

Prediction of in-hospital mortality in
exacerbations of chronic obstructive
pulmonary disease requiring assisted
ventilation, and patient-centred
outcomes over the subsequent year.

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Abstract

Background: COPD exacerbations account for over 141,000 hospitalisations annually in the UK, and 20% are complicated by respiratory acidaemia. In such cases non-invasive ventilation (NIV) substantially reduces mortality, but only 50% of patients receive NIV and delivery is often suboptimal. Prognostic pessimism may partially explain underuse. Little is known about the quality of life (QoL) of patients following ventilation.

Aims and Methods: The NIV Outcomes (NIVO) study aimed to validate a simple prognostic tool for inpatient mortality in this population and assess patient-centred outcomes over one year among those surviving to discharge. Prospective recruitment of patients occurred in 10 trusts. Model performance was assessed. QoL and mortality were tracked for one year following discharge.

Results: 733 patients were included. The NIVO score comprised eMRCD, acidaemia occurring >12 hours after admission, atrial fibrillation, chest x-ray consolidation, Glasgow coma scale ≤ 14 and pH < 7.25. Stepwise increase in inpatient mortality was observed, with a c-statistic of 0.79. The NIVO score significantly outperformed pre-identified comparator scores. 586 patients survived to discharge; QoL was assessed in 272 patients over one year. Symptom burden was substantial. QoL peaked 2-months after discharge and overall was well maintained subsequently. Most patients would accept NIV again. Poor outcome, defined as death within six months or poor QoL with a clinically significant deterioration, could be accurately predicted (c-statistic 0.81) using: LTOT, admission haemoglobin, left ventricular systolic dysfunction, diaphragm height, confusion, plus measures of depression and independence.

Discussion: Using six simple indices strong prediction of inpatient mortality was achieved. In most survivors, QoL remained stable over one year post-discharge. Predictors of patients likely to have poor outcome were identified. Clinical applications include facilitating informed discussions with patients and shared decisions about escalation to ventilation, challenging pessimism, comparing risk-adjusted outcomes between units (national audit), advance care planning and referral to specialist services.

Acknowledgements and dedication

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Dr Tom Hartley, I could not have wished for a better colleague to undertake this venture with and am pleased to have gained you as a friend. Dr Hartley had already completed the derivation study by the time I began work on the validation and longitudinal studies. We jointly undertook data collection, trial governance and site visits. Day-to-day running of the study was split 50/50 and we jointly undertook data verification and cleaning. The subsequent analysis presented in this thesis is all my own work.

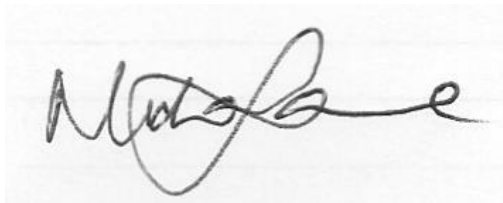
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Finally, I dedicate this thesis to my wonderful husband, James. Without your unwavering, unquestioning and unconditional support throughout I simply would not have been able to complete any of this. It is as much yours as it is mine. Thank you from the bottom of my heart.

Declaration

I declare that this thesis is my own work and effort. This work has not been submitted to this, nor any other university previously. Where other sources of information have been used they have been acknowledged.

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A handwritten signature in black ink, appearing to read 'Nicholas Lane', written on a light-colored background.

Nicholas David Lane

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Table of abbreviations

Abbreviation	Meaning
ABG	Arterial blood gas
ACOS	Asthma-COPD Overlap Syndrome
ADL	Activities of Daily Living
AECOPD	Acute exacerbation of Chronic Obstructive Pulmonary Disease
AF	Atrial Fibrillation
AHP	Allied health professional
AHR	Airway Hyperresponsiveness
ANOVA	Analysis of variance
APACHE II	Acute Physiology and Chronic Health Evaluation II Score
ARDS	Acute Respiratory Distress Syndrome
ARR	Absolute risk reduction
ATS	American Thoracic Society
AUROC	Area under the receiver operating characteristic curve
BADL	Basic activities of daily living
BDI	Baseline Dyspnoea Index
BMI	Body mass index
BNP/NT-pro-BNP	B-type natriuretic peptide/N-terminal-pro-hormone B-type natriuretic peptide
BP	Blood pressure
BPD	Bronchopulmonary dysplasia
bpm	Beats or breaths per minute
BTS	British Thoracic Society
BUR	Backup rate
CAG	Confidentiality advisory group
CAOS	Chronic Obstructive Pulmonary Disease and Asthma outcomes study
CAPS	Chronic Obstructive Pulmonary Disease and Asthma Physiology score

CAT	Chronic Obstructive Pulmonary Disease Assessment Tool
CD	Clinical Diagnosis [patients] (validation study)
CI	Confidence interval
cm	Centimetres
COPD	Chronic Obstructive Pulmonary Disease
CO₂	Carbon Dioxide
CPAP	Continuous positive airway pressure
CPR	Cardiopulmonary resuscitation
CRF	Case report form
CRN	Clinical Research Network
CRQ	The Chronic Respiratory Disease Questionnaire
CXR	Chest x-ray
DECAF	The Dyspnoea, Eosinopenia, Consolidation, Acidaemia, Atrial Fibrillation score
dL	Decilitre
DNACPR	Do not attempt cardiopulmonary resuscitation form
ECOPD	Exacerbation(s) of Chronic Obstructive Pulmonary Disease
ED	Emergency Department
EELV	End expiratory lung volume
EM	Expectation-Maximisation
eMRCD	Extended Medical Research Council dyspnoea score
EPAP	Expiratory positive airway pressure
EQ-5D-3L	EuroQol 5 domain, 3-level quality of life score
EQ-5D-5L	EuroQol 5 domain, 5-level quality of life score
ERS	European Respiratory Society
EU[28]	European Union [the 28 countries of the European Union]
FEF_{25/50/75}	Forced expiratory flow rate at 25/50/75% of vital capacity
FEV₁	Forced expiratory volume in one second
FEV₁/[F]VC	The ratio of forced expiratory volume in 1 second to [forced] vital capacity
FiO₂	Fraction of inspired oxygen

FN	False negative
FP	False positive
f_R	Frequency of respiration
FRC	Functional residual capacity
FVC	Forced vital capacity
g	Grams
GAI	Geriatric anxiety inventory
GCP	Good clinical practice module
GCS	Glasgow coma scale
GHQ-20	General Health Questionnaire
GOLD	Global Initiative for Chronic Lung Disease
GP	General practitioner
GRACE	Global registry of acute coronary events score
GST	Glutathione S-transferase gene
H⁺	Hydrogen ion
HADS	Hospital anxiety and depression scale
H@H	Hospital at Home
HCO₃⁻	Bicarbonate ion
HHANES	[The] Hispanic Health and Nutrition Examination Survey
HMV	Home mechanical ventilation
HR	Heart rate
HRA	Health research authority
HRQoL	Health related quality of life
hrs	Hours
H₂O	Water
H₂CO₃	Carbonic acid
IADL	Instrumental activities of daily living
IC	Inspiratory Capacity
ICS	Inhaled corticosteroid
IHD	Ischaemic Heart Disease
IMV	Invasive [mechanical] ventilation

IPAP	Inspiratory positive airway pressure
iPEEP	Intrinsic positive end expiratory pressure
IQR	Interquartile range
k	Respiratory constant
KCO	The rate of uptake of Carbon Monoxide
kPa	Kilopascal
L	Litres
LABA	Long acting beta-2 agonist
LAMA	Long acting muscarinic antagonist
LoS	Length of Stay
LRTI	Lower respiratory tract infection
LTOT	Long term oxygen therapy
LVRS	Lung Volume Reduction Surgery
LVSD	Left ventricular systolic dysfunction
MAR	Missing at random
MCAR	Missing completely at random
mins	Minutes
MNAR	Missing not at random
MCID	Minimum clinically important difference
mcg	Micrograms
mcg/m³	Micrograms per metre cubed
MI	Myocardial Infarction
mmHg	Millimetres of mercury
MMP12	Matrix Metalloproteinase 12
[m]MRCD	[modified] Medical research council dyspnoea score
NACAP	National [UK] Asthma and COPD audit program
NCROP	National COPD resources and outcomes project
NEADL	Nottingham extended activities of daily living scale
NHANES	[United States] National Health and Nutrition Examination Surveys
NHS	National health service
NICE	National Institute for Health and Care Excellence

NIHR	National institute of health research
NIV	Non-invasive ventilation
NIVO	Non-invasive ventilation outcomes study
NNT	Number needed to treat
NO₂	Nitrogen Dioxide
NYHA	New York Heart Association
OCD	Oxygen Cost Diagram
ONS	Office of national statistics
O₂	Oxygen
P2	Pulmonary second heart sound
p_[a/A]O₂	Partial pressure of oxygen [in arterial blood/Alveolar]
p_[a/A]CO₂	Partial pressure of carbon dioxide [in arterial blood/Alveolar]
Pb*	Barometric pressure minus water vapour pressure
PCV	Pressure controlled non-invasive ventilation
PDE4	Phosphodiesterase-4 inhibitor
PEARL	Previous admissions, extended medical research dyspnoea, age, right and left heart failure score
PEEP	Positive end expiratory pressure
pH	Potential of hydrogen
PI	Principle Investigator
PMC	Polymorphonuclear neutrophils
PM_{2.5}	Particulate matter under 2.5 micrometres
PM₁₀	Particulate matter under 10 micrometres
Q	Perfusion
QoL	Quality of life
R	Respiratory exchange ratio
RA	Respiratory acidaemia
RCP	Royal college of physicians
REC	Research ethics committee
REM	Rapid eye movement
RES	National research ethics service

ROC	Receiver operating characteristic (curve)
RR	Respiratory rate
RRR	Relative risk reduction
RSV	Respiratory Syncytial Virus
S	Spontaneous mode non-invasive ventilation
SD	Standard deviation
SGRQ	St Georges respiratory questionnaire
SNP	Single nucleotide polymorphism
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SpO₂	Peripheral oxygen saturation
SSRI	Selective-Serotonin Reuptake Inhibitor
S/T	Spontaneous-times non-invasive ventilation
TLC	Total lung capacity
TL_{co}	Diffusion capacity of carbon monoxide
TN	True negative
TP	True positive
TSC	Trial steering committee
TSP	Total suspended particles
UK	United Kingdom
USA	United States of America
VA	Alveolar volume
VC	Vital capacity
V_A	Alveolar ventilation
V_{DS}	Volume of physiological dead space
V_E	Minute volume
VIF	Variance inflation factor
V_T	Tidal Volume
VAS	Visual analogue scale
V/Q	Ventilation-Perfusion
WHO	World Health Organisation
α₁-antitrypsin	Alpha one antitrypsin

β	Regression coefficient
$^{\circ}\text{C}$	Degrees Celsius
χ^2	Chi-Squared test
μ	Micron
μg	Microgram
μm	Micrometre

1 Chronic Obstructive Pulmonary Disease (COPD)

1.1 Overview

Chronic obstructive pulmonary disease (COPD) is a disease of the lungs characterised by airflow obstruction due to small airways inflammation and parenchymal lung destruction.⁽¹⁾ Historically the terms 'chronic bronchitis' and 'emphysema' were used to describe the illness, however these refer more to the underlying pathological features and the term COPD is now preferred in clinical practice. COPD has an insidious onset, normally associated with a gradual deterioration in lung function.⁽²⁾ It presents as a heterogenous disease with a wide symptom burden including, but not limited to, breathlessness, cough and sputum production.⁽¹⁾ Exacerbations of COPD (ECOPD), during which symptoms acutely worsen, are common. These episodes are often triggered by infection and are the second most frequent cause of emergency hospital admission in the UK, occurring predominantly in older patients.⁽³⁾ COPD is preventable and treatable and is primarily caused by inhalation of noxious particles, typically cigarette smoke.^(1, 4-6) In contrast to asthma, airflow limitation (both the forced expiratory volume in one second, and the ratio of this to [forced] vital capacity) is not fully reversible in COPD.⁽⁵⁾

1.2 Incidence and prevalence

Accurate incidence and prevalence of COPD rates are difficult to calculate with a wide variation between countries.⁽⁷⁾ Official estimates suggest around three million people have COPD in the United Kingdom (UK), with total prevalence of around 13% of the population over 35 years of age; these estimates are for the whole population and include a significant portion of people where COPD remains undiagnosed.^(3, 4, 8) Cohorts from national GP databases suggest a diagnosed prevalence of 33.3/1000.⁽⁹⁾ In other developed countries, such as the United States of America (USA), Sweden, Spain and South Korea, there has been a reduction in the prevalence of COPD over recent years.⁽¹⁰⁻¹⁴⁾ This is thought to be in part due to reduction in smoking rates and improved workplace conditions. Smoking rates have also been falling in the UK for a number of years,⁽¹⁵⁾ although data from the British Lung Foundation suggests there has been an increase in the prevalence of COPD over this time, with a stable incidence of 185/100,000 since 2008. This may reflect improved diagnosis rates, or lower overall

mortality.⁽¹⁶⁾ There are predictions that the number of people living in England with COPD will increase 39% by 2030.⁽¹⁷⁾ Globally 251 million people live with COPD and 3.2 million deaths (5% of total) were caused by COPD in 2015; making it the 4th commonest cause of death worldwide.^(6, 18)

1.3 Aetiology

There are many causes of COPD. The inhalation of noxious compounds (most commonly tobacco smoke) is the primary trigger, although there are a number of other factors which contribute to the development of the disease.⁽¹⁾

1.3.1 Tobacco smoke

Tobacco smoke has long been established as a the most important causative factor for the development of COPD and decline in lung function; and is still the predominant worldwide factor.^(1, 2, 19) Forced expiratory volume in 1 second (FEV₁) declines as a normal part of ageing, however tobacco smoking accelerates this decline, and reduces the peak FEV₁ someone may achieve.^(2, 20) Passive inhalation of tobacco smoke in non-smokers may also be associated with increased prevalence of respiratory symptoms, compared to those without exposure.⁽²¹⁻²³⁾ Peto & Fletcher demonstrated in the 1970s that smoking cessation has a beneficial effect on the rate of decline of lung function, which was confirmed in the Framingham offspring cohort more recently.^(2, 20) In the 2014 UK national COPD audit, 37% of patients with COPD were current smokers and 61% ex-smokers.⁽²⁴⁾ Positively, there has been a slight improvement in this over time, with the 2019 national audit reporting 34.2% of patients as current smokers.⁽²⁵⁾

1.3.1.1 *Development of chronic bronchitis*

Host defence against tobacco smoke is conducted both by the adaptive and innate immune systems. Tobacco smoke causes increased inflammatory cellular migration (Polymorphonuclear neutrophils (PMC), macrophages, CD4+ & 8+ T lymphocytes and B cells) to the lung epithelium. There is an increase in cytokines as a result, and repeated exposure to tobacco smoke consequently causes chronic airway inflammation. This inflammation results in enlargement of mucous glands alongside aberrant healing, causing remodelling of the airway and production of excess mucous. Additionally,

resultant bronchial wall thickening and smooth muscle contraction contributes to airway obstruction.^(26, 27)

1.3.1.2 Development of emphysema

Tobacco smoke has a dose-relationship with the presence of emphysema, although the mechanism is less well understood than in chronic bronchitis. Smoking increases the number of circulating leucocytes, increases their size, and stimulates release of premature leukocytes from bone marrow. This results in an expansion of the leucocyte population in the pulmonary vasculature and thus into alveolar epithelium. The release of proinflammatory chemo and cytokines by the alveolar endo- and epithelium in response to this further worsens inflammation. There is a resultant imbalance of proteases (primarily produced by macrophages and neutrophils) and anti-proteases, which causes destruction of the lung parenchyma. Destruction of lung parenchyma is chemotactic in itself and creates a positive feedback loop. Tobacco smoke also inhibits histone deacetylase and results in oxidative stress – both cause an increase of proinflammatory cytokines and resultant development in emphysema.⁽²⁶⁻²⁸⁾

It is, however, important to note that less than half of smokers will go on to develop airflow obstruction and, given the variability in rates of lung function decline with similar smoke exposure, a group of patients who are susceptible to cigarette smoke or who have other environmental factors, must therefore exist.^(20, 29)

1.3.2 Non-Tobacco causes

Tobacco smoke is not the only cause of COPD. Data from the USA HHANES and NHANES I & II studies in the 1970-80s suggested between 4.7-5.1% of never-smokers reported they had been diagnosed with chronic bronchitis or emphysema (used as a surrogate for COPD).⁽³⁰⁾ More contemporary data from the UK shows a slightly higher proportion of never-smokers (5.7-8.2%) diagnosed with COPD.^(4, 31) Of note, this is different to the number of patients with COPD who have never smoked, which has been reported as being as high as 27% in some population studies.^(32, 33)

1.3.2.1 Air pollution and COPD

Links between air pollution and a higher burden of respiratory symptoms have long been established. In the UK in the 1960s this was demonstrated in surveys of both non-

smokers and smokers. Symptoms in smokers were worse- suggesting they are more susceptible than non-smokers to the adverse effects of environmental pollution.⁽³⁴⁾ Further large population studies such as the SAPALDIA and 7th day Adventists studies have shown that higher levels of pollution are associated with increased symptoms of cough, sputum production and dyspnoea.^(35, 36) The effects of <10µm diameter particles (PM₁₀), Nitrogen Dioxide (NO₂) and total suspended particles (TSP) are the most associated with detrimental effects on the lung, with atmospheric TSP >200mcg/m³ leading to the greatest risk for symptoms.^(35, 36)

Symptom development is not the only feature; increasing air pollution has a negative effect on lung function, with people in more polluted areas having a more rapid reduction in FEV₁ than those in less polluted areas.^(37, 38) This effect begins in childhood where high concentrations of PM₁₀ and NO₂ are associated with a 3.4% reduction in FEV₁ and 6.1% reduction in FEF₇₅ in 9-10 year olds living in more polluted areas. Reduction in FEV₁ and FEF₇₅ suggests damage to both large and small airways.⁽³⁹⁾ These findings are congruous with long term longitudinal follow up which showed in patients already diagnosed with respiratory disease, there was a 7.1% reduction in percent predicted FEV₁ when pollutant levels reached PM₁₀ >100mcg/m³ for more than 53 days per year. Similar patterns were found between FEV₁ reduction with Sulphates (1.5%) and Ozone (6.3%).⁽⁴⁰⁾

In never smoking males there was a small (1.5%), albeit significant, reduction in FEV₁/Forced Vital Capacity (FVC) but which is not replicated in females or ex-smokers.⁽⁴⁰⁾ The effect of environmental pollution is therefore likely to be a minor contributor to the overall development of COPD. It should be considered of greater importance in ex- or passive smokers, or people with other risk factors.

1.3.2.2 Genetics

A large and increasing number of genetic variances are thought to play a role in the development of, and susceptibility, to COPD.⁽⁴¹⁾ α₁-antitrypsin deficiency is a genetically inherited disorder due to mutations of the SERPINA1 gene, and the most common genetic cause of COPD. In the USA, 1.9% of patients with COPD have α₁-antitrypsin deficiency.⁽⁴²⁾ In people with α₁-antitrypsin deficiency who smoke, there is a compound effect with accelerated decline in lung function.^(42, 43) SERPINA1 encodes the α₁-

antitrypsin protein; a protease inhibitor which protects the lung against the effects of neutrophil elastase and other proteases. Deficiency in this protein can lead to emphysema, especially in severe deficiency.⁽⁴³⁾ There are a large number (>150) of different alleles associated with mutations in SERPINA1 resulting in the development of COPD, although the Z and S alleles are most associated with disease.⁽⁴⁴⁾ α_1 -antitrypsin deficiency is one of the most common genetic conditions worldwide (particularly in people of European Caucasian descent) with a prevalence of around 1 in 2500.⁽⁴³⁾ There are other recognised genetic abnormalities which are associated with COPD. Glutathione S-transferase (GST) gene M1/T1 polymorphisms reduce glutathione levels and therefore diminish protection against oxidative stress and the inflammatory response, contributing to the development of COPD.⁽⁴⁵⁾ Matrix Metalloproteinase 12 (MMP12) is a protease primarily produced by macrophages - which are prevalent in the lungs of smokers. Increase in MMP12 can lead to development of emphysema due to elastin breakdown – the fragments of which trigger a positive feedback loop with macrophages.⁽²⁸⁾ MMP12 gene polymorphisms can both help protect against the development of COPD (e.g. in the case of single nucleotide polymorphism (SNP) rs2276109)⁽⁴⁶⁾, or worsen emphysema through increased MMP12 activities (as in SNP rs652438)⁽⁴⁷⁾. Patients who are homozygous for the A/A allele are also overrepresented in the COPD population, with the minor (G) allele appearing to be relatively protective against the disease.^(46, 47)

1.3.2.3 *Childhood*

As already discussed, environmental factors such as exposure to sulphates, NO₂ and PM₁₀, along with other environmental pollutants can adversely affect childhood lung function.

1.3.2.3.1 *Exposure to tobacco smoke*

Exposure to environmental smoke in families where one or both parents smoke is common. Exposure to parental smoke causes small but significant reductions in children's lung function with meta analyses showing an overall 1.4% lower FEV₁ and reduced FEV₁/FVC ratios in smoke exposed children and which continue into adulthood.^(48, 49) Maternal smoking may have a more detrimental effect on children than paternal smoking.⁽⁴⁹⁾ Maternal smoking during pregnancy has negative effects on lung

function after birth, as well as the development of respiratory symptoms in childhood.⁽⁵⁰⁻⁵⁵⁾ Reductions in lung function are greatest in children exposed to cigarette smoke who go on to develop respiratory symptoms such as wheeze (FEV₁/FVC reductions between 2-4% at age 15), in contrast to increases in FEV₁/FVC in non-exposed, but symptomatic children.⁽⁵¹⁾ Children born to mothers who smoked during pregnancy show small but significant reductions in FEV₁, FEV₁/FVC, functional residual capacity (FRC) and FEV₂₅₋₇₅.⁽⁵²⁻⁵⁴⁾ Smoking during pregnancy presents a risk of reduction in childhood lung function, particularly small airways obstruction, separate to and not explained by continued maternal smoking post-partum.⁽⁵⁵⁾ In addition to the risks of passive smoke exposure stated above, children of smokers (including light or ex-smokers) are at least 3.5x more likely to smoke themselves. When an older sibling also smokes, this risk is increased to 15.4x that of a non-smoking family.⁽⁵⁶⁾ Smoking in adolescence not only damages the lungs as with adult smokers, but inhibits the rate of growth of FEV₁ and FVC, thereby potentially reducing peak/maximal attainable lung function achieved in adulthood.⁽⁵⁷⁾

1.3.2.3.2 Prematurity and birth weight

Prematurity and low birth weight is associated with reduction in lung function after birth when compared to infants of term-delivery.⁽⁵⁸⁻⁶⁰⁾ Pre-term/low birth weight children who develop bronchopulmonary dysplasia (BPD - a disease associated with the requirement for prolonged oxygen treatment and/or need for mechanical ventilation past 28 days or 36 weeks' gestation; and resulting in the possible development of hypoxaemia, hypercapnia, wheeze, increased secretions, hyperinflation, growth retardation, respiratory tract infections and Cor pulmonale) in particular have reductions of between 16.2 and 18.9% in their FEV₁ compared to those born at term (and without BPD).⁽⁵⁸⁾ This deficit is also seen in pre-term/low birth weight children who do not develop BPD, with an average 7.2% reduction in FEV₁ compared to term children.⁽⁵⁸⁾ Whether these effects last into later life and adulthood is less clear. Obstructive airways disease has been shown in premature/low birth weight children even much later in childhood.⁽⁶⁰⁾ These findings are backed up in a meta-analysis by Kotecha et al⁽⁵⁸⁾, however results are not conclusive. One British and one Australian study, for example, shows that by 14 years of age the respiratory health of low birth weight children is comparable to full term children.^(59, 61) British data, published in 1991, followed men

born from 1911-1930 into adulthood shows that adult FEV₁ was negatively associated with low birth weight, independent of smoking habit or social class, and that death from COPD was associated with low birth weight too.⁽⁶²⁾ This has to be interpreted with caution given the significant advances in neonatal and paediatric care over the last hundred years; but gives pause for thought as the majority of current patients were born in a similar era.

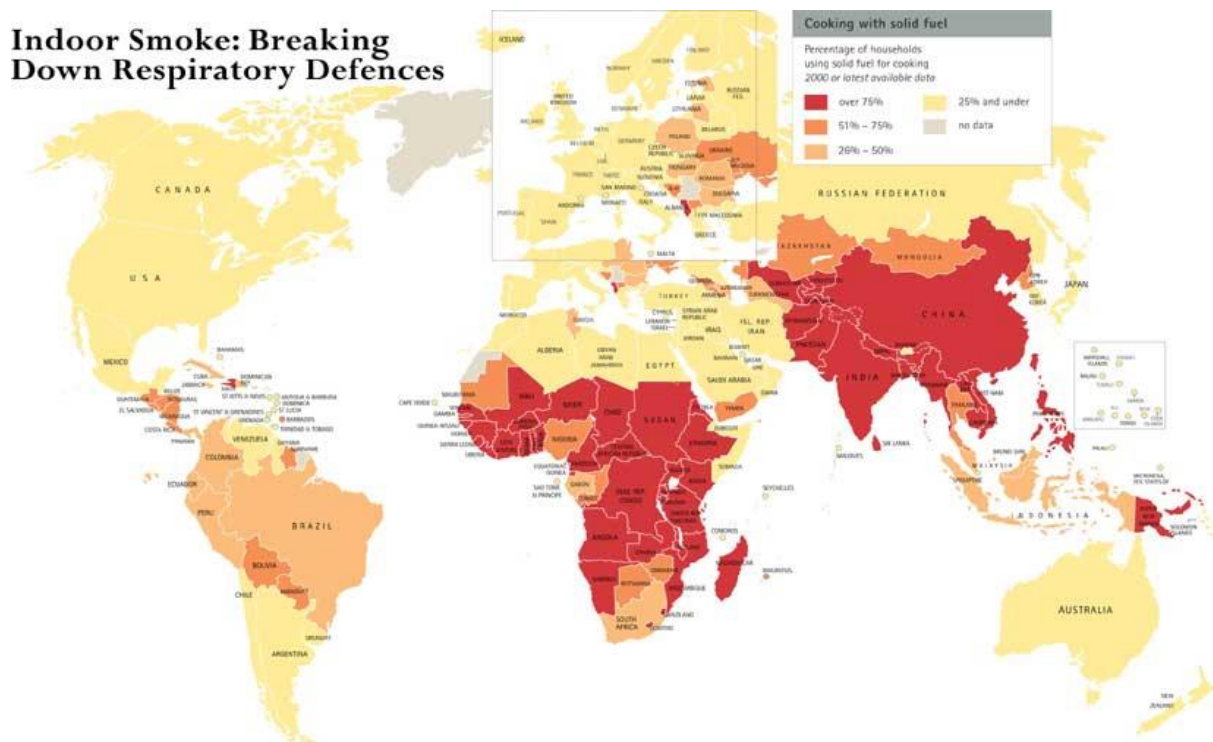
1.3.2.3.3 Childhood infection

Chest infections or pneumonia in childhood are also implicated in the development of airflow limitation or asthma, which may contribute to the development of COPD in adulthood. Childhood respiratory infection, and pneumonia in particular, has a lasting effect on the lung function of children. Castro-Rodriguez showed when children develop pneumonia under the age of 3 the subsequent rate of diagnosis of asthma is 3 fold at both 6 and 11 years of age. In this cohort 11 year old children who had had pneumonia, or non-pneumonic LRTI, had lower pre-bronchodilator FEV₁ and FEF₂₅₋₇₅ than those with no history of LRTI, although the statistical significance of these changes disappeared after bronchodilation.⁽⁶³⁾ In contrast, data tracking patients into adulthood shows that long term sequelae of childhood pneumonia includes reduction in lung function.^(61, 64, 65) Study results vary: Chan et al showed pneumonia has a pronounced effect, with a 2.5% reduction in FEV₁/FVC ratio at age 26, independent of other risk factors such as smoking.⁽⁶⁴⁾ Others have shown absolute decreases in the FEV₁ (-157 to 390ml) and FVC (-209 to 600ml) well into adulthood for people who had childhood pneumonia, but with no reduction in the FEV₁/FVC ratio itself.^(61, 65) When excluding patients who have a history of asthma the risk of developing COPD in people who had childhood chest infections is still approximately double that of people who didn't.⁽⁶⁶⁾ It is difficult to ascertain whether pre-existing defects in lung function (predisposing children to chest infection), parental smoke exposure increasing risk of infection, or infections themselves causing airway damage result in these long term defects. Whatever the exact mechanism is, there seems to be clear evidence that childhood respiratory infection has a long term effect on lung health and is implicated in the development of COPD, plus the attainment of maximal FEV₁.

1.3.2.4 Biomass fuel

Biomass fuels include animal waste/dung, crop residue, wood, charcoal, kerosene and coal amongst others. They are generally burnt indoors for heating and cooking and are a significant cause of indoor air pollution. These types of fuels are currently routinely used by around 3 billion people - 41% of the world's population.⁽⁶⁷⁾

Figure 1. World Health Organisation map of use of solid biofuels for cooking. (Year 2000 or latest data)⁶⁸



Use of biomass fuels is highest in low and middle income countries; with some populations having >95% reliance on them for household energy (Figure 1).^(67, 68)

Biomass fuel in general is highly polluting. The least efficient fuels (e.g. animal dung) tend to be the most polluting, but are also cheapest thus making them most desirable in poorer communities.⁽⁶⁹⁾ In addition to biomass fuel itself, traditionally built biomass stoves are inefficient and therefore more fuel is required for the same energy output, worsening pollution further.⁽⁷⁰⁾

Different fuels produce different pollutants, but biofuel pollution generally includes large quantities of small particulate matter (PM₁₀), Carbon Monoxide, Nitrogen and Sulphur Oxides, and Aromatic Hydrocarbons amongst others.^(69, 71) Tobacco smoke is an organic product, and therefore it is not necessarily surprising that other biomass smokes have a detrimental effect on health. Approximately 19.9% of the world's >15 year old population currently smoke tobacco products (33.7% of males and 6.2% of females).⁽⁷²⁾

The rate in the UK in 2018 was around 17.8% according to the world health organisation.⁽⁷²⁾ Whilst smoking is the greatest risk factor for development of COPD in the UK, it is arguable that use of biomass fuel is as big a risk factor internationally as smoking is – especially for women.

Indoor 24-hour average PM₁₀ concentrations in households burning biomass fuels are between 300-3000µg/m³ and can peak in excess of 30,000µg/m³ at times of cooking.^(69, 73) Biomass smoke pollution is a major factor in the development of symptoms such as wheeze, breathlessness and cough; it also causes COPD with odds ratio of between 1.38 and 2.27 compared to the non-exposed.⁽⁷⁴⁻⁷⁷⁾ Women and young children are the most affected by burning of biomass fuels, as they are most likely to be exposed to indoor pollution during cooking.^(69, 78, 79) In a study of Turkish, never-smoking females who burnt biomass fuels indoors the prevalence of COPD was as high as 23%.⁽⁷⁵⁾ Children born to mothers who are exposed to biomass fuels may also have lower birth weight, further increasing their risk of reduced lung function in later life.

The World Health Organisation 'Global burden of disease and risk factors' estimated in 2006 that 844,000 COPD deaths annually were attributable to biomass fuels, with women worst affected in each age category measured. In children there were an estimated 29.7million disability adjusted life years (DALYs) – a measure of 'a lost year of healthy life' – due to chest infection secondary to biomass fuels.⁽⁸⁰⁾ This may have a significant effect on achievement of maximal lung function and the subsequent development of COPD – particularly if in combination with ongoing tobacco smoke exposure.

While biomass fuel use is generally lower in the developed world a US study showed a self-reported 26% exposure to biomass fuel in over 2000 participants. After adjustment for co-variables exposure to wood-smoke was significantly associated with obstructive spirometry.⁽⁸¹⁾ In the UK, Kings College London undertook a 7 year study investigating environmental wood-smoke pollution. This showed that while there is an increasing number of wood burning stoves sold (~200,000/yr.), overall wood smoke pollution has slightly decreased over the years 2009-2016, though it still accounts for up to 31% of PM_{2.5} and PM₁₀ in urban areas and there is both day-to-night and summer-to-winter variation.⁽⁸²⁾

1.3.2.5 Recreational drug use

Use of some recreational drugs is associated with deterioration in lung function and the development of COPD. Cannabis is the most commonly used recreational drug used in the UK, with around 7.2% of adults using it within the last year, and 30% of UK adults having used cannabis at some point in their lifetime.⁽⁸³⁾ Cannabis has historically been illegal in most jurisdictions and therefore there have been difficulties in undertaking research on it. Problems include obtaining accurate usage statistics, no defined equivalent of a 'pack year' for cannabis, no standardised strength or purity, variations in whether cannabis is smoked alone, or in combination with tobacco and differences in grams of cannabis per cannabis cigarette.⁽⁸⁴⁾ In addition, cannabis can be 'smoked' in a number of different ways, such as cannabis cigarettes, waterpipes/hookah, pipes, or vaporised. Inhalation methods are not well defined in most of the literature. Despite difficulties, its effects on the airway function has been long reported, with evidence of small but significant obstructive defects (3% FEV₁ reduction) in heavy users over short periods of time – 6 to 8 weeks.⁽⁸⁵⁾ The same group also showed that cannabis smokers had an increase in symptoms such as cough, wheeze and sputum production compared to non-smokers – something which subsequent papers confirm.⁽⁸⁶⁻⁸⁹⁾ Cannabis is significantly associated with airway obstruction and may result in a fall of FEV₁ up to twice that of tobacco alone.^(87, 88) Aldington *et al* estimate that the effect of one cannabis cigarette on airway function is equivalent to between 2.5-5 traditional cigarettes.⁽⁹⁰⁾ When using cannabis in conjunction with tobacco there appears to be a synergistically detrimental effect on lung function and possible development of COPD.

