (SGRQ Activity and NEADL). This agrees with the findings of Almagro et al [58] who showed the SGRQ Activity subscale to be independently predictive of long-term mortality. Gudmundsson et al [255] showed all SGRQ domains to be associated with long-term mortality, a finding that we

have not replicated. There were, however, clinically important QoL differences in our study between patients who died and survived in terms of the SGRQ Impacts and Total subscores, and therefore a lack of statistical power (33 deaths in our study compared to 122 deaths in the study by Gudmundsson et al) may explain the non-significant results. In a second manuscript reporting on the same population, Gudmundsson et al [305] showed higher scores for all SGRQ domains except Symptoms to be significantly associated with rehospitalisation following discharge, and Osman et al [316] showed significant univariate associations between higher scores on all SGRQ domains and readmission. However, in both these populations, average QoL was better (i.e. lower SGRQ scores) than in the population reported here, which may further explain the lack of an association between SGRQ Symptoms and Impacts with outcome in the present study. Additionally, our results suggest patients with more depressive symptoms according to the HADS score were at higher risk of mortality ($p = 0.0825$): an association consistent with previous research.[58, 249, 262]

15.3.3 LONGITUDINAL CHANGE IN QUALITY OF LIFE FOLLOWING HOSPITAL DISCHARGE

We have shown that for all patients (n = 183), overall quality of life, measured using either SGRQ or CRQ, did not decline during follow-up and, for specific QoL domains (SGRQ symptoms and CRQ mastery), it improved by a clinically important amount (Table 13.7). Activity levels, however, did decline during follow-up, although for all patients (n = 183), the average decline was less than the MCID. For those not treated with assisted ventilation, individuals': symptoms, disease impact and total QoL (measured using the SGRQ); mastery of their condition (measured using the CRQ); and self-reported levels of anxiety (measured using the HADS) improved both more than the MCID and, for the SGRQ and CRQ indices, more than ventilated patients. Despite less improvement in QoL in ventilated patients compared to non-ventilated patients, it is noteworthy that for all QoL measures apart from SGRQ symptoms, ventilated patients' QoL was maintained at their baseline level and, in contrast to the previously reported prognostic pessimism in AECOPD,[104] did not inexorably decline.

We are not aware of any publications comparing change in QoL between ventilated and non-ventilated patients and, in general, there is little published data on longitudinal change in QoL in patients surviving hospital admission for AECOPD. Most studies assessing change in QoL over time in AECOPD discharged from hospital are either: cross-sectional and aim to identify predictors of quality of life at a single time-point; or measure QoL at only two time points and rely on patient recollection of their QoL during the intervening period.

Both of the studies which recorded QoL at more than two time points only assessed short term changes and therefore do not compare directly with our results. O'Reilly et al [131] showed that patient-reported activity limitation and psychological symptoms improved during hospital admission, but deteriorated between hospital discharge and three months post discharge although the statistical significance of these results is not stated. Patients were also asked to provide a global valuation of their perception of their QoL. Comparing patient valuations at three months to discharge levels confirms that, in the O'Reilly study, patients' perceived QoL exhibited a statistically significant decline. These results appear to conflict with the only other similar study [366] which showed that patients' symptoms improved progressively from admission (day 0) to day 40 (post-discharge). However, the latter study assessed symptoms whereas O'Reilly et al assessed activity limitation, and neither study interpreted the change in QoL in the context of an MCID for the instrument and therefore, although both studies show absolute changes in QoL, it is not known whether these changes are of clinical significance. Therefore, given the different time periods investigated, the different QoL components measured and the uncertainty over whether the changes identified were clinically important, it is uncertain how these results compare to our findings.

Comparisons can be drawn between our results on the change in QoL in patients treated with assisted ventilation and two previous studies: Wildman et al [177] asked patients to compare their QoL at six months following intensive care for an exacerbation of COPD or asthma with their recall of QoL prior to hospital admission; and Connors et al [102] asked a cohort of patients hospitalised with severe AECOPD to provide a global assessment of their QoL at six months following discharge. Wildman et al showed that in patients surviving intensive care following an exacerbation of

COPD or asthma, 73% of patients reported that their QoL was better than or equivalent to before hospital admission; and Connors et al reported that 51% of patients hospitalised with a severe AECOPD claimed to have good, very good or excellent QoL six months after discharge. Although it is not possible to compare our findings quantitatively with those of Wildman and Connors, the suggestion that patients hospitalised with underlying severe COPD and a severe exacerbation do not inevitably experience a decline in QoL following discharge is consistent with our findings regarding the mean change in ventilated patients (Table 13.7). The only other study investigating longer term QoL change in patients surviving hospitalisation for AECOPD [410] reported that six years after hospitalisation for AECOPD requiring IPPV, the majority (72%) of living patients were self-sufficient and there were no significant differences in QoL scores measured at baseline and six years post discharge. However, only a small number of patients completed follow-up (16.2%) and therefore, it is uncertain how these findings apply to most of the patients hospitalised with AECOPD and whether they can help clinical decision making at the time of hospital admission.

Andenæs et al [120] assessed QoL change (using the SGRQ) over a nine month period in patients hospitalised with AECOPD. It is not clear from the manuscript whether ventilated patients were included in the study, but given the low in-hospital mortality rate (3.9%) it is likely that most were not ventilated and therefore the results are comparable with the change in QoL in our patients not treated with assisted ventilation. Andenæs et al showed that, for all SGRQ components except the symptoms domain, QoL was significantly better (both statistically and clinically) at nine months following discharge than at admission. This differs only slightly from our findings (Table 13.7), where non-ventilated patients showed an overall improvement in all SGRQ domains except SGRQ activity. These minor discrepancies may be a result of two important differences: Andenæs et al only recorded QoL at two time-points and, compared to our methodology, this was less likely to reflect the typical fluctuation in individuals' symptoms; also, they recorded baseline QoL soon after hospital admission rather than at hospital discharge which, given that O'Reilly et al [131] showed patient-reported activity limitation improved during hospital admission and not after discharge, is likely to explain our finding of a lack of improvement in SGRQ activity.

In the present study, for most measures of QoL, patients reported their best QoL at three months following discharge. The time course of recovery in QoL following hospitalisation for AECOPD has not been previously reported with previous studies only recording QoL at a single time point after hospital discharge. In AECOPD treated in the community there are varying reports of the length of time taken for QoL to recover: Seemungal et al [106] showed that the median time to recovery of specific symptoms (cough, dyspnoea and coryzal symptoms) was seven days; however, Spencer et al [119] showed that overall QoL (measured using SGRQ) continued to recover up to 26 weeks following presentation with AECOPD. Therefore, although no direct comparisons are available, our findings are consistent with those reported in patients treated with AECOPD in the community.

In our study, the only measures of QoL which did not peak at the three month assessment were individuals' activity levels (SGRQ Activity and NEADL) which appeared to recover more rapidly within six weeks of discharge. However, it is possible that activity levels never fully recovered and the apparent early recovery is because activity levels deteriorated after six weeks (perhaps due to hospital readmission or further AECOPD). This hypothesis is supported by the mean decline in activity levels and the short period of time spent with activity levels better than baseline (Table 13.7) as well as the findings of a study of patients treated for AECOPD in the community.[119] The latter study showed that, in patients who experienced a further exacerbation following the initial episode, all domains of the SGRQ improved during the first four weeks following treatment but after this, the SGRQ Activity domain began to decline.

Longitudinal QoL, for almost all QoL measures, was significantly worse in patients who experienced an episode of rehospitalisation following discharge compared to those not readmitted. This agrees with the data from stable disease whereby patients who experienced a hospital readmission had worse QoL than those not hospitalised,[111] however the cause of this relationship is uncertain.

15.3.4 PREDICTING SUBSEQUENT POOR QOL FOLLOWING DISCHARGE

We identified 29 patients who, according to our definition outlined in section 13.6.1, had a poor QoL following discharge. These patients, compared to those with an

acceptable QoL, had more severe underlying COPD: higher levels of functional dependence; worse stable-state dyspnoea; greater lung function impairment; more frequent comorbid IHD ($p = 0.0621$) and peripheral vascular disease; a greater comorbidity burden; and worse baseline QoL. Most measures of acute physiological derangement and the proportion of patients treated with assisted ventilation were similar between the two groups suggesting that the severity of the index exacerbation was not associated with a subsequent poor QoL. There were significant differences in serum albumin concentration (lower albumin concentration in patients with a subsequent poor QoL), however given the lack of differences in other measures of acute illness, this difference may reflect poor nutritional status which was associated with subsequent poor QoL: patients experiencing a subsequent poor QoL had a non-significantly lower BMI ($p = 0.13$) and a higher proportion of recent unexplained weight loss ($p = 0.0194$) (Table 13.9).

We also found that lower serum sodium concentrations and higher serum potassium concentrations at admission to hospital were associated with post-discharge poor QoL. In Part 2 patients, higher potassium concentration was strongly positively correlated with hydrogen ion concentration at admission (Spearman's $\rho = 0.43$, $p < 0.0001$) which was non-significantly associated with poor QoL ($p = 0.26$) and, in Part 1, strongly associated with long-term mortality (Table 9.17). Therefore, although the two variables were not collinear, the relationship between high potassium and poor QoL may be via its relationship with hydrogen ion concentration. The relationship between lower serum sodium and subsequent poor QoL has a number of possible explanations: low serum sodium may be a marker of the presence of, or treatment for, underlying comorbidities (for example, cardiac, liver or renal failure) or cor pulmonale, although it is important to note that in our study there were no direct relationships between either cor pulmonale or pedal oedema and poor QoL; low serum sodium is also an adverse prognostic marker in patients with AECOPD requiring ventilation [158, 288] and its association with poor QoL may be via its relationship with mortality. At the time of hospital discharge, the only QoL measure associated with poor QoL, except those used its definition, was activity levels measured using the NEADL.

No previous studies have attempted to define and predict poor QoL in patients with COPD. The most comparable studies are those identifying factors associated with a lack of QoL recovery although it is important to note that this methodology is often biased by a 'floor effect' which occurs with all QoL measurement scales (section 15.2). Furthermore, very few of these studies have investigated patients hospitalised with AECOPD and most investigate stable disease.

QoL decline in stable COPD is associated with: lower activity levels,[362] more severe stable-state dyspnoea,[363, 364] greater comorbidity,[111, 361] and worse baseline QoL,[361] all of which are consistent with our results. In our study, lower FEV_1 was retained in the final regression model (p = 0.0523) which is consistent with data in both stable disease and following hospitalisation with AECOPD, where lower FEV_1 is an established predictor of QoL decline.[60, 111, 313, 364, 366] A single study in stable COPD [363] showed low BMI to be associated with QoL decline which is consistent with our strong association between recent weight loss and poor QoL.

Tsai et al [365] investigated short term (two week) recovery in QoL following hospital discharge with AECOPD and reported that comorbid coronary artery disease and previous episodes of AECOPD were associated with QoL decline. Although no relationship between prior AECOPD and poor QoL was found in our study, we did show that prior hospitalisation was non-significantly associated (p = 0.0817) with poor QoL. The biochemical abnormalities we reveal as being associated and independently predictive of mortality have not been previously described.

We identified six independent predictors of poor QoL ('Model 7'): comorbid IHD or PVD; lower serum sodium concentration; higher activity levels (according to NEADL); higher serum potassium concentration; lower serum albumin concentration; and lower FEV_1 % predicted (Table 13.13). Tests of model assumptions were satisfactory and the model showed good discrimination for poor QoL in its derivation cohort and on internal validation (bootstrapped AUROC = 0.828, 0.750 to 0.895). Although the NEADL was independently predictive of poor QoL, it is a cumbersome tool which may limit its use in clinical practice. If NEADL is omitted from multivariate analysis, eMRCD emerges as in independent predictor (OR 1.85, 1.05 to 3.28, p = 0.0336) and the other predictors remain in the model. The model including eMRCD was slightly less

generalisable (Nagelkerke's R^2 = 0.302), but remained a satisfactory fit of the overall dataset (HLGFT, p = 0.391) and had equivalent discrimination (AUROC = 0.836, 0.759 to 0.913) to Model 7 (p = 0.73). Therefore, our results suggest that clinicians could use the more pragmatic eMRCD instead of the NEADL for the prediction of poor QoL following hospital discharge.

15.4 CLINICAL APPLICATION

In a large population of older patients with severe exacerbations of severe underlying COPD, overall QoL does not deteriorate significantly following discharge, and in those not requiring assisted ventilation, it improves by a clinically important amount. Therefore, patients, carers and clinicians may be reassured by the knowledge that, despite high rates of mortality and readmission following discharge, it is likely that an individual's QoL will not deteriorate from the level experienced during the few weeks prior to hospital discharge. For clinicians, this may inform decision making with regards to escalation of care. For example, an inability to accurately prognosticate in AECOPD [411] has, consistent with national recommendations,[174] hitherto resulted in decisions regarding appropriate level of care being frequently made on the basis of clinicians' perceptions of individuals' QoL. It is our contention that many patients are denied potentially beneficial intensive care due to widespread beliefs that QoL inexorably declines following discharge. These results challenge this perception and may improve the access to intensive care for patients with AECOPD, which may result in improved clinical outcomes.

The use of the predictive indices described in Table 13.13 and Table 13.14 could enable clinicians to identify patients at risk of poor QoL following hospitalisation for AECOPD. Early identification of those at risk may permit an open and informed discussion of future treatment options. For example, given that the majority of patients will be rehospitalised during the subsequent year, and almost a third of ventilated patients and over 10% of non-ventilated patients will experience a readmission requiring assisted ventilation, patients whose QoL is expected to be poor may choose alternative treatment options to further hospitalisation or ventilatory assistance if the situation

arises. Furthermore, clinicians would be able to discuss end-of-life treatment options and, if acceptable, improve access to end-of-life services for appropriate patients.