Other recreational drugs associated with COPD include cocaine (primarily in its smokable form - crack cocaine) and heroin. These patients tend to have a younger age at diagnosis. Around 1/3 of crack cocaine users have a diagnosis of COPD (although 80% are also tobacco/marijuana smokers) and its use is frequently associated with bullous emphysema, although a number of other pulmonary manifestations, such as pneumonitis, also occur.⁽⁹¹⁻⁹³⁾ Similarly, ~28% of heroin smokers have a diagnosis of COPD and it is associated with early onset COPD, again with a predominant emphysematous pattern.^(94, 95) Few studies examine the use of inhaled methamphetamine, although exposure produces a similar inflammatory response to

other smokes such as tobacco and marijuana raising the potential for development of COPD.⁽⁹⁶⁾ Tsai *et al*, describe a lower risk of COPD in methamphetamine users compared to non-users. In this study methamphetamine users had a lower average age compared to non-users (35 vs. 52) and were more likely to be male (56% vs 37%). Prevalence of COPD in users increased from 6.6 to 12.7 per 1000, over a 5 year period – a trend not seen in non-users.⁽⁹⁷⁾ This suggests that ongoing Methamphetamine use may be well be a contributor to, or cause of COPD, and the lower baseline incidence could be explained by the large age discrepancy.

1.3.2.6 Diet and nutrition

There is a building body of evidence that dietary intake effects lung function, and therefore the potential to develop COPD. The evidence, however, is still conflicting. Fruit consumption in British children has been demonstrated to be associated with an 88ml increase in FEV₁ and a similar trend in FVC, suggesting that childhood lung development is at least partially reliant on good diet, and therefore potentially protective against COPD in later life.⁽⁹⁸⁾ This is congruent with earlier findings in British adults aged 18-69 years, which demonstrated a 78ml lower FEV₁ in those who consume the least quantities of fruits/fruit juices.⁽⁹⁹⁾ More recently, large Japanese and European studies have suggested significantly lower odds ratios for developing COPD (0.49-0.69) in people who eat higher quantities of vegetables – but found fruit to have no effect.^(100, 101) In a 20 year longitudinal follow up study, there was a trend towards lower risk of COPD with fruit (OR 0.86), but this was non-significant and no difference was seen with other dietary components.⁽¹⁰²⁾

In mice, Vitamin A deficiency has been associated with increased susceptibility to cigarette smoke and increased emphysema.⁽¹⁰³⁾ This this hasn't been demonstrated in longitudinal human studies. There is some evidence that high Vitamin C intake is associated with reduced risk of COPD, although in a retrospective, single country cohort.⁽¹⁰⁴⁾ High dietary Vitamin D intake is also associated with a higher FEV₁, FEV₁/FVC ratio and lower COPD risk – although this was not mirrored when examining participants' blood Vitamin D levels.⁽¹⁰⁵⁾ This finding points to a clear and pragmatic argument in a number of large studies: eating a 'prudent diet' with a balance of vegetables, fruits, proteins, fibres and fats is the most likely thing to protect against lung

function decline and COPD development, rather than concentrating on any individual component of diet.⁽¹⁰⁵⁻¹⁰⁸⁾

One difficulty of establishing individual dietary risks/benefits is the intrinsic link to other confounders such as socioeconomic status and BMI.^(98, 108) In addition to that, drawing conclusions in population-based studies may be difficult due to population-level factors. One recent American study of 6352 participants examined COPD and lung function in relation to the American heart association lifestyle recommendations. This study was unable to examine diet with adequate power as 95% of the population fell into the 'poor' diet group.⁽¹⁰⁹⁾

1.3.2.7 Asthma and airway hyper-responsiveness

Asthma is an inflammatory airway disease characterised by variable and reversible airflow obstruction, in contrast to COPD. Airways hyper-responsiveness to irritants is a characteristic feature of asthma. Asthma tends to have an episodic course with fluctuating intensity of symptoms, which present in a heterogenous manner.⁽¹¹⁰⁾ Asthma prevalence varies internationally with a self-reported history of asthma in 25.1% of UK teenagers.⁽¹¹¹⁾ Children with reduced lung function in infancy are more likely to develop childhood asthma and have increased airways hyperresponsiveness than those with normal lung function.^(112, 113) In those who develop asthma there is an accelerated decline in lung function throughout their childhood.⁽¹¹²⁾ When a cohort of unselected children were followed up longitudinally into adulthood those with a persistent diagnosis of asthma, or those without a formal diagnosis of asthma but who wheezed, had significantly lower FEV₁/FVC ratios than those who did not.⁽¹¹⁴⁾ These patients had a similar downward trajectory of FEV₁/FVC to non-asthmatic or non-wheezing subjects, but started from a lower baseline, suggesting asthmatic patients may never reach their 'peak' potential FEV₁. Factors which increased the likelihood of ongoing wheeze or asthma included smoking and increased airway hyperresponsiveness.⁽¹¹⁴⁾ This is important as when following people from childhood into middle-age: there is a clear association with reduced childhood lung function and risk of COPD. A recent Australian study of >8500 children followed to age 45 showed that 7 year olds with the lowest quartile of FEV₁/FVC measurements had a significantly increased risk (16.3x) for the coexistence of both asthma and COPD, and (5.8x) for COPD alone.⁽¹¹⁵⁾ This concurs with earlier work by Tai *et al* which describe a 32x higher rate of COPD at age 50 in asthmatic

children than in non-asthmatic children.⁽¹¹⁶⁾ Interestingly in this group, the rate of decline of FEV₁ was similar between the group that developed COPD and those that did not, in similarity with Sears' study.⁽¹¹⁴⁾ In the group diagnosed with COPD by age 50, 43% of patients had never smoked and a significant proportion of this population may have asthma with airways remodelling.⁽¹¹⁶⁾ Similar results were also found in the Tucson population study in which demonstrated a 17x increased risk for emphysema and 12.5x increased risk for COPD in asthmatic patients after correction for smoking and other potential confounders.⁽¹¹⁷⁾

A hallmark feature of asthma is airway hyperresponsiveness (AHR), although this can also be present outside of the formal diagnosis of asthma. In COPD presence of AHR is independently associated with both a more rapid decline in FEV₁ over time and appears to be associated with poorer prognosis and increased mortality.⁽¹¹⁸⁻¹²⁰⁾

When combined with other risk factors, such as low birth weight, passive smoking, environmental pollutants, or infection, asthmatic children and adolescents may never reach their maximal potential lung function. These 'childhood disadvantage' factors act cumulatively to permanently reduce FEV₁ and carry a significant risk for development of COPD later in life – as big as that of tobacco smoking.⁽¹²¹⁾

1.3.2.8 Occupational

Occupational exposure to dusts, vapours, fumes and gases contribute to both respiratory symptoms and the development of COPD. Non-organic dusts in particular are most associated with COPD.⁽¹²²⁾ Studies examining workers with particularly high non-organic exposure, such as mining⁽¹²³⁾, tunnel construction⁽¹²⁴⁾ and concrete manufacturing⁽¹²⁵⁾ demonstrate obstructive airflow limitation and increased respiratory symptoms. In broader population studies occupational exposure to biological dusts, insecticides/ herbicides/ pesticides, and other non-specific dusts, fumes, gases and vapours are associated with reductions in FEV₁, FEF₂₅₋₇₅ and increased diagnoses of COPD with risk double that of non-exposed workers.⁽¹²⁶⁻¹²⁹⁾ Workers in these professions who also smoke are particularly susceptible to development of COPD. Combined exposures to tobacco and dusts appears to act synergistically with an odds ratio for development of the disease increasing to 14.1 (2.11 for only dust exposed).^(127, 129) In addition to increasing the risk of developing COPD, workers with established COPD and occupational exposure have a worse symptom burden than those without occupational

exposure. Health related quality of life (measured by the St Georges Respiratory Questionnaire)⁽¹³⁰⁾, symptom burden (measured by the COPD Assessment Test)⁽¹³¹⁾, breathlessness (on the medical research council dyspnoea score) and 6-minute walk distances are all lower in occupationally exposed patients.⁽¹³²⁾

1.3.2.9 Socioeconomic status and poverty

COPD is significantly more common in areas with more poverty and lower socioeconomic standing, even amongst non-smokers, with a prevalence rate almost double that of non-poor areas.^(133, 134) People who finish secondary school, or that have a higher monthly household income are less likely to develop COPD.⁽¹³⁴⁾ Rural populations are at a greater risk than urban.^(133, 135) Rural populations are less likely to get a diagnosis of COPD made early – particularly if they are female or have lower educational attainment.^(133, 135) In addition to this, rural patients with COPD have a higher healthcare utilisation including hospitalisation rate, and overall lower quality of life than urban dwelling patients.⁽¹³⁶⁾ As discussed previously, the rate of COPD in rural populations could partly be explained by the increased use of biomass fuels in the home.^(67-69, 133) When looking at urban populations in rich western countries, lower education level, income and lower socioeconomic status are associated with reduced lung function, independent of smoking.⁽¹³⁷⁾ Between the poorest and wealthiest quintiles there is a 1.4 to 1.9 times higher lifetime risk of developing COPD.^(138, 139) Census level community poverty is associated with significantly increased rates of COPD (OR 1.12) than in communities not living in poverty; this is also replicated at household level (OR 1.08).⁽¹³³⁾ Smoking in lower socioeconomic populations is four times more prevalent than in more affluent populations and the chances of successfully quitting smoking are significantly lower.^(140, 141) British lung foundation statistics show that around 23% of people earning under £10,000 per year smoke compared with <11% of those earning over £40k. Smoking accounted for around an approximately 35% increase in death rates between the lowest and highest socioeconomic groups in London; and people born with smoking parents are more likely to smoke as well.⁽¹⁴²⁾ Homelessness is associated with both increased smoking rates (around 85% smoke), and homeless people are more likely to suffer with respiratory disease; COPD rates in this group are double the national average.⁽¹⁴²⁾ As well as increased risk of COPD and worse lung function, poverty is associated with an increased COPD mortality; particularly in countries with a gross

national income of under \$15000 per annum.⁽¹⁴³⁾ Interestingly, however, the BOLD cohort demonstrated that reduced FVC in these COPD populations impacts negatively on the mortality rate too.⁽¹⁴⁴⁾ It is likely that a combination of factors throughout life in poor populations – lower birth weights, exposure to pollutants, poor education, smoking, poor diet, work and reduced access to healthcare (delayed diagnoses and treatment) – impact the potential to ever reach peak lung function, and increase the rate of decline throughout life. It seems that COPD could be defined as, in many respects, primarily a disease of inequality and poverty.

Despite the description above of the various risk factors associated with COPD, within UK primary care cohorts only around 2% of patients with COPD are never-smokers.⁽¹⁴⁵⁾ This suggests that smoking, although intimately tied with various other socioeconomic factors, remains the single most important risk factor for the development of COPD in the UK.

1.4 Economic considerations

1.4.1 Healthcare Burden

COPD is the second most common cause of hospital admission in the UK and over 1 million bed days are taken by patients with COPD per annum.^(3, 24) There are an estimated 1.4 million COPD related consultations with General Practitioners per year in the UK.⁽¹⁴⁶⁾ Of patients admitted to hospital the average Length of Stay (LoS) is 4 days, which has not changed in the last few years. Readmission to hospital is an increasing problem in COPD; with the 2018 National COPD audit report demonstrated that 43% of patients hospitalised for COPD were readmitted within three months of discharge.⁽¹⁴⁷⁾

1.4.2 Economic Burden

The costs of COPD are enormous. Direct healthcare costs to the NHS are estimated to be around £1.8billion a year, and in England alone this is anticipated to rise to £2.32billion a year by 2030.^(17, 148) The cost of COPD to UK healthcare providers ranges from around £1523 to £3396 per annum, depending on the number of exacerbations a patient has, with an average cost of £2108. Primary care costs account for around 69% of this in patients with no exacerbations, to 47% in patients who have had multiple

exacerbations.⁽¹⁴⁹⁾ Non-direct healthcare costs of COPD have been estimated by the British Lung Foundation. In addition to the direct costs above, the estimated indirect (due to loss of production) and intangible (due to the impact of pain, anxiety & excess mortality) costs of COPD are in excess of £48.5billion/year.⁽¹⁴⁸⁾ These figures have to be interpreted with some caution as they are challenging to estimate, but may be inaccurately low due to under recognition and diagnosis of COPD. Patients with COPD also suffer in terms of their employment, worsening the associations with lower socioeconomic class and poverty (section 1.3.2.9, above). COPD accounts for around 29% of the economic costs of respiratory disease in the UK – the largest proportion of any respiratory disease. Patients with COPD are less likely to be in stable employment, have more time off work (approx. 464,000 work-days lost in the UK per annum), and have lower performance at work.^(142, 148, 150) More severe airflow obstruction (section 1.5.3) is also associated with lower likelihood of employment, although when adjusted for other factors (such as geography and comorbidities) this risk is more modest than it may initially seem.^(150, 151)

1.5 Diagnosis

The diagnosis of COPD should be considered in people who have been exposed to risk factors (Section 1.3) and who have symptoms typical of the disease. In order to make a firm diagnosis, confirmatory lung function testing is also required.⁽¹⁾

1.5.1 Symptoms and clinical features of COPD

1.5.1.1 Thoracic symptoms of COPD

The majority of patients with COPD present respiratory symptoms, although there is considerable variation between patients in presentation and severity of these. The most common symptoms of COPD are dyspnoea, cough, sputum production, wheeze and chest tightness. Symptoms are often under reported by patients and therefore may be under recognised by healthcare staff.^(1, 152) Whilst symptoms generally worsen with disease severity, this is not universally true. Around one third of patients with COPD may report no respiratory symptoms.⁽¹⁵³⁾

1.5.1.2 *Dyspnoea*

Dyspnoea is normally defined as an uncomfortable sensation or awareness of breathing, which can frequently be distressing.⁽¹⁵⁴⁾ It is the most common and significant symptom in COPD, and the primary reason people with COPD initially seek medical attention.⁽¹⁾

The sensation of dyspnoea is variable; differing both between patients, and within the same patients over time. This variability can make objectively quantifying dyspnoea challenging and unreliable. Patients with COPD, and other diseases causing dyspnoea, use a wide variety of terms to describe the sensation of breathlessness. The predominant feeling is that of 'air hunger' (the inability to breathe deeply, get enough air in, etc), although a number of other sensations are experienced.⁽¹⁵⁴⁾

The Medical Research Council Dyspnoea Score (MRCD) was developed to standardise measurement of dyspnoea and its effect on patients.⁽¹⁵⁵⁾ The MRCD assigns a score to patients based on their level of physical activity and associated dyspnoea and is commonly used in clinical practice. The lowest score, corresponding to the lowest limitation from dyspnoea, is 1 and the highest score is 5. The MRCD has been compared against multiple other variables associated with dyspnoea and disability in COPD. It correlates well with worsening morbidity and is a strong predictor of mortality in stable state COPD, as well as during exacerbations.^(156, 157) In addition, the MRCD score performs better than FEV₁ (Section 1.5.2) when predicting outcome in COPD.⁽¹⁵⁸⁾

Variants of the initial MRCD Score, such as the modified (mMRCD) or extended (eMRCD) MRCD score have been developed (Table 1).^(159, 160) The eMRCD (discussed further in section 2.3.2.2) provides increased discrimination at higher scores by extending the MRCD's traditional worst score, 5, into either 5a or 5b to include a marker of frailty. It also has defined time periods to assess dyspnoea over (3 months) and a patient must be as bad as the next level before scoring it. The eMRCD score is a stronger predictor of inpatient mortality for both pneumonic and non-pneumonic exacerbations of COPD than either the MRCD or mMRCD scores. Inpatient mortality approximately doubles between eMRCD scores of 5a and 5b, providing a prognostic benefit that is lost within the traditional MRCD score of 5.⁽¹⁶⁰⁾ In addition it is a strong independent predictor of post discharge mortality and readmission.⁽¹⁶¹⁻¹⁶³⁾

Other dyspnoea scores such as the Baseline Dyspnoea Index (BDI),⁽¹⁶⁴⁾ Oxygen Cost Diagram (OCD),⁽¹⁶⁵⁾ dyspnoea specific questions in the St Georges' Respiratory

Questionnaire (SGRQ),⁽¹³⁰⁾ or Chronic Respiratory Disease Questionnaire (CRQ)⁽¹⁶⁶⁾ perform similarly to the MRCD for measurement of dyspnoea but the MRCD score is easier to quickly calculate.⁽¹⁶⁷⁾ Another measure of dyspnoea, the modified BORG score, measures patient dyspnoea at a specific timepoint (or activity) rather than more generally, and though a useful and important measure, is more subjective and fluctuant than the MRCD score.^(167, 168)

Table 1. Comparison of the original MRC, mMRC and eMRC Dyspnoea scores. Differences between the MRC and mMRC relate to the score awarded for each level and the change of gender pronouns used. These moved from male to gender neutral but have been removed for simplicity of comparison in this table.

Description of limitation due to breathlessness	MRCD ⁽¹⁵⁵⁾	mMRCD ⁽¹⁵⁹⁾	eMRCD ⁽¹⁶⁰⁾
Breathless only with strenuous exertion	1	0	1
Breathless when hurrying on the level or walking up a slight hill	2	1	2
Walks slower than peers, or stops when walking on the flat at own pace	3	2	3
Stops after walking 100m, or for a few minutes, on the level	4	3	4
Too breathless to leave the house or I am breathless when dressing or undressing	5	4	n/a
<u>Too breathless to leave the house unassisted:</u>			
- But independent in washing and / or dressing	n/a	n/a	5a
- & dependent in washing <u>and</u> dressing	n/a	n/a	5b

1.5.1.3 Extra thoracic symptoms of COPD

COPD frequently presents with ‘non-respiratory’ symptoms and features in addition to those described above. These include weight loss (body mass index and free fat loss), osteoporosis, fatigue, anxiety and depression, anaemia and skeletal muscle dysfunction leading to weakness.^(169, 170)

1.5.1.4 Weight loss

Weight loss occurs in around 50% of patients with severe COPD and 25% of those with moderate COPD (section 1.5.2), with around 37% of patients with COPD being nutritionally deplete.^(169, 171) Patients with COPD are nearly twice as likely to lose weight unintentionally as those without.⁽¹⁷²⁾ The mechanisms behind weight loss in COPD are incompletely understood and likely multifactorial. Probable mechanisms include:

imbalance between calorie intake and burning (in part due to increased work of respiratory muscles), diffuse atrophy of muscles, tissue hypoxia, systemic inflammation, oxidative stress, and reduced anabolic hormone levels.^(173, 174) Whether measured as Body mass index (BMI) or fat free mass (lean body mass) low weight is associated with greater decline in lung function, more frequent exacerbations (section 1.9) and higher mortality.⁽¹⁷⁵⁻¹⁷⁹⁾ Fat free mass and arm or calf circumference may be more accurate measures of risk from weight loss than BMI, however are less widely understood and used in clinical practice.⁽¹⁶⁹⁾

Interestingly, there is an obesity paradox in COPD: a higher BMI ($>25 \text{ kg/m}^2$) than the normal range ($18.5\text{-}25.0 \text{ kg/m}^2$) is associated with reduced mortality from COPD, despite increased risk of diabetes, hypertension, heart failure and osteoarthritis.^(179, 180)

1.5.2 Lung function

1.5.2.1 Spirometry

Spirometry is a relatively simple lung function test which measures the volume of air a person can expire in relation to time; producing clinically meaningful lung volume and flow data. Spirometry is simple to perform, easily reproducible, and readily available.⁽¹⁸¹⁾ Spirometry should be performed in all people presenting with symptoms of COPD in order to make the diagnosis.⁽¹⁾ The two primary measurements taken in spirometry are the Forced Expiratory Volume in one second (FEV_1): the maximum volume of air that can be forcefully expelled in 1 second, and the [forced] Vital Capacity ([F]VC): the maximum volume of air that can be exhaled when blowing out as far as possible. The FEV_1 /[F]VC ratio is also calculated and is a measure of airflow obstruction. Normal values in spirometry are measured with adjustment for age, gender, ethnicity and height. Weight and smoking status should also be recorded to aid interpretation.⁽¹⁸¹⁾

The airflow limitation seen in COPD is that of airway obstruction, with a post-bronchodilator FEV_1 to [F]VC ratio (FEV_1 /[F]VC) of <0.70 .^(1, 182, 183) Decline in FEV_1 /[F]VC ratio occurs as part of the normal ageing process and using a strict cut off of <0.70 can lead to over-diagnosis of COPD in older people (particularly over 50 year olds) due to false positive tests. Using a cut-off below the statistical lower limits of normal can reduce over diagnosis in this population.⁽¹⁸⁴⁾ Despite this, the current joint European

Respiratory Society (ERS) and American Thoracic Society (ATS) guidance, as well as the Global Initiative for Obstructive Lung Disease (GOLD) and the National Institute for Health and Care Excellence (NICE) currently recommend the use of a static $FEV_1/[F]VC$ cut-off of <0.70 for diagnosis of COPD. In order to classify the severity of airflow obstruction the $FEV_1/[F]VC$ cut-off is used in combination with the % predicted FEV_1 (section 1.5.3).^(1, 182, 183)

1.5.2.2 Lung volumes and hyperinflation

Hyperinflation is common in COPD and accompanies airflow obstruction, contributing to morbidity. Hyperinflation occurs when the volume of gas in the lungs (or a constituent part of them) is greater than the predicted values.⁽¹⁸⁵⁾ Hyperinflation is due to a decrease in lung elasticity from emphysema with subsequent reduction in recoil pressure on the chest wall; resulting in an equilibrium with a higher than normal resting volumes. This causes a larger than normal functional residual capacity (FRC; the volume of air in the lungs at the end of expiration during tidal breathing) and a reduction in inspiratory capacity (IC; the volume of air available for inspiration after FRC is subtracted from the total lung capacity).^(185, 186)

Features of hyperinflation on clinical examination include increased anteroposterior diameter, reduced chest wall expansion, reduction of suprasternal-cricoid distance and paradoxical inward movement of the abdomen on inspiration.⁽¹⁸⁷⁾ Hyperinflation can also be seen on chest radiographs where it is exemplified by diaphragmatic flattening & depression (right hemidiaphragm lower than the anterior 7th rib) and increased transradiancy of the lung field.⁽¹⁸⁸⁾ Total lung volume, FRC or residual volume (RV) of $>120\%$ are generally regarded as likely to be of clinical relevance, although this figure should be used in combination with the standardised residual values.⁽¹⁸⁵⁾

In hyperinflated lungs the inspiratory muscles fibres are shorter than normal and there is diaphragmatic flattening (with resultant reduction in diaphragmatic apposition). This creates a mechanical disadvantage; the ability of these muscles to generate inspiratory pressure is reduced and work of breathing is increased, worsening symptoms. When hyperinflation occurs, there can be a positive intrathoracic end expiratory pressure, the intrinsic PEEP (iPEEP) which the respiratory muscles have to overcome prior to generating airflow into the lungs, again increasing work of breathing.^(186, 189, 190)

1.5.2.2.1 Dynamic hyperinflation

On exertion or during exacerbation lung hyperinflation can worsen. Lung emptying/expiratory airflow is determined by airway resistance and time allowed for expiration. In normal lungs expiratory airflow is sufficient to empty the lungs to FRC prior to the next inhalation. If minute ventilation needs to increase, tidal volume can expand by using more of the inspiratory capacity. In 'flow limited' patients the expiratory flow generated during tidal breathing is the maximal flow they can generate at that volume.

During exacerbation (or exertion) there is an increased minute volume demand. In exacerbation expiratory flow limitation, and thus airway resistance, is increased by airway narrowing due to a combination increased smooth muscle tone, mucus plugging and inflammation. This lengthens the time required to fully exhale and the demand for increased minute volume means the time needed to fully exhale may be insufficient before the next inhalation is required. This increases the end expiratory lung volume (EELV) and thus reduces the inspiratory capacity. Tidal breathing can consequently approach or hit the limit of minimum inspiratory reserve (IRV) capacity, near total lung capacity, and thus increases in minute volume are only possible by increasing respiratory rate, worsening the problem, causing significant breathlessness and eventually stopping any exertion. Work of breathing dramatically increases at higher lung volumes, with larger force required to reach the same tidal volume. This process is key to the failing of the respiratory pump, with decompensation and development of respiratory acidemia during ECOPD. (185, 186, 191)

1.5.2.3 Gas Transfer

Efficient gas transfer is reliant on matching of alveolar ventilation (V_A) and perfusion (Q), with any V_A/Q mismatch reducing gas transfer. In COPD the presence of emphysema increases V_A/Q mismatch. This can be measured by carbon monoxide transfer factor (TLCO) in the lung function laboratory. TLCO is the product of the alveolar volume (V_A) and rate of uptake of carbon monoxide (KCO) with reference to barometric and water pressure (P_b^*).

$$TL_{CO} = [KCO \times V_A] / P_b^*$$

In patients with COPD TL_{CO} is usually reduced. It can be used to help aid diagnosis, and monitor progression of disease.^(192, 193)

1.5.3 Severity of airflow obstruction

It is helpful to be able to objectively track progress and 'stage' airflow obstruction in COPD. A quick and reproducible way of doing this is to measure the degree of airflow obstruction (Table 2). This approach is widely accepted and helps predict, on a population level at least, health status, exacerbation risk and mortality.⁽¹⁸³⁾ It is also a simple way to convey information to patients and track change over time. COPD is not just characterised by dyspnoea, however, and other measures of disease impact should additionally be considered before categorising disease severity. On an individual level, FEV_1 measurements alone are not accurate at predicting outcome, particularly during exacerbation, and multidimensional scores are often used (Section 3.2) as they yield more accurate results. Despite this, measurement and quantification of airflow obstruction is recommended by GOLD, the ATS, ERS and NICE and is widely used in stable disease.^(1, 182, 183)

Table 2. Severity classification of COPD based on forced expiratory volume in 1 second

In patients with post-bronchodilator $FEV_1/[F]VC < 0.7$		
FEV_1 % predicted	Severity of airflow obstruction	GOLD Stage
$\geq 80\%$	Mild	1
50-79%	Moderate	2
30-49%	Severe	3
$< 30\%$	Very severe	4

1.5.4 Differentiation from asthma.

Asthma is a heterogenous disease characterised by chronic airway inflammation with variable airflow limitation and symptoms and over time.⁽¹¹⁰⁾ COPD and asthma share many similarities in presentation, such as breathlessness and wheeze, but it is important to recognise they are distinct conditions with different clinical and pathophysiological features (summarised in Table 3). Particularly as patients get older, however, these

features can be more difficult to tease apart. Some patients have persistent airflow limitation with the presence of features usually associated with both COPD and asthma, commonly referred to as the 'Asthma-COPD Overlap Syndrome' (ACOS).⁽¹¹⁰⁾ Poorly controlled asthma can also contribute to the development of COPD in later life (see section 1.3.2.7).

Table 3. Clinical features differentiating COPD and asthma^(110, 182)

Feature	COPD	Asthma
Age of onset	Usually >35	Usually childhood, but can be any age
Smoking	Nearly all	Possible
Symptom pattern	Chronic, usually continuous, symptoms present with 'good' and 'bad' days.	Variability in symptoms over time.
Chronic Cough	Common, often productive	Uncommon
Breathlessness	Persistent, often progressive. Almost universally worse with exercise	Variable. Often worse with exercise
Symptom triggers	Exertion is the primary trigger	Often triggered by exercise, emotion including laughter, dust and allergen exposure
Diurnal variation	Uncommon	Common
Night time symptoms	Uncommon	Common
Lung Function	Obstructive. Gradual decline over time. No/small response to bronchodilators/steroid treatment	Variable obstructive limitation or Normal. Improvement often seen with bronchodilator or steroid treatment.

Feature	COPD	Asthma
Family History	Variable (often family members have smoked)	Common
Atopy	Uncommon	Common
Chest x-ray	Often abnormal	Normal
Immunoglobulin E	Normal	Often raised
Airway inflammatory cells	Eosinophils +/- Neutrophils	Neutrophils, Lymphocytes +/- Eosinophils

1.5.5 Missed and inaccurate diagnosis.

COPD is common and has significant impact not only on patients, but also the NHS with economic implications (section 1.4). Despite this, there is a significant problem with case-recognition and misdiagnosis. Around one million patients are estimated to have been diagnosed with COPD in the UK, however the real prevalence is thought to be much higher with approx. 2 million further undiagnosed patients in the community.⁽³⁾ By the time a patient is eventually diagnosed with COPD it is very likely that they will have had a number of missed opportunities for diagnosis. Jones et al showed that at the point of COPD diagnosis 85% of patients have presented with respiratory symptoms and had missed opportunities to have made the COPD diagnosis in the preceding 5 years.⁽¹⁹⁴⁾ Targeted case finding of undiagnosed patients has been shown to be over 7 times more effective than routine care, but has yet to have been widely adopted in the UK.⁽¹⁹⁵⁾ Incorrect diagnosis is also a significant problem. The UK national asthma and COPD audit (NACAP) has shown that, of those who had had previous spirometry, 1 in 8 patients admitted to hospital for 'COPD' did not have evidence of airway obstruction, and therefore were misdiagnosed.⁽¹⁴⁷⁾ This has clear implications for treatment (including harms of mistreating), patient expectations of disease prognosis, cost, and the potential under-recognition of other comorbid conditions. Overdiagnosis, especially in the older population, is problematic. As people get older lung function naturally declines and can lead to an FEV1/[F]VC <0.70 even in the absence of airways disease. Up to 45% of >60 year old males have an obstructive defect on spirometry.⁽¹⁸⁴⁾ As discussed in the spirometry section (1.5.2.1) using LLN cut offs for diagnosis reduces overdiagnosis in this

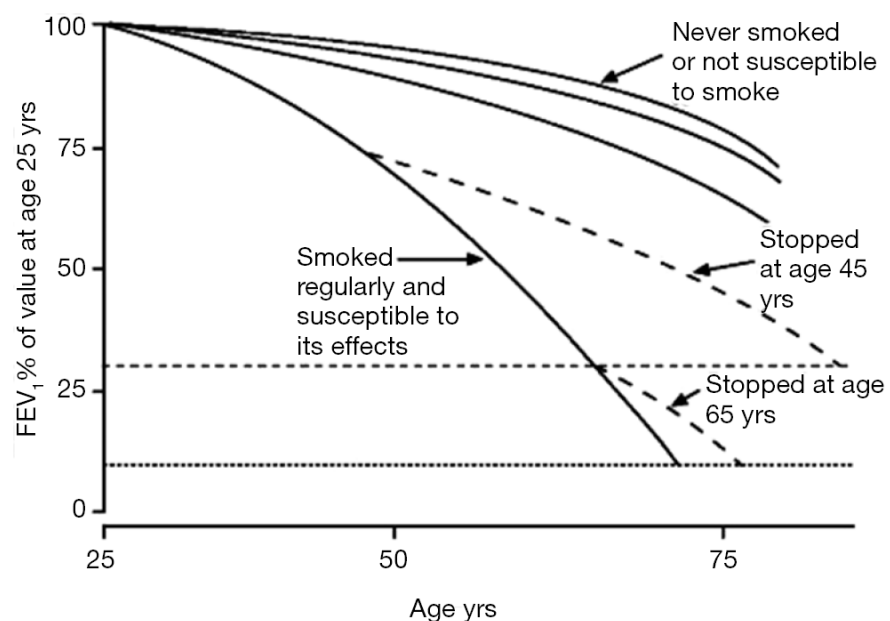
situation, though is not always used in clinical practice as a static cut off is simpler and is in line with the GOLD guidelines.⁽¹⁾

1.6 Prognosis

1.6.1 Natural history of disease

The natural history of COPD varies substantially between patients, although in general there is a gradual decline in lung function over time. The traditional view was first identified by Fletcher and Peto in a study on working men from London in 1977. They described a gradual decline in FEV₁ in the population over time, with normal ageing including in never smokers, plus a population of 'susceptible' smokers who have accelerated decline in lung function. They additionally describe the reduction in the rate of deterioration in FEV₁ in people who stop smoking (Figure 2).⁽²⁾ This theory is widely used as a simple way to explain lung function deterioration and smoking to patients in clinical practice.

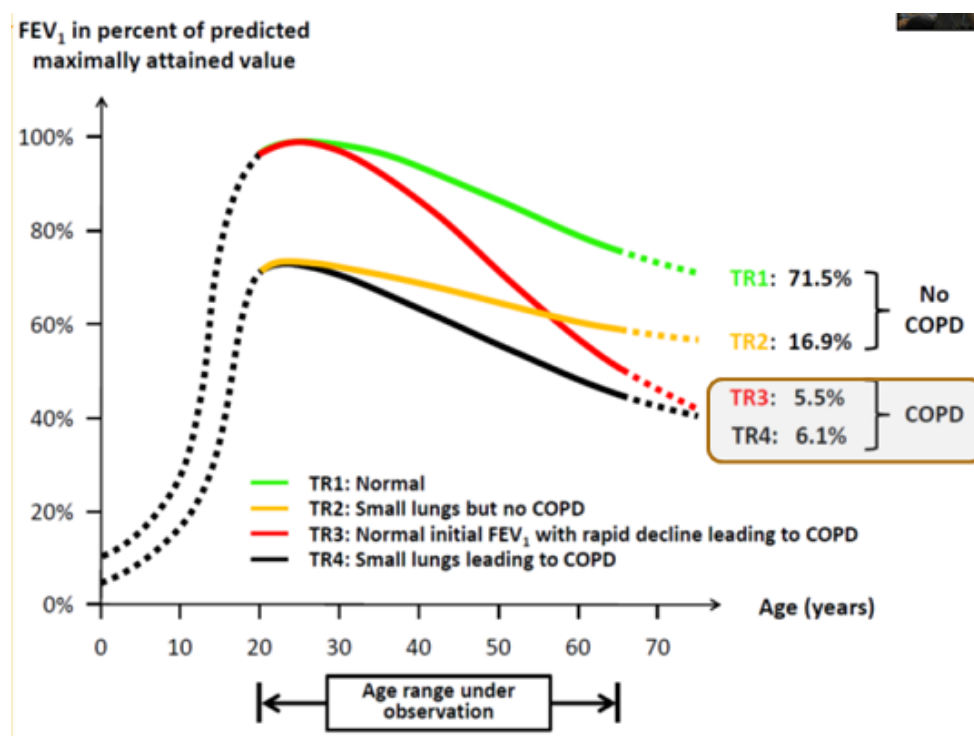
Figure 2 The 1977 Peto-fletcher curve demonstrating the risks of lung function decline in men who smoke⁽²⁾



The reality of the development and natural history of COPD is more complex than that described above. As discussed in section 1.3, there are multiple contributory factors to the development of obstructive airflow limitation. Peak lung function is attained by early adulthood and is an important factor for the development of COPD in later life, along

with the rate of decline of FEV₁. In healthy lungs the rate of change of FEV₁ is around -20ml/year.⁽²⁰⁾ Lange *et al* describe four broad trajectories of lung function dependent on these parameters (Figure 3). In people who achieve their predicted peak FEV₁ in early life most will have a slow decline in FEV₁ and will not develop COPD. A small percentage will have a rapid decline in lung function leading to COPD. A similar trend is seen in patients who do not achieve their peak predicted lung function in younger life, although the relative loss of FEV₁ to COPD in this group is smaller (Figure 3).⁽¹⁹⁶⁾ Even in COPD diagnosed patients, not all have sustained or accelerated deterioration in their FEV₁. In one study of 2163 patients 31% had a normal decline in FEV₁ (-20 to 40ml/year), 23% (+20 to -20ml/year) and 8% (>+20ml/year).⁽¹⁹⁷⁾ This study also showed that milder (GOLD 2) disease had more rapid decline than more severe (GOLD 4) disease, a finding also seen in the BODE follow up cohort.^(197, 198) This is perhaps unsurprising – in milder disease there is more ‘potential’ lung function decline and by the time severe disease occurs this lung function has already been lost.

Figure 3. Lung function trajectories leading to COPD as described by Lange *et al*. TR1&3 had baseline FEV₁ of >79% predicted, with TR2&4 having baseline FEV₁ <80% predicted. At the conclusion of the study TR3&4 had COPD. Dotted lines represent hypothetical trajectories.



Whilst conceptually useful, the reality is that patients do not fit neatly into one of these groups; there is significant heterogeneity and spread between patients' individual

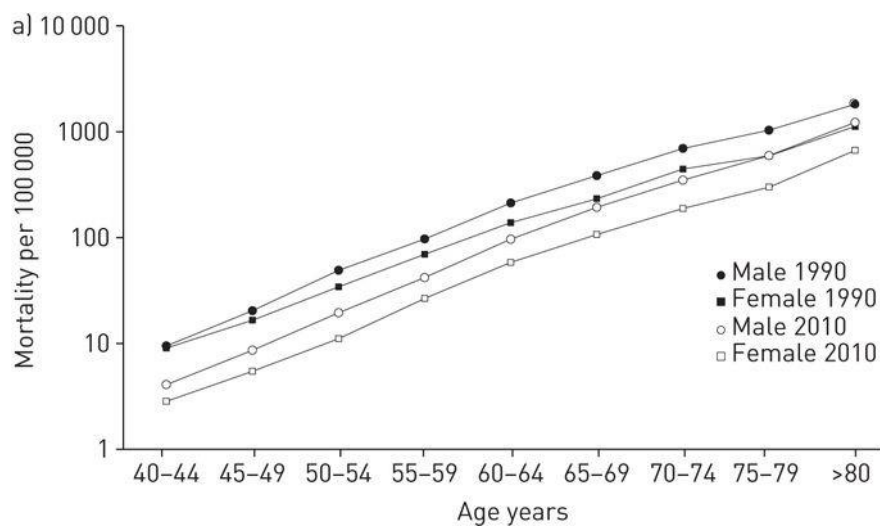
disease trajectories and these curves describe populations rather than individuals. Continued smoking increases the rate of decline of FEV₁ and is associated with increased hospitalisations and mortality.^(199, 200) Pharmacological treatments for COPD can increase absolute lung function values but the UPLIFT, TORCH and SUMMIT trials do not appear to have a large effect on the rate of change of lung function over the longer term.⁽²⁰¹⁻²⁰³⁾ Health related quality of life in COPD also deteriorates over time. This occurs in a similar manner to FEV₁, but decline it is independent of lung function. Whilst smokers tend to have worse overall quality of life, smoking does not affect the rate of change of quality of life in COPD.^(204, 205) Quality of life in COPD will be discussed in more detail in chapter 2.

The course of patients with COPD may also be punctuated with exacerbations, sometimes requiring hospitalisation, which can worsen both lung function (exacerbations are also more common in patients with quickly declining lung function) and quality of life.^{(199) (206)} Exacerbations will be discussed further in section 1.9.

1.6.2 Mortality

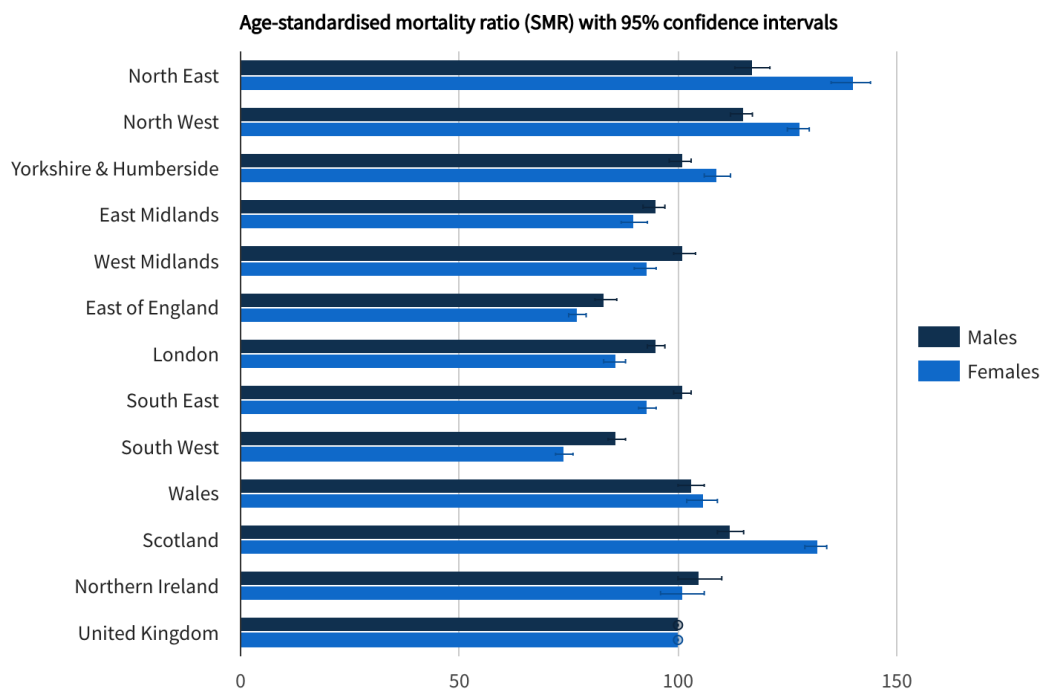
Mortality in COPD is difficult to accurately quantify and is likely to be underestimated due to underdiagnoses in the missing millions. The World Health Organisation (WHO) attributed around 3.17million (5% of global) deaths to COPD in 2015.⁽⁶⁾ COPD is predicted to become the 4th leading cause of death worldwide by 2030, with poorer countries having the highest burden.^(6, 207, 208) The worldwide adjusted mortality rate for COPD has fallen over the last 30 years (Figure 4), although the relative rate of decline is low compared to non-COPD all-cause mortality. COPD mortality between 1990-2010 fell by 5.5%, compared to an all-cause reduction by 17%.⁽²⁰⁸⁾

Figure 4. Worldwide COPD mortality rates 1990-2010 by age.⁽²⁰⁸⁾



In the UK, there is excess mortality when compared to other European countries (Age standardised mortality rate: UK= 58.8; EU28= 34.9 deaths per 100,000).⁽²⁰⁹⁾ There is geographical variation in the prevalence and mortality from the disease too. The North East and North West of England and Scotland have the highest COPD prevalence and mortality in the UK (Figure 5). North East COPD prevalence is nearly 1000 people per 100,000 higher than the South East. Reflecting the worldwide picture, COPD diagnosis in the UK has a strong association with living standards and deprivation.⁽²¹⁰⁾

Figure 5. COPD mortality ratios by UK region, male and female 2008-12.⁽²¹⁰⁾



Prediction of outcome (including hospital mortality) in patients with COPD who develop decompensated respiratory failure during exacerbation, and who require assisted ventilation, is the main focus of this thesis and will be discussed further in Chapter 3.

1.7 Treatment of stable disease

The primary goals of treatment in COPD are to minimise disease progression, improve symptoms, maximise quality of life, reduce exacerbation frequency and improve survival. All of this should be performed with ongoing patient education to maximise their understanding and allow informed decisions to be made by them. A broad overview of COPD treatments is described below.

Smoking cessation is the primary and most important step in disease modification. In the UK around 1/3 patients hospitalised with COPD are current smokers, and of those only 67.1% are offered smoking cessation pharmacotherapy, with a poor uptake in those offered (25.7%).⁽²¹¹⁾ Smoking cessation is associated with a reduction in the rate of decline of lung function, fewer exacerbations and lower mortality.^(20, 200, 212)

Vaccination against Influenza reduces exacerbation frequency, hospitalisations, outpatient department visits and all-cause mortality with the most pronounced benefit

in the older (≥ 65 year old) COPD population.⁽²¹³⁻²¹⁵⁾ Similarly, Pneumococcal vaccination reduces both exacerbation and pneumonia frequency.⁽²¹⁶⁾

Pulmonary rehabilitation is effective at improving quality of life, dyspnoea, exercise capacity, reducing fatigue and it improves perception of control over the disease.⁽²¹⁷⁾

Unfortunately, access remains a problem. There are prolonged waiting times and under recognition of the need to refer patients to the program (at least 44% of patients do not get referred following hospitalisation).^(218, 219) Even when in pulmonary rehabilitation, only 62% of patients complete the program.⁽²¹⁸⁾

Anxiety and depression is common in COPD and is associated with adverse outcomes.^(220, 221) Treatments such as cognitive behavioural therapy are effective,⁽²²²⁾ and whilst use of pharmacotherapy (such as Selective Serotonin Reuptake Inhibitors (SSRI)/Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)) is commonplace, there is little evidence that they are effective in improving either depressive or anxiety related symptoms in COPD.^(223, 224) Pharmacotherapies have additionally been associated with small increases in respiratory morbidity and mortality in one large observational study.⁽²²⁵⁾

The mainstay of pharmacological treatment for COPD is with inhaled bronchodilators and corticosteroids. The two primary classes of bronchodilator used in COPD are Long-Acting-Muscarinic-Antagonists (LAMA) and Long-Acting-Beta-2-Agonists (LABA), which must be given on a regular basis to maintain efficacy.⁽¹⁾ There are various preparations of these available. They are often prescribed in combination, with or without inhaled corticosteroid (ICS) agents. Inhaled medications can improve lung function, reduce exacerbation frequency and hospitalisations, improve health related quality of life, reduce dyspnoea, and lower mortality.^(1, 201-203, 226, 227) There is, however, a significantly increased risk of pneumonia associated with the use of inhaled corticosteroids such as Fluticasone or Budesonide.^(202, 227-229) In addition to inhaled medications oral macrolide therapy (primarily Azithromycin), oral mucolytic agents, and phosphodiesterase-4 inhibitors (PDE4) may improve exacerbation frequency and quality of life in patients with COPD; PDE4's also have a positive effect on lung function.⁽²³⁰⁻²³²⁾

Cor Pulmonale occurs when pulmonary vascular resistance increases, usually in response to chronic hypoxaemia or destruction of the pulmonary vascular bed by emphysema, resulting in chronic pulmonary arterial hypertension (most frequently caused by COPD,

but occurring in other respiratory disorders too). This causes impairment and dilatation of the right side of the heart, with resultant symptoms and signs of right heart failure (raised venous pressures, parasternal heave, loud P2, peripheral oedema, dyspnoea, fatigue).⁽¹⁹³⁾ When this occurs recommended treatment is with oxygen if severely hypoxaemic and, where patients have peripheral oedema, diuresis.⁽¹⁸²⁾ Long term oxygen therapy (LTOT) works to counteract chronic hypoxaemia in Cor Pulmonale, and can result in a partial reversal of the pulmonary hypertension by reducing pulmonary vascular bed resistance.⁽²³³⁾ In patients with chronic hypoxaemia (with or without Cor Pulmonale) LTOT reduces work of breathing, improves exercise tolerance, improves mental state and reduces mortality.⁽²³⁴⁾ In those without Cor Pulmonale, it helps delay onset of this.⁽²³³⁾ For treatment with oxygen to have any substantial effect, it should be worn for ≥ 15 hours a day – the longer worn, the better the effect.^(235, 236) Treatment is often recommended overnight to minimise excess desaturation during REM sleep and for the ease of patients.⁽²³⁴⁾

Lung Volume Reduction Surgery (LVRS), as well as other lung volume reduction methods such as endobronchial valves, improves elastic recoil, respiratory muscle function, airflow limitation, and dynamic hyperinflation in COPD. This leads to improvement in exercise capacity and reduces exacerbation frequency, but is only viable in selected groups of patients with COPD.^(237, 238) COPD is the most common reason for lung transplantation internationally, with double lung transplantation resulting in better survival than single.^(239, 240)

1.7.1 Home ventilation

Acute assisted ventilation – primarily non-invasive ventilation (NIV) – for exacerbations of COPD requiring admission to hospital, and outcome following these episodes is the main focus of this thesis and will be discussed in more depth in 1.10.2. However, home ventilation is often used as a treatment for stable COPD and is discussed here.

Costello *et al* described that patients demonstrating reversible hypercapnia had similar outcomes to normocapnic patients, but that those with persistent hypercapnia had significantly higher mortality, suggesting a group in which intervention could be targeted toward.⁽²⁴¹⁾ Patients with chronic respiratory failure may benefit from long term domiciliary NIV by means of reduction in primary care attendances and hospital

admissions, improvement in blood gases, and improvement in health related quality of life.⁽²⁴²⁻²⁴⁴⁾ Whilst the HOT-HMV trial demonstrated improvement in time to readmission or death at 1 year, despite improvements in arterial blood gas tensions and quality of life, the RESCUE trial did not.^(244, 245) The selection criteria in HOT-HMV were stricter, including only patients with evidence of ongoing persistent hypercapnia 2-4 weeks following correction of respiratory acidaemia and when weaned from NIV; the patient group Costello *et al* had identified as having the worst outcome. Köhnlein *et al* similarly demonstrated significant improvement in mortality (12% at one year) for hypercapnic COPD patients treated with NIV compared to usual care (33% at one year) in a prospective multicentre RCT.⁽²⁴⁶⁾ In a retrospective long term follow up of patients with COPD who were on home ventilation around 25% had died by one year, with a median survival of 2.7 years; similar to that seen in the fourth quartile of the BODE index.⁽²⁴⁷⁾ Outcomes were worse where ventilation was commenced in patients aged >60 or in those set up following an acute admission.

The benefits of home ventilation are probably limited to a selected cohort of patients with more severe COPD who have persistent hypercapnia. Whilst home ventilation is likely to benefit such patients, consideration of transplantation referral (where appropriate), involvement of specialist palliative care services and the undertaking of advance care planning should probably be performed when commencing HMV.

1.8 Multimorbidity

Comorbidity is traditionally thought of as the presence of a separate disease or condition in addition to the primary disease of interest.⁽²⁴⁸⁾ This definition can be complicated when the comorbid disease may have occurred as a consequence of the primary disease, such as in the development of Cor Pulmonale (described in section 1.7). In patients with multiple medical conditions the term multimorbidity is perhaps a better term as symptom burden, quality of life and prognoses are contributed to by all conditions and does not assume a 'dominant' disease. COPD shares common risk factors with a number of diseases, particularly cardiovascular, such as smoking and ageing, but systemic inflammation observed within COPD may itself contribute to the development

of multimorbid conditions.⁽²⁴⁹⁾ The presence of COPD does not, of course, mean that it is the cause of all symptoms a patient suffers.

1.8.1 Respiratory disease

There is a strong association between asthma and COPD diagnosis (discussed in more detail in sections 1.3.2.7 and 1.5.4), with a UK primary care cohort of >38,000 patients revealing 34% of patients having been diagnosed with asthma at the diagnosis of COPD (albeit that some 'asthma' may have been misdiagnosed COPD).⁽¹⁹⁴⁾ Similar overlap is seen with bronchiectasis, with 29% of patients with COPD having evidence of bronchiectatic change on high resolution CT, and an increasing recognition of a COPD-Bronchiectasis overlap syndrome phenotype.^(250, 251) Patients with COPD also have significantly increased risk of thoracic malignancy^(1, 252-254) and respiratory infections including both pneumonia and non-tuberculous mycobacterial disease.^(253, 255, 256)

1.8.2 Cardiovascular disease

COPD and cardiovascular illness share combined risk factors and, perhaps unsurprisingly, there is extensively reported comorbid cardiovascular disease in patients with COPD.⁽¹⁾ The range of prevalence of all cardiovascular disease is reported to be between 19-70% in patients with COPD, with an overall RR of 3.81 that of non-COPD patients.^(255, 257, 258) Heart failure appears to be a particular risk with an RR of 4.09 and overall prevalence of 31-54%.^(258, 259) Zvezdin et al reported in 2009 that heart failure was the primary cause of death in COPD, accounting for 37.2% of cases analysed at post-mortem.⁽²⁶⁰⁾ Arrhythmia has also been reported with a wide range of both relative risk (1.2 to 5.6) and prevalence (0.3-29%).⁽²⁵⁸⁾ Atrial Fibrillation (AF) in COPD is associated with worse quality of life, high levels of heart failure and higher all-cause and cardiovascular mortality in both univariate analysis and multivariate models.^(161, 261) Whilst the risk of coronary heart disease is higher in COPD than non-COPD, myocardial infarction (MI) itself is less clear. Rodriguez et al showed no increased risk of MI in a UK cohort compared to the non-COPD population,⁽²⁵⁴⁾ whilst others have demonstrated both increased prevalence of MI (RR 1.61) and death from MI (RR 1.51).⁽²⁵⁹⁾ Once MI occurs, it appears to have a significant effect on COPD mortality. One large study of patients undergoing

percutaneous intervention for myocardial infarction demonstrated a significantly ($p<0.001$) increased unadjusted mortality for COPD vs. non-COPD patients (27% vs. 9%) over the three years following treatment.⁽²⁶²⁾ Rates of other cardiovascular diseases such as hypertension,^(253, 257) peripheral vascular disease^(253, 255) and Stroke⁽²⁵⁸⁾ are more common in COPD.

1.8.3 Bone mineral density and fractures

COPD is associated with significantly increased risk of reduced bone mineral density, osteopenia, osteoporosis and osteoporotic fracture.^(255, 263-266) The use of systemic glucocorticoids⁽²⁶⁵⁾ and long term, high dose (>4yrs of 1000micrograms/daily fluticasone equivalent) inhaled glucocorticoids⁽²⁶⁷⁾ are contributing factors to development of these conditions, although COPD itself is also a driver of disease. In a Brazilian cohort of patients with COPD, 87.7% of the total population and 51% of non-steroid using patients with COPD had decreased bone mineral density, with 94.7% also being either vitamin D insufficient or deficient.⁽²⁶⁶⁾ Patients with COPD have significantly lower bone mineral density in the spine and femur than control groups of healthy patients, and importantly, non-COPD smokers.⁽²⁶³⁾

The risk of either osteopenia or osteoporosis in obstructive lung disease is higher in females and is particularly high risk in >65 year old patients; broadly in keeping with non-COPD patients.^(255, 268) In a large UK cohort, the high rates of major osteoporotic or hip fracture in patients with COPD was attributed to high use of oral corticosteroids, BMI and smoking. Despite the freely available use of accurate risk prediction models for osteoporotic fracture, the same study found only 1.3% of UK patients with COPD have these performed.⁽²⁶⁴⁾

1.8.4 Depression and anxiety

COPD is associated with a high prevalence of both clinically relevant anxiety and depression. A number of studies show prevalence as high as 50% in patients with COPD.⁽²⁶⁹⁻²⁷¹⁾ Where depression and/or anxiety is present it can contribute to worsening dyspnoea, lower quality of life, increased exacerbation rates and increased hospitalisation and subsequent readmission.⁽²⁷⁰⁻²⁷⁴⁾ Symptoms of dyspnoea worsen,

even in early stages of COPD, if patients have coexistent anxiety and/or depression. Their presence can create a vicious cycle of COPD worsening anxiety & depression and these in turn then worsening COPD symptoms.⁽²⁷²⁾ Unsurprisingly the more severe the COPD, the higher the prevalence of clinically significant anxiety and depression.⁽²⁶⁹⁾ This is of particular importance as emotional status of one of the most important determinants of patients' quality of life.⁽²⁷⁵⁾

1.8.5 Other diseases

A number of other co-morbidities are common in COPD (Table 4), including Diabetes,^(194, 257) Chronic pain,⁽¹⁹⁴⁾ Cataracts & Glaucoma,⁽²⁵⁵⁾ and Gastroesophageal reflux⁽²⁷⁶⁾ amongst others.

Table 4. Rate per 10,000 and Relative Risk by major organ systems in COPD. (Source: Soriano et al, 2005)⁽²⁵⁵⁾

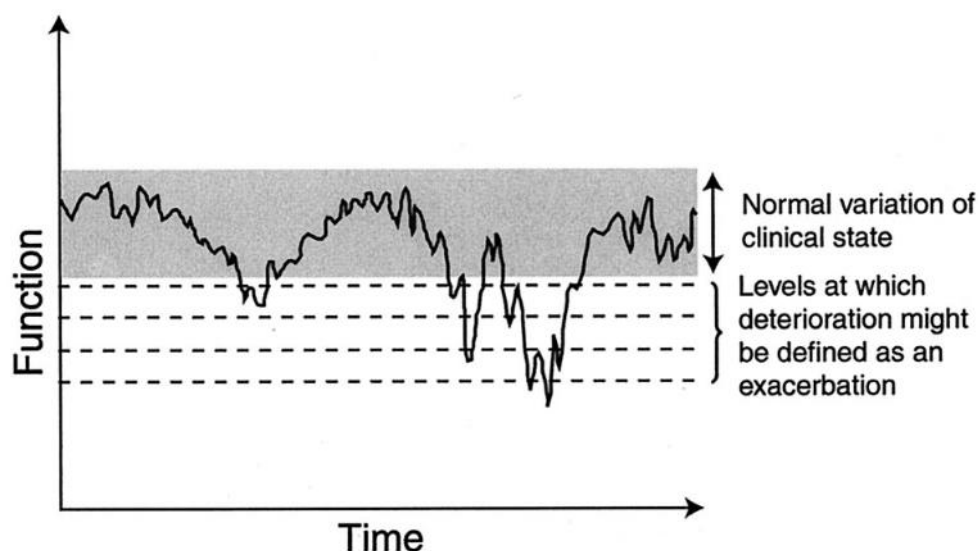
Disorders	COPD	RR (95% CI)
Blood and lymphatic system	277.8	1.74 (1.4–2.1)
Cardiac	2,256.3	4.01 (3.6–4.4)
Congenital, familial, and genetic	48.1	1.18 (0.8–1.8)
Ear and labyrinth	881.8	1.44 (1.3–1.6)
Endocrine	385.3	1.22 (1.1–1.4)
Eye	870.69	1.32 (1.2–1.5)
GI	2,756.5	1.69 (1.6–1.8)
General and administration site	2,252.6	1.75 (1.6–1.9)
Hepatobiliary	96.33	2.89 (1.9–4.3)
Immune system	481.6	1.78 (1.5–2.1)
Infections and infestations	3,923.6	2.13 (2.0–2.2)
Injury, poisoning	607.6	1.23 (1.1–1.4)
Metabolism/nutrition	485.3	1.66 (1.4–1.9)
Musculoskeletal and connective tissue	2,867.7	1.45 (1.4–1.5)
Neoplasms benign, malignant, and unspecified	385.3	1.09 (0.9–1.3)
Nervous system	1,207.8	1.48 (1.3–1.6)
Pregnancy, puerperium, and perinatal	11.1	0.43 (0.2–0.9)
Psychiatric	1,063.3	1.98 (1.8–2.2)
Renal and urinary	566.8	1.53 (1.3–1.7)
Reproductive system and breast	377.9	1.17 (1.1–1.4)
Respiratory, thoracic, and mediastinal	2,897.3	3.14 (2.9–3.4)
Skin and subcutaneous tissue	1,726.5	1.57 (1.4–1.7)
Social circumstances	292.7	1.80 (1.5–2.2)
Surgical and medical	2,315.6	1.51 (1.4–1.6)
Vascular	926.2	1.41 (1.3–1.6)

1.9 Exacerbations of COPD

1.9.1 Definition of exacerbation

There is no widely or internationally accepted and agreed definition of what an exacerbation of COPD (ECOPD) is. This is reflected in much of the literature, with varying definitions in different papers. The GOLD guide is particularly vague in its own definition: 'periods of acute worsening of respiratory symptoms'.⁽¹⁾ One of the difficulties in defining exacerbation is agreeing the 'cut off' in which worsening of symptoms should be regarded as abnormal, as patients with COPD tend to have daily variation in symptoms (Figure 6).

Figure 6. The day to day variability of a patient with COPD and levels at which exacerbation could be defined. From Rodriguez-Roisin, 2000⁽²⁷⁷⁾



In 2000 a consensus statement was produced which has been adapted by NICE in their definition of COPD exacerbation: *"a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD"*.^(182, 277)

The most commonly reported symptoms during exacerbation are worsening dyspnoea, increased sputum purulence and/or volume and increasing cough and/or wheeze.^(1, 278)

Other symptoms, however, are common. These frequently include fatigue, reduced exercise tolerance, general malaise, worsening of peripheral oedema, confusion and inability to manage activities of daily living within the home.^(182, 279) Given there is no internationally agreed definition of exacerbation there are differences in the

delineations between exacerbation severity. Most clinical trials, plus NICE and GOLD split patients into three broad categories although other severity grades exist (Table 5). The EXACT scale uses a 27 item symptom diary to assess various aspects of a patients' health status out of 100. This is then used to determine exacerbation and severity, but is not widely used in clinical practice and is more complicated than those outlined in Table 5.^(280, 281)

Table 5. Primary COPD Exacerbation severity categories.

Severity	GOLD Guide ⁽¹⁾	Burge & Wedzicha ⁽²⁸²⁾	NICE ⁽¹⁸²⁾	Rodriguez Consensus ⁽²⁷⁷⁾
Mild	Treated with short acting bronchodilators only	An exacerbation treated with antibiotics but no systemic corticosteroid. If no blood gases are available the absence of respiratory failure is assumed	The person has an increased need for medication, which they can manage in their own normal environment	The patient has an increased need for medication, which he/she can manage in own normal environment
Moderate	Treated with short acting bronchodilators plus antibiotics and/or oral corticosteroids	An exacerbation treated with parenteral corticosteroids with or without an antibiotic. If no blood gases are available the absence of respiratory failure is assumed	The person has a sustained worsening of respiratory status that requires treatment with systemic corticosteroids and/or antibiotics	The patient has an increased need for medication and feels the need to seek additional medical assistance
Severe	Patient required hospitalisation or visits the emergency department. May also be associated with respiratory failure.	Type 1 respiratory failure with hypoxaemia but no carbon dioxide retention or acidosis; $P_{a,O_2} < 8$ kPa (60 mmHg) and $P_{a,CO_2} < 6$ kPa (45 mmHg)	The person experiences a rapid deterioration in respiratory status that requires hospitalisation.	The patient/caregiver recognises obvious and/or rapid deterioration in condition, requiring hospitalisation.

Severity	GOLD Guide ⁽¹⁾	Burge & Wedzicha ⁽²⁸²⁾	NICE ⁽¹⁸²⁾	Rodriguez Consensus ⁽²⁷⁷⁾
Very Severe		Type 2 respiratory failure, compensated with hypoxia, carbon dioxide retention but no acidosis; $P_{a,O_2} < 8$ kPa (60 mmHg), $P_{a,CO_2} > 6$ kPa (45 mmHg) and hydrogen ion concentration < 44 nM ($pH > 7.35$)		
Life Threatening		Type 2 respiratory failure, decompensated with acidosis and carbon dioxide retention; $P_{a,CO_2} > 6$ kPa (45 mmHg) and hydrogen ion concentration > 44 nM ($pH < 7.35$)		

1.9.2 Aetiology of exacerbations

The majority of COPD exacerbations are caused by either viruses, bacteria or a combination of both. Papi et al found that 78% of exacerbations were infective in nature, with a slight (54.7%) preponderance for bacterial infection, although a quarter of exacerbations were co-infective with both bacterial and viral triggers.⁽²⁸³⁾ When coinfection occurs, the severity of infection is worse and is more likely to result in hospitalisation.⁽²⁸³⁾ The predominant bacterial causes of exacerbation are *Haemophilus Influenzae*, *Moraxella Catarrhalis* and *Streptococcus Pneumoniae*; however other common species are *Pseudomonas Aeruginosa*, *Enterobacteria* species and *Staphylococcus Aureus*.⁽²⁸³⁻²⁸⁵⁾ When patients are colonised with lower airway bacteria if the strain within a species changes this is a common and important trigger for exacerbation.⁽²⁸⁵⁾

The most common virus in exacerbations is rhinovirus, accounting for 58% of viral isolates.⁽²⁸⁶⁾ Other common viruses are Influenza A/B, Respiratory Syncytial Virus (RSV), Coronavirus, Adenovirus, Picornavirus and Parainfluenza.⁽²⁸⁶⁻²⁸⁹⁾

Non-infective causes of exacerbation include cold and wintery weather (which also tends to coincide with the viral season), as well as air pollution. Air pollution is thought to cause up to 9% of all hospital attendances for ECOPD.^(290, 291) Multimorbid conditions are also associated with exacerbations of COPD. Heart failure, atrial fibrillation, depression, poor vision/blindness, gastroesophageal reflux, osteoporosis, prostatic dysfunction and peripheral vascular disease are all non-respiratory conditions significantly associated with increased exacerbations. Pulmonary cancers, along with other respiratory conditions such as asthma or bronchiectasis are, unsurprisingly, associated with increased exacerbation and respiratory symptoms.⁽²⁹²⁾ Although the majority of exacerbations are infective, in clinical practice the underlying causative factor is often unproven.