15.5 FURTHER RESEARCH QUESTIONS

We have attempted to define poor QoL in patients surviving hospitalisation for AECOPD, however, to validate our definition, comparison with patients' illness perceptions would be both informative and interesting. Furthermore, a detailed qualitative exploration of the wishes and expectations of patients with, or at risk of, a poor QoL would help inform end-of-life decision making in COPD. It is also uncertain whether individuals' views regarding treatment options and future care changes as QoL improves or deteriorates and understanding this relationship may help clinicians assess the impact of treatments and future events on patients' wishes and expectations. Therefore, potential future research questions include:

- ★ For patients who are expected to experience a poor QoL following discharge, what are their preferences and expectations with regards to future care?
- ★ Is there a relationship between patient-reported QoL and patient preferences regarding treatment, future care and end-of-life care?

The results reporting here may also have implications for future therapies. Treatments may be more clinically or cost-effective if directed at patients most at risk of poor outcome. Certain treatments may prevent QoL decline and others may be particularly effective at preventing or reversing the decline in QoL experienced by certain patients. Consequently, potential future research questions include:

- ★ Many patients, particularly ventilated patients, experience an early and significant decline in activity levels. Can pulmonary rehabilitation, commenced during the in-hospital stay, result in sustained improvements in QoL post discharge?
- ★ Given the effect of subsequent readmission on longitudinal QoL (Table 13.8), can therapies aimed at reducing readmission risk (i.e. treatments aimed at reducing AECOPD frequency) alter longitudinal QoL in patients surviving hospitalisation for AECOPD?

CHAPTER 16 FINAL CONCLUSIONS

This detailed study of a large cohort of patients hospitalised with AECOPD has many important findings, some in agreement with the published literature and some not previously reported. The most important results are summarised below:

- ★ Prognostication in AECOPD requiring hospitalisation can be improved using routinely available clinical indices.
- ★ The extended MRC Dyspnoea Score is a particularly strong predictor of subsequent outcome (mortality, readmission and poor QoL) and should routinely be recorded in all patients hospitalised with an exacerbation.
- ★ We have shown the DECAF score to be an accurate clinical prediction tool whose appropriate utilisation could result in improved patient outcomes.
- ★ A longer time between admission and the development of acidaemic respiratory failure is a strong independent predictor of mortality in patients requiring treatment with assisted ventilation.
- ★ The CRUSHED predictive tool appears to be a stronger predictor of readmission than two other commonly used predictive tools (the LACE and PARR tools) developed to predict readmission in general hospitalised patients.
- ★ Following discharge, most patients' QoL did not decline and for certain QoL domains, improved by a clinically important amount.
- ★ Clinical application of the clinical predictors of poor QoL may assist clinicians in the identification of, and reasoned discussion with, patients at greatest risk of poor recovery following discharge. This may improve clinical and patient decision making, and perhaps improve access to end-of-life services for those most in need.

CHAPTER 17 ACKNOWLEDGEMENTS

I am forever thankful to my supervisors, Dr Stephen C. Bourke and Professor G. John Gibson, for their unending enthusiasm, patience, knowledge and guidance that ensured this project was informative, rewarding and enjoyable with a final result of which I am proud. Nick Steen and Keith Gray were always available for the many and varied statistical questions thereby greatly enhancing my knowledge of statistical techniques and methodologies. Without the assistance of the Respiratory Specialist Nursing team and Respiratory Physicians at Northumbria Healthcare NHS Foundation Trust this project would not have been so productive and I am therefore most grateful. Victoria Ferguson's dedication and accuracy with regards to data management was of immeasurable help and ensured the project ran smoothly. I must also thank the agencies involved in study funding: Northumbria Healthcare NHS Foundation Trust Teaching and Research Fellow Programme; Breathe North; and the National Institute of Health Research, through the Comprehensive Local Research Network.

Lastly, I am indebted to my wife, Anna, for her unquestioning support, in the absence of which, none of this work would have been possible.

APPENDICES

APPENDIX A. CHARLSON COMORBIDITY INDEX (CCI)

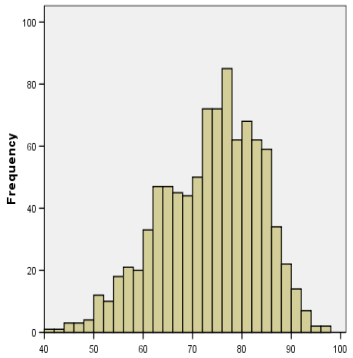
Table 17.1 Charlson comorbidity index

Comorbidity	Relative score
Metastatic solid tumour	6
AIDS	6
Moderate-to-severe liver disease	3
Hemiplegia	2
Moderate-to-severe renal failure	2
Diabetes with end organ damage	2
Neoplasia	2
Leukaemia/lymphoma	2
Myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Connective tissue disease	1
Peptic ulcer disease	1
Mild liver disease	1
Diabetes	1

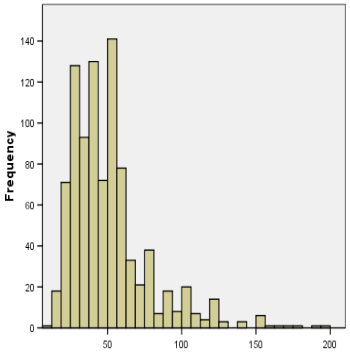
APPENDIX B. VARIABLE DISTRIBUTION

APPENDIX B.1. PART 1

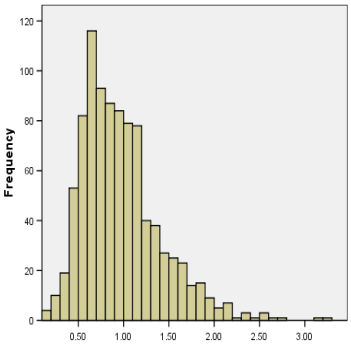
The distributions of all independent variables collected at the time of hospital admission are shown below. Assessment of normality was performed using the methods described in section 6.7.2.



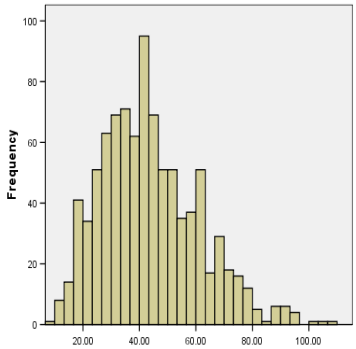
Age



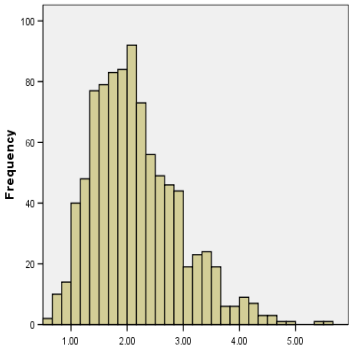
Cigarette pack years



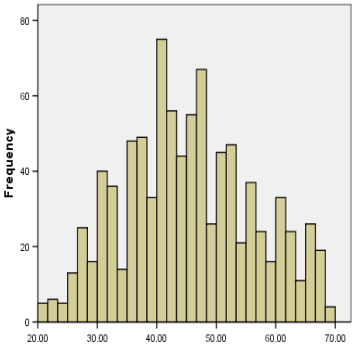
FEV_1 (litres)



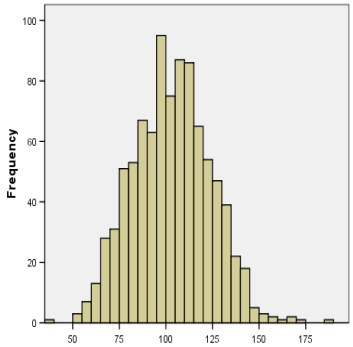
FEV_1 % predicted



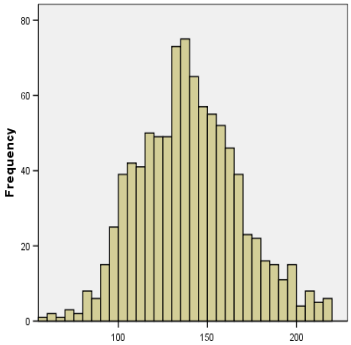
FVC (litres)



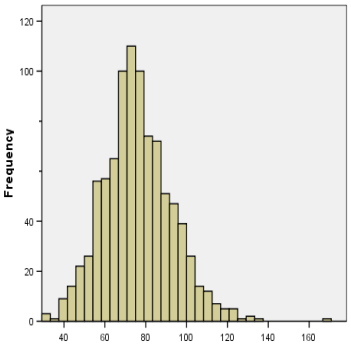
FEV_1/FVC ratio



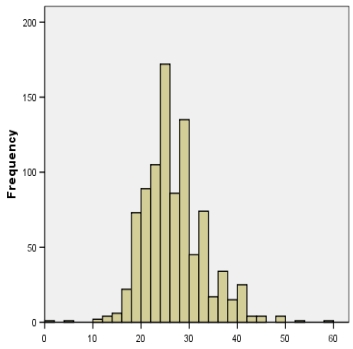
Heart rate



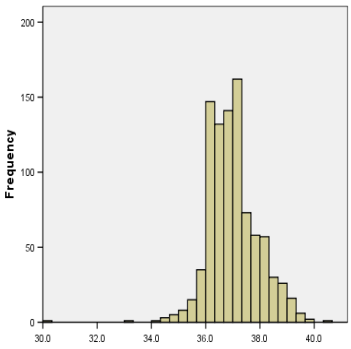
Systolic blood pressure



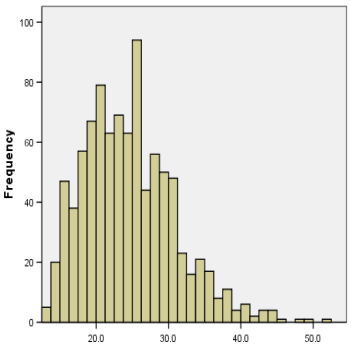
Diastolic blood pressure



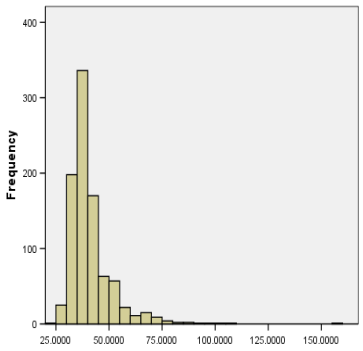
Respiratory rate



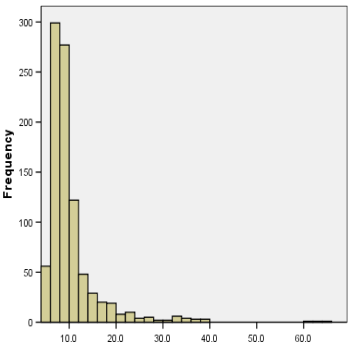
Temperature



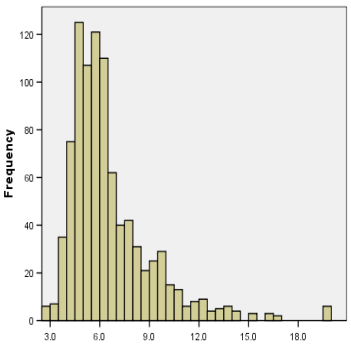
BMI



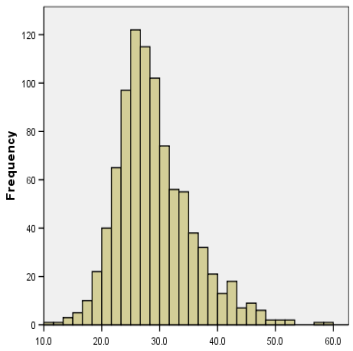
Hydrogen ion concentration



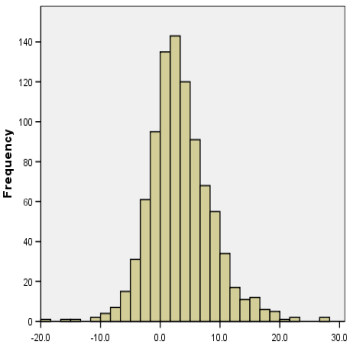
P_aO_2 (mmHg)



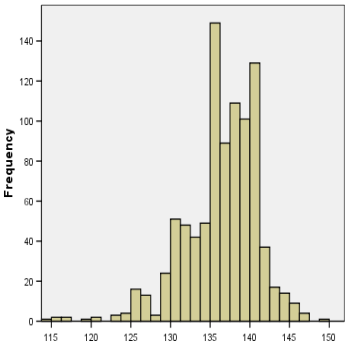
P_aCO_2 (mmHg)