1.9.2.1 *Pneumonia in ECOPD*

Community acquired pneumonia is an acute illness in which there is an alveolar inflammation with pus build up. Pneumonia has a broad clinical presentation including tachypnoea, dyspnoea, cough, sputum, fever, pleural pain, malaise and can result in sepsis. Pneumonia classically causes chest x-ray shadowing, although a considerable

amount of community acquired pneumonia is diagnosed in primary care and without radiology.⁽²⁹³⁾

Some contention exists as to whether pneumonia constitutes ECOPD or is a separate entity. Non-pneumonic exacerbations and pneumonia have similar clinical presentation and can therefore be challenging to separate from each other. Admission chest x-rays in patients ultimately diagnosed with pneumonia are negative in ~21% of patients, but 55% of those go on to develop infiltrates consolidation on follow up x-ray in the 48 hours following admission.⁽²⁹⁴⁾ Additionally, 27% of 'non-pneumonic' chest radiographs have evidence of consolidation on CT scan.⁽²⁹⁵⁾

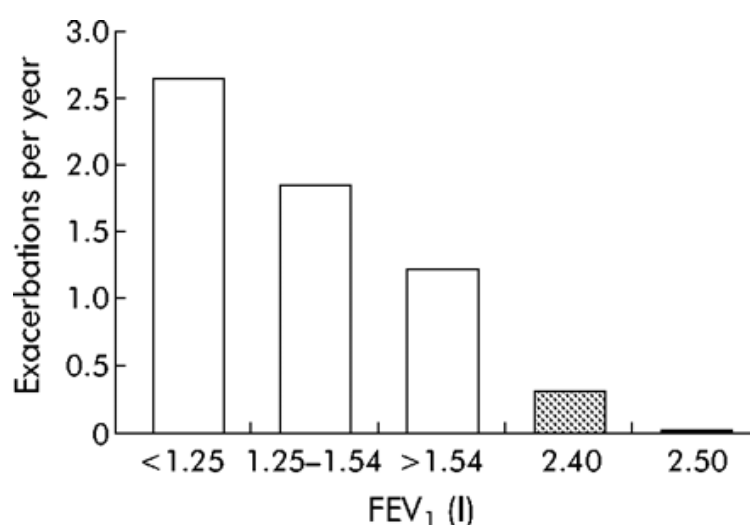
The rate of development of pneumonia in patients with COPD is significantly higher than non-COPD patients.^(253, 296) Reported incidence in the literature range from 8% to over 36% of exacerbations.^(258, 297) In the UK, the rate of pneumonia in hospitalised ECOPD has been falling over time in observational studies.^(161, 162, 298) but remains the second most common reason for readmission after discharge with COPD both at 30- and 90- days.⁽²⁹⁹⁾ Risks for the development of pneumonia in COPD include older age^(296, 297, 300, 301), more severe disease,^(297, 300, 302) use of inhaled corticosteroid (particularly high dose fluticasone),⁽²²⁸⁾ and in patients with multimorbidity.⁽²⁹⁷⁾ Where pneumonia occurs, it tends to be more severe in patients with COPD than non-COPD patients,^(301, 303) and is associated with increased mortality.^(161, 253, 297, 303) In a study of post mortem analysis, 27.9% of COPD deaths were attributed to pneumonia.⁽²⁶⁰⁾

1.9.3 Prevalence and frequency

The true prevalence of exacerbations is likely to be underestimated. Around half of all exacerbations recorded on symptom cards are not reported to healthcare professionals, even within research studies examining them.^(206, 286, 304) It is therefore likely, especially given self-medication with rescue packs, that exacerbations are even less frequently reported to healthcare professionals in real-life clinical practice. Nonetheless, COPD exacerbations represent the second most common reason for hospital admission, and 5th biggest cause of death in England.⁽⁵⁾

Exacerbations frequency increases in more severe disease (Figure 7) and tend to be clustered in time with 27% of exacerbations having a second exacerbation within 2 months.^(282, 289, 305, 306)

Figure 7. Mean incidence of exacerbations in relation to FEV₁. Data compiled from the placebo arm of multiple studies.⁽²⁸²⁾



COPD exacerbations and hospitalisations occur more frequently in winter months than summer months.⁽³⁰⁶⁻³⁰⁸⁾ Pneumonia is also more common, and exacerbations have a longer recovery period than in the summer months.^(307, 309) Within individual patients the proportion of individual/single-event versus clustered exacerbations does not change with season.⁽³⁰⁶⁾

1.9.4 Treatment of exacerbation

The mainstay of treatment for exacerbations of COPD is short acting bronchodilators, systemic oral corticosteroids and antibiotics. Bronchodilators can be administered effectively via nebuliser or handheld inhalers. When nebulisers are used compressed air should be used to drive them, and return to the patient's normal inhaler device is recommended as soon as is practicable.⁽¹⁸²⁾ Corticosteroids are recommended by NICE, the ERS and ATS. These should be given as a short oral course, normally in the form of 30mg Prednisolone daily. NICE recommends a 5 day course, whereas the joint ATS/ERS guidance is less prescriptive, suggesting <14 days treatment.^(182, 310) Corticosteroid use improves symptoms, lung function and reduces hospitalisation.⁽³¹⁰⁾ Antibiotics are used where there is evidence of infection (such as raised inflammatory markers or worsening purulent sputum) and can help increase time between exacerbation. New and previous culture results and local sensitivity patterns should inform antimicrobial choice;

recurrent exacerbation leads to the use of more second line antibiotics such as Ciprofloxacin.^(182, 306, 310)

In hypoxic patients supplementary oxygen therapy may be required,⁽³¹¹⁾ although this should be used with caution (discussed further in section 1.10.1.3). Where sepsis occurs, prompt supportive treatment such as intravenous fluids and antibiotics is recommended and can improve mortality.⁽³¹²⁾ Where acute, or acute on chronic respiratory failure occurs, non-invasive ventilation (NIV) is recommended. Outcomes following exacerbations of COPD in which patients require NIV is the main focus of this thesis and respiratory failure will be discussed in more detail in the next section (1.10).

In clinical practice around 43% of patients experiencing exacerbation get both antibiotics and corticosteroids, with 38% receiving antibiotics alone and 19% corticosteroids alone.⁽³⁰⁸⁾ The majority of exacerbations are managed by patients themselves or by primary care providers.^(306, 308, 313) The decision to admit a patient to hospital for an exacerbation of COPD is multifactorial; to aid decisions on community or hospital care, NICE recommends consideration of various factors (Table 6).

Table 6. NICE recommended considerations for place of care in treatment of ECOPD⁽¹⁸²⁾

Factor	Treat at home	Treat in hospital
Able to cope at home	Yes	No
Breathlessness	Mild	Severe
General condition	Good	Poor/deteriorating
Level of activity	Good	Poor/confined to bed
Cyanosis	No	Yes
Worsening peripheral oedema	No	Yes
Level of consciousness	Normal	Impaired
Already receiving LTOT	No	Yes
Social circumstances	Good	Lives alone/not coping
Acute confusion	No	Yes
Rapid rate of onset	No	Yes
Significant multimorbidity (particularly cardiac disease and insulin-dependent diabetes)	No	Yes

Factor	Treat at home	Treat in hospital
SpO ₂ < 90%	No	Yes
Changes on chest radiograph	No	Present
Arterial pH	≥ 7.35	< 7.35
Arterial PaO ₂	≥ 7 kPa	< 7 kPa

Where possible, ‘hospital at home’ (H@H) programs are recommended for ECOPD.^(182, 310, 314) H@H programs provide hospital-level, specialist respiratory care, but delivered in the patients’ own home. These programs have been shown to be safe, effective, preferred by patients and cheaper to the healthcare provider, even with considerably simpler selection criteria than those outlined above.⁽³¹⁵⁾

1.10 Respiratory failure in exacerbations of COPD

1.10.1 Definition and prevalence

Measurement of arterial blood gas tensions is recommended in all patients admitted to hospital with an exacerbation of COPD and should include documentation of the fraction of inspired oxygen (FiO₂) at the time of the blood gas.⁽¹⁸²⁾ Respiratory acidaemia (synonymous with acute hypercapnic respiratory failure or acute type two respiratory failure) during exacerbations of COPD is conventionally defined as a potential of Hydrogen (pH) <7.35 and partial pressure of Carbon Dioxide PaCO₂ of either >6.0 or 6.5kPa. Current British Thoracic Society (BTS) guidelines⁽³¹⁶⁾ recommend the latter as the cut off for defining hypercapnic respiratory failure, although multiple studies have used 6.0kPa as this is the upper limit of normal PaCO₂ in healthy patients.^(193, 316-320) The occurrence of a pH <7.25 (in the presence of hypercapnia) represents severe acidaemia, and is sometimes used as a threshold for consideration of invasive mechanical ventilation (IMV). Co-existent hypoxaemia is often present, although this may be masked by the administration of oxygen therapy.⁽³¹⁶⁾

Development of respiratory acidaemia in COPD exacerbation is a signal of both severe underlying COPD and severe exacerbation (see section 1.9.1).⁽³¹⁸⁾ Respiratory acidaemia occurs in around 20% of patients presenting to hospital with exacerbation, and is associated with an inpatient mortality rate of 20-25%.^(318, 320, 321) Where respiratory

acidaemia occurs, around 1 in 5 patients quickly improve with medical therapy alone,⁽³²¹⁾ but many will require treatment with assisted ventilation - either invasively or non-invasively (Section 1.10.2).

The two main mechanisms leading to hypercapnic respiratory failure and acidosis are; 1) failure of the respiratory pump and 2) failure of the lungs ability to exchange gas.^(316, 322)

The respiratory pump comprises the chest wall and respiratory musculature, central nervous system controls (CNS) and associated peripheral nerves which connect the CNS to the respiratory muscles.^(322, 323) Very broadly 'failure of the lungs' leads to hypoxaemia, or type 1 respiratory failure, and can be caused by a number of diseases such as pneumonia, interstitial lung disease or emphysema. Failure of the respiratory pump results in alveolar hypoventilation, and therefore hypercapnia – type 2 respiratory failure. Both of these can exist within the same person, as is common in severe COPD.^(193, 322, 324)

1.10.1.1 Mechanisms of type 1 respiratory failure

Type 1 respiratory failure is generally caused by ventilation-perfusion mismatch (V/Q mismatch), increased right-to-left shunt, diffusion impairments or alveolar hypoventilation. Of these, V/Q mismatch is the most common. This occurs where ventilation is reduced to a normally perfused area of lung, if there is greater relative reduction in ventilation than in perfusion to a region of lung, or if there is reduction in perfusion to a normally ventilated area of lung. Diffusion impairments occur due to decreased capillary surface area, shortened transit time of blood through the alveolar capillaries, or increase the alveolar-capillary membrane thickness.^(322, 324) With the exception of right-to-left shunt, supplementary oxygen can often relatively quickly correct the hypoxaemia caused by these conditions.^(316, 324)

1.10.1.2 Mechanisms of type 2 respiratory failure

Failure of the respiratory pump leads to alveolar hypoventilation, with subsequent fall in PaO₂ and rise in PaCO₂.^(322, 324) In steady state, humans breathe out around the same amount of CO₂ that they produce (V_{CO2}) from respiration.^(322, 325) PaCO₂ is dependent on alveolar ventilation (V_A), V_{CO2} and a constant, k (=0.863)

$$\text{PaCO}_2 = k \times (\text{V}_{\text{CO}_2} / \text{V}_A)$$

V_A is calculated as minute volume (V_E) minus physiological dead space (V_{DS}). Minute volume is itself calculated by tidal volume (V_T) multiplied by respiratory frequency (f_R). Therefore

$$PaCO_2 = k (V_{CO_2} / (V_E - V_{DS}))$$

Or

$$PaCO_2 = k (V_{CO_2} / (V_T f_R - V_{DS}))$$

This demonstrates that an increase in V_{CO_2} or physiological dead space; or reductions in either respiratory frequency or tidal volume will result in increased $PaCO_2$. This, roughly, means that when alveolar ventilation is halved, $PaCO_2$ doubles.^(322, 324, 325)

The alveolar gas equation is also important when considering hypercapnia and hypoxaemia, as partial pressure of oxygen is related to the partial pressure of carbon dioxide. Carbon dioxide is highly diffusible across the alveolar membrane the alveolar gas equation assumes $P_{ACO_2} = PaCO_2$

$$PAO_2 = (F_iO_2 \times (P_{atm} - P_{H_2O})) - (P_{aCO_2} / R)$$

P_{atm} = barometric pressure (around 760mmHg at sea level) minus the P_{H_2O} partial pressure water pressure vapour (around 47mmHg). R = Respiratory exchange ratio (0.8).

Therefore, rises in CO_2 will result in reduction in partial pressure of oxygen and contribute to hypoxia.^(324, 326)

Respiratory pump failure leading to alveolar hypoventilation can be caused by 3 major mechanisms.

- 1) Reduction in central respiratory drive. This can be reduced by suppressant drugs, such as opioids or benzodiazepines (sometimes used to treat the sensation of dyspnoea in severe COPD⁽³²⁷⁾), barbiturates and anaesthesia; or intrinsic diseases of the medulla.
- 2) Defects of the chest wall. For example, the mechanical muscular disadvantage of hyperinflation plus diaphragmatic flattening is common in COPD.⁽³²⁸⁾
- 3) Respiratory muscles may easily fatigue despite a normal respiratory drive and chest wall. Airflow obstruction – which worsens during exacerbation – the

presence of dynamic hyperinflation (section 1.5.2.2.1), increased iPEEP, increased respiratory rate, and reduced inspiratory/expiratory times increase both the work of breathing and oxygen cost, leading to respiratory muscle fatigue.^(189, 322)

In clinical practice, most patients presenting with respiratory failure associated with exacerbations of COPD have a combination of factors leading to their respiratory failure.

Normal acid-base balance is maintained at a pH of between 7.35-7.45. This is maintained by both the lungs and kidneys. Carbon dioxide and water in the blood combine to produce carbonic acid which quickly dissociates into bicarbonate and hydrogen ions



In acute respiratory acidaemia, such as during exacerbations of COPD, the rapid occurrence of alveolar hypoventilation causes a rise in CO₂, which is itself acidic, and reduces the HCO₃⁻/CO₂ ratio, lowering blood pH. There is some increase in bicarbonate production to compensate, and the kidney will increase reabsorption of bicarbonate ions and excretion of H⁺ ions. Whilst sensitive to changes in pH, renal compensation of respiratory acidosis is slow (hours to days) compared to the sudden increase in CO₂ and acidosis can therefore persist.^(322, 324, 325, 329)

1.10.1.3 Oxygen therapy in ECOPD and respiratory failure

Oxygen therapy is frequently administered to patients with ECOPD when they are admitted to hospital. Oxygen is a treatment for hypoxia, not breathlessness – although it is often improperly used for this purpose.⁽³¹¹⁾ When oxygen is prescribed and administered for COPD, tailored target peripheral oxygen saturations should be set. Whilst there is debate about the most appropriate target saturation for patients, a level of 88-92% is often adopted in COPD to reduce the risk of oxygen induced hypercapnia.⁽³¹¹⁾

Oxygen causes hypercapnia in COPD via a number of mechanisms. V/Q matching is maintained in part by hypoxic pulmonary vasoconstriction (HPV), which ensures that perfusion is not maintained to under-ventilated regions of lung.^(311, 330) When

supplemental oxygen is provided the FiO_2 , and therefore P_{AO_2} , is increased even in under-ventilated areas of lung. This reverses HPV and increases blood flow to that unit of lung.^(311, 330, 331) Alveolar hypoventilation, and therefore high $\text{P}_{\text{A/aCO}_2}$, in that alveolar unit persists despite the increased blood flow and P_{AO_2} . The overall resultant effect is that whole lung V/Q mismatch increases, and less CO_2 is blown off.^(311, 331-333) Another cause of O_2 induced hypercapnia is the loss of hypoxic ventilatory drive.⁽³¹¹⁾ When given high flow oxygen there is initially a reduction in tidal volume and respiratory rate which worsens alveolar hypoventilation in COPD. The effect of this is higher in patients who retain CO_2 although in both retainers and non-retainers is relatively transient, partially correcting to ~93% of predicted within 20 minutes or so.^(332, 333)

Hypoxaemia drives increased ventilation, therefore correcting this with supplemental oxygen causes a decrease in ventilation, which is inversely proportional to PaCO_2 (see section 1.10.1.2). This effect is primarily seen in severe hypoxia, where $\text{PaO}_2 < 8.0\text{kPa}$, and is mostly attenuated once PaO_2 rises above 13kPa . Therefore, any PaCO_2 rises past this PaO_2 are not due to loss of hypoxic drive, and are more likely due to loss of HPV.^(311, 332, 334) Other contributing causes include the Haldane effect (where oxygenated blood has less affinity for carbon dioxide, leading to higher PaCO_2),⁽³¹¹⁾ absorption atelectasis (where mechanically unstable alveoli distal to airway obstruction collapse due to increased absorption of O_2 in high P_{AO_2} , worsening V/Q mismatch further still)⁽³³⁵⁾ and increased viscosity of air with higher oxygen concentrations.

Liberal use of oxygen has, therefore, been implicated in the clinical presentation of respiratory acidosis in patients with ECOPD. Since the 1960s it has been clear that patient outcomes are better with the use of controlled rather than uncontrolled oxygen.⁽³³⁶⁾ Conservative oxygen administration is associated with lower rates of requirement for ventilatory support (22% vs. 9%; $p < 0.001$) and mortality (11.1% vs. 7.2%; $p < 0.001$) in hospital.⁽³¹⁸⁾ Austin *et al* demonstrated this benefit extends to prehospital care. Where paramedics titrated oxygen treatment to target SpO_2 88-92% rather than 'usual care' of high flow (8-10L/min) there was reduction in COPD mortality from 9% to 2%, higher average pH, and reduction in hypercapnia.⁽³³⁷⁾ Aiming for a P_{aO_2} under 10kPa is associated with less hypercapnia, and consequently less acidosis, and using lower target SpO_2 (such as 88-92%) in all patients with COPD is safe.^(321, 338) This is particularly pertinent given that in the national confidential enquiry into patient

outcome and death 2017, which examined NIV use across the UK reported that oxygen toxicity was implicated in 26.9% of cases, and inappropriate oxygen therapy was delivered to 32.3% of patients.⁽³³⁹⁾ These data add credence to the use of more conservative oxygen saturation targets, such as the 88-92% target, for all patients with COPD.

1.10.1.4 Sleep and breathing

Patients with COPD are at higher risk of respiratory failure overnight. Of patients with daytime hypercapnia 43% have worsening hypercapnia overnight.⁽³⁴⁰⁾ During sleep there is loss of the wakefulness drive to breathe, an increase in airway resistance (and therefore obstruction), and hypotonia of the respiratory muscles. In the supine position this exerts greater than normal reliance on the diaphragm which, as discussed in 1.5.2.2, is at a mechanical disadvantage in patients with hyperinflation. These result in worsening hypoventilation (which is more exaggerated than that of the general population), with associated increase in PaCO₂ and fall in PaO₂. Rapid Eye Movement (REM) sleep is the phase of sleep during which these changes are most pronounced as there is almost total reliance on the diaphragm, due to suppression of intercostal and accessory muscles.^(341, 342) Increases in PaCO₂ above baseline are most pronounced in patients with high daytime PaCO₂, increased BMI, higher apnoea-hypopnoea index and the more time spent in REM sleep.⁽³⁴⁰⁾ The long term consequences of nocturnal hypoventilation and hypercapnia upon patient outcomes are currently unclear.

1.10.2 Assisted ventilation

When respiratory acidaemia occurs, it can be treated by either non-invasive ventilation or invasive mechanical ventilation. Non-invasive ventilation (NIV) is the provision of bi-level positive pressure ventilation normally using a face mask, or similar, via the patients' upper airway.⁽³⁴³⁾ NIV is distinct from IMV in which the patients' upper airway is bypassed by an endotracheal tube, tracheostomy or laryngeal mask. When providing NIV there are two primary modes of delivery of ventilatory support: pressure-targeted or volume-targeted. In volume-targeted ventilation the V_T to be delivered by the ventilator and the inspiratory time to deliver this volume. The ventilator then generates the required pressure to deliver the predetermined tidal volume.

In pressure-targeted ventilation the maximal and minimal pressures the ventilator should deliver are mandated (see section 1.10.2.1 & 1.10.2.2). This method has advantages over volume-targeted ventilation as it compensates for leak and reduces sudden changes in pressure – making it more comfortable for the patient. Additionally, the constant expiratory pressure expels CO₂ by reducing rebreathing. Pressure-targeted ventilation can be delivered in spontaneous mode (S) in which the ventilator is entirely triggered by a patients' breath; spontaneous-timed mode (S/T) in which a backup ventilatory rate is programmed into the ventilator; or pressure-controlled ventilation mode (PCV) in which the length of inspiratory support is also programmed. S/T ventilation is the most common form of ventilation used in ECOPD with respiratory failure; likely due to patient comfort, the safety of a backup rate, and ease of configuration of the ventilator.⁽³¹⁶⁾

1.10.2.1 Expiratory positive airway pressure

Expiratory positive airway pressure (EPAP) is the provision of a positive pressure throughout expiration. It is similar in many respects to positive end expiratory pressure (PEEP) on an invasive ventilator. EPAP assists in overcoming iPEEP and therefore reduces inspiratory muscle work. It additionally recruits under-ventilated areas of lung, thus generally improving oxygenation.⁽³⁴³⁻³⁴⁶⁾ Continuous positive airway pressure (CPAP) devices essentially provide EPAP alone (but throughout the respiratory cycle) and are most often used in clinical practice for medical conditions such as Pulmonary Oedema. CPAP does not, however, provide inspiratory ventilatory support and is therefore distinct from NIV.

1.10.2.2 Inspiratory positive airway pressure

Inspiratory positive airway pressure (IPAP) is a second, higher level of pressure support provided in addition to EPAP. IPAP provides inspiratory ventilatory support and assists by allowing relative rest of the inspiratory muscles during inspiration, thus reducing work of breathing and improving physiological parameters.^(343, 345-349)

1.10.3 NIV in exacerbations of COPD

In patients who have respiratory acidosis due to an exacerbation of COPD, NIV is long established as the gold standard treatment to provide in parallel with medical therapy.^(1, 316, 319) In multiple clinical trials, NIV has been shown to significantly reduce the need for invasive ventilation,^(320, 350-352) reduce length of hospital stay,^(350, 353) improve blood gas parameters,^(320, 353) improve the sensation of breathlessness,^(321, 351, 354) and reduce mortality from exacerbation by up to 50%.^(321, 350, 354) Cochrane reviews from both 2003 and 2017 are broadly unchanged in their conclusion that NIV provides a mortality risk reduction of 46% compared to standard medical treatment. Similarly, invasive ventilation is reduced by 65% and there is an average 3.4-day reduction in length of stay.^(317, 355) The number needed to treat to prevent a death is 12.⁽³¹⁷⁾ A number of NIV trials have excluded patients with severe acidosis ($\text{pH} < 7.25$); Carerra et al, however, demonstrated greater improvement in the requirement for IMV in patients with $\text{pH} \leq 7.30$ compared to those with $\text{pH} > 7.3$. This is in contrast to an earlier UK study which showed a trend towards a worse outcome in this group. The ventilatory times are notably longer (11-13hrs vs. 5-9hrs) in the Carerra study, which is likely to have impacted on outcome. It stands to reason that sicker patients, with a more significant acidosis, have 'more to gain' from well delivered ventilation but that outcome would be worse.^(320, 352) Cochrane conclude that the magnitude of improvement in NIV is similar in patients with more severe ($\text{pH} < 7.30$), or milder acidosis.⁽³¹⁷⁾

In clinical practice the mortality of NIV is increasing; this is likely to, in part, due to the increasing likelihood of ventilating sicker patients with more severe acidosis. Results from consecutive BTS NIV audits 2010-13 (See Table 7) show lower mean pH and increasing use in patients with consolidation on chest x-ray (CXR). Looking at the overall ABG results in these audits, the reductions in PaCO_2 and improvement in pH across the board are comparable with RCTs, as are the number of hours of NIV delivered: this suggests good delivery of acute NIV. There is, however, an increase in 'NIV failure' ($\text{pH} < 7.30$, PaCO_2 reduction $< 0.5\text{kPa}$ or need for intubation) but broadly similar numbers of patients intubated – suggesting that NIV may be being used more liberally on patients who are not deemed fit for invasive ventilation.

Table 7. Aggregated results from British Thoracic Society Audits 2010-2013, adapted from Bourke *et al*⁽³⁵⁶⁾

Year	Mean Age	Consolidation	Median PaCO ₂	Median pH	NIV failure	IMV	Mortality	
							All cause	Respiratory
2010	71	30%	10.2	7.30	27%	2.3%	29%	22%
2011	71	38%	10.1	7.26	33%	3.8%	30%	25%
2012	72	40%	10.2	7.25	31%	2.7%	31%	26%
2013	72	40%	10.2	7.24	33%	3.0%	34%	27%

Non-invasive ventilation is not without its pitfalls. Positive pressure ventilation can have an adverse, pressure-related effect on cardiac output. This is most pertinent in patients with hypotension, intravascular depletion or atrial fibrillation and requires increased monitoring and careful fluid balance management.⁽³⁵⁷⁾ NIV masks can cause claustrophobia, discomfort, gastric distension, be intolerably noisy (particularly if there is a significant leak from poor mask fit), and can cause facial trauma – most commonly over the nasal bridge.^(357, 358)

1.10.3.1 NIV Failure

As mentioned above, NIV failure (pH remains <7.30, PaCO₂ reduction <0.5kPa or requirement for invasive ventilation) can also occur. NIV failure is associated with delayed commencement of initial NIV treatment, inappropriate ventilatory settings, the experience of the treating team (inversely), increasing baseline disease severity, and multi-organ failure.⁽³⁵⁷⁾ Where NIV failure does occur there is evidence that early transition to invasive ventilation may be beneficial.⁽³⁵⁹⁾ Chandra *et al*, however, described a large cohort with high mortality in patents transitioned to IMV from NIV, but that overall NIV-only and IMV-only mortality rates both fell significantly over time, suggesting generally good quality ventilatory care. There was, unfortunately, no assessment of illness severity assessment nor monitoring of response to NIV.⁽³⁶⁰⁾ Similar findings of poor outcome in patients failing NIV and subsequently being invasively ventilated have been replicated in other studies.^(361, 362)

Early NIV failure – within the first few hours of treatment – is more common in patients who are unable to tolerate the ‘non-invasive’ interface. In this situation the treating clinician should ensure mask fit and ventilator settings are appropriate, but transition to

invasive ventilation may result in a better outcome. Late failure – generally >48hours from NIV commencing, following an initially successful response – occurs in around 15-20% of patients treated with NIV and is more common in severe underlying disease.^(359, 363) Moretti demonstrated significant inpatient mortality risk (68% died) in this population.⁽³⁵⁹⁾ It may be that a population who fail despite good quality NIV (with appropriate medical therapy) represent a group in which transition to IMV is unlikely to improve outcome, not due to a failure of the ventilatory interface itself, but the acute illness and severity of underlying lung disease.^(298, 356, 364) Similarly patients who develop their first respiratory acidosis as an inpatient, despite receiving medical therapy, have higher mortality than (whether ventilated or not) than those who present most acidotic at admission (32.9% vs 12.4%).⁽³¹⁸⁾

1.10.3.2 Problems with NIV delivery

Despite clear guidelines and evidence, and widespread availability of NIV in UK hospitals (92% in 2003⁽³⁶⁵⁾; 97% in 2008⁽³⁶⁶⁾ and 99.8% in 2014⁽²⁴⁾) there is significant mis- and under- use of ventilation in patients with COPD with respiratory acidosis. The 2011 ‘national COPD resources and outcomes project’ (NCROP) report demonstrated that 11% of patients with pure metabolic acidosis received NIV treatment despite this not being an indication for NIV. Of patients admitted to hospital with respiratory acidosis due to COPD, only 30% received treatment within an hour. Additionally, a large minority (42%) of patients with new or progressively worsening acidosis did not have NIV provided.⁽³¹⁸⁾ This has not improved over time. NACAP reports between 2008-2018 show that despite 26% of patients having acidosis during their hospital admission, only 12% were ventilated in 2008/2014 and 10.9% in 2018.^(24, 299, 366) Early application of NIV is independently associated with increased survival, yet in 2018 only 21% of patients received NIV within two hours of admission.^(211, 367, 368)

The National Confidential Enquiry into Patient Outcome and Death (NCEPOD) reported on the use of acute NIV in COPD in 2017. The mortality rate for patients with COPD was 25.1% - higher than the original studies into NIV on the ward.^(320, 339) Worryingly 1 in 5 patients were deemed to be inappropriately treated with NIV, and in 80.7% of cases there was room for improvement in care. Additionally, nearly two thirds of decisions about commencing treatment with NIV are not made by Respiratory physicians or Intensivists (those who generally have the greatest knowledge and experience in COPD

and NIV treatment), and 72% are by doctors more junior than consultant grade. When consultants do review these patients, there were changes to treatment in 53% of cases.⁽³³⁹⁾ Specialist respiratory input into COPD care is known to improve delivery of evidence based treatment, as well as outcomes such as mortality and length of stay.^(24, 298, 369)

1.11 Outcomes of COPD exacerbation

Exacerbations of COPD result in worse outcomes for patients and mortality following severe exacerbation is high. Inpatient mortality for all COPD was 3.8% in 2018, and 25.1% for NIV patients.^(299, 339) In those who survive to discharge, 6.1% die within 30 days and 11.3% within 90 days; but if a patient requires ventilation the OR for mortality is 3.85 and 2.62 respectively.⁽²⁹⁹⁾ Mortality rates have been falling across consecutive national audits, but there is still higher mortality in the UK compared to other European countries (age standardised mortality rate: UK=58.8; EU28 34.9/100,000).⁽²⁰⁹⁾

Exacerbations, particularly 3 or more in a year, are independently associated with a worse prognosis, and readmission rates are rising – over 40% of patients are readmitted by 90 days.^(298, 299, 370) The leading causes of death following exacerbation are respiratory failure, pneumonia, lung cancer, and cardiac failure/ischaemic heart disease (IHD).^(248, 253, 299) Aside from mortality and readmission risk, COPD exacerbations confer an increased risk of myocardial infarction and stroke in the month following their onset.⁽³⁷¹⁾ Patients with more frequent exacerbations also lose FEV₁ at a faster rate than those without.⁽³⁷²⁾

Exacerbations also have a negative effect on patients' quality of life with worsening ability to perform activities of daily living, reduction in mood, increased frustration at health status, and worsening COPD symptom severity; moreover, worse quality of life is associated with increased risk of exacerbation.^(206, 373-377) Prediction of outcome in individuals will be discussed in more detail in Chapter 3.

1.12 Chapter summary

COPD is a common disease with increasing prevalence throughout the world. It is a common cause of morbidity and mortality and its causes are multifactorial. Although smoking remains the principal cause in the UK, it is strongly associated with lower socioeconomic class and poverty. It is a complex, systemic, disease with a wide variety of manifestations; these have a significant impact upon patients diagnosed with the disease. Hospital admissions due to exacerbations are common, account for the bulk of healthcare utilisation cost of COPD, carry increased risk for patients and have poor outcome. Patients with respiratory acidaemia are at particularly high risk of both inadequate care and death, both as an inpatient and following discharge from hospital. These patients are treated with complex ventilatory support but often decisions are made by non-specialists and junior doctors, who may not be appropriately trained or experienced in NIV delivery and complex, evidence-based COPD management. Multiple factors play into the success, or failure, of NIV and a simple tool, which accurately predicts outcome would be beneficial in guiding treatment decisions and discussions about prognosis vs. treatment burden for patients and their families.

2 Defining and measuring quality of life in COPD

2.1 Quality of life

Quality of life (QoL) is a difficult concept to define, partly as it cannot be directly observed.⁽³⁷⁸⁾ Traditionally it was defined by the absence of disease and a persons' health status. This 'biological' view has been replaced more recently by a biopsychosocial model of health. Quality of life should be broadly thought of as the holistic evaluation of a persons' current circumstance in the culture in which they live and which is based on their own perception and value system.⁽³⁷⁹⁾ The WHO define quality of life as *"an individual's perception of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns"*.⁽³⁸⁰⁾ Quality of life is subjective, changeable, and encompasses a persons' psychological, physical, spiritual and social situation; it is not purely 'health status', 'lifestyle', 'mental state' or 'overall wellbeing'.⁽³⁷⁹⁻³⁸¹⁾

2.1.1 Health-related quality of life

In healthcare settings, the term QoL is used interchangeably with 'Health related quality of life' (HRQoL). HRQoL comprises the above attributes, but normally also with a focus on the impact of a physical or mental diseases effect on a patients' ability to function: their level of ability or disability.^(381, 382) Focussing on ability and disability alone is not without its flaws, as ill health can insidiously effect almost all aspects of a persons' life, even if they are not instinctively associated directly with health (e.g. financial security) but can have significant impact on quality of life, despite not often being measured.⁽³⁸³⁾ Given the complexity of 'HRQoL', multiple approaches to measuring it – covering different aspects of QoL - are recommended to improve the accuracy of results and ensure they are truly representative.^(379, 383) Traditionally, the measurement of HRQoL has been at a single timepoint: this is not representative of the reality of living with a chronic disease, such as COPD, which has natural variation and fluctuation in its burden over time.⁽³⁸¹⁾ Longitudinal measurement of HRQoL can therefore improve understanding of the true effect on patients, and better reflects their burden of illness. It is important to recognise that in a multimorbid population HRQoL can be affected by more than one condition and distinguishing between the relative effects of each illness

can be challenging, if not impossible. Quality of life measurements are particularly important in diseases which have high symptom burden or disability but relatively low overall mortality, such as COPD (in the UK, 3 million people live with COPD; ~30,000 per year die from it).^(4, 210, 381) These patients may need increased support and if QoL is deteriorating, more intense follow up; poor patient-perceived HRQoL is associated with increased mortality.⁽³⁸⁴⁾

2.1.2 Activities of daily living

Activities of daily living (ADL) refer to what a person has to do in order to function day-to-day. These are split into basic activities of daily living (BADL) and instrumental activities of daily living (IADL). BADLs are those considered essential for self-care such as continence, washing, dressing and walking or transferring. IADLs refer to more complex tasks required for a patient to be independent in the community, such as managing their money and the ability to undertake their own shopping, meal preparation and housework tasks.^(385, 386) The term 'functional status' is used as a description of how well a patient can perform their ADLs.⁽³⁸⁷⁾

2.2 Quality of life in COPD and following acute NIV.

COPD carries a high symptom burden, which can be significantly worse than that of inoperable lung cancer.⁽³⁸⁸⁾ The James Lind Alliance has established that the ability to identify and determine the palliative care needs of non-malignant disease (including COPD) patients as a top 10 priority, but other questions in the area of COPD are lacking currently. A priority setting survey in exacerbations of COPD opened in 2019 and has since been completed; this may include improving measures of quality of life but has not yet reported its findings.