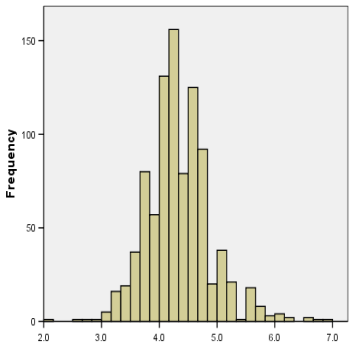
Bicarbonate



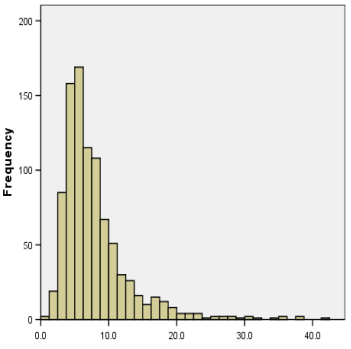
Base excess



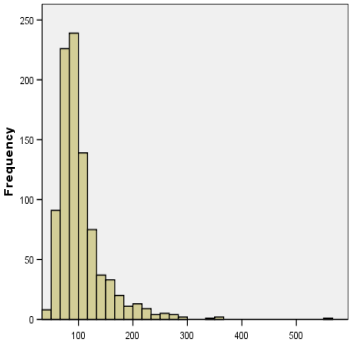
Sodium



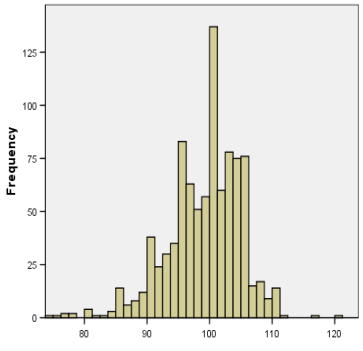
Potassium



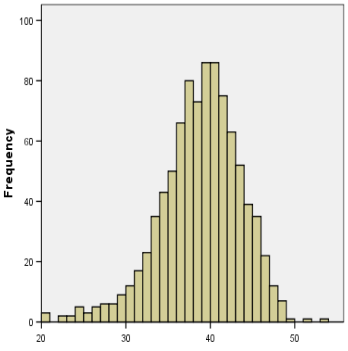
Urea



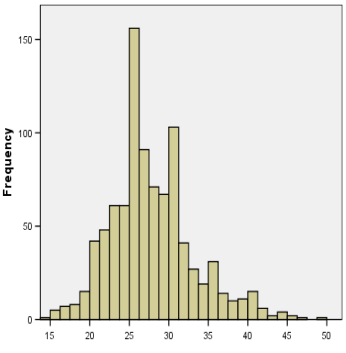
Creatinine



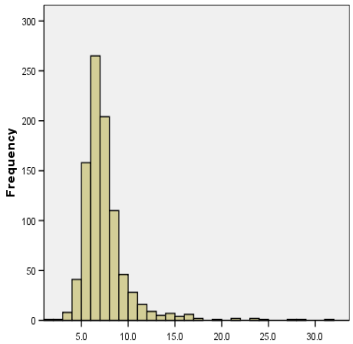
Chloride



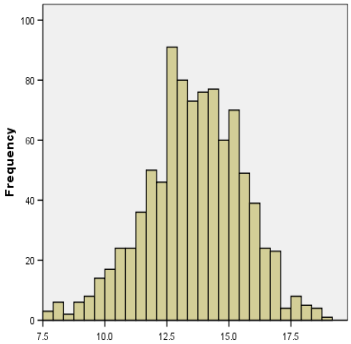
Albumin



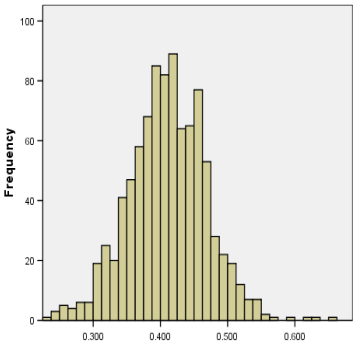
Serum bicarbonate



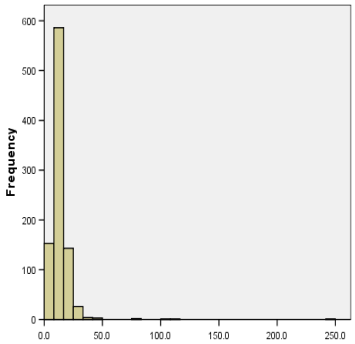
Serum glucose



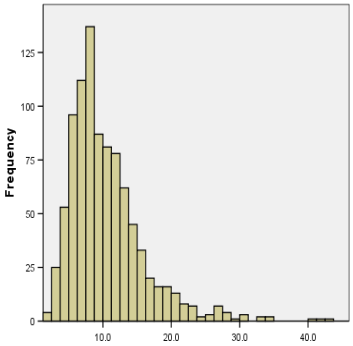
Haemoglobin



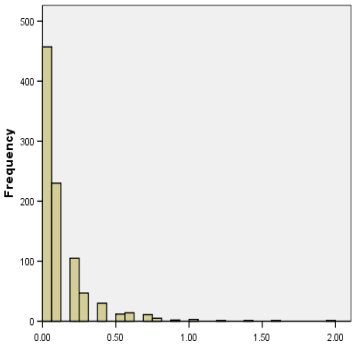
Haematocrit



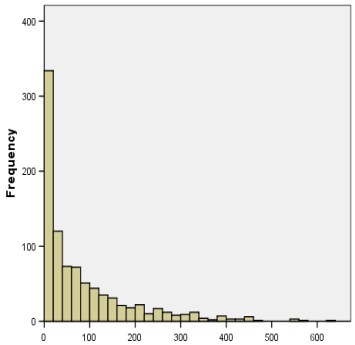
White cell count



Neutrophil count

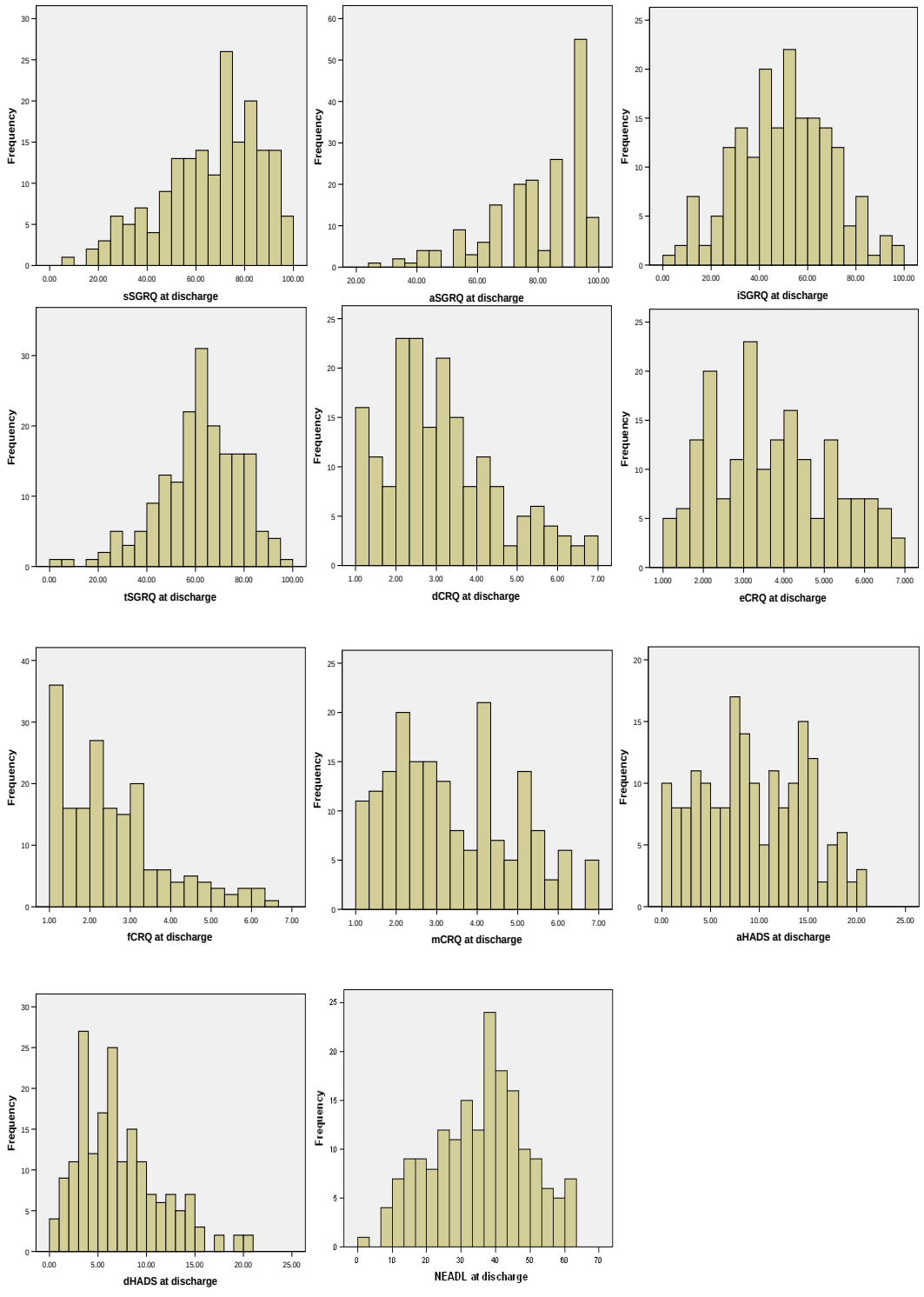


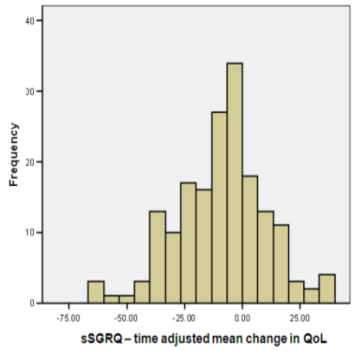
Eosinophil count

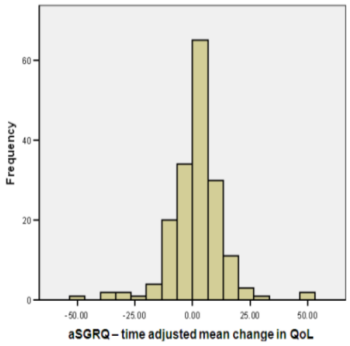


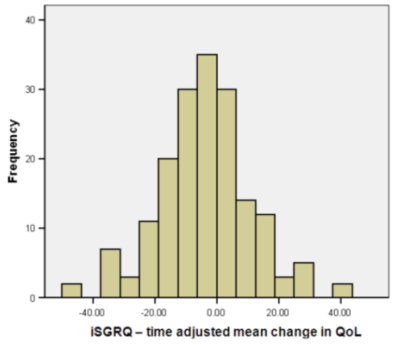
C-reactive protein

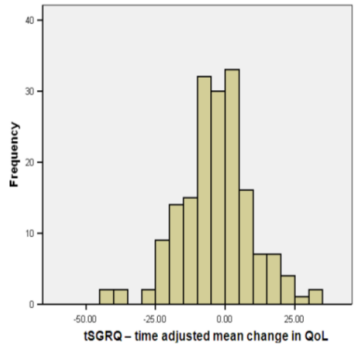
APPENDIX B.2. PART 2

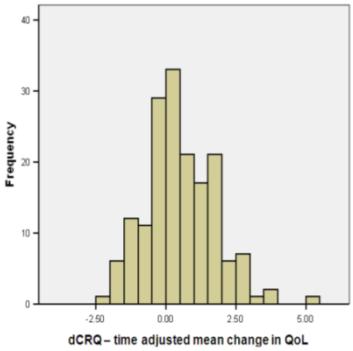


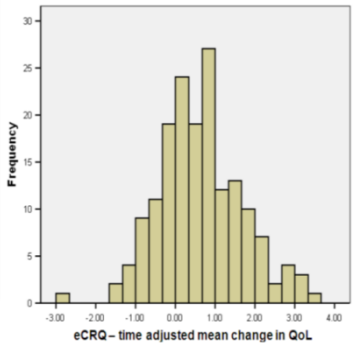

Frequency
sSGRQ – time adjusted mean change in QoL

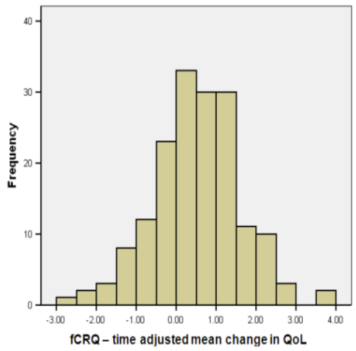

Frequency
aSGRQ – time adjusted mean change in QoL

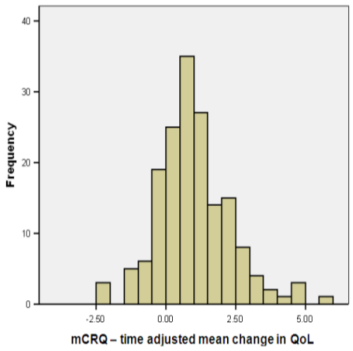

Frequency
iSGRQ – time adjusted mean change in QoL

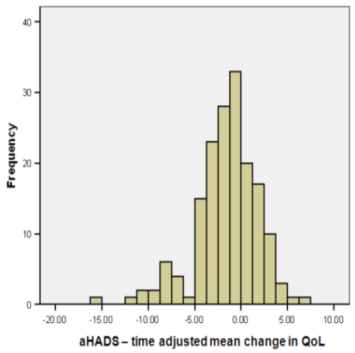

Frequency
tSGRQ – time adjusted mean change in QoL

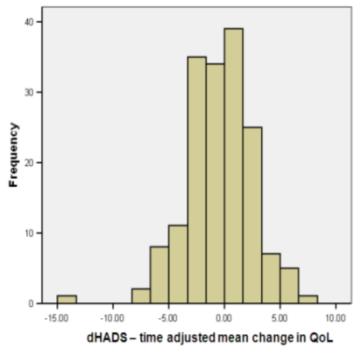

Frequency
dCRQ – time adjusted mean change in QoL

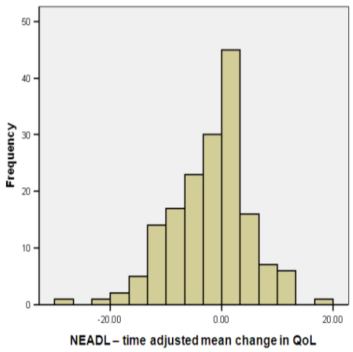

Frequency
eCRQ – time adjusted mean change in QoL

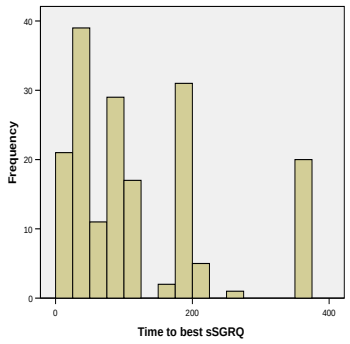

Frequency
fCRQ – time adjusted mean change in QoL

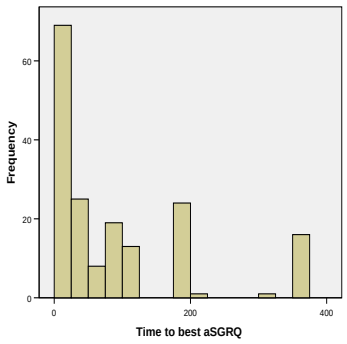

Frequency
mCRQ – time adjusted mean change in QoL

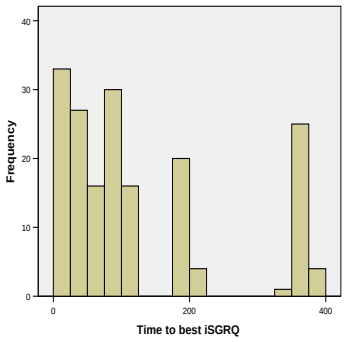

Frequency
aHADS – time adjusted mean change in QoL

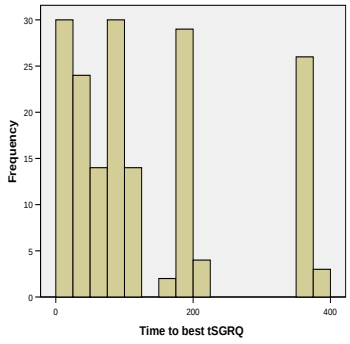

Frequency
dHADS – time adjusted mean change in QoL

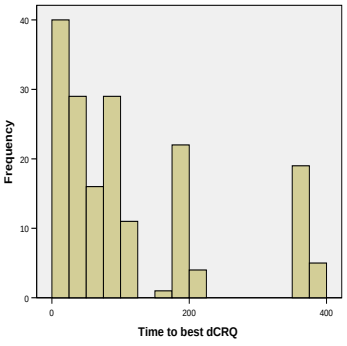

Frequency
NEADL – time adjusted mean change in QoL

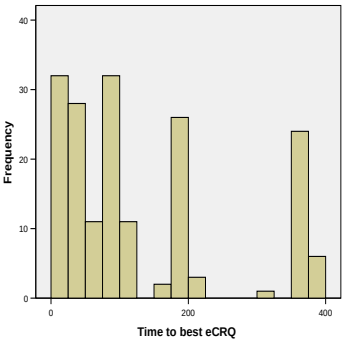

Frequency
Time to best sSGRQ

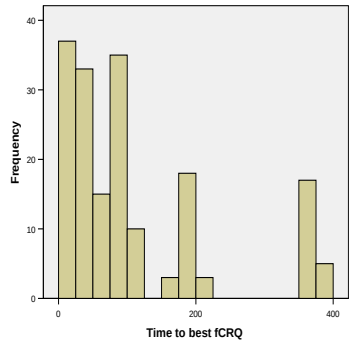

Frequency
Time to best aSGRQ

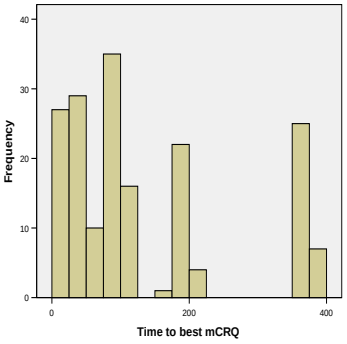

Frequency
Time to best iSGRQ

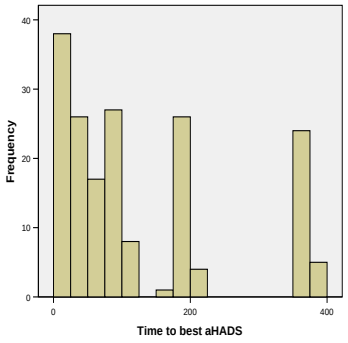

Frequency
Time to best tSGRQ

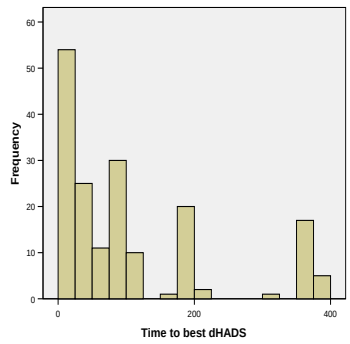

Frequency
Time to best dCRQ

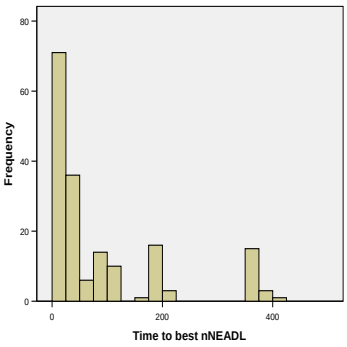

Frequency
Time to best eCRQ

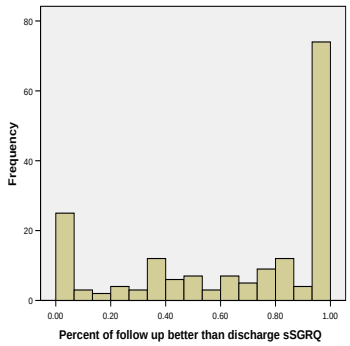

Frequency
Time to best fCRQ

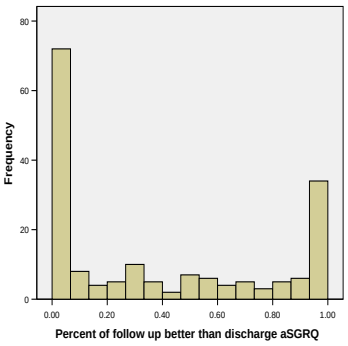

Frequency
Time to best mCRQ

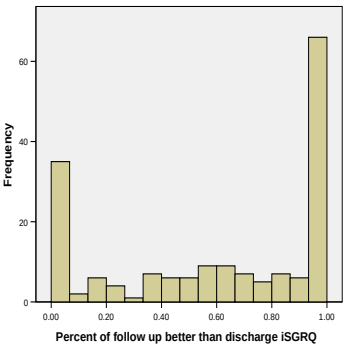

Frequency
Time to best aHADS

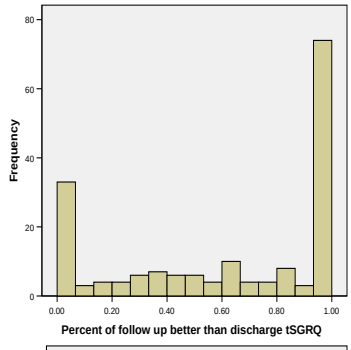

Frequency
Time to best dHADS

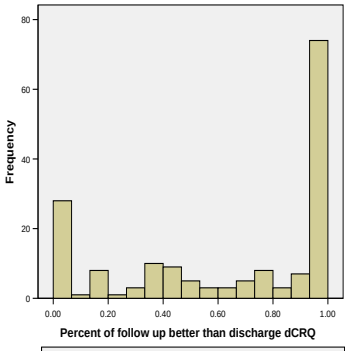

Frequency
Time to best nNEADL

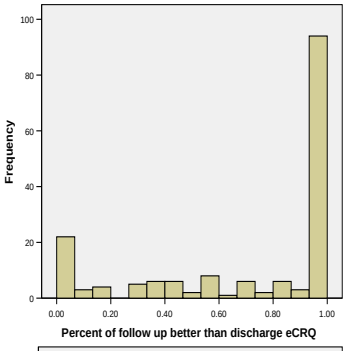

Frequency
Percent of follow up better than discharge sSGRQ

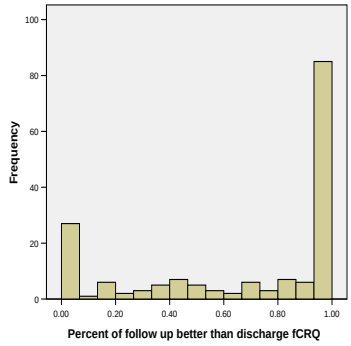

Frequency
Percent of follow up better than discharge aSGRQ

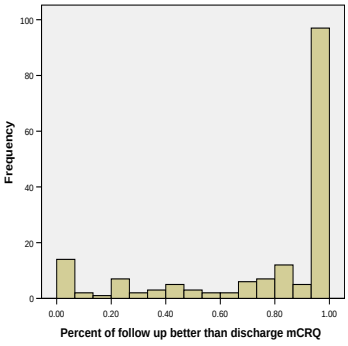

Frequency
Percent of follow up better than discharge iSGRQ

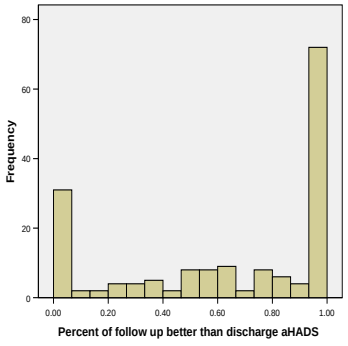

Frequency
Percent of follow up better than discharge tSGRQ

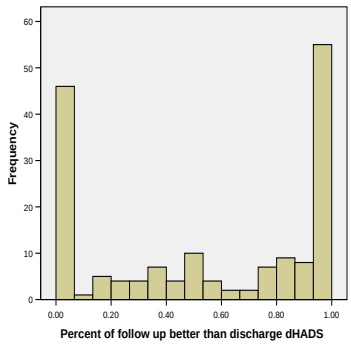

Frequency
Percent of follow up better than discharge dCRQ

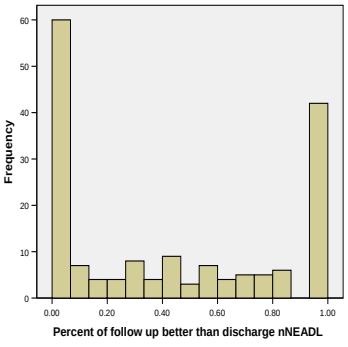

Frequency
Percent of follow up better than discharge eCRQ


Frequency
Percent of follow up better than discharge fCRQ


Frequency
Percent of follow up better than discharge mCRQ


Frequency
Percent of follow up better than discharge aHADS


Frequency
Percent of follow up better than discharge dHADS


Frequency
Percent of follow up better than discharge nNEADL

APPENDIX C. MISSING DATA AND DATA IMPUTATION

Table 17.2 Characteristics of patients with missing data

Variable	% missing	Age, years (mean)		Female (%)		FEV_1 % predicted (mean)		CCI (median)		BMI (mean)		MRCD (median)		Length of stay, days (median)		Death in-hospital, %	
		P	M	P	M	P	M	P	M	P	M	P	M	P	M	P	M
Glucose	19.3	73.3	72.2	52.8	58.4	44.4	43.1	2	2	24.8	23.8	4	4	6	7	10.6	9.6
AECOPD in past year	15.2	72.3*	77.3*	55.9*	42.9*	43.7	47.2	2*	2*	24.8*	23.1*	4*	5*	6	6	6.9*	30*
Spirometry$^{\Delta}$	14.3	72.1*	78.6*	53.7	55.3	n/a	n/a	2*	2*	24.9*	22.6*	4*	5*	6	7	7.2*	29.5*
Albumin	7.3	73.1	72.0	54.0	52.2	44.1	44.9	2	2	24.6	24.2	4	4	6*	5*	11.1*	1.5*
HCO_3^-, BE	6.8	73.0	74.3	54.7	42.9	43.9	47.4	2	2	24.6	24.2	4	4	6	5	10.7	6.3
pH (H^+), pO_2, pCO_2	6.3	73.0	74.7	54.6	43.1	43.8	49.1	2	2	24.6	24.0	4	4	6.5*	4*	10.7	6.9
BMI	4.3	72.9*	76.2*	54.3	45	44.3	40.2	2*	1*	n/a	n/a	4*	5*	6	5.5	9.1*	40*
K^+	1.3	73.0	74.5	53.7	66.7	44.1	47.2	2	1.5	24.6	25.5	4	4	6	7.5	10.5	8.3

P – Data present; M – data missing; AECOPD – acute exacerbations of COPD; HCO3- - bicarbonate; BE – base excess; BMI – body mass index; K+ - potassium; CCI – Charlson Comorbidity Index; MRCD – MRC Dyspnoea Scale; * significant difference between 'present' and 'missing', $p<0.05$; $^{\Delta}$including FEV1, FEV1 % predicted, FVC and FEV1/FVC

Table 17.3 Details of missing data and results of EM imputation

Variable	% missing	Original dataset			Complete dataset†		
		mean	SD	SE mean	mean	SD	SE mean
Glucose	19.3	7.49	2.96	0.11	7.45	2.71	0.089
Number of AECOPD in past year	15.2	3.02	2.64	0.095	3.02	2.47	0.082
FEV_1*	14.3	0.99	0.45	0.016	0.97	0.44	0.014
FEV_1 % predicted*	14.3	44.1	18.0	0.64	43.6	17.2	0.57
FVC*	14.3	2.19	0.81	0.029	2.15	0.78	0.026
Albumin	7.3	38.2	5.20	0.18	38.3	5.06	0.17
H^+	6.3	41.4	10.8	0.369	41.2	10.6	0.348
pCO_2	6.3	6.62	2.60	0.088	6.56	2.55	0.084
pO_2	6.3	10.3	6.21	0.21	10.3	6.02	0.20
HCO_3^-	6.8	29.2	6.47	0.22	29.1	6.52	0.21
BE	6.8	3.47	5.23	0.18	3.42	5.27	0.17
BMI	4.3	24.6	6.42	0.22	24.6	6.31	0.21
K^+	1.3	4.32	0.56	0.019	4.32	0.56	0.018