Emotional status and the ability to perform activities of daily living are the most important determinants of QoL in COPD, and those patients who have high levels of anxiety or depression in particular have a lower overall QoL.^(222, 275) The more severe the disease is, the higher the likelihood of clinically significant anxiety.⁽²⁶⁹⁾ Extrinsic life stresses (e.g. bereavement) in patients with COPD result in worse QoL outcomes, and greater symptoms of depression than non-COPD controls.⁽³⁸⁹⁾ Patients suffering with

depressive symptoms, and with worse psychosocial factors in QoL questionnaires, are at higher risk of admission and readmission to hospital.^(270, 271)

Patients with COPD often subconsciously reduce the intensity and number of ADLs they undertake to reduce the intensity of dyspnoea they experience. However, in a similar manner to lung function, quality of life has varying severity and trajectory between patients. It is important to note that while lung function and exacerbation frequency may correlate with it, they cannot be used as surrogates for QoL in COPD.^(387, 390)

Positively, a Dutch study by Tiemensma *et al* demonstrated that when patients were well informed and educated about COPD, they had better coping strategies and better self-management, which in turn improved their QoL.⁽³⁹¹⁾ This study highlights the importance of how the clinician describes and explains COPD to patients, as well as the importance of ongoing review to ensure both accurate understanding and to reinforce positive self-management.

Exacerbations of COPD resulting in hospitalisation are associated with significant deterioration in the QoL of patients.^(274, 377, 392, 393) There is surprisingly little data regarding longitudinal QoL following severe exacerbation of COPD and even less in patients who have had acute NIV. Steer *et al* studied longitudinal outcomes in 183 patients following discharge for severe COPD exacerbation; most patients improved from baseline measurements (inpatient, but after clinical stability had been reached) by 3 months, with a quarter taking 6 months or longer. In the 83 patients who were ventilated, there was no overall decline in QoL over the year after discharge, with respiratory symptoms improving. Ventilated patients had more severe COPD, but with less severe pre-hospital respiratory symptoms than non-ventilated patients. This may be due to their lower functional status masking the severity of symptoms. Poor functional status was associated with increased risk of both readmission and mortality.⁽³⁷⁶⁾ Patients from the CAOS cohort, which included both non-invasively and invasively ventilated patients treated in critical care units, demonstrated that by 6-months post discharge, 73% had recovered to the same or better QoL than prior to hospitalisation. Despite this improvement, three quarters had trouble mobilising around the house due to dyspnoea, two thirds complained of moderate to extreme discomfort, and over half had anxiety and/or depression. In total, 83% felt their chest disease limited the 'fullness of their

lives’.⁽³⁹⁴⁾ Patients suffering with chronic respiratory failure can have significant and substantial benefit in QoL from long-term domiciliary NIV.⁽³⁹⁵⁾

2.3 Measurement of quality of life

Given the complexity of defining QoL, it is unsurprising that there are many tools available to help measure it. Good quality, well designed measurement tools should yield valid (the tool actually measures what it is supposed to), reliable (results which are reproducible across time, researchers and items in the tool) and interpretable results which distinguish differences between different patients.^(378, 381) QoL measurement tools, in general, can be discriminative (those which differentiate between patients at a point in time) or evaluative (measure longitudinal changes in patients over a period time) and should be sensitive to either positive and negative change in quality of life.^(381, 383) Measuring distinct domains associated with quality of life, for example mobility or self-care, make tools more discriminative, irrespective of whether a disease specific or generic tool is being used.⁽³⁸³⁾

2.3.1 Challenges

Whilst many tools exist to measure quality of life, the complexity of the subject results in a number of challenges. Many of these can be overcome, though acknowledgement of these challenges is important.

2.3.1.1 Recorder effects

Some errors can occur when the ‘recorder’ of the patients’ quality of life is not the patient themselves. This is particularly important in tick-box style questions, where the veracity of the patients’ response can be underappreciated by the recorder.

Additionally, there can be a desire by the patient to match what they believe to be the ‘ideal’ or ‘expected’ response for the recorder, to appear happier than they really are, or to represent themselves in a ‘good light’, thus not accurately representing their true QoL. These effects would not really matter if they occurred equally, but elderly patients and those with lower educational attainment are more likely to respond in this manner than others. This is more often than not a coping mechanism rather than intentionally

malicious or malign behaviour, but is important to realise, especially in light of the demographic of patients most likely to suffer with COPD.⁽³⁷⁸⁾

Tick box style questions often have “objective indicators” of quality of life, but these observations may be being made by someone other than whom they are relevant to, again potentially misrepresenting the experience of the patients QoL.^(379, 381) Patients with COPD also have day-to-day or hour-to-hour changes on their own assessment of their QoL based on their mood. Low mood exaggerates symptoms in COPD and thus if patients are asked QoL questions whilst experiencing this, the results may be worse.^(379, 390)

The mode of administration of a QoL questionnaire is also important each with strengths and weaknesses. This is summarised below, in Figure 8.

Figure 8. Relative strengths and weaknesses of various modes of administration of QoL tools. Taken from Guyatt et al.⁽³⁸³⁾

Mode of Administration	Strengths	Weaknesses
Interviewer	Maximizes response rate Few, if any, missing items	Requires many resources, training of interviewers May reduce willingness to acknowledge problems Limits format of instrument
Telephone	Minimizes errors of misunderstanding Few, if any, missing items Minimizes errors of misunderstanding Less resource intensive than interviewer-administered mode	
Self	Minimal resources required	Greater likelihood of low-response rate, missing items, misunderstanding
Surrogate responders	Reduces stress for target group (very elderly or sick)	Perceptions of surrogate may differ from target group

Many tools also carry the assumption that each of the assessed domains are of equal importance to the patient, as many are scored with equal weighting, but different domains or symptoms may well not be of equal importance to the patient.

2.3.1.2 Ceiling and floor effects

Using questionnaires that demonstrate responsiveness to changes in a patients’ QoL is important; even when those changes may be small. To yield clinically-useful, interpretable assessments of QoL, ceiling and floor effects of the survey need to need to be minimised. Ceiling effects occur when patients with the ‘best score’ in a survey may still have substantial impairment with room to improve further; but this cannot be distinguished from the surveys score. Similarly, a floor effect occurs when patients with the ‘worst score’ may still deteriorate further.^(166, 383, 396) Avoiding the ceiling effect is

particularly important when measuring recovery from an assumed 'worse than usual' baseline reading, such as during or immediately following an exacerbation of COPD.

2.3.1.3 Recall bias and reconceptualization

Recall bias is a common phenomenon in QoL studies and questionnaires. Recall bias occurs when there is an inability of the patient to accurately recognise a previous disease state (e.g., their symptoms last month), most commonly due to memory effects. In this scenario patients may over- or under- estimate their previous disease state. It is, therefore, most helpful to ask questions which are based on a timescale, "on average over the last month...". Often recall bias fluctuates, resulting sometimes in better, sometimes worse responses; these effects can cancel out over time, however this is not always the case.⁽³⁹⁷⁾ Judging retrospective timescales accurately is a significant difficulty; particularly when there have been no pertinent life events, such as birthdays or hospital admissions, to frame the memory around; this worsens recall bias.^(397, 398) Recall is founded in memory, and if patients can't remember a situation then they may have to 're-construct' their symptoms based on their current situation and another time that they do remember.^(397, 399) Where a period of time is questioned, for example one month, there is a tendency for patients not to think of the whole period of being assessed, but to focus on the best or worst time(s) within it. Often patients can overlook significant impairments which have since subsided, and therefore can over-rate their QoL, or vice versa.⁽³⁹⁹⁾ Emotional response also contributes and recall bias is often increased in attitudinal questions more than in behavioural. Recall bias can be minimised by using well designed tools which use shorter periods of recall time, frequent visits or surveys (which may act as points for a patient to frame memory), and increasing numbers of respondents in a study.

In addition to recall bias itself, patients may reconceptualise their illness over time. That is, change their definitions or expectation of their QoL as their disease progresses, thus changing their responses to QoL questionnaires. For example, a healthy teenager may consider independence as their primary measure of QoL. If they then go blind and require assistance with ADLs this would worsen their QoL. However, 20 years after going blind their redefined or new primary QoL measure may be simply to appreciate the help of others and help others as they are able. Whilst the patients' objective impairment or disability has not changed in that time, their QoL is now higher as their definition of QoL

has changed.^(397, 398) Whilst a real phenomenon, the overall effect size of reconceptualization in studies with longitudinal follow up periods has been shown to be relatively small in a meta-analysis by Schwartz et al.⁽⁴⁰⁰⁾

Despite the difficulties in measuring QoL there are a large number of commonly used and validated, responsive and interpretable tools available for measuring quality of life.

2.3.2 Generic and disease specific tools

Different types of QoL measurement tools exist. Generic QoL tools are widely useable for populations across a range of diseases, but may not be sensitive to changes in specific conditions. Specific instruments focus on particular diseases, populations or areas of function and are more sensitive to changes in that area than generic tools might be, but can't be applied more broadly.⁽³⁸³⁾ For the remainder of this chapter I will only discuss the QoL tools that are being used in my study, accepting that others (both generic and COPD specific) are available.

2.3.2.1 *EuroQol-5D-5L*

The EuroQol EQ-5D-3L quality of life score was initially introduced in 1990. It asked about 5 domains of quality of life (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), with 3 levels of severity ('no problems', 'some problems', 'extreme problems') within each domain. Additionally a 0-100 visual analogue scale (VAS) was used to assess the patients' view of their overall health.⁽⁴⁰¹⁾

It was updated in 2009 to the EQ-5D-5L, where patients have '5 levels' of severity to answer for each domain ('no problems', 'slight problems', 'moderate problems', 'severe problems' or 'unable to [perform that domain]/Extreme [for anxiety/depression and pain]').⁽⁴⁰²⁾ Expanding to 5-levels reduces the ceiling effect of the 3L tool, improving its ability to discriminate between different levels of health, and increases reliability of the score.⁽⁴⁰³⁾ The EQ-5D-5L is not a COPD specific tool, and it has been validated in a number of diseases.⁽⁴⁰³⁻⁴⁰⁵⁾ COPD specific studies have demonstrated correlations with EQ-5D-5L and both lung function and other COPD-validated health-related quality of life scores.^(406, 407) The resultant output is split into two constituents: the 'Utility Index', which is calculated from the scores of the 5 level questions, and the VAS. These scores are adjusted to reflect experience by country, with this study using the score for England

validated by Devlin *et al.*⁽⁴⁰⁸⁾ The minimum clinically important difference (MCID) for the UI is a change of 0.051 and for the VAS is a change of 6.7.⁽⁴⁰⁷⁾

2.3.2.2 *The extended Medical Research Council Dyspnoea score*

The MRCD dyspnoea score and its variants have been briefly discussed in section 1.5.1.2. The eMRCD defines dyspnoea based on physical activity on the patient's best day over the last three months. The lowest score, corresponding to the lowest limitation from dyspnoea, is 1 and the highest score is 5. The extended MRCD (eMRCD) dichotomises level 5 in the MRCD score into 5a and 5b, dependent on whether a patient is too breathless to leave the house independently but able to wash and/or dress independently (5a); or is dependent for both washing and dressing (5b). By splitting level 5 to involve personal care tasks the eMRCD incorporates a measure of frailty. In exacerbations of COPD requiring hospitalisation the risk of inpatient mortality from 5a to 5b doubles.^(160, 162) The eMRCD is a component in both the DECAF Score,⁽¹⁶¹⁾ which predicts inpatient mortality in ECOPD, and the PEARL score,⁽¹⁶³⁾ which predicts 90-day readmission or death following admission with ECOPD. In both of these scores the eMRCD is the strongest independent predictor of outcome.⁽¹⁶¹⁻¹⁶³⁾ There is no defined MCID for eMRCD in the literature, though the MRCD and mMRCD have a defined MCID of a change of 1.⁽⁴⁰⁹⁾

2.3.2.3 *Hospital Anxiety and Depression Scale*

The Hospital anxiety and depression scale (HADS) is a screening tool which has been widely used since it was first developed in the 1980s. Symptoms of anxiety and depression are assessed separately with a score out of 21 for each (where 21 is the largest symptom burden). Clinical significance is reached at a score of 8 or more in either domain. HADS is acceptable for use in both inpatient and outpatient settings.^(410, 411) The MCID for either anxiety or depression in the HADS is a change of 1.5 (with each domain being scored separately).⁽⁴¹²⁾

HADS has been validated in COPD and has been used to assess symptoms in a number of studies where patients had mild through to very severe COPD.^(269, 413-416) There are disputes about HADS' sensitivity and specificity for both anxiety and depression in COPD. In some studies it shows only a moderate accuracy for diagnosing depression in COPD (AUROC 0.68), though tends to perform better with anxiety (AUROC 0.79) and is still

comparable or better than other screening tools, such as the Geriatric Anxiety Inventory (GAI), Beck depression and anxiety indices and the General Health Questionnaire (GHQ-20).⁽⁴¹⁵⁻⁴¹⁸⁾ Pragmatically, it is a common screening tool used in UK hospitals in a variety of specialities, and one that medical teams are very familiar with.

2.3.2.4 Nottingham Extended Activities of Daily Living scale

The Nottingham Extended Activities of Daily Living Scale (NEADL) was first designed for use in stroke patients to assess disability and improvement in their physical abilities following rehabilitation.^(419, 420) The NEADL measures both basic and instrumental ADLs. The original NEADL scores from 0-22, where 22 is the least disabled and 0 the most. This is achieved by the two highest functioning options for each question scoring one, with the two lowest functioning scoring zero. This scoring has more recently been updated to score from 0-3 from least to most functionally able, with a resultant score from 0-66.^(421, 422) There is a mixture of these two scoring systems currently used in the literature. Both scores were assessed, but the 0-66 score is presented in analysis given its increased responsiveness. The MCID for NEADL is 2 (using the 0-22 score) and 5 (using the 0-66 score).^(420, 423)

Although not designed for use in COPD, the NEADL questions are relevant for multiple medical conditions. It has been investigated in other chronic diseases such as hip arthritis,⁽⁴²⁴⁾ multiple sclerosis⁽⁴²⁵⁾ and has been used to assess disability in other COPD studies.^(275, 426, 427) NEADL has also been shown to have good inter-user reliability and, importantly for this project, can be answered by both medical and non-medical personnel.⁽⁴²⁸⁾ The NEADL has previously been used in a study investigating patient attitudes toward ventilation in COPD: younger, more able patients (assessed via NEADL) were more likely to be willing to receive ventilatory support than older or less able patients.⁽⁴²⁷⁾

2.3.2.5 The COPD Assessment Tool

The COPD assessment Tool (CAT) was developed as a short, simple, COPD specific, health-related QoL score which could be completed by patients and/or health professionals. The score identifies eight domains which are rated 0 (best) to 5 (worst). Individual domain scores are then added to give a total out of 40.⁽¹³¹⁾ A high burden of symptoms is defined as a score of 21 or more. The minimum clinically important

difference for the CAT is 2 points.⁽⁴²⁹⁾ The CAT has good repeatability and can discriminate between milder and more severe disease in a similar manner to the St Georges Respiratory Questionnaire and is sensitive to changes in symptom burden around exacerbations of COPD, including improvements following recovery.^(131, 373, 430-432)

The CAT test is reliable with either telephone or face-to-face interviews and can be filled in by either patient or interviewer without affecting the score.^(433, 434) It is more sensitive to changes than MRCD, particularly at the milder end of the disease spectrum.⁽⁴³⁵⁾

2.4 Chapter summary

Quality of Life is complex and multifaceted, with changes in response to symptoms, mood and multiple external factors. Despite the challenges in measuring quality of life, there are many well designed measurement tools available for both generic QoL and disease specific aspects; a number of these are validated in patients with COPD. The burden of symptoms and effect COPD has on the quality of life of patients living with it is enormous. Unfortunately, though predictably, QoL is substantially worsened by exacerbation(s). In the fifth of patients who develop acidotic respiratory failure and require treatment with NIV the effect on quality of life appears to be even greater still, but very little literature on this exists despite how common it is. Patients suffering with acute respiratory failure due to ECOPD are at an already low point in their quality of life. Better understanding of trends in their condition, functional status and symptom burden following acute NIV is of great importance; it would facilitate more accurate conversations with patients and their families about prognosis. In patients who were likely to further deteriorate, or to suffer prolonged worsening of their symptoms, it may facilitate improved or more intensive outpatient follow up, including referral to services such as specialist palliative care or cognitive behavioural therapy for symptoms such as anxiety and depression.

3 Prediction in ECOPD with acute respiratory failure

3.1 Importance and difficulty of accurate prognostication

The accurate prediction of outcome is fundamental to the decision to provide any medical intervention. Accurate prognostication is the foundation of truly informed consent and is therefore a prerequisite for a clinician to respect a patients' autonomy, avoid maleficence and provide patient centred care.^(436, 437) Predicting outcome in any given situation, however, is complex for a clinician to do objectively and accurately. When contemplating which treatments to discuss with a patient, let alone provide, clinicians have to judge what they believe a 'successful outcome' would be for the patient; treatment must then be tailored to the individual circumstance, taking into account all the possible consequences of that particular treatment for that patient. To do this, clinicians' have to pull together the total knowledge of their previous experience alongside the application of research results, however these often don't reflect the demographic of the population they're treating. Frequently they then have to apply this in an area in which they are not a specialist. This whole process is very likely to introduce subjective bias into their decision making and as a result clinicians rarely have accurate expectations of benefit and harm; this is not a failing of the clinician per se, but simply reflects the complex world of acute medicine.⁽⁴³⁶⁻⁴³⁸⁾ Additionally complexity arises from the fact that most prognostic research reports mortality as the outcome, with little in the way of predicting ongoing morbidity or quality of life.⁽⁴³⁶⁾

The decision to start assisted ventilation in a patient with acute respiratory failure from ECOPD is a significant moment. Outcomes are poor, with over 25% dying.⁽³³⁹⁾ Decisions are normally preceded by a discussion about whether ventilation is appropriate, and what to do for the patient in the case of failure of ventilation.^(316, 339, 356) There are various indices independently associated with increased risk in ECOPD requiring NIV. Inaccurate or excessive weighting by a clinician on any given one of these indices, or any other index not associated with increased risk, could lead to inappropriate treatment decisions being made, patients being misinformed of prognosis or even the withholding of potentially life-saving treatment.

3.1.1 Patient understanding of prognosis

Explaining risk and prognosis to patients and their families can also be challenging. Communication of statistics, such as percentages, is generally not well understood; framing statistics in more understandable terms (e.g., '4 in 10 people' instead of '40%') can help understanding. It is important to recognise that patients' previous experience, the experience of people around them, and their interpretation of external factors (such as media reports) can influence their opinion and expectation of treatment.⁽⁴³⁹⁾ The statistics a doctor uses to explain benefit and risk also influences their willingness to undertake treatment. Using Relative Risk Reduction (RRR) as opposed to Absolute Risk Reduction (ARR) or Number Needed to Treat (NNT) can provide a much more compelling argument when discussing treatment plans.⁽⁴³⁹⁾ This is important in NIV treatment: using Plant et al's⁽³²⁰⁾ data from 2000, the conversation could be phrased in the following three ways, of which RRR is clearly the most persuasive.

- "Treatment with this ventilator will half your risk of dying" (RRR)
- "Treatment with this ventilator will reduce your risk of dying by 10%" (ARR)
- "If we treat 100 people with this, 10 will die instead of 20" (NNT)

RRR in particular can, however, be misleading in conditions with a low absolute risk of death and is better used in the setting of a condition with high risk. Similar to healthcare professionals, patients can find judging risk difficult and sometimes have unrealistic optimism: "It'll never happen to me".⁽⁴⁴⁰⁾ This is not a phenomenon specific to medicine – similar optimism and denial has been observed in people who felt well after the Chernobyl nuclear disaster: some individuals assumed they would be fine, even when accepting others with a similar dose exposure were at risk of radiation sickness.⁽⁴⁴¹⁾ This has also been found in flood awareness studies; people with a lower socioeconomic background, shorter exposure to their environment and who hadn't previously experienced flooding were much less likely to accept that their property was at risk of it.⁽⁴⁴²⁾ Expectation of future risk for the general public, in any discipline, is based primarily on their past experience, and that their future will emulate this.⁽⁴⁴²⁾ The parallels with the experience of developing respiratory failure are clear: lower socioeconomic status is associated with poorer disease state, and those with less exposure to healthcare and who have not previously needed NIV are less likely to accept and understand the risks of the situation.

When clinicians' explain risk using an information that is tailored to that patient (rather than the broad results of, for example, a research study), it is more easily understood and feels more relevant to the patient – improving their ability to process the information and reach an informed decision, and to be able to better cope with their illness.^(391, 439) In order to achieve this, however, more personalised risk calculations need to be available to treating teams.

3.1.2 Clinician prognostication and communication

Judging risk or prognosis in clinical situations is challenging. Inherently, the risk of a situation is determined by a degree of uncertainty in the outcome. Risk assessment incorporates the recognition of one or more 'dangers' (for instance, the danger might be massive haemorrhage, or the death of the patient), the probability of that danger occurring, and the seriousness of the danger(s).⁽⁴⁴³⁾ This is not a recent phenomenon; Pearlman demonstrated 30 years ago that physicians interpret similar scenarios differently, potentially leading to variability in practice in patients with the same condition; that physicians were not well skilled at using known predictors of mortality to formulate predictions of survival, and that they frequently put excessive weight on the patients' social factors.⁽⁴⁴⁴⁾

Prognosis is complex to predict, complicated to explain, and varies from patient to patient. Clinicians may avoid discussing it for a multitude of reasons; such as increased specialization, mis- or non-understanding of research in the area, a disinterest in the condition or the patient, time and workload pressures, no recognition of the need to discuss it, fears of patient or family reactions, failure to recognise deterioration of a condition, or the desire to avoid the appearance of prophesising.^(436, 437)

When prognosis is discussed, 'defensive pessimism' is often employed by the clinician – the setting of low expectations for outcome, as not to disappoint should a poor outcome occur. This is often employed subconsciously and is more common when the treating clinician feels like they are out of control, stressed or anxious – such as when treating a condition they are not expert in. This is relevant to the treatment of ECOPD with NIV – approximately 2 out of 3 of decisions are made by non-respiratory doctors, and nearly 75% are made by non-consultant doctors.^(339, 445) This pessimism is not a completely senseless approach – it can make life easier for the clinician (e.g., if a family have been

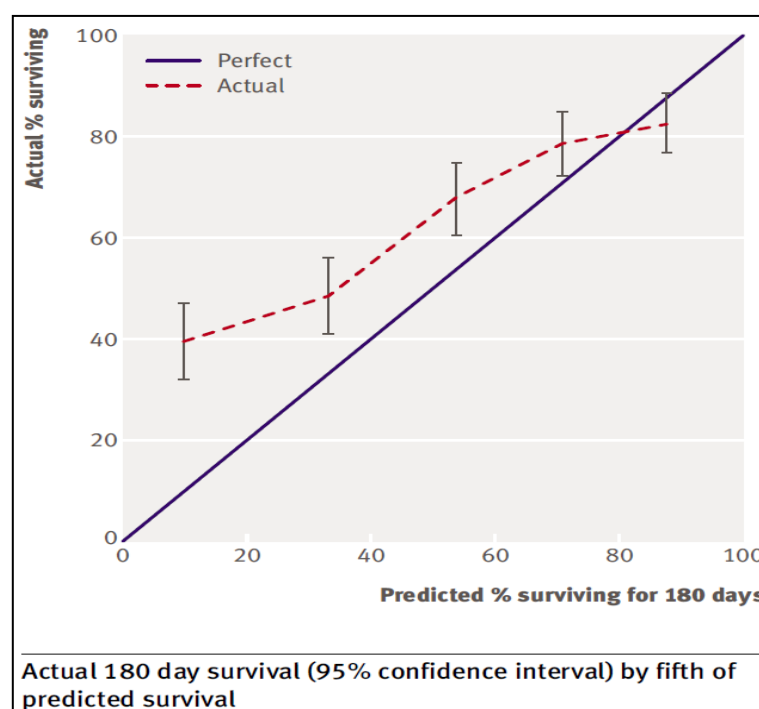
told there is high chance the patient is going to die, they will know to expect this as a possible outcome and are less likely to be shocked if it occurs. If the patient was to get better, it may also appear like the team ‘pulled out all the stops’ to save their loved one. If the family was told ‘everything is going to be fine’ and the patient then died, subsequent conversations may be much more difficult and time consuming for the clinician). Additionally, pessimism can improve the patient-doctor relationship. When doctors discuss potential negative outcomes it can build trust in the doctor, as the patient feels they are being honest with them.⁽⁴⁴⁶⁾

During the COVID-19 pandemic there was widespread reporting of the use of non-invasive respiratory support (principally CPAP) and invasive ventilation in treating COVID-19. This may have an effect on the attitudes of the public towards ventilation (including for exacerbations of COPD) in the future, as well as how clinicians communicate with patients about NIV, but is this yet to be seen.

3.1.3 Prognostic pessimism in COPD

In addition to communicating with defensive pessimism, medical teams are inaccurate at predicting survival and outcomes in acutely unwell patients, including in COPD, and tend toward overly pessimistic prognoses, particularly with regards to quality of life.⁽⁴⁴⁷⁻⁴⁴⁹⁾ The CAOS study examined 832 COPD and asthma patients across 92 critical care centres in the UK and demonstrated a six-month survival of 62.1% overall.⁽³⁹⁴⁾ Overall, and in most subgroups, clinicians demonstrated prognostic pessimism. Figure 9 illustrates this by breaking down the CAOS cohort into quintiles; anything above and to the left of the ‘perfect prediction’ line represents prognostic pessimism by the treating clinicians.

Figure 9. From the CAOS study showing clinician predicted vs. actual survival at 180 days following discharge.⁽⁴⁴⁸⁾



In the lowest expected survival quintile estimated 6 month survival was 10%, but actual survival was 40%. This overestimation of mortality was even more stark in the 10% of patients with the poorest clinician predicted six-month survival: clinician estimated survival was approx. 3% in this group with actual survival 10-fold higher, at 36%.⁽⁴⁴⁸⁾ Prognostic pessimism is particularly worrying in the context of the withholding of potentially life saving treatments. In a study of critical care consultants considering the intubation of patients with COPD in their mid 70's with respiratory failure (who had already had NIV), consultants would not, on average, proceed to intubate when the clinician predicted survival fell below 22%. There was a wide variation in 'cut off' between different physicians presented with the same scenario, and 16.3% of consultants would not intubate even where estimated survival was >30%.⁽⁴⁵⁰⁾ When combining the theoretical denial of treatment in this study with the predicted/observed mortality quintiles from CAOS shown in Figure 9, it becomes clear that prognostic pessimism towards patients with COPD is likely to result in substantial withholding of ventilatory treatment, based wholly on inaccurate physician predicted outcomes. Patients also disagree with these clinician impressions. At six months following discharge 73% of patients stated their QoL was the either the same or better than before admission, and 96% would be willing to undergo the treatment again.

A particular concern with prognostic pessimism is the effect of a 'decision makers' attitude to treatment on the wider medical team. Role modelling is one of the most powerful, though under-recognised and potentially corrosive, teaching methods in clinical medicine with observed behaviours and attitudes integrated into a learners' own practice. Therefore, if prognostic pessimism is frequently observed and remains unchallenged, it becomes the norm and can become reflected in the attitude of the wider team and even into organisational culture.⁽⁴⁵¹⁾

Prognostic pessimism and inaccuracy is not unique to patients with ECOPD. It has been demonstrated in a number of studies following acute illness including stroke rehabilitation,⁽⁴⁵²⁾ estimating exercise tolerance in rehabilitation,⁽⁴⁵³⁾ and outcome following cardiopulmonary resuscitation.⁽⁴⁵⁴⁾ Positively, both defensive and prognostic pessimism are adaptable and can be changed. When a clinician has access to relevant and understandable prognostic data their anxiety, stress and feelings of being out of control are mitigated, and evidence based expertise is increased. This means they are less likely to employ defensive pessimism as a coping strategy in their practice, and prognostic pessimism is challenged by objective findings.^(444, 445)

3.2 Clinical prediction tools

Clinical prediction models or prognostic tools employ a mathematical algorithm to a combination of risk factors resulting in an estimate of probability of a medical outcome.^(455, 456) They can be applied in a variety of situations, such as prediction of the development of a disease, prediction of the risk of a side effect, or the prediction of an outcome of an illness. Using prognostic tools to calculate outcomes from illness, based on clinical information or pre-morbid status, can give more accurate estimates of short, medium and long term results than doctors' own predictions.⁽⁴⁵⁷⁻⁴⁵⁹⁾ The strength, and potential clinical utility, of a tool is improved if only a limited number of variables are required to use it, that these variables are readily available to the clinician, and there is no need for complex computation to get a result. Clinical prediction models are not designed to act as a replacement for clinical judgment; but given their objective nature, many are commonly utilised to aid clinical reasoning and decision making in a number of

fields of medicine.^(455, 456) Commonly used examples of predictive models are the CHA₂DS₂-VAsC score for stroke risk in Atrial Fibrillation,⁽⁴⁶⁰⁾ the HASBLED score for bleeding risk with anticoagulation,^(461, 462) the Glasgow-Blatchford Score (GBS) for acute gastrointestinal bleed management,⁽⁴⁶³⁾ and the Wells criteria for risk stratification in Pulmonary Embolism,⁽⁴⁶⁴⁾ although many more in various fields exist.

3.2.1 Healthcare system benefits

The effect of good clinical prediction tools on healthcare delivery can be profound. In some situations these type of tools can be balanced against each other to guide treatment; in the case of the CHA₂DS₂-VAsC and HASBLED their use has been mandated in national guidance for assessment of patients with Atrial Fibrillation, with judgements about anticoagulation based on their scores.⁽⁴⁶⁵⁾ Within Respiratory medicine predictive tools are also regularly used to guide treatment decisions. The CURB65 score⁽⁴⁶⁶⁾ measures the severity of community acquired pneumonia and is widely used to inform both location of care (community, hospital or critical care) and the prescription of either single or dual antimicrobial therapy. Similarly, the DECAF score^(161, 162) not only predicts inpatient mortality in ECOPD but has also been used to guide patient enrolment into hospital at home programs. This has demonstrated patient preference toward hospital at home, equality of safety and significant healthcare cost reductions.⁽³¹⁵⁾

3.3 Design of prognostic tools

The TRIPOD and PROBAST guidelines lay out steps to aid the development of high quality prognostic tools.^(467, 468) There should be clear pre-identification of the question to be answered (or at least clarified) by the proposed model prior to development.⁽⁴⁵⁶⁾ There are a number of specific considerations which should be addressed during the development of a tool, covered below.