Only includes variables with >1% missing. Variables with less than 1% missing inc: RR, Temp, Na, Hb, WCC, Haematocrit, Urea, Creatinine, CRP, eosinophils. *within 2 years of admission; † includes original and imputed data

APPENDIX D. UNIVARIATE ANALYSES USING ORIGINAL (I.E. INCOMPLETE) VARIABLES

Table 17.4 Univariate relationships between original, incomplete variables and mortality following hospital admission

Variable	n (% of 920)	In-hospital mortality, p value	12-month mortality, p value
AECOPD in past year	780 (85)	0.85	0.52
FEV_1	788 (86)	0.0178	0.0001
FEV_1 % predicted	788 (86)	0.17	0.0009
FVC	788 (86)	0.0075	<0.0001
BMI	880 (96)	0.0011	<0.0001
Hydrogen ion concentration	862 (94)	0.0024	<0.0001
p_aO_2	862 (94)	0.87	0.99
p_aCO_2	862 (94)	0.0128	0.0002
HCO_3^-	857 (93)	0.44	0.0208
Albumin	853 (93)	<0.0001	<0.0001
K^+	908 (99)	0.0021	<0.0001
Glucose	742 (81)	0.0313	0.28

Table 17.5 Univariate relationships between original, incomplete variables and readmission following hospital discharge

Variable	n (% of 824)	90-day readmission or death, p value	Frequent readmission, p value
AECOPD in past year	726 (88)	<0.0001	<0.0001
FEV_1	731 (89)	0.0171	0.0112
FEV_1 % predicted	731 (89)	0.0043	0.0006
FVC	731 (89)	0.0116	0.0836
BMI	800 (97)	0.13	0.56
Hydrogen ion concentration	770 (93)	0.47	0.23
p_aO_2	770 (93)	0.56	0.81
p_aCO_2	770 (93)	0.26	0.27
HCO_3^-	765 (93)	0.40	0.50
Albumin	758 (92)	0.0013	0.0159
K^+	813 (99)	0.26	0.62
Glucose	663 (80)	0.0435	0.37

APPENDIX E. CORRELATION MATRICES FOR POTENTIAL PREDICTOR VARIABLES FOR REGRESSION ANALYSES

APPENDIX E.1. CORRELATION MATRIX OF POTENTIAL CONTINUOUS PROGNOSTIC VARIABLES, FOR BOTH IN-HOSPITAL AND 12-MONTH MORTALITY, IN ALL PATIENTS HOSPITALISED WITH AECOPD

Table 17.6 Correlations between potential continuous prognostic variables in all patients hospitalised with AECOPD (n = 920)

	Age	Previous admissions	FEV_1 % pred	FVC	eMRCD	dBP	RR	Temp	S_pO_2	H^+	p_aO_2	HCO_3^-	K^+	Urea	Creatinine	Albumin	Glucose	Hb	nØ	eØ	CRP
Age	1	0.09†	0.14‡	-0.28‡	0.33‡	-0.14‡	0.13‡	-0.03	-0.06	-0.01	-0.02	-0.02	0.07*	0.33‡	0.28‡	-0.27‡	0.02	-0.33‡	0.03	-0.07*	0.14‡
Previous admissions		1	-0.06	-0.03	0.23‡	0.04	0.06	-0.03	0.01	-0.06*	0.02	-0.01	-0.03	-0.06	-0.06	-0.03	-0.03	-0.15‡	0.00	0.16‡	-0.09†
FEV_1 % pred			1	0.43‡	-0.26‡	-0.08*	-0.05	0.07*	0.04	-0.24‡	0.01	-0.40‡	-0.15‡	0.12‡	0.23‡	-0.03	0.01	-0.12‡	-0.03	-0.02	0.01
FVC				1	-0.39‡	0.05	-0.09†	-0.02	0.08*	-0.25‡	0.02	-0.39‡	-0.02	-0.02	0.19‡	0.09†	-0.09†	0.16‡	-0.05	0.02	-0.07*
eMRCD					1	-0.10†	0.14‡	-0.05	-0.05	0.14‡	0.05	0.19‡	0.14‡	0.17‡	0.00	-0.25‡	0.02	-0.18‡	0.10†	-0.03	0.08*
dBP						1	0.13‡	-0.01	0.11†	0.09†	0.09†	0.03	0.02	-0.23‡	-0.17‡	0.31‡	0.01	0.22‡	-0.09†	0.10†	-0.28‡
RR							1	0.07*	-0.08*	0.17‡	0.07*	-0.08*	0.05	0.04	0.06	-0.03	0.10†	0.01	0.06	-0.06	0.08*
Temp								1	-0.10†	-0.13‡	-0.11†	-0.07*	-0.13‡	-0.06	-0.01	0.01	0.06	-0.02	0.24‡	-0.17‡	0.24‡
S_pO_2									1	-0.09†	0.37‡	-0.13‡	-0.02	-0.12‡	-0.01	0.15‡	-0.10†	0.05	-0.09†	0.13‡	-0.15‡
H^+										1	0.10†	-0.21‡	0.42‡	0.12†	0.03	0.08*	0.19‡	0.08*	-0.09†	0.04	-0.09†
p_aO_2											1	-0.08*	0.01	-0.01	0.03	0.08*	0.02	-0.06	-0.05	0.04	-0.04
HCO_3^-												1	0.04	-0.10†	-0.32‡	-0.03	0.07*	0.03	-0.07*	-0.02	-0.05
K^+													1	0.21‡	0.14‡	-0.01	0.04	-0.02	0.05	0.02	0.00
Urea														1	0.67‡	-0.31‡	0.12†	-0.24‡	0.18‡	-0.17‡	0.24‡
Creatinine															1	-0.14‡	0.10†	-0.16‡	0.10†	-0.02	0.15‡
Albumin																1	0.11†	0.34‡	-0.20‡	0.17‡	-0.52‡
Glucose																	1	-0.01	0.13‡	-0.19‡	0.03
Hb																		1	-0.10†	0.00	-0.21‡
nØ																			1	-0.24‡	0.43‡
eØ																				1	-0.29‡
CRP																					1

Pearson's r or Spearman-ρ correlation coefficient used depending on underlying variable distribution; RR – respiratory rate; dBP – diastolic blood pressure; temp – temperature; K^+ - potassium; Hb – haemoglobin; nØ – neutrophil count; eØ – eosinophil count; *p<0.05; † p<0.01; ‡p<0.001

APPENDIX E.2. CORRELATION MATRIX OF POTENTIAL CONTINUOUS PROGNOSTIC VARIABLES IN PATIENTS RECEIVING ASSISTED VENTILATION

Table 17.7 Correlations between potential continuous prognostic variables in patients receiving assisted ventilation (n = 199)

	Age	eMRCD	BMI	Urea	Albumin	Hb	nØ	eØ	CRP	RR*	$H^{+~}$	Time from admission to acidosis
Age	1	0.29‡	-0.17*	0.42‡	-0.23†	-0.31‡	-0.09	-0.12	0.12	0.09	0.09	0.21†
eMRCD		1	-0.19†	0.08	-0.16*	-0.08	0.05	-0.04	0.11	0.11	0.03	0.05
BMI			1	0.08	0.06	0.13	-0.06	0.11	0.05	-0.06	-0.05	-0.01
Urea				1	-0.38‡	-0.23†	0.17*	-0.27‡	0.29‡	0.02	0.19†	0.06
Albumin					1	0.30‡	-0.16*	0.33‡	-0.41‡	0.01	0.02	-0.19†
Hb						1	-0.10	-0.02	-0.08	-0.01	-0.14*	-0.12
nØ							1	-0.23†	0.46‡	0.09	0.14*	-0.01
eØ								1	-0.35‡	-0.01	-0.05	-0.11
CRP									1	0.10	-0.02	0.13
$RR^{~}$										1	0.21†	-0.07
$H^{+~}$											1	-0.18†
Time from admission to acidosis												1

Pearson's r or Spearman-ρ correlation coefficient used depending on underlying variable distribution; RR – respiratory rate; Hb – haemoglobin; nØ – neutrophil count; eØ – eosinophil count; H^+ - hydrogen ion concentration; ~ at the time of commencement of assisted ventilation; *p<0.05; † p<0.01; ‡p<0.001

APPENDIX E.3. CORRELATION MATRIX OF POTENTIAL CONTINUOUS PROGNOSTIC VARIABLES, FOR BOTH SINGLE AND FREQUENT READMISSION, IN PATIENTS SURVIVING TO DISCHARGE

Table 17.8 Correlations between potential continuous prognostic variables in patients surviving to discharge (n = 824)

	Age	Previous admissions	Previous AECOPD	Smoking load	FEV_1 % pred	FVC	eMRCD	Na	Urea	Albumin	Glucose	Eosinophils	CRP	Length of stay
Age	1	0.08*	-0.09*	-0.12†	0.14‡	-0.27‡	0.30‡	0.06	0.41‡	-0.30‡	0.01	-0.04	0.12†	0.19‡
Previous admissions		1	0.36‡	0.07*	-0.08*	-0.03	0.22‡	0.02	-0.07	-0.01	-0.04	0.16‡	-0.09†	0.05
Previous AECOPD			1	0.06	-0.07*	-0.09*	0.25‡	0.04	-0.08*	0.06	-0.07*	0.14‡	-0.05	0.06
Smoking load				1	-0.06	0.13‡	0.04	-0.07	-0.07*	0.00	-0.08*	0.05	0.01	-0.02
FEV_1 % pred					1	0.43‡	-0.27‡	-0.07*	0.13‡	-0.04	0.01	-0.03	0.02	-0.12‡
FVC						1	0.40‡	-0.10†	-0.01	0.10†	-0.08*	0.00	-0.06	-0.24‡
eMRCD							1	0.03	0.13‡	-0.20‡	0.01	0.02	0.04	0.25‡
Na								1	0.13‡	0.07*	-0.08*	0.17‡	-0.15‡	0.02
Urea									1	-0.29‡	0.10†	-0.13‡	0.21‡	0.19‡
Albumin										1	0.10†	0.14‡	-0.53‡	-0.22‡
Glucose											1	-0.21‡	0.03	0.06
Eosinophils												1	-0.27‡	-0.12‡
CRP													1	0.17‡
Length of stay														1

Pearson's r or Spearman-ρ correlation coefficient used depending on underlying variable distribution; *p<0.05; † p<0.01; ‡p<0.001

APPENDIX E.4. CORRELATION MATRIX OF POTENTIAL CONTINUOUS PROGNOSTIC VARIABLES FOR POOR QOL IN PATIENTS SURVIVING TO DISCHARGE

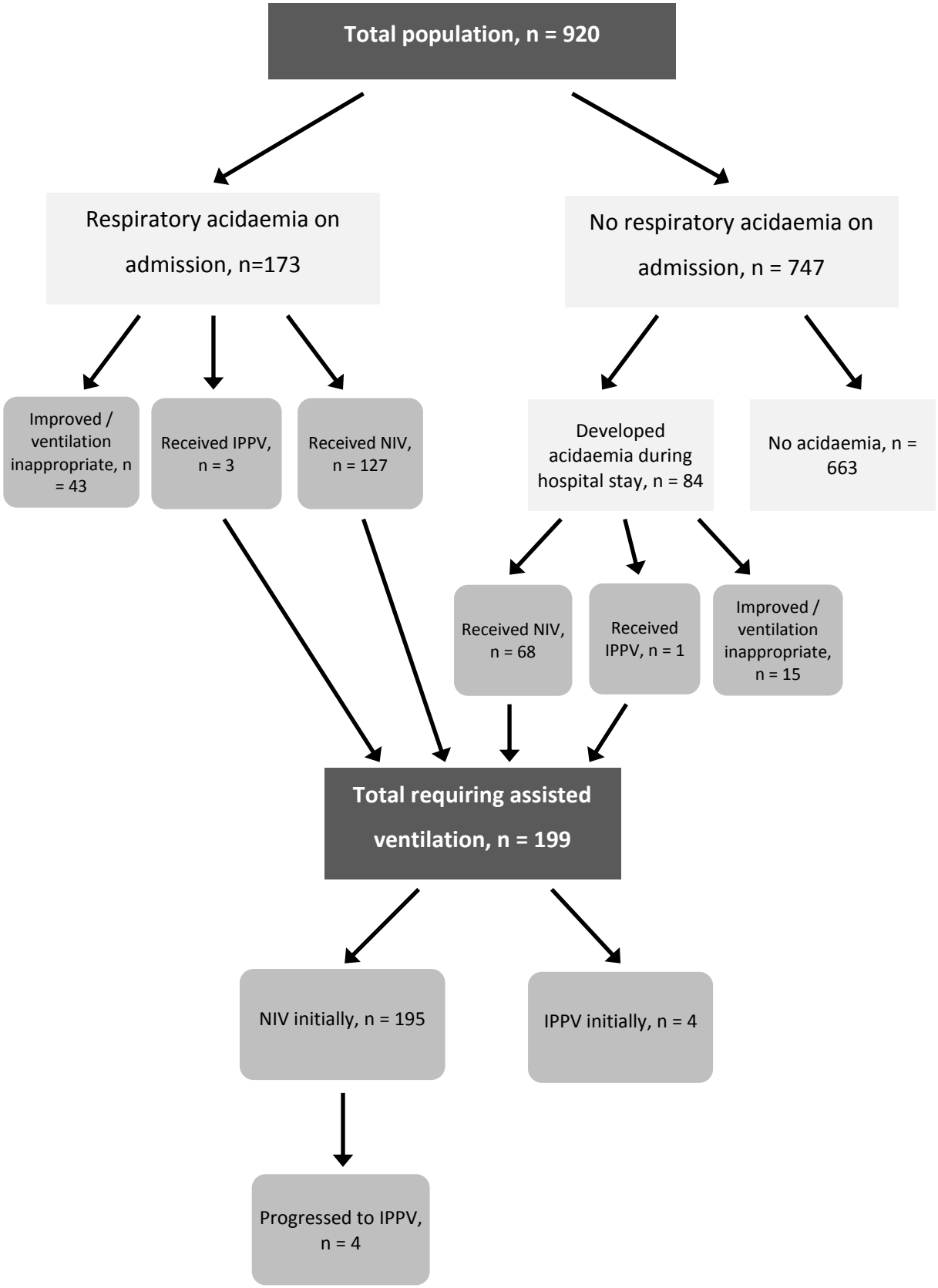
Table 17.9 Correlations between potential continuous prognostic variables for poor QoL in patients surviving to discharge (n = 183)

	Age	Previous admissions	FEV_1 % pred	FVC	eMRCD	BMI	Diastolic BP	P_aCO_2	Na	K	Albumin	Hb	Length of stay	Baseline NEADL
Age	1	0.05	0.10	-0.32‡	0.20†	-0.01	-0.12	0.08	0	0	-0.21†	-0.21†	0.17*	-0.12
Previous admissions		1	-0.14	-0.02	0.28‡	-0.05	0.07	0.04	0.04	0.05	0.02	-0.12	0.12	-0.26‡
FEV_1 % pred			1	0.37‡	-0.34‡	0.30‡	-0.01	-0.37‡	-0.01	-0.29‡	0.05	-0.10	-0.19*	0.37‡
FVC				1	-0.41‡	0.13	0.09	-0.39‡	0.06	-0.07	0.19*	0.17*	-0.28‡	0.47‡
eMRCD					1	-0.07	-0.11	0.35‡	-0.08	0.15*	-0.09	-0.12	0.28‡	-0.65‡
BMI						1	-0.08	-0.04	0.22†	-0.08	0.05	0.06	0.03	0.13
Diastolic BP							1	0.05	0.02	0.01	0.36‡	0.27‡	0	0.05
P_aCO_2								1	0.05	0.35‡	-0.02	0.05	0.28‡	-0.37‡
Na									1	0.03	0.06	0.12	-0.09	0.02
K										1	0.07	0.11	0.03	-0.15*
Albumin											1	0.30‡	0.15*	0.15*
Hb												1	-0.14	0.18*
Length of stay													1	-0.30‡
Baseline NEADL														1

Pearson's r or Spearman-ρ correlation coefficient used depending on underlying variable distribution; *p<0.05; † p<0.01; ‡p<0.001

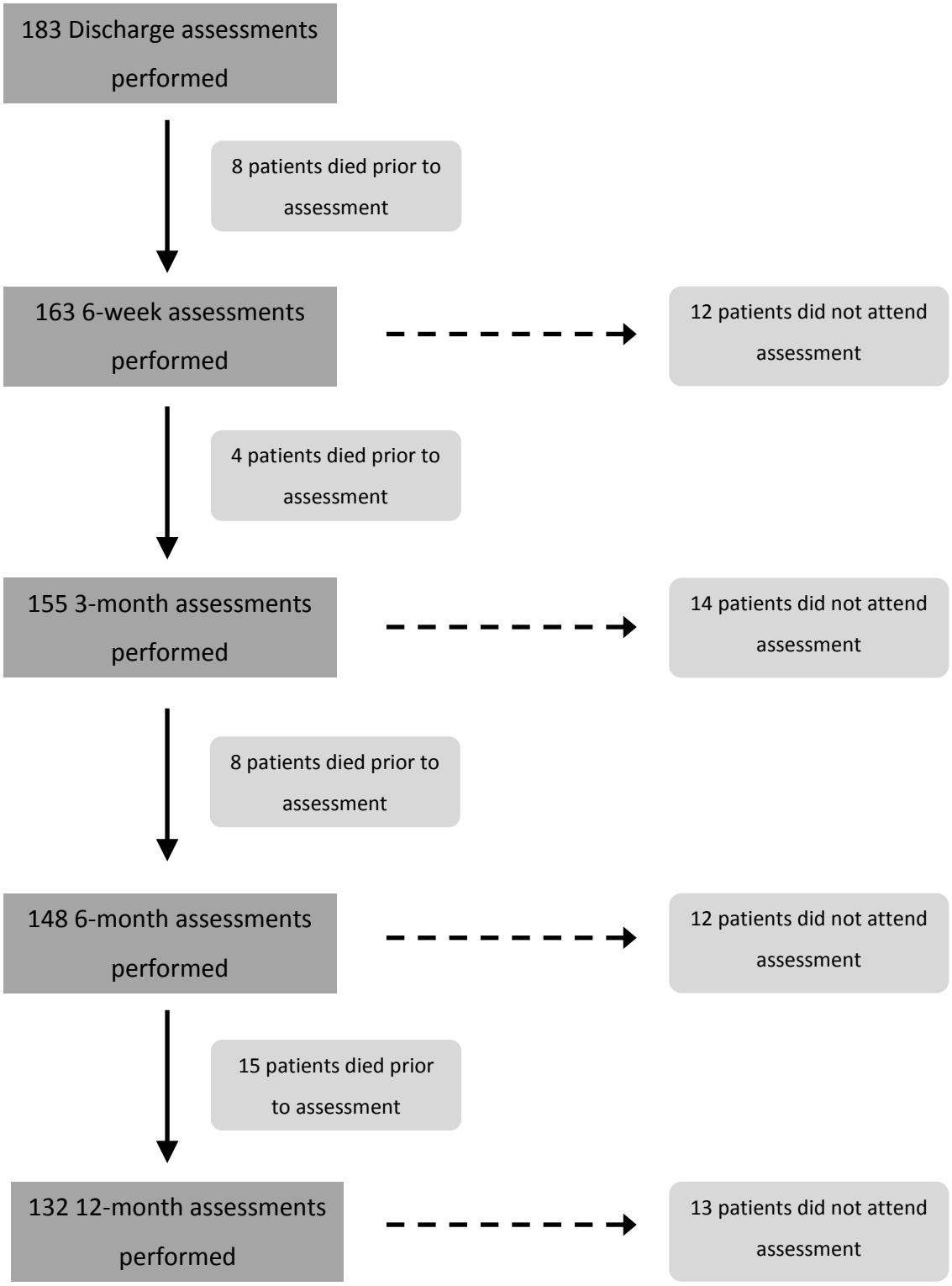
APPENDIX F. ACIDAEMIC RESPIRATORY FAILURE DURING HOSPITAL ADMISSION

Figure 17.1 Development and management of acidaemic respiratory failure



APPENDIX G. ATTENDANCE AT FOLLOW-UP ASESSEMENTS FOR PART 2

Figure 17.2 Flowchart detailing attendance at longitudinal assessments of quality of life and health resource use following hospital discharge (Part 2)



APPENDIX H. QUESTIONNAIRES

APPENDIX H.1. THE CHRONIC RESPIRATORY QUESTIONNAIRE

For Internal Use Only

PATIENT INITIALS _____ _____ _____
FIRST MIDDLE LAST

TODAY'S DATE _____/_____/_____

Admin Self

PATIENT ID ☐☐–☐☐☐☐

CHRONIC RESPIRATORY QUESTIONNAIRE
FIRST ADMINISTRATION

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. In the first section, you will be asked to answer questions about activities which make some people feel short of breath. In the next section, you will answer questions about your mood and how you have been feeling.

Please read these instructions for completing this questionnaire:

1. **Please read each question carefully and then circle the answer that best describes you. If you are unsure about how to answer a question, please give the best answer you can.**
2. **Remember, there are no right or wrong answers.**
3. **Your answers to this questionnaire will be kept confidential and will be used only for research purposes.**

Please continue to the next page.

Page 1

PATIENT ID

CRQ FIRST ADMINISTRATION TODAY'S DATE ___/___/___

These first questions ask you to think of the activities that you have done during the LAST 2 WEEKS that have made you feel short of breath.

Please read the following list of activities which make some people with lung problems feel short of breath. Circle the letter adjacent to each activity that you do frequently and that makes you feel short of breath. After you have read the list, please add any additional activities that you have done during the LAST 2 WEEKS that have made you feel short of breath. These should be activities which you do frequently and which are important to your day-to day-life.

(Circle all that apply)

a. BEING ANGRY OR UPSET
b. HAVING A BATH OR SHOWER
c. BENDING
d. CARRYING, SUCH AS CARRYING GROCERIES
e. DRESSING
f. EATING
g. GOING FOR A WALK
h. DOING YOUR HOUSEWORK
i. HURRYING
j. MAKING A BED
k. MOPPING OR SCRUBBING THE FLOOR
l. MOVING FURNITURE
m. PLAYING WITH CHILDREN OR GRANDCHILDREN
n. PLAYING SPORTS
o. REACHING OVER YOUR HEAD
p. RUNNING SUCH AS FOR A BUS
q. SHOPPING
r. WHILE TRYING TO SLEEP
s. TALKING
t. VACUUMING
u. WALKING AROUND YOUR OWN HOME
v. WALKING UPHILL
w. WALKING UPSTAIRS
x. WALKING WITH OTHERS ON LEVEL GROUND
y. PREPARING MEALS

z. _____(Additional activity)

aa. _____(Additional activity)

bb. _____(Additional activity)

cc. _____(Additional activity)

dd. _____(Additional activity)

Of the activities circled above, please select the 5 most important activities and write them on the lines provided below. You can choose any of the items, from a to z, or aa to dd. Then, for each activity, circle the number indicating how much shortness of breath you have had while doing that activity during the LAST 2 WEEKS.

	(Circle one number on each line)						
Activities:	Extremely short of breath	Very short of breath	Quite a bit short of breath	Moderate shortness of breath	Some shortness of breath	A little shortness of breath	Not at all short of breath
A._____	1	2	3	4	5	6	7
B._____	1	2	3	4	5	6	7
C._____	1	2	3	4	5	6	7
D._____	1	2	3	4	5	6	7
E._____	1	2	3	4	5	6	7

CRQ FIRST ADMINISTRATION TODAY'S DATE ___/___/___ PATIENT ID [ ][ ][ ]-[ ][ ][ ][ ]

These next questions ask you about your energy in general and how your moo has been during the LAST 2 WEEKS. Please circle the number, from 1 to 7, tha best describes how you have felt.

Q5. In general, how much of the time during the **LAST 2 WEEKS** have you felt frustrated or impatient?

All of the time.....1
Most of the time.....2
A good bit of the time.....3
Some of the time.....4
A little of the time.....5
Hardly any of the time.....6
None of the time.....7

(Circle one number.)

Q6. How often during the **LAST 2 WEEKS** did you have a feeling of fear or panic when you had difficulty getting your breath?

All of the time.....1
Most of the time.....2
A good bit of the time.....3
Some of the time.....4
A little of the time.....5
Hardly any of the time.....6
None of the time.....7

(Circle one number.)

Q7. How tired have you felt over the **LAST 2 WEEKS**?

Extremely tired.....1
Very tired.....2
Quite a bit of tiredness.....3
Moderately tired.....4
Somewhat tired.....5
A little tired.....6
Not at all tired.....7

(Circle one number.)

Please continue to the next page.

Q8. How often during the **LAST 2 WEEKS** have you felt embarrassed by your coughing or heavy breathing?

All of the time 1
Most of the time 2
A good bit of the time 3
Some of the time 4
A little of the time 5
Hardly any of the time 6
None of the time 7

(Circle one number.)

Q9. In the **LAST 2 WEEKS**, how much of the time did you feel very confident and sure that you could deal with your illness?

None of the time 1
A little of the time 2
Some of the time 3
A good bit of the time 4
Most of the time 5
Almost all of the time 6
All of the time 7

(Circle one number.)

Q10. How much energy have you had in the **LAST 2 WEEKS?**

No energy at all 1
A little energy 2
Some energy 3
Moderately energetic 4
Quite a bit of energy 5
Very energetic 6
Full of energy 7

(Circle one number.)

Please continue to the next page.

Q11. In general, how much of the time did you feel upset, worried, or depressed during the **LAST 2 WEEKS**?

All of the time.....1
Most of the time.....2
A good bit of the time.....3
Some of the time.....4
A little of the time.....5
Hardly any of the time.....6
None of the time.....7

(Circle one number.)

Q12. How often during the **LAST 2 WEEKS** did you feel you had complete control of your breathing problems?

None of the time.....1
A little of the time.....2
Some of the time.....3
A good bit of the time.....4
Most of the time.....5
Almost all of the time.....6
All of the time.....7

(Circle one number.)

Q13. How much of the time during the **LAST 2 WEEKS** did you feel relaxed and free of tension?

None of the time.....1
A little of the time.....2
Some of the time.....3
A good bit of the time.....4
Most of the time.....5
Almost all of the time.....6
All of the time.....7

(Circle one number.)

Please continue to the next page.