3.3.1 Population and covariate selection

Predictive tools should be derived in populations which are representative of the population that the resultant tool will be used in.⁽⁴⁵⁶⁾ Data collected from the derivation population should result in a list of candidate predictors (covariates) of the prespecified

outcome.⁽⁴⁵⁶⁾ This step can be problematic if covariates are selected from retrospective, or 'non disease specific' datasets, such as intensive care databases. Using these data sources can result in the exclusion of potentially strongly predictive covariates [from the final model] if they were not present in the derivation dataset, as well as high levels of missing data if they were poorly recorded in that dataset.^(455, 456) Whilst imputation methods can be employed for missing data, they are not as good as ensuring more complete data collection from prospective data capture, with comprehensive collection of any/all potential indices, where possible.⁽⁴⁵⁶⁾

3.3.2 Developing a model from covariates

Once covariates have been identified there are various statistical methods for development of the eventual tool, but there is no agreed consensus on exactly how the final model is developed.⁽⁴⁵⁶⁾ A 'full model' approach enters all covariates into a multivariate regression model, although this is often unfeasible or impractical due to the large numbers of covariates that can be identified by researchers. Typically, univariate associations with the outcome in question are brought forward to a multivariable analysis following the removal of highly correlated covariates. Ideally, univariate associations entered into the multivariable model should not be solely limited to those which are statistically significant ($p < 0.05$) as this could remove some indices with potentially important predictive power.^(456, 469) The use of a higher p value for inclusion into the multivariate model (e.g. $p < 0.1$) can be instituted, or the inclusion of indices from previous research which are known to have a strong relationship with outcome. Conversely, a covariate which is strongly related to outcome but is difficult to capture, not routinely used in clinical practice, or uncommon in the target population, could arguably be removed as its inclusion may limit the generalisability or utility of the resultant model. Using a non-full model approach is more likely to result in 'overfitting' of the model – where the resultant predictive tool is too specific to the population it was derived in, and is not as generalisable to a wider population.^(455, 456, 468)

3.3.3 Calibration

Model calibration refers to whether the predicted probabilities from the model are reflective of the outcomes that were observed. A well calibrated tool will accurately estimate risk for the population in question, whereas a poorly calibrated tool will over- or underestimate this.^(455, 469) Calibration inaccuracy can be systematic (over- or underestimating risk in the whole population), may only affect certain combinations of component indices, may be poor in only a certain part of the risk range (e.g. poor at estimating risk in very low or very high risk patients), or in certain groups of individuals. Any of these scenarios can lead to false expectations for both patients and clinicians, and potentially over or under treatment, even if overall discrimination (section 3.3.4) is good. If the tool excludes a significant group of people with a particularly high risk of an outcome (e.g., obesity) during its development, then it may not be accurate when applied to that group of patients; this highlights the need to ensure that the derivation population is representative of the population it will be used in. Calibration of a tool can be shown graphically and by using Hosmer and Lemeshow calculations.^(456, 469, 470)

3.3.4 Discrimination

Discrimination is the ability of the tool to differentiate between individuals experiencing the outcome and those who did not – i.e. to be able to identify between high and low risk.^(456, 468, 469) The most common method of measuring discrimination is by using the area under receiver operation characteristic (AUROC) curve (this is discussed further in Section 5.9.7), and this method also allows for a simple statistical comparison with other predictive scores to be performed.

3.3.5 External validation

Prognostic models should be externally validated in different participants: both temporally (different time) and geographically (different place); ideally by a different research team.^(455, 468-473) This assesses the performance of the tool in a new and different group of similar patients to those in which it was developed, and is the gold standard for ensuring a tool is fit for purpose. It is important to note that external validation is not the same as randomly splitting a derivation population into two,

developing the tool in one half and testing it in the other half, though is often mis-sold as such. Temporal validation can occur at a later timepoint within the same institution that the derivation population was studied.⁽⁴⁷¹⁾ Geographic validation ensures the generalisability of the performance of the tool to the population of other institutions or countries. In combination, these external validation measures can act as a strong proof of concept for the predictive tool.^(469, 471)

3.4 Prediction tools used in COPD

A number of prediction tools have been developed for use in the COPD population and are used in a variety of circumstances; a summary is shown in Table 8. The majority of these tools are used to calculate outpatient stable state prognosis, or inpatient mortality for ECOPD and common themes in their variables emerge (see Table 9). It is as interesting to see what is not included in final tools as what is included, highlighting the importance of inclusion of all potential clinical variables into the model selection process. Whilst tools may have included patients with acute respiratory failure, only three are specific to that population and only one of these has undergone external validation.

Table 8. Summary of clinical prognostic tools used to predict outcome in COPD in different settings.

Tool name	Author	Design	N	Outcome measure	COPD only	NIV only	Variables in model	Discrimination*	Validation
OUTPATIENT TOOLS									
ADO	Puhan ⁽⁴⁷⁴⁾	Prospective moderate to severe COPD patients	574	3 year mortality risk	Yes	No	Age, dyspnoea, airflow obstruction	AUROC 0.63	Internal and external
B-AE-D-[C]	Boeck ⁽⁴⁷⁵⁾	Retrospective. GOLD II-IV COPD	530	2 year all-cause mortality	Yes	No	BMI, exacerbation frequency, mMRC [copeptin]	AUROC 0.74 <i>0.77 with copeptin</i>	Internal validation
BODE	Celli ⁽⁴⁷⁶⁾	Prospective. Stable COPD outpatients	859	2 year mortality (any cause and respiratory cause)	Yes	No	BMI, % predicted FEV ₁ , mMRC, exercise capacity	AUROC 0.74	Internal and external
BODEX	Soler-Cataluña ⁽⁴⁷⁷⁾	Prospective. Stable COPD, all male	185	Mortality (all cause) over 5 years	Yes	No	BMI, % predicted FEV ₁ , mMRC, exacerbation frequency	AUROC 0.74	Internal and external
BARC	Bloom ⁽⁴⁷⁸⁾	Retrospective. COPD patients in primary care	54990	1 year mortality	Yes	No	Age, BMI, Creatinine, Haemoglobin, FEV ₁ , Comorbidities, Smoking status, Gender, Number of hospitalisations, Albumin, MRCD, Platelet count	0.781	Internal and external

Tool name	Author	Design	N	Outcome measure	COPD only	NIV only	Variables in model	Discrimination*	Validation
-	Bertens ⁽⁴⁷⁹⁾	Prospective	1033	Exacerbation prediction	Yes	No	Previous exacerbations, % predicted FEV ₁ , Smoking pack years, comorbid vascular disease	AUROC 0.75	Internal and external
DOSE	Jones ⁽⁴⁸⁰⁾	Retrospective. COPD patients in primary care dataset	375	COPD severity	Yes	No	MRCD, % Predicted FEV ₁ , Smoking status, Exacerbations per year	Not reported	Internal and external
READMISSION (+/- DEATH) TOOLS									
CODEX	Almagro ⁽⁴⁸¹⁾	Retrospective. Hospitalised ECOPD patients	679	All-cause mortality or readmission at 3 months and one year	Yes	No	Charlson index, % predicted FEV ₁ , mMRCD, number of severe exacerbations	AUROC (3 month) 0.72 AUROC (12 month) 0.68	Internal and external
PEARL	Echevarria ⁽¹⁶³⁾	Prospective. Hospitalised ECOPD patients	2417	Readmission or death within 90 days of discharge	Yes	No	≥2 admissions, eMRCD, ≥80 years old, Right or Left heart failure	AUROC 0.73	Internal and external

Tool name	Author	Design	N	Outcome measure	COPD only	NIV only	Variables in model	Discrimination*	Validation
LACE	van Walraven ⁽⁴⁸²⁾	Prospective. Patients discharged from medicine or surgery	4812	Death of readmission within 30 days of discharge	No	No	Length of stay, acuity of admission, Charlson comorbidity score, number of emergency admissions in last 6 months	AUROC 0.711	Internal and external
PARR-30	Billings ⁽⁴⁸³⁾	Retrospective. All patients admitted	576868	Readmission within 30 days of discharge	No	No	Age, Number of admissions in last 12 months, Admission within last 30 days, current admission emergency, deprivation (IMD) band, comorbidities, hospital specific variable	AUROC 0.699	Internal
INPATIENT MORTALITY TOOLS									
APACHE II	Knaus ⁽⁴⁸⁴⁾	Prospective. General intensive care admissions	5815	Intensive care unit mortality	No	No	Severe organ failure, Age, temperature, MAP, pH, HR, RR, Sodium, Potassium, Creatinine, Acute renal failure, Haematocrit, White cell count, GCS, FiO2	AUROC 0.863	Internal and external

Tool name	Author	Design	N	Outcome measure	COPD only	NIV only	Variables in model	Discrimination*	Validation
SAPS II	Le Gall ⁽⁴⁸⁵⁾	Prospective medical/surgical critical care admissions	13152	Inpatient mortality	No	No	Age, HR, SBP, Temperature, GCS, PaO ₂ /FiO ₂ , Serum Urea, Urine output, Potassium, Bicarbonate, Bilirubin, White Cell Count, Chronic Disease Comorbidities, Type of admission,	AUROC 0.88	External
BAP-65	Tabak ⁽⁴⁸⁶⁾	Retrospective. Hospitalised ECOPD patients	88074	Inpatient Mortality	Yes	No	Serum Urea, GCS <14, Heart Rate >109/min, Age >65	AUROC 0.72	External
DECAF	Steer ⁽¹⁶¹⁾	Prospective. Hospitalised ECOPD	920	Inpatient mortality	Yes	No	eMRCD, eosinopenia (<0.05x10 ⁹ /L), CXR consolidation, pH<7.3, Atrial Fibrillation	AUROC 0.86	Internal and external
CAPS	Wildman ⁽⁴⁸⁷⁾	Retrospective. Critical care admissions with COPD or asthma	8527	Inpatient mortality	No	No	Heart Rate, Blood pressure, pH, Sodium Urea, Creatinine, Albumin, White Cell Count	AUROC 0.718	Internal
-	Roche ⁽¹⁵⁷⁾	Prospective. ED attendances for ECOPD. Excluded immediate need for ventilation or critical care	794	Inpatient mortality	Yes	No	Age 70+, clinical severity index, dyspnoea grade	AUROC 0.79	Internal

Tool name	Author	Design	N	Outcome measure	COPD only	NIV only	Variables in model	Discrimination*	Validation
-	Ruiz-Gonzales ⁽⁴⁸⁸⁾	Prospective. Hospitalised ECOPD	147	Mortality, admission to critical care or cardiac failure	Yes	No	CRP, Confusion, Smoking status, 2+ comorbidities	AUROC 0.80	None
-	Tsimogianni ⁽⁴⁸⁹⁾	Prospective. Consecutive ECOPD admissions	106	3 year mortality	Yes	No	MRCD, BMI	AUROC 0.83	None
-	Incalzi ⁽⁴⁹⁰⁾	Prospective. Patients discharged for ECOPD	288	5 year mortality	Yes	No	Chronic renal failure, RVH/overload or ischaemic change on ECG, FEV ₁ <590ml, Age	Sensitivity 63.4% Specificity 76.6%	None
COPD & VENTILATION SPECIFIC TOOLS									
-	Chung ⁽⁴⁹¹⁾	Retrospective. ECOPD requiring NIV	100	5 year survival	Yes	Yes	Age, BMI, domiciliary oxygen	Not presented	None
-	Anton ⁽⁴⁹²⁾	Prospective. ECOPD requiring NIV	49	NIV failure	Yes	Yes	Level of consciousness, Baseline PaCO ₂ , %predicted FEV ₁ , change in PaCO ₂ on NIV, pH after 1hr of NIV	Sensitivity 0.97 Specificity 0.9	Internal validation

Tool name	Author	Design	N	Outcome measure	COPD only	NIV only	Variables in model	Discrimination*	Validation
Confalonieri Risk Chart	Confalonieri ⁽⁴⁹³⁾	Prospective. COPD requiring NIV	1033	NIV failure (intubation or death)	Yes	Yes	APACHE II indices, pH, RR and GCS	AUROC 0.81	External

*Derivation result shown unless otherwise stated.

Definitions of abbreviations: N=number of patients in study; COPD=Chronic Obstructive Pulmonary Disease; NIV= Non-invasive ventilation. AUROC= area under the curve of the receiver operating characteristic; GOLD = Global initiative for chronic obstructive lung disease; BMI= Body Mass Index; [m/e]MCRD= [modified/extended]medical research council dyspnoea score; FEV₁= Forced Expiratory Volume in 1 second; ECOPD = exacerbation of Chronic Obstructive Pulmonary Disease; IMD= Index of multiple deprivation; MAP= mean arterial pressure; pH= potential of Hydrogen; HR= Heart rate in beats per minute; RR= respiratory rate in breaths per minute; GCS= Glasgow Coma Scale; FiO₂ = Fraction of inspired oxygen; SBP= Systolic Blood Pressure; PaO₂ = Partial pressure of arterial oxygen; CXR= Chest X-Ray; ED= Emergency Department; CRP= Blood C-Reactive Protein level; RVH= Right ventricular hypertrophy; ECG= Electrocardiogram; PaCO₂= Partial pressure of arterial Carbon Dioxide

Tool name abbreviations: ADO Score= age, dyspnoea, airflow obstruction tool; B-AE-D-[C] Score= body mass index, number of severe ECOPD in the last year, dyspnoea score, copeptin at inclusion; BODE index= body mass index, airflow obstruction, dyspnoea, exercise capacity index; BODEX index= body mass index, airflow obstruction, dyspnoea, exacerbation frequency index; BARC index= blood results, age, respiratory variables and comorbidities index; DOSE index= dyspnoea, obstruction, smoking and exacerbation index; CODEX index= comorbidity, obstruction, dyspnoea and severe exacerbation index; PEARL score= previous admissions, eMRCd, age, right heart failure, left heart failure score; LACE index= length of stay, acuity of admission, comorbidity and emergency admissions index; PARR-30 score= patients at risk of readmission within 30 days score; APACHE II Score= acute physiology and chronic health evaluation two score; SAPS II score= simplified acute physiology score two; BAP-65 score= blood urea nitrogen, altered mental status, pulse and age over sixty five score; DECAF score= dyspnoea, eosinopenia, consolidation, acidosis and atrial fibrillation score; CAPS score= COPD and asthma physiology score.

Table 9. Summary table of the predictive indices used in COPD scores.

Tool	Dyspnoea	Age	FEV1	U&E*	Comorbidities*	FBC*	GCS*	BMI	Exacerbation Frequency	ABG*	Obs*	Smoking*	Cardiovascular disease	Hospitalisations	LFTs*	Type of admission	Organ failure	6MWT	Gender	Radiology	Copeptin	Length of stay	Social Status	Hospital location	Severity index	LTOT
ADO	X	X	X																							
BARC	X	X	X	X	X	X		X				X		X	X				X							
Roche tool	X	X																							X	
PEARL	X	X							X				X													
BODE	X		X					X										X								
BODEX	X		X					X	X																	
DOSE	X		X						X			X														
CODEX	X		X		X				X																	
DECAF	X					X				X			X							X						
Tsimogianni tool	X							X																		
B-AE-D-C	X							X	X												X					
PARR30		X			X									X		X							X	X		
Incalzi tool		X	X		X								X													
Chung tool		X						X																		X
APACHE II		X		X		X	X			X	X						X									
Confalonieri		X		X		X	X			X	X						X									
SAPS II		X		X	X	X	X			X	X				X	X										
BAP65		X		X			X				X															
Bertens tool			X						X			X	X													
Anton tool			X				X			X																
CAPS				X		X				X	X				X											
Ruiz-Gonzales' tool				X	X		X					X														
LACE					X									X		X						X				
TOTAL USES	11	11	9	7	7	6	6	6	6	6	5	4	4	3	3	3	2	1	1	1	1	1	1	1	1	1

FEV1= Forced expiratory volume in 1 second; U&E= Urea and electrolytes; FBC= Full blood count; GCS= Glasgow coma score; BMI=Body mass index; ABG= Arterial blood gases; Obs= Clinical/bedside observations; LFTs= Liver function tests; 6MWT= 6 minute walk test; LTOT= long term/domiciliary oxygen.

*FBC includes haemoglobin, white blood cells including eosinophils, haematocrit, platelets. LFTs includes albumin, bilirubin. U&E includes urea, creatinine, acute kidney injury, potassium, sodium, and CRP. Obs includes respiratory rate, heart rate, temperature, systolic, diastolic or mean arterial blood pressure, fraction of inspired oxygen, urine output. Comorbidities includes any reference to general comorbidities, the Charlson score or other comorbidity index but excludes specific mention of cardiovascular diseases (which are categorised separately). ABG refers to PaO₂, PaCO₂, HCO₃⁻, Base Excess and pH. GCS refers to formal calculation of the 15 point Glasgow coma score, or another other consciousness scale, or to the development of confusion. Smoking includes any reference smoking status or smoking pack year history. Dyspnoea refers to any objective measure used to quantify breathlessness (for example the mRC score).

If a predictive score requires more than one value from the same category to be calculated, they are only counted once in that category on this chart.

3.4.1 Predictive tools in ECOPD with respiratory acidaemia

Most currently used prognostic tools applicable to the ECOPD with RA population are not condition specific and thus offer modest performance. They tend to be complex to calculate (APACHE II, as an example, contains 14 indices⁽⁴⁸⁴⁾) and have generally been developed in the intensive care setting from pre-existing large datasets (e.g. the CAPS score⁽⁴⁸⁷⁾) which makes them less applicable to ward based NIV care and leads to the exclusion of strong predictors of outcome, such as recent performance status and timing of acidaemia. In the UK only 7% of patients with ECOPD are reviewed by critical care, and only 29% of those patients (1.9% of total admissions) are subsequently transferred to critical care.⁽²⁴⁾ The prognostic tool developed from the largest study specifically looking at ECOPD with RA was undertaken by Confalonieri, but has only moderate performance for the prediction of NIV failure.⁽⁴⁹³⁾ The Confalonieri risk chart is complicated to calculate: firstly the APACHE II score must be calculated, then the GCS, pH and respiratory rate must be rescored and correlated against a results matrix (Figure 10) to reveal the lowest predicted chance of NIV failure. This can also be rescored with updated values after two hours of ventilation, yielding different prediction results.

Figure 10. Failure risk chart of NIV at admission from the Confalonieri paper (the values in each cell correspond to the percentage of patients who fail in each category)⁽⁴⁹³⁾

		pH admission <7.25		pH admission 7.25–7.29		pH admission >7.30		
		RR	APACHE ≥29	APACHE <29	APACHE ≥29	APACHE <29	APACHE ≥29	APACHE <29
GCS 15	<30	29	11	18	6	17	6	
	30–34	42	18	29	11	27	10	
	≥35	52	24	37	15	35	14	
GCS 12–14	<30	48	22	33	13	32	12	
	30–34	63	34	48	22	46	21	
	≥35	71	42	57	29	55	27	
GCS ≤11	<30	64	35	49	23	47	21	
	30–34	76	49	64	35	62	33	
	≥35	82	59	72	44	70	42	

This study was prospective, included 1178 patients (1033 consecutive patients in derivation, 145 in external validation), and had an external validation cohort with promising receiver operation characteristic (ROC) curves: admission score in derivation=0.81 and external Validation=0.71. However, its outcome measure was NIV failure and not mortality. The predictive capability of the tool was markedly better when scored at 2hrs after ventilation commenced, rather than at admission. Accurate scoring of outcome after starting treatment is of little use to clinicians weighing up the potential

benefits to inform a decision and discussions about commencing NIV in the first place. Similarly, the study by Anton requires ventilation to have been commenced and indices collected after one hour of ventilation.⁽⁴⁹²⁾ In both of these tools it is perhaps unsurprising that a lack of improvement in pH, PaCO₂, conscious level and respiratory rate after ventilation has commenced correlates with an increased likelihood of NIV failure. The tools currently available to predict mortality were not derived solely in patients with RA in ECOPD specifically; though some, such as DECAF, are specific to severe ECOPD and included patients with respiratory acidaemia in tool development and validation.^(161, 162)

A pilot study predicting mortality in 199 patients with ECOPD requiring NIV at Northumbria Healthcare showed that development of a simple tool is possible, and identified variables associated with increased mortality.⁽³⁶⁷⁾ This study described an inpatient mortality rate of 24.6%. Variables independently associated with mortality were increasing age, ineffective cough, eMRCD score, serum bicarbonate, time to acidosis, neutrophils, previous stroke, recent weight loss, anxiety or depression, and maintenance carbocysteine prescription.⁽³⁶⁷⁾ Whilst some studies have examined healthcare utilisation, mortality and change in quality of life over a number of months following discharge in COPD, data specific to the NIV population is scant. These are sicker patients with a higher likelihood of poor outcomes than the general COPD population. Interestingly, however, there is also local data in this population suggesting QoL does not significantly decline in the months directly following ventilation, in keeping with the CAOS findings.^(376, 394)

3.5 Potential benefits of an ECOPD and NIV prognostic tool

There is no real, equally efficacious, alternative treatment to NIV (or invasive ventilation) in the management of respiratory failure in exacerbations of COPD; reflected in the fact that 99.8% of UK hospitals have the capability to provide NIV if required.⁽²⁴⁾ Despite this widespread ability to provide treatment, NIV remains under-utilised. Non-NIV care provision, such as early inpatient palliative care provision, may be less uniformly provided.

A prognostic tool which is simple to use and designed specifically for the ECOPD with RA population could aid accurate clinical decision making, predicting inpatient mortality as well as longer term measures such as six-month mortality and changes in quality of life. Additionally, it may facilitate more appropriate conversations regarding outcome with patients, helping them reach truly informed decisions about their own care. The aim of a robust predictive tool would be multifactorial, but incorporating it into routine clinical use may be challenging. Accurate, objective prediction of inpatient mortality will allow treating clinicians to have honest, informed conversations with patients and families about their treatment. Given the underutilisation of NIV repeatedly demonstrated in national audit programs, some of which is due to prognostic pessimism, a tool should challenge this attitude in treating clinicians. Thus, the provision of NIV should increase in this group of patients who otherwise have a substantial risk of mortality. Reducing the marked variability of decision making between clinicians treating identical patients is another factor, similar but subtly different to the effect of prognostic pessimism, which objective prediction models may help reduce by improving equity of resources.⁽⁴⁵⁰⁾ Additionally, a tool may help reduce institutional biases and inequalities in provision of care: a recent study by our research group has demonstrated that the strongest predictor of whether a patient with respiratory acidosis actually ends up treated with NIV is the institution they attend. Moreover, the predictors of receiving NIV were not those indices most strongly associated with eventual outcome.⁽⁴⁹⁴⁾ This is in keeping with demographic data from the CAOS study which demonstrated substantial inter-unit variation in the age and performance status of the patients they treated; with relative 'within-unit' consistency in practice.⁽³⁹⁴⁾ Conversely, such a tool could identify patients who are at particularly high risk of mortality and contribute to decisions to withhold NIV in situations where futility of this (often uncomfortable) treatment is likely. This could also act as a trigger to refer patients to specialist palliative care services, and to discuss resuscitation decisions and advanced care plans at an earlier point than they are currently addressed. It is feasible that mortality results at 90- or 180- days might influence inpatient decisions to withhold, or for a patient to refuse, treatment (if there was a very high mortality at these points), but outcomes beyond this are less likely to. A tool which integrates longitudinal follow up of patients with quality of life, readmissions and attitudes toward ventilation would add weight to all of the above

benefits, allowing for not only inpatient but deeper mid- to longer-term discussions and planning to occur. These outcomes, rather than inpatient mortality, may well be the most important factors for patients.

3.6 Chapter summary

Calculating and communicating accurate prognosis around medical conditions is challenging for clinicians, but is essential to ensure that patient autonomy is maintained and that patients can reach fully informed decisions about their treatment(s). The way in which clinicians communicate benefit and risk to patients can also have a profound effect on patients' decisions. Unfortunately, prognostic pessimism is likely to be playing a significant role in the underutilisation of NIV in patients with ECOPD complicated by respiratory acidaemia. Well-designed prognostic clinical tools can significantly simplify and improve prognostication; in turn aiding clinical decision making and communication with patients. Importantly, the objective nature of these tools challenges prognostic pessimism and empowers clinicians by improving their understanding of a disease. Prognostic tools should, however, undergo thorough external validation to ensure they work, before being used in clinical practice. A number of prognostic tools exist for use in the COPD population for a variety of purposes. Perhaps surprisingly there are few designed for those requiring NIV and the only externally validated tool is both complex to score and predicts the failure of treatment, rather than patient centred outcomes alone. A clinical tool designed specifically for this population may challenge prognostic pessimism, improve equity of NIV delivery, improve communication with patients about their condition and facilitate longer term (than just inpatient mortality) planning and shared decision making. In a select group of patients who may be at very high risk of poor outcome or death, it may also open discussions around a more palliative approach and conservative treatment options.

4 Research Aims

The principle aim of this research is the prospective external validation of a prognostic tool aimed at accurately predicting survival, plus assessment of other outcomes in patients hospitalised with ECOPD who require acute NIV due to type two respiratory failure, and is referred to as the NIV Outcomes (NIVO) study.

For ease of understanding and ongoing context, the NIVO study is split into two constituent parts: the 'validation study' (which includes all patients) and the 'longitudinal study' (which includes only consenting patients who survive to discharge). The aims of each of these arms of the study are laid out below, and study design will be further discussed in Chapter 5.

4.1 Aims of the Validation study

1. Prediction of inpatient mortality
 - a. Validation of the derived tool (the derivation study is described in section 5.1)
2. Assessment of inpatient and post discharge survival, plus readmission rates to one year post discharge in:
 - a. The whole study population
 - b. Patients with late failure of NIV
 - c. Patients receiving long term oxygen therapy
 - d. Patients on domiciliary ventilation at discharge
 - e. Patients with Eosinopenia at discharge
 - f. Persistent (post ventilation) hypercapnia

4.2 Aims of the Longitudinal study

1. Longitudinal assessments of activities of daily living, functional status, quality of life and breathlessness as measured by:
 - a. CAT
 - b. The EQ-5D-5L
 - c. NEADL
 - d. eMRCD

2. Assessment of anxiety and depression as measured by the HADS score.
 - a. Relationship with readmission and mortality
3. Patient attitudes towards their experience of NIV and their willingness to undergo similar treatment again during severe exacerbation.
4. Identification of predictors of poor outcome (poor baseline quality of life with subsequent clinically significant deterioration, or death within 6 months).

5 Patients and Methods

5.1 The derivation study

This section (5.1) is not my own work but is fundamental to the project and design so has been included for context. This work has been undertaken by Dr Tom M Hartley and is presented in detail in his doctoral thesis. It is reproduced with his permission.

Retrospective data on 489 consecutive patients meeting selection criteria from two acute admitting hospitals in the same NHS trust was collected. Patients were identified from a combination of previous research, coding searches and ventilation database. Multiple coding searches were tested against a period of known consecutive admissions to maximize sensitivity/specificity of coding searches. Some 400 indices were routinely collected: These comprise key timings, demographics, population descriptors, admissions in last year, comorbidity, medications, observations, investigations, ABGs, details of index and previous ventilation, outcomes, readmissions and a further late failure case report form (CRF) if required. Within this the components of comparator tools are included.

Variables related to mortality ($p < 0.1$) on univariate analysis have been identified using student's t-test, Mann Whitney U or Fisher's Exact test for parametric, non-parametric and categorical data respectively. Multicollinearity was assessed. Continuous variables were dichotomised or categorised, with groups identified by the following hierarchy:

- Inspection of the receiver operating characteristic curve
- A clinically relevant threshold
- Median split

Variables with <10% of the population in one category were excluded. Eligible variables were entered into backward stepwise logistic regression with in-hospital mortality as the dependant variable.

To ensure that the final model could be easily applied at the bedside, the final number of variables was reduced to the minimum required to maintain good, or very good, prediction of in-hospital mortality. Weightings of the individual prognostic indices was assigned according to the regression coefficient (β). Nine indices remained to be taken forward to the validation study:

- eMRCD Score (0-4, 5a, 5b)
- Timing of acidaemia >12hours
- Eosinopenia
- Any history of Atrial Fibrillation up to the point of ventilation
- pH <7.25
- Negative base excess
- Consolidation on chest radiograph
- Glasgow Coma Score <15
- Long term oxygen therapy

Performance of the model was assessed by area under the receiver operating characteristic curve, which was 0.85.

5.2 Study design

The study design for each aspect of the research is detailed below. A schematic of the overall study design is shown in (section 14.1). The study design and delivery was supported by the National Institute for Health Research (NIHR) clinical research network (CRN) portfolio.

5.2.1 Validation study design

Unique, consecutive patients meeting selection criteria (Section 5.5) were prospectively identified at each site by daily screening of admissions units and areas in which ventilation is delivered. Patients receiving either NIV or invasive ventilation were accepted, but identified separately. Descriptive and demographic indices were gathered in a similar manner to the derivation study, plus indices in the comparator tools (APACHE II, CAPS and Confalonieri risk chart) and ventilation settings. For patients experiencing late failure of NIV or relapse (the recurrence of respiratory acidaemia following the cessation of NIV), additional data was collected including continuation of treatment, arterial blood gas values around these events and any changes in ventilator settings. In all patients that survived to discharge readmissions, commencement of home ventilation and mortality data was tracked in the year following discharge.

Key to the development of an accurate predictive model of mortality is the inclusion of patients at both extremes of mortality risk. The most unwell patients, or patients with reduced consciousness, are unlikely to be able to provide informed consent; these patients are treated with NIV or IMV in real life, and therefore exclusion from the study would introduce selection bias and render the predictive model inaccurate and not generalisable, significantly weakening its utility. All of the indices captured in the validation study are usually readily available in routine clinical care of patients receiving ventilation and would not influence changes to usual care. Mortality and readmission data following discharge was captured electronically. Therefore, the validation study did not require individual patient consent for inclusion.

The results of the derivation study were not disseminated to treating or research teams in the validation study as to minimise any change in usual practice from undertaking the study.

5.2.1.1 Clinical diagnosis patients

There are a significant number of patients in clinical practice who are treated for ECOPD with NIV by clinicians who either do not have access to, or have not had, spirometry; these patients are still treated as 'ECOPD' by clinicians. It is probable that the NIVO tool would be applied to such patients in future practice and therefore we collected an additional, reduced dataset on these patients. This comprised demographic and survival data, and the components of the derivation study tool. These patients do not count towards the number for power.

5.2.2 Longitudinal study design

The longitudinal study collects quality of life data, functional status and additional home NIV data on patients up to one year after discharge from their index admission.

Individual patient consent to participate in this aspect of NIVO is sought for all patients in the validation study surviving to discharge, aside from clinical diagnosis patients.

External sites are designated as either 'a', or 'b' sites and this determined the data that was collected.

5.2.2.1 Type 'a' sites

Type 'a' sites collected all data required for the validation study but undertook a substantially reduced longitudinal study. The only questions asked were patients' attitudes toward ventilation before discharge (baseline), which was repeated at three months following discharge.

- "Considering your recent experience on ventilation and how you feel at present and about the future, are you glad that you received ventilation?"
- "Based on your recent experience, if faced with a similar severe exacerbation in the future would you choose to receive ventilation again?"
- "Are you satisfied with your current overall quality of life?"

These questions were phrased in this manner in order to be easily comparable to those in the CAOS study, but could be construed as leading towards a positive response.⁽³⁹⁴⁾

Type 'a' sites were created to facilitate a wider demographic and geographic spread and to involve institutions which may not have the necessary resources to undertake the full longitudinal study assessments which 'b' sites performed.

5.2.2.2 Type 'b' sites

Type 'b' sites collected the same data as 'a' sites, plus additional longitudinal elements.

Measurement of the CAT, EQ-5D-5L, HADS, eMRCD & NEADL scores were collected at baseline and monthly following discharge. At baseline, 3, 6 and 12 months sites also collected: weight/body mass index, peripheral oxygen saturations (plus fraction of inspired oxygen), spirometry and patient reported healthcare resource utilisation.

Researchers undertook face-to-face interviews at baseline, 3, 6 and 12 months. At the other monthly intervals data could be completed with or without researcher presence (e.g., postal, telephone). If domiciliary ventilation was started from or subsequent to the index admission, ventilation pressures and compliance were captured. Follow up visits (aside from 0, 3, 6, 12 month) were primarily performed by telephone with the research teams at each site; a minority were undertaken by the patient returning in the post. A study flow diagram is shown in Appendix A, section 14.1.

5.3 Ethical approval and research governance

5.3.1 Ethical approvals

National research ethics service approval was sought and granted on the 11th of July 2016 by the North East – Tyne & Wear South Research Ethics Committee.

- Reference number 16/NE/0213
- Integrated Research Application Service ID 206694.

Ethical approval for the transfer of confidential readmission and mortality data, using identifiable information in non-consenting patients, was sought separately from the Health Research Authority Confidentiality Advisory Group (CAG). This was approved under Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002 ('section 251 support') to process confidential patient information without consent on the 18th of September 2019.

- Reference number 19/CAG/0072

5.3.2 Health Research Authority approval

Health Research Authority approval to undertake the study was granted on the 27th of July 2016.

5.3.3 Caldicott approval

Caldicott approval was granted by the Northumbria Healthcare NHS Foundation Trust Caldicott guardian for all aspects of the NIVO study. References C3104 and RPI-1065.

5.3.4 Good Clinical Practice

I have undertaken the NIHR 'Good Clinical Practice' (GCP) module, last completed on the 26th March 2020.