TODAY'S DATE ___/___/___

PATIENT ID ☐☐-☐☐☐☐

Q14. How often during the **LAST 2 WEEKS** have you felt low in energy?

All of the time.....1
Most of the time.....2
A good bit of the time.....3
Some of the time.....4
A little of the time.....5
Hardly any of the time.....6
None of the time.....7

(Circle one number.)

Q15. In general, how often during the **LAST 2 WEEKS** have you felt discouraged or down in the dumps?

All of the time.....1
Most of the time.....2
A good bit of the time.....3
Some of the time.....4
A little of the time.....5
Hardly any of the time.....6
None of the time.....7

(Circle one number.)

Q16. How often during the **LAST 2 WEEKS** have you felt worn out or sluggish?

All of the time.....1
Most of the time.....2
A good bit of the time.....3
Some of the time.....4
A little of the time.....5
Hardly any of the time.....6
None of the time.....7

(Circle one number.)

Please continue to the next page.

Q17. How happy, satisfied, or pleased have you been with your personal life during the **LAST 2 WEEKS?**

Very dissatisfied, unhappy most of the time ... 1
Generally dissatisfied, unhappy ... 2
Somewhat dissatisfied, unhappy ... 3
Generally satisfied, pleased ... 4
Happy most of the time ... 5
Very happy most of the time ... 6
Extremely happy, could not be more satisfied or pleased ... 7

(Circle one number.)

Q18. How often during the **LAST 2 WEEKS** did you feel upset or scared when you had difficulty getting your breath?

All of the time ... 1
Most of the time ... 2
A good bit of the time ... 3
Some of the time ... 4
A little of the time ... 5
Hardly any of the time ... 6
None of the time ... 7

(Circle one number.)

Q19. In general, how often during the **LAST 2 WEEKS** have you felt restless, tense, or uptight?

All of the time ... 1
Most of the time ... 2
A good bit of the time ... 3
Some of the time ... 4
A little of the time ... 5
Hardly any of the time ... 6
None of the time ... 7

(Circle one number.)

Please continue to the next page.

For Internal Use Only

PATIENT INITIALS _____ _____ _____
FIRST MIDDLE LAST

TODAY'S DATE _____/_____/_____

Admin: Self

PATIENT ID | | | – | | | | |

CHRONIC RESPIRATORY QUESTIONNAIRE FOLLOW-UP ADMINISTRATION

You have previously completed a questionnaire containing questions on how you have been feeling and how your lung disease was affecting your life. This is a follow-up questionnaire designed to ask you how you have been since that time.

With today's follow-up questionnaire, you have also received a copy of your previous questionnaire. The five activities you chose before have been written in for you on this follow-up questionnaire. When you provide your responses to the follow-up questionnaire, feel free to refer to your prior responses.

Please read these instructions for completing this questionnaire:

1. **Please read each question carefully and then circle the answer that best describes you.**
2. **Refer to the copy of the first questionnaire to see how you answered each question last time. If you are unsure about how to answer a question, please give the best answer you can.**
3. **Remember, there are no right or wrong answers.**
4. **Your answers to this questionnaire will be kept confidential and will be used only for research purposes.**

Please continue to the next page.

Page 1

CRQ FOLLOW-UP ADMINISTRATION TODAY'S DATE ___/___/___ PATIENT ID [ ][ ][-][ ][ ][ ][ ]

The first question asks you about how much shortness of breath you have experienced during the last 2 weeks.

For each of the five activities, please indicate how much shortness of breath you have had during the **LAST 2 WEEKS** while doing <u>each</u> activity. Please keep in mind the answers you chose when you last completed the questionnaire.

(Circle one number on each line.)

Activities:	Extremely short of breath	Very short of breath	Quite a bit short of breath	Moderate shortness of breath	Some shortness of breath	A little shortness of breath	Not at short breat
4A. _____	1	2	3	4	5	6	7
4B. _____	1	2	3	4	5	6	7
4C. _____	1	2	3	4	5	6	7
4D. _____	1	2	3	4	5	6	7
4E. _____	1	2	3	4	5	6	7

These next questions ask you about your energy in general and how your mood has been during the LAST 2 WEEKS. Please circle the <u>number</u>, from 1 to 7, that best describes how you have felt.

Q5. In general, how much of the time during the **LAST 2 WEEKS** have you felt frustrated or impatient? Please keep in mind the answer you chose on the last questionnaire.

All of the time.....1
Most of the time.....2
A good bit of the time.....3
Some of the time.....4 (Circle one number.)
A little of the time.....5
Hardly any of the time.....6
None of the time.....7

Please continue to the next page.

CRQ FOLLOW-UP ADMINISTRATION TODAY'S DATE ___/___/___ PATIENT ID [ ][ ]-[ ][ ][ ][ ]

Q6. How often during the **LAST 2 WEEKS** did you have a feeling of fear or panic when you had difficulty getting your breath? Please keep in mind the answer you chose on the last questionnaire.

All of the time 1
Most of the time 2
A good bit of the time 3
Some of the time 4
A little of the time 5
Hardly any of the time 6
None of the time 7

(Circle one number.)

Q7. How tired have you felt over the **LAST 2 WEEKS**? Please keep in mind the answer you chose on the last questionnaire.

Extremely tired 1
Very tired 2
Quite a bit of tiredness 3
Moderately tired 4
Somewhat tired 5
A little tired 6
Not at all tired 7

(Circle one number.)

Q8. How often during the **LAST 2 WEEKS** have you felt embarrassed by your coughing or heavy breathing? Please keep in mind the answer you chose on the last questionnaire.

All of the time 1
Most of the time 2
A good bit of the time 3
Some of the time 4
A little of the time 5
Hardly any of the time 6
None of the time 7

(Circle one number.)

Please continue to the next page.

Q9. In the **LAST 2 WEEKS**, how much of the time did you feel very confident and sure that you could deal with your illness? Please keep in mind the answer you chose on the last questionnaire.

None of the time 1
A little of the time 2
Some of the time 3
A good bit of the time ..... 4 (Circle one number.)
Most of the time 5
Almost all of the time 6
All of the time 7

Q10. How much energy have you had in the **LAST 2 WEEKS**? Please keep in mind the answer you chose on the last questionnaire.

No energy at all 1
A little energy 2
Some energy 3
Moderately energetic ..... 4 (Circle one number.)
Quite a bit of energy 5
Very energetic 6
Full of energy 7

Q11. In general, how much of the time did you feel upset, worried, or depressed during the **LAST 2 WEEKS**? Please keep in mind the answer you chose on the last questionnaire.

All of the time 1
Most of the time 2
A good bit of the time 3
Some of the time ..... 4 (Circle one number.)
A little of the time 5
Hardly any of the time 6
None of the time 7

Please continue to the next page.

Q12. How often during the **LAST 2 WEEKS** did you feel you had complete control of your breathing problems? Please keep in mind the answer you chose on the last questionnaire.

None of the time 1
A little of the time 2
Some of the time 3
A good bit of the time 4
Most of the time 5
Almost all of the time 6
All of the time 7

(Circle one number.)

Q13. How much of the time during the **LAST 2 WEEKS** did you feel relaxed and free of tension? Please keep in mind the answer you chose on the last questionnaire.

None of the time 1
A little of the time 2
Some of the time 3
A good bit of the time 4
Most of the time 5
Almost all of the time 6
All of the time 7

(Circle one number.)

Q14. How often during the **LAST 2 WEEKS** have you felt low in energy? Please keep in mind the answer you chose on the last questionnaire.

All of the time 1
Most of the time 2
A good bit of the time 3
Some of the time 4
A little of the time 5
Hardly any of the time 6
None of the time 7

(Circle one number.)

Please continue to the next page.

Q15. In general, how often during the **LAST 2 WEEKS** have you felt discouraged or down in the dumps? Please keep in mind the answer you chose on the last questionnaire.

All of the time 1
Most of the time 2
A good bit of the time 3
Some of the time 4
A little of the time 5
Hardly any of the time 6
None of the time 7

(Circle one number.)

Q16. How often during the **LAST 2 WEEKS** have you felt worn out or sluggish? Please keep in mind the answer you chose on the last questionnaire.

All of the time 1
Most of the time 2
A good bit of the time 3
Some of the time 4
A little of the time 5
Hardly any of the time 6
None of the time 7

(Circle one number.)

Q17. How happy, satisfied, or pleased have you been with your personal life during the **LAST 2 WEEKS**? Please keep in mind the answer you chose on the last questionnaire.

Very dissatisfied, unhappy most of the time .. 1
Generally dissatisfied, unhappy 2
Somewhat dissatisfied, unhappy 3
Generally satisfied, pleased 4
Happy most of the time 5
Very happy most of the time 6
Extremely happy, could not be more satisfied or pleased 7

(Circle one number.)

Please continue to the next page.

CRQ FOLLOW-UP ADMINISTRATION TODAY'S DATE ____/____/____ PATIENT ID [| | | – | | | | |]

Q18. How often during the **LAST 2 WEEKS** did you feel upset or scared when you had difficulty getting your breath? Please keep in mind the answer you chose on the last questionnaire.

All of the time 1
Most of the time 2
A good bit of the time 3
Some of the time ..... 4 (Circle one number.)
A little of the time 5
Hardly any of the time 6
None of the time 7

Q19. In general, how often during the **LAST 2 WEEKS** have you felt restless, tense, or uptight? Please keep in mind the answer you chose on the last questionnaire.

All of the time 1
Most of the time 2
A good bit of the time 3
Some of the time ..... 4 (Circle one number.)
A little of the time 5
Hardly any of the time 6
None of the time 7

Q20. Since the last time you completed this questionnaire, would you say your lung problems have ...

Improved 1
Remained the same ..... 2 (Circle one number.)
Worsened 3

THANK YOU VERY MUCH FOR YOUR TIME!

Survival, quality of life and health resource use following exacerbations of COPD

ST-GEORGE RESPIRATORY QUESTIONNAIRE (SGRQ)

Patient identification number:

Study number:

Follow-up ID number:

Date of assessment

Discharge

6 weeks

3 month

6 month

12 month

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you the most problem.

Please read the instructions carefully and ask if you do not understand something. Do not spend too long deciding about your answer.

Part 1

Questions about how much chest trouble you had over the last month Please fill in the relevant number next to each activity.

1- Over the last month I have coughed : ☐

1- Most days a week
2- Several days a week
3- A few days a week
4- Only with chest infections
5- Not at all

2- Over the last month I have brought up phlegm (sputum) : ☐

1- Most days a week
2- Several days a week
3- A few days a week
4- Only with chest infections
5- Not at all

3- Over the last month I have had shortness of breath : ☐

1- Most days a week
2- Several days a week
3- A few days a week
4- Only with chest infections
5- Not at all

ST-GEORGE RESPIRATORY QUESTIONNAIRE (SGRQ)

Patient ID no **Study number** **Follow up ID no**

4- Over the last month I have had attacks of wheezing : ☐
1- Most days a week
2- Several days a week
3- A few days a week
4- Only with chest infections
5- Not at all

5- During the last month how many severe unpleasant attacks of chest trouble have you had : ☐
1- More than 3 attacks
2- 3 attacks
3- 2 attacks
4- 1 attack
5- No attack

GO TO QUESTION 7 IF YOU HAD NO SEVERE ATTACKS.

6- How long did the worst attack of chest trouble last : ☐
1- A week or more
2- 3 or more days
3- 1 or 2 days
4- Less than a day

7- Over the last month in an average week, how many good days (with little chest trouble) have you had : ☐
1- No good days
2- 1 or 2 good days
3- 3 or 4 good days
4- Nearly every day is good
5- Every day is good

	No	*Yes*	*Not applicable**
8- If you have a wheeze, is it worse in the morning :	☐	☐	☐

* CHECK « NOT APPLICABLE » IF ANSWERED 5-NOT AT ALL TO QUESTION 4.

Part 2

SECTION 1

9- How would you describe your chest condition : ☐
1- The most important problem I have.
2- Causes me quite a lot of problems.
3- Causes me quite a few problems.
4- Causes me no problem.

ST-GEORGE RESPIRATORY QUESTIONNAIRE (SGRQ)

Patient ID no **Study no** **Follow-up ID no**

10- If you have ever had paid employment, please choose one of these answers : ☐

1- My chest trouble made me stop work.
2- My chest trouble interferes with my work or made me change my work.
3- My chest trouble does not affect my work.

SECTION 2

Questions about what activities usually make you feel breathless these days. For each item, please answer either true or false as it applies to you.

		True	*False*
11-	*Sitting or lying still.*	☐	☐
12-	*Getting washed or dressed.*	☐	☐
13-	*Walking around the house.*	☐	☐
14-	*Walking outside on level ground.*	☐	☐
15-	*Walking up a flight of stairs.*	☐	☐
16-	*Walking hills.*	☐	☐
17-	*Playing sports or games.*	☐	☐

SECTION 3

Some more questions about your cough and breathlessness these days. For each item, please answer either true or false as it applies to you.

		True	*False*
18-	*My cough hurts.*	☐	☐
19-	*My cough makes me tired.*	☐	☐
20-	*I am breathless when I talk.*	☐	☐
21-	*I am breathless when I bend over.*	☐	☐
22-	*My cough or breathing disturbs my sleep.*	☐	☐
23-	*I get exhausted easily.*	☐	☐

SECTION 4

Questions about other effects that your chest trouble may have on you these days. For each item, please answer true or false as it applies to you.