5.3.5 Trial steering committees

Trial steering committees were undertaken throughout the recruitment period of the NIVO study. They were all chaired by Professor John Gibson (who was not otherwise involved in the running of the study) and an independent patient representative was invited to all meetings. All members of the research team at each site, not just the

principal investigators, were invited to participate. Meetings took place on the following dates:

- 31st Jan 2017
- 10th May 2017
- 27th September 2017
- 29th November 2017
- 23rd January 2018

5.3.6 Funding sources

Funding for the study was provided by grants from Philips Respironics, Pfizer OpenAir, The ResMed Foundation and Bright Northumbria. All funding was via an open, clinician initiated and competitive process. The work was also supported by the UK Clinical Research Network (CRN), via its portfolio adoption. These funders had no input into design, analysis or reporting of the study.

5.4 Data handling

5.4.1 Data verification

Data for the NIVO study were uploaded to a bespoke online database. When entering data points onto this database upper and lower bounds had been pre-defined in order to minimise anomalous results. If a result lay outside these bounds the study centre had to contact the sponsor site in order to override the limit. In addition, throughout the study real time data verification was performed and unusual or potentially anomalous results were queried with sites by email. Following completion and locking of the database, data were sorted by value and outliers examined.

5.4.2 Data monitoring

Following completion of recruitment data monitoring visits were undertaken at external sites contributing >5% of the NIVO population. At these visits key indices were checked against source documentation. Where discrepancies occurred, these were raised with the principal investigator who made the final decision on whether to action these and make changes.

5.4.3 Database analysis

The finalised online database was exported first to Microsoft Excel, and then into IBM SPSS Statistics V.24.

5.5 Inclusion criteria

Inclusion criteria were intentionally designed to be broad, to reflect real life clinical practice in the treatment of patients with ECOPD and respiratory acidaemia.

- Age 35 or over
- A minimum 10 pack year history of smoking
- Obstructive spirometry performed prior to admission
 - Defined as an FEV1/[F]VC ratio <0.70
- The primary diagnosis is an exacerbation of COPD
- Respiratory acidaemia treated with either NIV or IMV
 - Defined as a blood gas showing pH <7.35 AND pCO₂ >6.5kpa

5.6 Exclusion criteria

Exclusion criteria for the study are listed below. Like inclusion these are designed primarily to ensure that the study is capturing real life clinical practice. Excluding other diseases likely to limit prognosis to under a year avoids 'expected deaths' by non-COPD diseases which may skew or bias the cause and/or prediction of death data, or their influence on quality of life outcomes.

- Previous inclusion in the study
- Another illness (not COPD) likely to limit survival to less than one year
- Inability to give informed consent (relevant only to the longitudinal study)

5.7 Institutions and site selection

Ten NHS hospital trusts recruited to the study. Sites were chosen with a wide geographical spread across England and Wales (Figure 11), and with a mix of urban, suburban and rural populations. The total population coverage of the trusts in NIVO was >6,390,000. To be selected as a site each trust had to demonstrate a liberal NIV policy

(i.e., not routinely deny treatment with ventilation based on presumed futility) to minimise selection bias; each potential site submitted their audit data which the chief investigator reviewed. As an example, at Northumbria Healthcare 86% of patients who meet criteria for NIV with an eMRCD score of 5b (unable to leave the house unassisted and require help with both washing and dressing) are treated with ventilation. The following sites recruited to the study:

Figure 11. Geographical distribution of NIVO sites



1. Northumbria Healthcare NHS Foundation Trust
2. South Tyneside NHS Foundation Trust
3. Gateshead Health NHS Foundation Trust
4. Leeds University Hospitals NHS Trust
5. Nottingham University Hospitals NHS Trust
6. Oxford University Hospitals NHS Foundation Trust
7. Hywel Dda University Health Board
8. Guys and St Thomas' (Lane Fox Unit), NHS Foundation Trust
9. Taunton and Somerset NHS Foundation Trust
10. University Hospitals Plymouth NHS Trust

5.8 Data collected

The indices collected were all readily available clinical data for the admitting care team. There was no mandated change to usual care, nor extra indices required over and above usual care. Using only readily available clinical indices will facilitate future utilisation of the tool in routine care.

5.8.1 Validation Study

Copies of the CRFs for each aspect of the study and the longitudinal study consent form and GP letter are shown in appendices F to J (sections 14.6 to 14.10, pages 307 to 313).

5.8.1.1 *Pre-admission demographics*

Data were collected on: type of residence prior to admission; smoking status (ex-smoker was defined as no cigarettes for >6 weeks prior to date of admission); smoking exposure history (in cigarette pack years); the number of hospital admissions (any cause) over the preceding 12 months; level of dyspnoea measured by the eMRC score; whether they had previous episodes of treatment with NIV before this admission (if yes, the total number of episodes in the preceding year and the date of their first episode); baseline creatinine (lowest value in the preceding 3 months), and whether they were treated with long term oxygen therapy or domiciliary ventilation prior to admission.

5.8.1.2 *Spirometry*

To be eligible to enter the study the patient must have had pre-admission obstructive spirometry performed and documented. Spirometry was looked for in medical notes, lung function laboratory databases and primary care records. Obstructive spirometry was defined as an $FEV_1/[F]VC$ ratio <0.70 . If a relaxed VC had been performed in lieu of a forced VC, this was accepted. If both were performed, the higher vital capacity value was included as this is more reflective of the true size of the patients' vital capacity. On occasion patients may have demonstrated obstructive spirometry but the absolute values are unavailable. In this situation if the patient had clinic letters from a respiratory physician directly referencing obstructive spirometry, this was accepted. If spirometry was referred to, but an obstructive defect was not specifically mentioned, this was not accepted as having diagnostic spirometry for inclusion.

5.8.1.3 Background multimorbidity

Medical records and electronic primary care records were reviewed to assess for comorbid conditions. Patients were considered to have these if they were documented in primary care records, outpatient clinic letters, if an investigation confirmed diagnosis or it was noted in admission clerking documents. Conditions specifically captured in the study were: left ventricular systolic dysfunction (confirmed by echocardiography, cardiac MRI or on clinical grounds: B-type natriuretic peptide (BNP) level >2000, episodes of pulmonary oedema with cardiomegaly, or a cardiologist confirmation). Where left ventricular systolic dysfunction (LVSD) is present the New York heart association (NYHA) class⁽⁴⁹⁵⁾ was documented; ischaemic heart disease (defined as any previous myocardial infarction or diagnosis of angina pectoris); cerebrovascular disease (any previous diagnosis of transient ischaemic attack, ischaemic stroke or haemorrhagic stroke); cognitive impairment (any diagnosis resulting in chronic confusion, cognitive impairment or any form of dementia); cor pulmonale; depression; APACHE II liver failure (biopsy proven cirrhosis and documented portal hypertension; episodes of upper gastrointestinal bleeding attributed to portal hypertension; previous episodes of hepatic encephalopathy/failure/coma); renal failure treated with either peritoneal or haemodialysis; immunocompromise (defined as receiving therapy which would suppress resistance to infection within four weeks of admission e.g. immunosuppressive therapy, chemotherapy, radiotherapy, high dose steroid (>1.5mg/kg); presence of immunosuppressing disease such as leukaemia, acquired immunodeficiency syndrome, lymphoma); atrial fibrillation (any history of chronic/permanent, historic, new/acute or paroxysmal disease). Presence of atrial fibrillation (AF) was assessed at two time points: prior to admission and up to ventilation. This differentiates between people with a history of AF and those who develop it for the first time after being admitted, but prior to ventilation.

5.8.1.4 Prescribed Medication

Prescription of selected medications prior to admission (even if stopped acutely) and discharge were recorded for the following: long term steroid use (≥ 1 month of continuous use immediately prior to admission); any diuretic; any beta blocker; angiotensin converter blockers or angiotensin II receptor blockers; any statin; any long acting beta two agonist; any long acting muscarinic antagonist; any inhaled

corticosteroid; carbocisteine; azithromycin, or theophylline. Specific generic drug or brand names were not recorded.

5.8.1.5 Admission related

Data were collected on: the time and date of emergency department (ED) arrival, medical ward arrival and of senior (consultant physician/intensivist, but not ED consultant) review; the effectiveness of their cough (subjectively judged by the treating clinician as the ability for the patient spontaneously to clear secretions, accepting that this is substantially limited by its subjective nature and variability between clinicians); height in centimetres; weight in kilograms (BMI was accepted if other values unavailable); whether the patient was deemed suitable for invasive ventilation; whether the patient was for cardiopulmonary resuscitation in the event of cardiorespiratory arrest; the highest level of care received; and the worst observations recorded at two different timepoints. For the recording of observations the first timepoint was 0-4 hours/commencement of ventilation, whichever came first. The second timepoint was the 24 hours before ventilation is commenced. More often than not these timepoints were expected to be the same. The observations recorded were blood pressure (lowest), heart rate (greatest deviation from 70bpm), respiratory rate (highest), temperature (greatest deviation from 37.0 Celsius), Glasgow coma score (lowest), peripheral oxygen saturation (lowest) and associated fraction of inspired oxygen and the presence of confusion.

5.8.1.6 Investigations

The results of certain investigations performed during the admission were recorded, these were: the presence of chest X-ray consolidation (at admission and at the time of ventilation, and in the eyes of the treating clinician); diaphragm height on chest x-ray (measured at the maximum height of the dome from a line between the medial and lateral insertion points; ideally on the right side); blood tests at admission, ventilation and the final set prior to discharge (sodium, potassium, urea, creatinine, albumin, bilirubin, C-reactive protein, glucose, haemoglobin, platelet count, haematocrit, white cell count, eosinophil count); blood gas results at admission, first respiratory acidaemia, time of decision to ventilate, 24 hours after ventilation was commenced, and in the steady period following the discontinuation of ventilation (termed post-wean).

5.8.1.7 Ventilation related

Details of ventilation recorded were: time and date ventilation was initiated and discontinued; the time and date of pH correction; IPAP, EPAP and backup rate after 1 hour of ventilation and the maximum attained; the reason ventilation was discontinued; whether the patient was invasively ventilated (and if yes, the duration of invasive ventilation and whether they had NIV prior or following IMV; if the patient developed late failure of NIV (defined as the recurrence of respiratory acidaemia prior to discontinuation of ventilation with pH falling below 7.35 having previously corrected for ≥ 24 hours, plus a climb in $p\text{CO}_2$ of $\geq 1\text{kPa}$ from the lowest recorded post correction, to $>6.5\text{kPa}$); or developed relapse (defined as the recurrence of respiratory acidaemia more than 24 hours after NIV cessation). Door-to-mask (the time from arrival of the patient to the commencement of NIV) and door-to-acidosis (time from arrival to the development of the first respiratory acidaemia) times were calculated.

5.8.1.8 Survival and post discharge

Survival to discharge, plus the date of discharge from hospital or death were recorded. Patients who died within a week of discharge, where the death was expected or planned for (such as discharged on an end of life care pathway), were not classed as having survived to discharge. These patients would usually die in hospital and moving home is a place of care preference, rather than survival of the acute episode. In patients who did survive to discharge we collected data on the number and cause of readmissions (plus whether NIV was provided again) and if home ventilation was started (and if yes, the reason). If a patient died at any point during the study we captured date, place and cause of death (as documented on medical certificate of death).

5.8.2 Longitudinal Study

All patients surviving to discharge were offered the opportunity to enter the longitudinal study. Reasons for non-entry were documented (ineligible + reason ineligible or declined). The remainder of data collected in the longitudinal study is laid out in section 5.2.2. The only addition was that, in longitudinal study patients starting home ventilation (HNV) in the year following discharge, ventilation pressures and compliance data were also collected.

5.8.3 Clinical Diagnosis patients

The data collected for clinical diagnosis patients was significantly smaller than that of the validation study - primarily the indices in the tool from the derivation study.

Collected data were: Time and date of admission; eMRCd score; BMI; prescription of LTOT prior to admission; presence of LVSD, depression, or AF (up to ventilation); observations in the 24hours prior to ventilation (blood pressure, respiratory rate, GCS); the pH and base excess of the ventilation decision blood gas; blood results (haemoglobin, haematocrit, white cell count, eosinophils, urea, potassium, albumin, c-reactive protein); and survival to discharge. If performed, spirometry data in the year post discharge was obtained.

5.9 Statistical Methods

5.9.1 General approach

Data collected in the study were quantitative and analysis was conducted with IBM SPSS statistics version 24 (IBM, New York, USA) and Stata (StatCorp, Texas, USA). P-values were considered as statistically significant when $p < 0.05$; exact p-values were used where appropriate. Means are presented with the standard deviation, mean (SD), and medians with the interquartile range median (IQR). Categorical variables are presented with proportions. For AUROC and ORs the 95% confidence intervals are presented.

5.9.2 Power calculation

To estimate the sensitivity of the predictive tool (and assuming a standard error of 5%), 85 deaths needed to be studied in the validation. Assuming the population had a mortality rate of 20% in the validation cohort, a minimum of 425 patients were required in the validation study.

5.9.3 Missing data

Throughout the validation and longitudinal study great lengths were gone to, to minimise missing data. Missing data rates highlighted in relevant results sections and are also shown in Appendix B (Section 14.2), but in the validation study the variables associated with outcome in the derivation tool were low. In the longitudinal study there

were higher levels of missing data, which was not unexpected. If there was no initial response (in the case of the longitudinal questionnaires) multiple attempts to collect data were made.

Patterns of missing data exist and are important to consider when trying to deal with missing data. The three types of missing data are missing at random (MAR), missing completely at random (MCAR) and missing not at random (MNAR).^(496, 497)

- MCAR data: the missing data is totally unrelated to any of the other variables, measured or missing. I.e., the probability of missing data is not dependent on anything else.
 - E.g., A questionnaire is lost in the post, or a blood sample is spilt in the analysing laboratory and therefore can't be used.
- MAR data: the missing data is dependent on (or could be predicted by) one or more of the observed variable(s) but is not dependent on the missing data itself. I.e., if there is 'a pattern' to the missing data based on the observed data
 - E.g., A man may not fill in a questionnaire; not to do with any reason in the questionnaire itself, but because he is male.
- MNAR data: The probability of missing data is dependent on the missing variable itself.
 - E.g., The participant in a study would not fill in the questionnaire because they are affected by the subject of the questionnaire itself (wouldn't fill in a HADS *because* they are too depressed).

When data is MCAR there is little chance of introducing bias, though high rates can result in loss of statistical power.⁽⁴⁹⁶⁾ MAR and MNAR can introduce bias, with a larger effect of bias the larger the missingness of data.⁽⁴⁹⁷⁾ In an observational study missingness is generally beyond the researchers' control, and therefore MAR is an assumption, but not easily testable.⁽⁴⁹⁷⁾ While MAR and MNAR may both occur in observational data they are indistinguishable from each other, though departures from MAR are possible, these are not large enough to invalidate the use of MAR-based analysis.^(497, 498)

When handling missing data and imputing replacement variables (by any means) it is important not to redefine the characteristics of the population being studied, as this can introduce bias.⁽⁴⁹⁷⁾ Traditional methods of imputation, such as mean substitution (where

the missing data is replaced by the mean score for that population), or simply not analysing individuals with any missing data, may reduce standard error and introduce bias.⁽⁴⁹⁷⁾ In this study expectation-maximisation (EM) methods were used to impute missing data. The expectation step, 'E', estimates values for the missing data using existing variables and creates a probability of distribution of data. The maximisation step, 'M', feeds the new data into a statistical model and checks if the estimated values is the most likely value by tweaking the probability distribution. These steps repeat (by re-imputing a more likely value for missing data in the E step) until there is stability between the values in the E and M steps; giving a 'best fit value' for the missing data. This method uses the assumption of MAR and results in a complete data set (allowing individuals without complete data to be included in analysis) with production of nearly unbiased results and smaller underestimation of standard error than other methods.^(496, 497, 499) Whilst multiple imputation can be employed, the EM algorithm is acceptable in datasets with low rates of missing data, such as expected in this study. EM only results in one dataset and it is therefore substantially simpler to analyse resultant data. In the results section EM data is presented unless otherwise specified.

5.9.4 Normality

Normality can be assessed quantitatively by using either the Kolmogorov-Smirnoff or Shapiro-Wilk tests; although in large sample sizes these can produce significant results (i.e. state data is not normally distributed) even for small, unimportant deviations from a perfect normal distribution.⁽⁵⁰⁰⁾ Therefore, normality was principally assessed by visual inspection of the histogram as well as by examining skewness, kurtosis, the mean (plus SD) and median (plus IQR). Parametric tests were applied to normally distributed data and non-parametric tests to non-normally distributed data. When presenting averages, mean (SD) is presented for normally distributed, and median (IQR) for non-normally distributed data. Histograms of population descriptors are shown in Appendix C (section 14.3, page 286).

5.9.5 Univariate comparisons

Univariate comparisons were made with chi-squared or Fisher's exact test for categorical variables, students t-test for parametric data and Mann-Whitney-U for non-parametric variables. ANOVA was used for parametric data, and Kruskal-Wallis for non-parametric data when examining trends within a group. Two sided tests were used unless specified otherwise and when using independent t-tests variance was assessed with Levene's test and the appropriate t-test result reported accordingly.

5.9.6 Logistic regression

Logistic regression analysis in any form attempts to recognise predictive, but unknown, data on a dependent variable from a set of otherwise known (independent) variables. The dependent variable is often known as the outcome variable. The simplest form of regression is linear regression in which a straight 'line of best fit' is drawn between data. If you had knowledge of the equation to create that line and results of new data, it would be possible to predict outcome. In multivariate regression there are multiple independent variables used in the regression model to predict outcome of the dependent variable.

In the NIVO validation study, only predictors previously identified in the derivation study (section 5.1) were examined in two multivariate logistic regression analyses; a 'forced entry' and a 'backwards stepwise' analysis. The same methodology was used for selecting candidate predictors of poor quality of life in the longitudinal study. One important thing to consider is that all variables collected cannot simply be added into a regression equation as this may result in overfitting of the model – where the regression results are too closely influenced by the indices of the original dataset and fail to predict new outcomes in different datasets with a similar population well.

5.9.6.1 *Forced entry regression*

Forced entry, or 'enter', regression analysis ensures all entered variables stay within the regression model and that none are removed; the user therefore has to ensure that there is logic behind the variables entered into the model in the first place. This allows a complete assessment of the variables entered, as well as comparison of their relative value against each other.⁽⁵⁰⁰⁾

5.9.6.2 *Backwards stepwise regression*

In this regression type the user enters all the independent variables to be assessed. When the model is tested the weakest independent predictor of outcome is dropped from the model. The new model is then retested and steps are repeated until only significantly predictive (significance level is defined pre-test) variables remain in the model.⁽⁵⁰⁰⁾ In NIVO the pre-specified significance level was set at <0.05 and removal significance level of the predictors was set at 0.10.⁽⁴⁶⁹⁾ Odds ratios are presented with 95% confidence intervals.

5.9.6.3 *Assessment of the model*

Once the regression model has been developed it needs to be assessed to ensure it is an accurate representation of the data.

5.9.6.3.1 *Model fit*

The most important aspect of ensuring good model fit is careful consideration of variables being entered into it. However, statistical methods should also be employed to ensure that model fit is good. When the regression analysis is calculated it creates a prediction of outcome. This can be measured against observed outcome, the difference between these is a 'residual value', of which studentized residuals are considered the most reliable. If more than 5% of studentised residuals fall outside $> \pm 1.96$ this suggests an unacceptable amount of error in the model.⁽⁵⁰⁰⁾ Additional analysis is undertaken by assessment of the Cook's distance, which measures the influence of individual cases on the regression model. Any cases in which the Cook's distance is > 1 suggest that that case could be overly influential. Finally, model fit was also tested with Leverage values. Similarly to a Cook's score, leverage values > 3 times the mean leverage could be exerting influence on the model. The expected mean leverage is calculated from the model and number of cases (expected mean leverage = number of variables in the final regression + 1 / number of cases).⁽⁵⁰⁰⁾

5.9.6.3.2 *Calibration and Discrimination*

Calibration (see section 3.3.3) assessment was performed by two methods. First, by the Hosmer-Lemeshow goodness of fit test, where a non-significant value suggests good calibration of the model to the data.^(469, 470, 500) Secondly the R^2 was calculated, which describes how much of the variability of the outcome is accounted for by the model

itself. An R^2 of 1.00 would mean all variation in outcome is accounted for by the model.⁽⁵⁰⁰⁾ Additionally, a calibration plot of observed versus predicted mortality was plotted. Discrimination is tested by the assessment of the AUROC curve, discussed in more detail below.

5.9.7 Specificity, sensitivity and receiver operating characteristic curves

In a simple dichotomous test it possible to assess its 'diagnostic' accuracy with a 2x2 table (Table 10). This will reveal the tests sensitivity (the correct detection of a truly positive case) and specificity (the correct detection of a truly negative case). The sensitivity is calculated by examining all subjects in which the disease is present

Table 10. Simple 2x2 contingency table

	DISEASE PRESENT	DISEASE ABSENT
TEST POSITIVE	True positive (TP)	False positive (FP)
TEST NEGATIVE	False negative (FN)	True Negative (TN)

(Sensitivity=TP/TP+FN) and specificity where disease is absent Specificity=TN/TN+FP).^{(501,}

⁵⁰²⁾ In tests which are ordinal or continuous (such as predictive models outcome assessment), 2x2 tables cannot be used, but receiver operation characteristic (ROC) curves can be. ROC curves are essentially demonstrating the relationship between sensitivity and 1-specificity across a number of discrete cut off points for the test; measured by the 'area under the ROC' (AUROC/C-statistic). This yields a score between 0-1; the maximum score (1.00) equates to the perfect prediction of outcome, with a score of 0.50 would suggest no better prediction than that of chance.⁽⁵⁰¹⁾ When considering 'how good' the predictive ability of a test is AUROC can be very helpful: a score of >0.9 is considered highly accurate, with 0.7-0.9 moderately accurate and 0.5-0.7 of low accuracy.⁽⁵⁰³⁾ It's worth noting that in predictive modelling, rather than diagnostic

testing, AUROCs are generally lower: 0.6-0.85 is common, and scores of 0.75-0.85 are considered to be good.^(469, 504) The ROC curves (of the predictive tool and other predictive models) were calculated in the validation cohort of patients to assess discrimination of the tools, and comparisons of these AUROCs were made using the method of DeLong.⁽⁵⁰⁵⁾

5.9.8 Ensuring validity of the tool

The validation study of NIVO was prospective, temporally separated (a later time period) from the derivation study, and had geographic validation across England and Wales (ensuring variation in disease prevalence, socioeconomic status and rurality), as well as a mix of hospital types (district general and tertiary centres; with acute NIV provision in a range of settings). Consecutive patients were recruited to reduce bias. Additionally, treating clinicians and external investigators were blind to the derivation tool indices, in keeping with the PROBAST and TRIPOD gold standards for predictive model design.^(467, 468)

5.9.9 Subgroup analysis

Mortality and readmission rates were compared by Chi Squared/Fisher's exact tests in patients with (and without) the following characteristics

- Late failure of NIV, as defined in section 5.8.1.7
- Persistent hypercapnia
- Long term oxygen therapy
- Domiciliary ventilation at discharge
- Eosinopenia ($<0.05 \times 10^9/L$) on discharge

In addition, survival analysis by Kaplan-Meier estimator was performed for both time to readmission and time to mortality in each of these groups and statistical significance between curves was compared by the log-rank test.⁽⁵⁰⁶⁾

5.9.10 Longitudinal study QoL

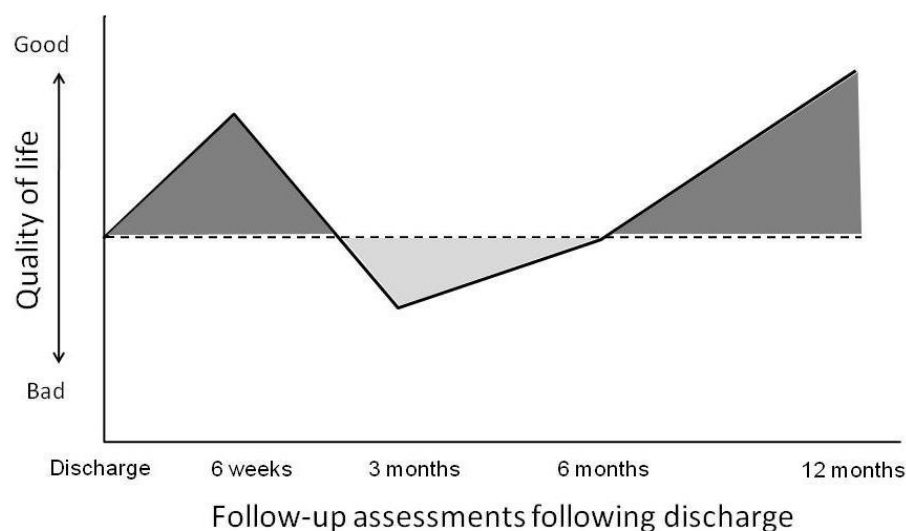
Changes in longitudinal quality of life were measured in three ways: mean change over follow up, time to best score and time equal to or better than baseline. Changes were

assumed to occur in a rectilinear fashion; where patients missed follow-up appointments (with resultant missing data), there was an assumption of a linear change between the last recorded result and the next available either side of the missing data. Death was equated to the worst outcome possible in each questionnaire (with the exception of the EQ-5D-5L which specifies death as a score of zero). If a patient consented into the longitudinal study but had no follow up data they were excluded from longitudinal analysis. Univariate comparisons were performed as in the validation study. Changes for time for binary questions over time were measured using McNemar's test and changes between groups measured by ANOVA.

5.9.10.1 Mean change in QoL

The mean change in QoL for each tool was measured over the longitudinal period to provide a global measure comparable to the minimum clinically important difference (MCID). This is a relatively novel approach and takes into account the whole period of follow up, as opposed to simply stating the result of repeated assessments at finite time points. A schematic of this is shown in Figure 12. The mean change is the area above baseline (shaded in dark grey) minus the area lower than baseline (shaded in light grey), where baseline is the dotted line.

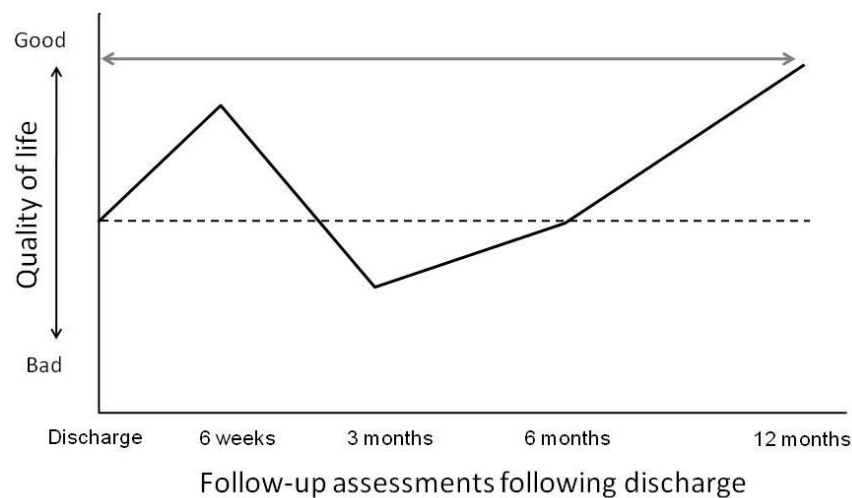
Figure 12. Schematic of how mean change was calculated over the longitudinal study.



5.9.10.2 Time to best

The time taken for the patient to reach their best QoL, functional status and HADS score following discharge was calculated and is considered 'time to recovery' from discharge. This is represented in Figure 13.

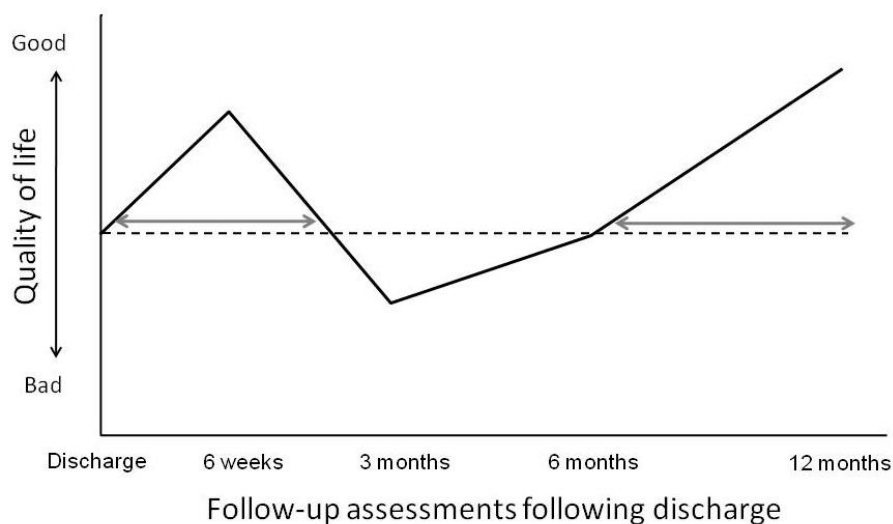
Figure 13. Schematic of how 'time to best' was calculated over the longitudinal study.



5.9.10.3 Time above baseline

This measures the amount of time the patients spent with a QoL better than their baseline score. This is of importance as there can be concern (from patients, carers and healthcare teams) that patients 'never get better' or will have a downward trajectory in their QoL following admission and ventilation – these beliefs can influence clinical decisions. This is a simple measure which can be easily communicated. This is shown as a schematic in Figure 14..

Figure 14. Schematic of how time better than baseline (arrows) was calculated over the longitudinal study.



6 Results of the validation study

The results of the validation study are described in this section. The derivation study, which produced the candidate variables for the clinical predictive tool has been discussed in brief earlier (section 5.1) and is the subject of another doctoral thesis. The results in this section refer solely to the validation study or clinical diagnosis patients (section 5.2.1.1) where specified. Data for this aspect of the NIVO project were collected jointly by Dr Tom Hartley and myself. All analyses performed below have been undertaken by myself.

6.1 Missing data

Missing data rates for the variables in the derivation study model were low, and are as follows: eMRCD 0%, Atrial Fibrillation 0%, chest x-ray consolidation 0%, Long term oxygen therapy 0%, pH 0%, time to acidaemia 0%, Eosinophil count 2.9%, Glasgow coma score 2.6%. Missing data rates for variables are detailed in Appendix B (Section 14.2).

6.2 Headline data

The NIVO study opened to recruitment on 14/10/2016 and closed to recruitment on 28/2/2018, with a total recruitment time of 503 days. In this time period 733 patients were recruited to the validation study, exceeding the power target of 425. Internal recruitment closed at 200 patients (27.3% of total). External centres closed to recruitment either when a pre-agreed target was met, or when the study closed on 28/2/18. The follow up period ended one year from the day of discharge, or at the death of the patient if this occurred in the interim period. Inpatient mortality overall was 20.1%.

An additional 111 patients were recruited to the clinical diagnosis group. Of these, 22 (19.8%) were recruited locally.

6.2.1 Recruitment and targets

Recruitment targets for each site, and therefore performance relative to these, have been withheld. Three sites recruited to $\geq 100\%$ of their target, 5 sites recruited to $\geq 80\%$

of their target and two sites recruited <80% of their target. Overall recruitment was 94% of target. No specific targets were set for the clinical diagnosis (CD) group. Table 11 summarises recruitment across all sites.

Table 11. NIVO validation and clinical diagnosis (CD) recruitment by site

Recruiting site	Number	% of NIVO	Recruitment per day	CD recruits
Northumbria Healthcare	200	27.3%	0.57	22
Nottingham University Hospitals	77	10.5%	0.21	23
Derriford Hospital, Plymouth	37	5.0%	0.17	7
Lane Fox Unit, St Thomas' hospital	60	8.2%	0.13	5
Leeds Teaching Hospitals	116	15.8%	0.28	20
Oxford University Hospitals	14	1.9%	0.07	0
Hywel Dda University Health Board	44	6.0%	0.09	14
Queen Elizabeth Hospital, Gateshead	69	9.4%	0.18	6
South Tyneside District General Hospital	67	9.1%	0.15	8
Musgrove Park Hospital, Taunton	49	6.7%	0.14	6
Total	733	100%	1.46	111

6.3 Population description

Results from here will only refer to the validation patients. Clinical diagnosis patients will not be discussed again until Chapter 8.

The average patient in NIVO is a white, current smoker, female in their early 70s. They are likely to have been admitted to hospital (for any reason) within the previous year, and have a substantial cigarette pack year history (see Table 12). The overwhelming ethnicity in NIVO was Caucasian. This may appear to be initially unrepresentative given the UK population is 86% Caucasian. When examining only those age 60 or over 95.3% are white, so the NIVO population is more representative than it initially appears.⁽⁵⁰⁷⁾ A surprising number of patients were smokers at admission. There was no significant difference between people who had previously been admitted and who currently smoked (≥ 1 admission + smoker=62.9% vs. no admissions + smoker=63.4%; $p=0.934$).

The same was seen for those who had had previous NIV (previous NIV + smoker=64.1% vs. no previous NIV +smoker=62.5%; p0.690).