		True	*False*
24-	*My cough or breathing is embarrassing in public.*	☐	☐
25-	*My chest trouble is a nuisance to my family, friends or neighbours.*	☐	☐
26-	*I get afraid or panic when I cannot get my breath.*	☐	☐
27-	I feel that I am not in control of my chest problems.	☐	☐
28-	*I do not expect my chest to get any better.*	☐	☐
29-	*I have become frail or an invalid because of my chest.*	☐	☐
30-	*Exercise is not safe for me.*	☐	☐
31-	*Everything seems too much of an effort.*	☐	☐

ST-GEORGE RESPIRATORY QUESTIONNAIRE (SGRQ)

Patient ID no **Study no** **Follow-up ID no**

SECTION 5

Questions about your medication. If you are receiving no medication go straight to **section 6**. For each item, please answer either « true » or « false » as it applies to you.

		True	*False*
32-	*My medication does not help me very much.*	☐	☐
33-	*I get embarrassed using my medication in public.*	☐	☐
34-	*I have unpleasant side effects from my medication.*	☐	☐
35-	*My medication interferes with my life a lot.*	☐	☐

SECTION 6

These are questions about how your activities might be affected by you breathing. For each question, please answer « true » if one or more parts applies to you because or you breathing. Otherwise, answer « false ».

		True	*False*
36-	*I take a long time to get washed or dressed.*	☐	☐
37-	*I cannot take a bath or shower, or I take a long time.*	☐	☐
38-	*I walk slower than other people, or else I stop for rests.*	☐	☐
39-	*Jobs such as housework take a long time, or I have to stop for rests.*	☐	☐
40-	*If I walk up one flight of stairs, I have to go slowly or stop.*	☐	☐
41-	*If I hurry or walk fast, I have to stop or slow down.*	☐	☐
42-	*My breathing makes it difficult to do things such as walking up hills, carrying things up stairs, light gardening such as weeding, dance, play bowling or play golf.*	☐	☐
43-	*My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles (8 km) per hour, play tennis or swim.*	☐	☐
44-	*My breathing makes it difficult to do things such as carry heavy manual work, run, cycle, swim fast or play competitive sports.*	☐	☐

SECTION 7

We would like to know how your chest trouble usually affects your daily life. Please answer either « true » or « false » as it applies to you because of your chest trouble. (remember that « **true** » only applies to you if you cannot do something **because of your breathing**.)

		True	*False*
45-	*I cannot play sports or games.*	☐	☐
46-	*I cannot go out for entertainment or recreation.*	☐	☐
47-	*I cannot go out of the house to do the shopping.*	☐	☐
48-	*I cannot do the housework.*	☐	☐
49-	*I cannot move far from my bed or chair.*	☐	☐

ST-GEORGE RESPIRATORY QUESTIONNAIRE (SGRQ)

Patient ID no **Study no** **Follow-up ID no**

51- Now, would you choose (one only) which you think best describes how your chest trouble affects you:

1- It does not stop me doing anything I would like to do.
2- It stops me doing one or two things I would like to do.
3- It stops me doing most of the things I would like to do.
4- It stops me doing everything I would like to do.

Time at the end of the questionnaire [:] on 24:00

Hospital Anxiety and Depression (HAD) scale

Health professionals are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he will be able to help you more. This questionnaire is designed to help your doctor to know how you feel. Read each item and circle one number beside the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought-out response.

Circle only one response in each section

I feel tense or wound up: *3* Most of the time *2* A lot of the time *1* Time to time *0* Not at all	**I feel as if I am slowed down:** 3 Nearly all the time 2 Very often 1 Sometimes 0 Not at all
I still enjoy the things I used to enjoy: 0 Definitely as much 1 Not quite so much 2 Only a little 3 Hardly at all	**I get a sort of frightened feeling like butterflies in the stomach:** *0* Not at all *1* Occasionally *2* Quite often *3* Very often
I get a sort of frightened feeling as if something awful is about to happen: *3* Very definitely and quite badly *2* Yes, but not too badly *1* A little, but it doesn't worry me *0* Not at all	**I have lost interest in my appearance:** 3 Definitely 2 I don't take so much care as I should 1 I may not take quite as much care 0 I take just as much care as ever
I can laugh and see the funny side of things: 0 As much as I always could 1 Not quite as much now 2 Definitely not so much now 3 Not at all	**I feel restless as if I have to be on the move:** *3* Very much indeed *2* Quite a lot *1* Not very much *0* Not at all
Worrying thoughts go through my mind: *3* A great deal of the time *2* A lot of the time *1* From time to time but not too often *0* Only occasionally	**I look forward with enjoyment to things:** 0 As much as ever I did 1 Rather less than I used to 2 Definitely less than I used to 3 Hardly at all
I feel cheerful: 3 Not at all 2 Not often 1 Sometimes 0 Most of the time	**I get sudden feelings of panic:** *3* Very often indeed *2* Quite often *1* Not very often *0* Not at all
I can sit at ease and feel relaxed: *0* Definitely *1* Usually *2* Not often *3* Not at all	**I can enjoy a good book or radio or TV programme:** 0 Often 1 Sometimes 2 Not often 3 Very seldom

Scoring: Even questions (scores in blue) are for depression. Odd questions (scores in red italics) are for anxiety. Score each separately. A score of 8 or more is significant, a score of 11 or more highly significant.

NOTTINGHAM EXTENDED ACTIVITIES OF DAILY LIVING (EADL) INDEX

PATIENT'S NAME:

HOSPITAL NUMER:

0 = Not at all
1 = With help
2 = Alone with difficulty
3 = Alone easily

DO YOU.....

	Comments	*Date*				
MOBILITY						
- walk around outside?						
- climb stairs?						
- get in and out of the car?						
- walk over uneven ground?						
- cross roads?						
- travel on public transport?						
TOTAL						
IN THE KITCHEN						
- manage to feed yourself?						
- make yourself a hot drink?						
- take hot drinks from one room to another?						
- do the washing up?						
- make yourself a hot snack?						
TOTAL						
DOMESTIC TASKS						
- manage your own money when out?						
- wash small items of clothing?						
- do your own shopping?						
- do a full clothes wash?						
TOTAL						
LEISURE ACTIVITIES						
- read newspapers and books?						
- use the telephone?						
- write letters?						
- go out socially?						
- manage your own garden?						
- drive a car?						
TOTAL						
GRAND TOTAL						

Will you involve my General Practitioner?

With your consent, we will inform your GP of your participation in the study. We will contact your GP 12 months after you enter the study in order to keep track of how your condition is progressing.

Will my taking part in the study be kept confidential?

Yes.

All of your data will be handled in the strictest of confidence and we will adhere to the NHS Code of Confidentiality. All data will be anonymised after collection and there will be no potential identifiable information involved in the final study analysis. Your personal data will only be accessible by the research team and it will not be shared with any third party organisations. Once the study is compiete, all personal data will be destroyed.

What if there is a problem?

If you have a concern about any aspect of this study then you should speak to the researchers on the contact numbers provided. If you wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be provided at your request.

Who is organising and funding the research?

The project has been planned by Dr Stephen Bourke, and it has been extensively reviewed by 2 other experts within this field. The project has been funded by Northumbria Healthcare NHS Foundation Trust.

How will I be informed of the results?

Once the study has been completed, the results will be displayed on a poster within the Respiratory department of NTGH. We will also distribute a summary of the results to all participants as well as informing you of the scientific publication of the research.

Survival and quality of life following exacerbations of chronic obstructive pulmonary disease.

Invitation to participate.

We are inviting you to take part in the above-titled research project. Please take time to read this information sheet carefully.

Investigators

Dr. Stephen Bourke– Principle Investigator

Professor John Gibson

Dr. John Steer-- Research Fellow

Further information & questions

If it any time you require further information, or if you have any questions regarding this form, then please contact:

Dr. John Steer
Teaching and Research Fellow
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Rake Lane
Newcastle
NE29 8NH
Tel: 0844-811-8111 ext 2819
Email: john.steer@northumbria-healthcare.nhs.uk

Why are we undertaking this research?

COPD is one of the most frequent causes of admissions to hospital and hospital admissions become more common as the disease becomes more severe. Exacerbations can affect patients' quality of life but we are currently unable to predict which patients are going to experience the most significant change in their quality of life following discharge.

Some patients with a severe exacerbation of COPD require treatment with a machine to help them breathe (non-invasive ventilation - NIV). We currently know very little about patients' quality of life following treatment with NIV and we do not know which patients benefit the most from treatment with NIV.

We understand that exacerbations will affect a patient's quality of life and that some patients with COPD can have severe and disabling symptoms that are improved by input from the palliative care services. Therefore, if we are able to predict the effect that an exacerbation of COPD will have on a patient's quality of life, or if we could predict which patients will need palliative care input in the near future, then we can target extra help to those patients most at need of it, improving their symptoms and quality of life.

What are we planning to do?

We intend to study groups of patients with an exacerbation of COPD not requiring NIV and those who do require NIV. We hope to identify factors, and develop a clinical tool, that help predict quality of life after discharge and identifies which patients are most at risk of recurrent exacerbations.

We will assess the current provision of palliative care services and try and develop a model that will help predict which patients are most in need of referral to palliative care services.

We also intend to validate a breathlessness scoring system which we hope will be useful in predicting which patients have the most disabling symptoms and are most at risk of readmission to hospital.

Patient information leaflet Version 1.3

Do I have to take part?

It is entirely up to you to decide. We will describe the study and go through this information sheet, which we will then give to you. If you are happy to participate, we will then ask you to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

What will taking part involve?

Following recruitment to the study we intend to keep track of various aspects of your condition for up to 1 year. A lot of this information would normally be routinely collected as part of your medical care.

We will be performing assessments, which will last approximately 30 minutes in total, at our outpatient department or in your home if you prefer. **These will occur on discharge from hospital, and then at six weeks, 3 months, 6 months, and 12 months** after discharge. At these assessments we will use **4** questionnaires where you have to answer questions regarding your quality of life, your ability to function independently, and your levels of anxiety and depression. These questionnaires are simple and straightforward and can be completed by yourself. We will also assess your oxygen levels, breathing tests, degree of breathlessness, height, weight and nutrition.

What are the potential disadvantages of taking part?

We do not anticipate that you would experience any harm if you participate.

What are the potential benefits?

We cannot promise the results of this study will directly help you but we hope the information we get from this study will help to greatly improve the treatment people with COPD receive.

Northumbria Healthcare NHS Foundation Trust

Survival and quality of life following exacerbations of chronic obstructive pulmonary disease.

CONSENT FORM

Please initial box

1. I confirm that I have read and understand the information sheet (version 1.3) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation in this study is entirely voluntary and I am free to withdraw my consent at any time without giving any reason, without my medical or legal rights being affected. ☐

3. I understand that relevant parts of my medical records will be accessed by the individuals within the research team. No other third parties will be granted access. ☐

4. I agree to being telephoned, or visited, at home if any further details require clarification. ☐

5. I agree to my GP being informed of my participation in the study. ☐

6. I agree to taking part in the study ☐

Name of patient	Date	Signature

Name of person taking consent	Date	Signature

APPENDIX J. PUBLICATIONS AND PRESENTATIONS

APPENDIX J.1. PUBLISHED MANUSCRIPTS

1. Steer J, Gibson J, Bourke SC. The DECAF Score: predicting hospital mortality in exacerbations of chronic obstructive pulmonary disease. Thorax 2012.

2. Steer J, Norman EM, Afolabi OA, Gibson GJ, Bourke SC. Dyspnoea severity and pneumonia as predictors of in-hospital mortality and early readmission in acute exacerbations of COPD. Thorax 2012;**67**(2):117-21.

3. Steer J, Gibson GJ, Bourke SC. Predicting outcomes following hospitalization for acute exacerbations of COPD. Qjm 2010;**103**(11):817-29.

APPENDIX J.2. PRESENTED ABSTRACTS AND PRESENTATIONS

1. Effect of hospitalisation for acute exacerbations of COPD on subsequent quality of life. Accepted for BTS Winter Meeting 2012 – poster presentation.

2. Relations of different quality of life tools to subsequent mortality and readmission of patients surviving hospitalisation for acute exacerbations of COPD. Accepted for BTS Winter Meeting 2012 – poster presentation.

3. Predicting mortality in patients hospitalised with acute exacerbations of COPD (AECOPD) requiring assisted ventilation. ERS Annual Congress: Vienna 2012 – oral presentation.

4. Predicting hospital readmission in patients discharged following acute exacerbations of COPD (AECOPD). ERS Annual Congress: Vienna 2012 – poster discussion.

5. The DECAF Score: predicting in-hospital mortality in acute exacerbations of COPD. BTS Winter Meeting 2011 – oral presentation.

6. Late ventilation is associated with high in-hospital mortality in patients hospitalised with acute exacerbations of COPD. BTS Winter Meeting 2011 – poster presentation

7. A novel prognostic score for COPD. Invited speaker at Joint Yorkshire Thoracic Society and North of England Thoracic Society Meeting, York 2011.

8. CURB-65 and mortality in pneumonic and non-pneumonic exacerbations of COPD. ERS Annual Congress: Amsterdam 2011 – poster presentation.

9. Eosinopenia independently predicts in-hospital mortality in patients hospitalised with acute exacerbations of COPD. British Association of Lung Research Summer Meeting: Newcastle 2011 – poster presentation.

10. Comparison of indices of nutritional status in prediction of in-hospital mortality and early readmission or patients with acute exacerbations of COPD. BTS Winter Meeting 2010 – poster presentation.

11. Evaluation of the MRC dyspnoea scale and a novel extended version in prediction of in-hospital death and early readmission in acute exacerbations of COPD. BTS Winter Meeting 2010 – oral presentation.

12. Comparison of indices of nutritional status in prediction of in-hospital mortality and early readmission of patients with acute exacerbations of COPD. Irish Thoracic Society Annual Congress 2010 – oral presentation.

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