Table 12. Selected population descriptors from the NIVO validation cohort

Variable	Result
Age*	70.5 (9.3)
Female	58.3%
Caucasian	98%
Current Smoker	63.1%
Cigarette Pack Years*	45.5 (22.6)
≥1 admission in the last 12 months	68.9%
Number of admissions in last 12 months [†]	1 (0-3)

*Mean (SD) [†]Median (IQR)

6.3.1 Home circumstances

The vast majority of patients in NIVO were admitted from their own home (92.3%). Only 17.5% of patients were recorded as having formal carers. This is unlikely to be truly reflective of the actual burden of care for these patients: 56% of patients in NIVO could not get out of the house unassisted and 21.8% require assistance with both washing and dressing (eMRCD 5b) (results in section 6.3.4). There is likely to be a significant amount of ‘informal’ care being performed for these patients which is unrecognised.

Table 13. The home circumstances immediately preceding the index admission in the NIVO study.

Admitted from	% of NIVO patients
Home	74.8%
Home (with carers)	17.5%
Sheltered accommodation	1.4%
Sheltered accommodation (with carers)	1.0%
Residential care	3.1%
Nursing care	1.6%
Community hospital	0.4%
Homeless	0.3%

6.3.2 Coexistent conditions

Comorbid conditions collected in the validation study were limited to those which showed univariate association with mortality in the derivation study, or that were required for calculation of the APACHE II score. Table 14 shows the prevalence of these in the NIVO population. There is a substantial amount of comorbid disease in this population, in keeping with the literature. When examining the prevalence of cardiovascular disease captured (LVSD, AF, IHD, Stroke, Cor Pulmonale) in the validation population 14.5% had 2 cardiovascular diseases, 6.3% had 3 cardiovascular diseases and 2.5% had >3 cardiovascular diseases; illustrating the idea that COPD is associated with multimorbidity.

Table 14. Percentage of patients diagnosed with co-morbid disease at index admission

Condition	% of NIVO patients diagnosed
Cor Pulmonale	22.5%
Left ventricular systolic dysfunction	14.1%
NYHA Class[†]	3 (2-3)
Atrial Fibrillation	18.7%
Ischaemic Heart disease	22.5%
Cerebrovascular disease	9.7%
Cognitive impairment	7.8%
Depression	23.6%
Liver failure*	0.5%
Renal failure*	0.3%
Immunocompromise*	1.8*

[†]Median (IQR) *as defined by the APACHE II score⁽⁴⁸⁴⁾ NYHA= New York Heart Association

6.3.3 Medication

Similarly to comorbidity recording, in the validation study only selected medications were recorded at admission (Table 15). The median (IQR) number of medications prescribed was 4 (3-6). With regard to inhaled COPD therapy 12.1% were on LABA+LAMA; 14.2% on LABA+ICS; 61.9% on triple therapy (LABA+LAMA+ICS); 5.1% on single agent LABA or LAMA or ICS; 1.9% on LAMA+ICS and 4.8% had no inhaled

medication documented. It is possible that a proportion of patients were on nebulised short acting bronchodilators, although this was not captured.

Table 15. Percentage of patients prescribed selected medication at admission

Medication	% of NIVO patients prescribed
Long term oral steroids	10.2%
Diuretic	36.7%
Beta blocker	23.2%
ACEi or ARB	26.9%
Statin	44.2%
Long acting beta-2-agonist	89.5%
Long acting muscarinic antagonist	78.9%
Inhaled corticosteroid	79.0%
Oral Carbocisteine	47.3%
Maintenance Azithromycin	12.3%
Oral Theophylline	10.0%

ACEi = Angiotensin converting enzyme inhibitor; ARB= angiotensin receptor blocker

6.3.4 Extended MRC dyspnoea scores

The eMRCD score was the strongest predictor of mortality in the derivation study and remains significantly associated in the validation (Mann-Whitney U test= $p<0.0001$). In the validation study, 56% of patients had an eMRCD score of 5a or 5b; meaning they were unable to get out of the house independently on their best day within the preceding 3 months.

Table 16. eMRCD score in the validation study, with inpatient and 90-day mortality.

eMRCD Score	Number of patients	% of NIVO patients	Inpatient mortality	90-day mortality
1	9	1.2%	0%	11.1%
2	18	2.5%	0%	11.1%
3	53	7.2%	3.8%	13.2%
4	242	33.0%	11.2%	19.4%
5a	251	34.2%	24.7%	37.8%
5b	160	21.8%	35.0%	52.5%

eMRCD Score	Number of patients	% of NIVO patients	Inpatient mortality	90-day mortality
Total	733	100%	20.1%	32.2%

There is a clear incremental increase in both inpatient, and 90-day post discharge mortality, with higher eMRCD scores (Table 16). The jump in mortality from inpatient to 90 days in eMRCD 1 and 2 patients at first appears striking, though the numbers are very low and 90-day mortality represents only three deaths across both categories.

6.3.5 COPD severity

Lung function results for the cohort are demonstrated in Table 17. Splitting the cohort by severity of airflow obstruction shows over 80% of the NIVO cohort had severe or very severe airflow obstruction (Table 18).

Table 17. Lung function, body mass index and other respiratory history at admission.

Variable	Result
FEV₁[*]	0.84L (0.36)
Percentage predicted FEV₁[*]	37.2% (15.39)
FVC[*]	1.96L (0.71)
FEV₁/FVC[*]	0.44 (0.12)
Body mass index[†]	24.1 (19.6-29.7)
On LTOT at admission	28.6%
Previous NIV treatment	35.9%
On home NIV at admission	8.7%

*Mean (SD) †Median (IQR). FEV₁=forced expiratory volume in one second; FVC=forced vital capacity; LTOT=long term oxygen therapy; NIV=non-invasive ventilation.

Where patients had either or both the absolute values of FEV₁ or FVC missing, but there had been confirmation of the presence of airflow obstruction in a pre-admission document by a physician (such as a respiratory outpatient clinic letter) this could be declared, and patients could be entered included; 35 such patients were included in the validation study. If there were missing lung function values and there was no prior

documentation about airflow obstruction, patients were only eligible for the clinical diagnosis group.

Table 18. NIVO population categorised by severity of airflow obstruction.

COPD severity by FEV₁ % predicted	Percentage of NIVO population
Mild	0.9%
Moderate	18.8%
Severe	43.6%
Very Severe	36.8%

6.3.6 Mortality by site

There was some variation in both the inpatient (lowest 12.2%, highest 28.4%) and 90-day (lowest 24.3% and highest 40.3%) mortality between NIVO sites (Table 19).

However, across the 10 sites as a whole there was no statistically significant difference (χ^2) in either inpatient $p=0.471$) or 90-day ($p=0.643$) mortality.

Table 19. Mortality by recruiting site

Recruiting site	N	Inpatient Mortality	90-day mortality
Northumbria Healthcare	200	18.0%	31.0%
Nottingham University Hospitals	77	19.5%	40.3%
Derriford Hospital, Plymouth	37	13.5%	24.3%
Lane Fox Unit, St Thomas' hospital	60	18.3%	26.7%
Leeds Teaching Hospitals	116	19.8%	32.8%
Oxford University Hospitals	14	21.4%	28.6%
Hywel Dda University Health Board	44	25.0%	36.4%
Queen Elizabeth Hospital, Gateshead	69	26.1%	33.3%
South Tyneside District General Hospital	67	28.4%	27.3%
Musgrove Park Hospital, Taunton	49	12.2%	24.5%
Total	733	20.1%	32.2%

6.3.7 Mortality by time of recruitment

Patients were only included in NIVO once. Patients recruited near the beginning of the study at each site could be over representative of patients who frequently attend hospital; therefore, mortality may be lower in that recruitment period compared to patients recruited later. This was not consistently seen across NIVO sites – no site had a statistically significant difference in either inpatient or 90-day mortality rates split by quarter (of total patients at that site), nor in 1st quarter vs remaining patients (Table 20 and Table 21).

Similarly, when the whole cohort of patients was ordered by recruitment dates and split into groups of 50 patients, there is no clear pattern in mortality rate changes although the staggered start of recruitment of each site, plus seasonal variation in recruitment complicates this (Table 22).

Table 20. Inpatient and 90-day mortality by recruitment quarters at each site

Site	N	Inpatient Mortality rate (%)					90-day mortality rate (%)				
		Quarter 1	Quarter 2	Quarter 3	Quarter 4*	P value [†]	Quarter 1	Quarter 2	Quarter 3	Quarter 4*	P value [†]
Northumbria	200	12.0%	22.0%	20.0%	18.0%	0.594	26.0%	38.0%	26.0%	34.0%	0.471
Nottingham	77	25.0%	10.0%	10.0%	35.3%	0.145	40.0%	30.0%	50.0%	41.2%	0.643
Plymouth	37	0.0%	20.0%	10.0%	28.6%	0.336	20.0%	40.0%	10.0%	28.6%	0.454
London	60	33.3%	6.7%	13.3%	20.0%	0.273	40.0%	20.0%	20.0%	26.7%	0.563
Leeds	116	20.7%	13.8%	13.8%	31.0%	0.304	34.5%	27.6%	24.1%	44.8%	0.349
Oxford	14	25.0%	25.0%	25.0%	0%	0.888	25.0%	25.0%	50.0%	0.0%	0.626
Llanelli	44	36.4%	9.1%	27.3%	27.3%	0.512	45.5%	27.3%	27.3%	45.5%	0.666
Gateshead	69	23.5%	47.1%	11.8%	22.2%	0.117	35.3%	47.1%	23.5%	27.8%	0.483
South Tyneside	67	35.3%	23.5%	17.6%	37.5%	0.529	41.2%	29.4%	35.3%	43.8%	0.831
Taunton	49	0.0%	8.3%	16.7%	23.1%	0.323	8.3%	33.3%	25.0%	30.8%	0.479
Total	733	20%	18.9%	16.2%	25.3%	0.181	31.9%	33.0%	28.1%	36.0%	0.453

*Quarter 4 may contain a different number of patients to other quarters due to rounding; [†]Chi squared test

Table 21. Inpatient and 90-day mortality by first quarter recruitment vs. remaining patients across at each site.

Site	N	Inpatient Mortality (%)			90-day mortality (%)		
		Quarter 1	Quarter 2-4	P value*	Quarter 1	Quarter 2-4	P value*
Northumbria	200	12.0%	20%	0.287	26.0%	32.7%	0.480
Nottingham	77	25.0%	17.5%	0.518	40.0%	40.4%	1.000
Plymouth	37	0.0%	18.5%	0.295	20.0%	25.9%	1.000
London	60	33.3%	13.3%	0.122	40.0%	22.2%	0.195
Leeds	116	20.7%	19.5%	1.00	34.5%	32.2%	0.823
Oxford	14	25.0%	20.0%	1.00	25.0%	30.0%	1.000
Llanelli	44	36.4%	21.2%	0.425	45.5%	33.3%	0.492
Gateshead	69	23.5%	26.9%	1.000	35.3%	32.7%	1.000
South Tyneside	67	35.3%	26.0%	0.538	41.2%	36.0%	0.775
Taunton	49	0.0%	16.2%	0.314	8.3%	29.7%	0.247
Total	733	20.0%	20.1%	1.00	31.9%	32.3%	1.000

*Two tailed Fishers' exact test

Table 22. Mortality by each 50 patients in order of recruitment, recruitment start for each site and months of recruitment

Patient by date	Inpatient Mortality	90-day mortality	Sites recruiting (first recruited patient number)	Months
1-50	18.0%	28.0%	Northumbria (from 1) London (from 28) Llanelli (from 31) Gateshead (from 39)	Oct 2016, Nov, Dec
51-100	24.0%	34.0%	South Tyneside (from 73)	Dec
101-150	22.0%	38.0%	Leeds (from 119)	Dec, Jan 2017
151-200	24.0%	38.0%		Jan, Feb

Patient by date	Inpatient Mortality	90-day mortality	Sites recruiting (first recruited patient number)	Months
201-250	18.0%	22.0%	Nottingham (from 228) Taunton (from 235)	Feb, March
251-300	16.0%	30.0%		March, April
301-350	18.0%	30.0%		April, May
351-400	20.0%	26.0%		May, June
401-450	12.0%	30.0%		June, July
451-500	12.0%	22.0%	Plymouth (from 459) Oxford (from 466)	July, Aug
501-550	26.0%	42.0%		Aug, Sept, October
551-600	18.0%	42.0%		Oct, Nov
601-650	14.0%	28.0%		Nov, Dec, Jan 2018
651-700	32.0%	38.0%		Jan
701-733	30.3%	36.4%		Feb

6.3.8 Seasonality of mortality

Mortality rates for ECOPD vary by season and wintery weather is associated with higher exacerbation rates.⁽²⁹⁰⁾ NIVO was open to recruitment over two autumn/winter periods, and one spring/summer period. Mortality by season is shown in Table 23.

Table 23. Mortality rate by season.

Season	N	Mortality rate
Winter	309	24.3%
Spring	164	18.3%
Summer	111	11.7%
Autumn	149	19.5%

6.4 Admission specific descriptors

6.4.1 Observations

These variables are the worst (most abnormal) recorded in the 24 hours preceding the commencement of assisted ventilation. The average NIVO patient was normotensive, tachycardic, tachypnoeic and apyrexial, with low oxygen saturations (Table 24). Around a quarter of patients were confused prior to ventilation. The Glasgow coma score was 14 or less in 260 (35.5%) patients and <8 (the level which BTS guidelines specify increases risk of NIV failure⁽³¹⁶⁾) in 31 (4.2%) patients.

Table 24. Worst observations recorded in the 24 hours prior to the commencement of assisted ventilation.

Variable	Result
Systolic blood pressure* (mmHg)	133.3 (34.2)
Diastolic blood pressure* (mmHg)	75.4 (20.7)
Heart rate* (bpm)	109.9 (21.4)
Respiratory rate* (bpm)	28.4 (7.4)
Temperature* (°C)	36.7 (1.0)
Oxygen Saturations† (%)	87 (81-90)
Glasgow Coma Score†	15 (14-15)
Confusion present	25.1%
Effective cough	84.9%

*Mean (SD) †Median (IQR).

6.4.2 Chest x-ray

The BTS NIV guideline states that NIV is not indicated in patients with pneumonia, and is associated with increased failure rate.⁽³¹⁶⁾ Despite this, in NIVO a significant minority of patients had consolidation on CXR in the opinion of the treating clinician. Of the 279 patients with CXR changes at the point of ventilation, 262 had the changes at admission (Table 25). One patient with CXR consolidation at admission had resolution of changes by the point of ventilation. Diaphragm height on CXR was measured as a surrogate marker of hyperinflation (which is associated with worse mortality⁽⁵⁰⁸⁾); this measurement has some limitation in terms of a patients' ability to breath hold whilst in respiratory distress, but is simple to measure on an already routinely performed

examination. It was not, however, significantly different between patients who died as an inpatient (mean height in survivors 2.41cm vs. non survivors 2.327cm; t-test $p=0.362$) or those who died up to 90 days (mean height in survivors 2.44cm vs. non-survivors 2.30cm; t-test $p=0.066$), although a trend towards smaller height in non-survivors was seen. Remaining results refer to ventilation CXRs, unless otherwise specified.

Consolidation was more common in older patients (Mean (SD) age with consolidation 72.4 (9.3) vs no consolidation 69.4 (9.2); t-test $p<0.001$)

Table 25. Chest x-ray findings at admission and ventilation.

Variable	Result
Chest x-ray consolidation at admission	35.9%
Chest x-ray consolidation at ventilation	38.1%
Diaphragm Height* (cm)	2.4cm (1.0)

*Mean (SD) †Median (IQR). Chest x-ray consolidation in the opinion of the treating senior clinician; Diaphragm height was measured in centimetres from a line drawn between the lateral and medial insertion points and the maximal height of the dome on chest X-ray.

6.4.2.1 Consolidation and eMRCD

Whilst the prevalence of CXR consolidation in the eMRCD 1 population appears substantially lower than the other MRCD scores (Table 26), there were only 9 patients with this eMRCD therefore reducing the validity of this result. There was no significant difference between eMRCD grade and presence of pneumonia ($\chi^2 p=0.484$)

Table 26. eMRCD score and the percentage of patients with chest x-ray consolidation at the point of ventilation.

eMRCD Score	Presence of consolidation n (%)
1	1 (11.1%)
2	7 (38.9%)
3	16 (30.2%)
4	94 (38.8%)
5a	99 (39.4%)
5b	62 (38.8%)

6.4.2.2 Consolidation and home circumstance

Similarly to the eMRCD score, the background residence of the patient had no bearing on the likelihood of having CXR consolidation at the time of ventilation (χ^2 p=0.636, Table 27).

Table 27. Background residence and rate of chest x-ray consolidation.

Admitted from	Presence of consolidation n (%)
Home	204 (37.2%)
Home (with carers)	54 (42.2%)
Sheltered accommodation	3 (30.0%)
Sheltered accommodation (with carers)	3 (42.9%)
Residential care	11 (47.8%)
Nursing care	3 (25.0%)
Community hospital	0 (0%)
Homeless	1 (50.0%)

6.4.2.3 Consolidation and comorbidity

Atrial Fibrillation, Ischaemic heart disease and cognitive impairment were all significantly associated with increased risk of consolidation, but other comorbid conditions were not (

Table 28). It may be that the infiltrates seen in IHD and AF were not only pneumonic change, but increased opacification from heart failure; although this may then have been expected in LVSD too. Cognitive impairment may be associated due to the increased risk of aspiration pneumonia, and whilst not statistically significant there is a trend in cerebrovascular disease which may also reflect this.

Table 28. Prevalence of CXR consolidation by presence or absence of comorbidity

	Comorbidity not present	Comorbidity present	P value*
Cor Pulmonale	221 (38.9%)	58 (35.2%)	0.413
LVSD	242 (38.4%)	37 (35.9%)	0.663
Atrial Fibrillation	207 (35.1%)	72 (50.3%)	0.001
IHD	201 (35.4%)	78 (47.3%)	0.006

	Comorbidity not present	Comorbidity present	P value*
CVD	244 (36.9%)	34 (47.9%)	0.073
Cognitive impairment	249 (36.9%)	30 (52.6%)	0.023
Depression	212 (37.9%)	67 (38.7%)	0.858
Immunocompromise[^]	274 (38.1%)	5 (38.5%)	1.000
Renal Failure[^]	278 (38.0%)	1 (50.0%)	1.000
Liver Failure[^]	278 (38.1%)	1 (25.0%)	1.000

*Fishers exact test. [^]As defined in the APACHE II score. LVSD= Left ventricular systolic dysfunction; IHD= Ischaemic heart disease; CVD= cerebrovascular disease.

6.4.2.4 Consolidation and observations

Patients with consolidation had statistically lower systolic blood pressure, higher temperature, lower oxygen saturations and GCS, all in keeping with findings in pneumonia and sepsis, although the values do not demonstrate obvious clinically important differences (Table 29). The other observations associated with sepsis (RR, HR) were statistically similar with or without consolidation, though still physiologically abnormal.

Table 29. Observations between patients with and without CXR consolidation

Variable	No consolidation	Consolidation	P value
Systolic blood pressure (mmHg)	135.4 (35.4)	129.9 (31.9)	0.036*
Diastolic blood pressure (mmHg)	76.4 (21.7)	73.8 (18.9)	0.097*
Heart rate (bpm)	110.2 (20.1)	109.4 (23.3)	0.670*
Respiratory rate (bpm)	28.4 (7.3)	28.5 (7.6)	0.908*
Temperature (°C)	36.6 (0.9)	36.8 (1.1)	<0.001*
Oxygen Saturations (%)	87 (81-91)	86 (80-90)	0.039†
Glasgow Coma Score	15 (14-15)	15 (13-15)	0.002†

*Students T-test with variables presented as Mean (SD); †Mann-Whitney-U test with variables presented as Median (IQR)

6.4.2.5 Consolidation and outcome

The presence of chest x-ray consolidation was associated with both a higher inpatient mortality and a higher 90-day mortality (Table 30); in keeping with the findings of both the NIVO derivation study and the DECAF score.⁽¹⁶²⁾

Table 30. Mortality rates with and without CXR consolidation.

	Consolidation present	No consolidation	P value*
Inpatient mortality	73 (26.2%)	74 (16.3%)	0.002
90-day mortality	103 (36.9%)	133 (29.3%)	0.034

*Chi-squared test

6.4.3 Blood results

Blood tests were recorded both at admission within the in the 24hrs prior to ventilation 'NIV decision' (Table 31). There is a sizable overlap in these results where patients came into hospital and were ventilated soon after admission – only 17.9% of patients developed acidaemia >24hrs from admission. No obviously anomalous results appear, and the results represent what might be expected from a patient presenting in type two respiratory failure from ECOPD.

Table 31. Blood results at admission and at NIV decision

Investigation	At admission	At NIV decision
Haemoglobin (g/dL)*	13.8 (2.1)	13.7 (2.1)
Haematocrit (L/L)*	0.43 (0.06)	0.43 (0.06)
Platelets (x10⁹/L)*	272.1 (107.4)	271.9 (107.5)
White Cell Count (x10⁹/L)*	12.9 (6.8)	13.1 (6.8)
Eosinophil Count (x10⁹/L)[†]	0.0 (0.0-0.1)	0.0 (0.0-0.1)
Eosinophil count <0.05 (%)	52.9%	53.5%
Sodium (mmol/L)*	136.7 (5.5)	136.9 (5.5)
Potassium (x10⁹/L)*	4.6 (0.6)	4.6 (0.6)
Urea (x10⁹/L)[†]	6.9 (5.0-10.2)	7.0 (5.1-10.3)
Creatinine (x10⁹/L)[†]	74 (58-99)	74 (57-99)
Baseline creatinine*	70.6 (28.8)	n/a
Albumin (g/L)*	37.9 (5.1)	37.7 (5.2)
Bilirubin[†] (μmol/L)	8.0 (6.0-12.1)	8.0 (6.0-12.0)
Glucose (mmol/L)*	8.3 (3.3)	8.2 (3.4)
CRP (mg/L)[†]	39 (13-105)	40 (13-110)

* Mean (SD) [†]Median (IQR)

6.4.4 Arterial blood gases

Blood gases were recorded at various time points: admission, the first documented respiratory acidaemia, NIV decision, 24hrs after ventilation commenced, and 'post-wean' from ventilation. The first respiratory acidaemia ABG frequently overlapped with admission gases and is primarily used to calculate timings (e.g., door-to-acidosis time) and is not shown below. There is no missing data for the NIV decision gas (used as an inclusion criterion and in the derived tool), therefore the results in Table 32 are raw, not EM data.

Table 32. Blood gas results

Time of gas	Missing data	pH [†]	PaO ₂ [†]	PaCO ₂ [†]	HCO ₃ ^{-*}	Base Excess [*]
Admission	2.7%	7.29 (7.24-7.35)	7.70 (6.12-9.72)	9.00 (7.40-10.90)	30.3 (6.7)	4.9 (6.5)
NIV gas	0%	7.27 (7.22-7.30)	8.00 (6.72-9.80)	9.60 (8.20-11.60)	30.5 (6.8)	4.6 (6.6)
24hr gas	14.5%	7.37 (7.33-7.41)	8.15 (7.30-9.28)	7.20 (6.20-8.50)	30.3 (6.3)	5.7 (6.2)
Post-wean	43.7%	7.41 (7.38-7.45)	7.80 (6.90-8.90)	6.85 (6.09-8.02)	32.8 (5.7)	8.3 (5.7)

*Mean (SD) †Median (IQR)

The NIVO blood gases have a slightly higher pH and lower PaCO₂ than those of the 2013 national audit (7.24 and 10.2kPa respectively); though only 62% of patients in this audit had COPD.⁽⁵⁰⁹⁾ This could be due to prompt treatment and more judicious oxygen therapy (PaO₂ in 2013 audit 9.7kPa) resulting in less severe respiratory failure; or may reflect liberal ventilation policies for patients with less severe respiratory failure in NIVO. The results of the 2019 national NIV audit (conducted after NIVO had completed recruitment) demonstrated a similar median pH (7.26), PaO₂ (8.1kPa) and PaCO₂ (9.3kPa) to NIVO, suggesting the above may be more widespread in current practice.⁽⁵¹⁰⁾ Similarly to 2013, however, only 67% of the 2019 national audit patients had COPD. NIVO was observational, and as such did not specify when ABGs should be taken, explaining the high number of missing post-wean (and to a lesser extent 24hr) blood gases.

6.5 Descriptors of Ventilation

6.5.1 Escalation and cardiopulmonary resuscitation decisions

Decisions about both escalation to invasive ventilation and if the patient was for cardiopulmonary resuscitation (CPR) were recorded (Table 33). If no 'do not attempt cardiopulmonary resuscitation' (DNACPR) form, or nothing about suitability for invasive ventilation was documented, the patient was assumed to be 'for' the respective treatment. If a change to this was made by a senior clinician up to 24hours after ventilation had commenced this was accepted. Changes made >24hours were not recorded.

Table 33. Number of patients for invasive ventilation and cardiopulmonary resuscitation.

Variable	Percentage 'for'
Cardiopulmonary resuscitation	328 (44.7%)
Invasive ventilation	294 (40.1%)

Overall, fewer than half of the patients in NIVO were for deemed 'for' either CPR or IMV. There was a significant difference between intubation and ventilation decisions between sites (both IMV and CPR decisions χ^2 $p < 0.001$), shown in Figure 15.

When breaking into selected demographics similar patterns are seen between sites (see Table 35 and Table 36). 60.7% of patients had a decision to withhold at least one of IMV/CPR. Where a decision was made to withhold IMV or CPR, the decision was congruous with the other treatment in 89.7% of cases. Mortality was higher in patients who had treatment withheld (Table 34), reflecting that clinicians are able to identify those who may be likely to benefit from these treatments and who may not. No record of patient decision or opinion was made, so this aspect cannot be further explored.

Figure 15. Percentage of NIVO patients considered for invasive ventilation or CPR by recruiting site.

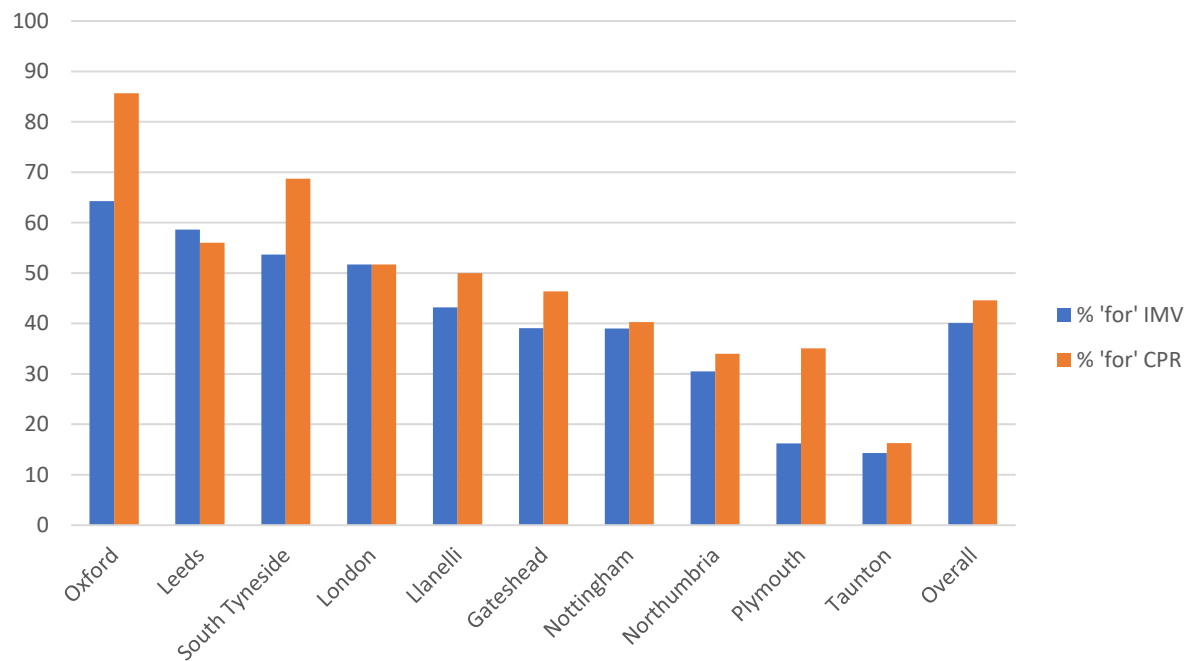


Table 34. Number of patients with IMV or CPR treatment decisions with associated mortality.

Variable	Number (%)	Inpatient Mortality	90-day mortality
For CPR & IMV	288 (39.3%)	10.1%	17.7%
Not for CPR nor IMV	399 (54.4%)	27.8%	44.1%
Decision to withhold treatment	445 (60.7%)	26.5%	41.6%

Table 35. Percentage of NIVO patients 'for' CPR split by selected demographics and site.

	% 'For' Cardiopulmonary resuscitation										
Site	Overall	eMRCD 1-4	eMRCD 5a	eMRCD 5b	Age 80+	LTOT	Prev. NIV	GCS ≤10	AF	Consolidation	Eosinopenia
Oxford	85.7	100	33.3	n/a	100.0	100.0	66.7	66.7	50.0	100.0	100.0
South Tyneside	68.7	91.3	66.7	45.0	50.0	50.0	56.5	100	60.0	64.3	63.9
Leeds	56.0	74.5	51.1	27.3	44.4	42.9	39.5	55.6	40.0	60.0	60.9
London	51.7	61.3	44.4	36.4	28.6	47.8	34.3	100	42.9	47.4	20.0
Llanelli	50.0	62.5	41.7	25.0	22.2	28.6	33.3	50.0	37.5	45.8	50.0
Gateshead	46.4	63.9	33.3	20.0	15.0	34.8	45.0	16.7	16.7	50.0	44.7
Nottingham	40.3	58.6	37.9	15.8	33.3	25.0	36.4	0	23.5	42.1	35.4
Plymouth	35.1	69.2	25.0	8.3	0	15.4	35.7	66.7	42.9	37.5	30.4
Northumbria	34.0	63.8	19.7	4.5	17.9	8.0	22.5	18.2	20.5	32.0	29.8
Taunton	16.3	21.4	8.3	11.1	0	0	14.3	0	13.3	0.0	18.5
OVERALL	44.7	64.3	35.9	19.4	24.8	29.5	33.8	39.6	29.9	43.0	42.0

Table 36. Percentage of NIVO patients 'for' IMV split by selected demographics and site.

	% 'for' Invasive Mechanical Ventilation										
Site	Overall	eMRCD 1-4	eMRCD 5a	eMRCD 5b	Age 80+	LTOT	Prev. NIV	GCS ≤10	AF	Consolidation	Eosinopenia
Oxford	64.3	72.7	33.3	n/a	100	100	66.7	66.7	50	100	71.4
Leeds	58.6	74.5	53.2	36.4	55.6	48.6	46.5	88.9	40	65.7	62.5
South Tyneside	53.7	73.9	62.5	20.0	42.9	37.5	43.5	66.7	46.7	32.1	50
London	51.7	61.3	44.4	36.4	28.6	47.8	34.3	100	42.9	47.4	20
Llanelli	43.2	50.0	41.7	25.0	22.2	28.6	22.2	50	25	41.7	45.5
Gateshead	39.1	58.3	22.2	13.3	10.0	26.1	30	16.7	16.7	45.8	36.2
Nottingham	39.0	58.6	37.9	10.5	33.3	25	31.8	0	23.5	36.8	33.3
Northumbria	30.5	61.3	13.2	4.5	12.8	6	21.3	9.1	17.9	28	27.9
Plymouth	16.2	38.5	8.3	0.0	0.0	7.7	7.1	16.7	14.3	18.8	13.0
Taunton	14.3	17.9	8.3	11.1	0.0	0	14.3	0.0	13.3	0	14.8
OVERALL	40.1	58.4	32.3	15.6	22.3	27.1	30.0	35.8	25.5	36.9	37.1

6.5.2 Timing of acidaemia

The time from attendance at hospital to the NIV decision gas was just over two hours, although the wide interquartile range reflects the inclusion of patients who deteriorated and become acidotic late into their admission (see Table 37). The door-to-mask-time is a measure used to assess the quality of NIV being delivered across the UK; the recent BTS quality standards set a target of ≤ 120 minutes (in those who are acidotic at admission).⁽⁵¹¹⁾ For the 535 NIVO patients who were acidotic at admission door to mask time was just over two hours. There was no difference in either inpatient (Fisher's exact $p=0.144$) or 90-day ($p=0.505$) mortality if the door-to-mask-time was above or below 120min. Length of stay was similar, irrespective of DTMT, in all patients (DTMT ≤ 120 min= 8 (5-13) days vs. DTMT >120 min= 8 (5-14.5) days; $p=0.725$) and in only those who survived to discharge (DTMT ≤ 120 min= 8 (6-12) days vs. DTMT >120 min= 8 (5-15) days; $p=0.669$).

Table 37. Timings from admission to arterial blood gases and mask.

Variable	Time in minutes*
Attendance to first ABG	31 (12-79)
Attendance to NIV decision gas	137 (41-767)
Attendance to 1 st respiratory acidosis	53 (14-287)
Door to mask time [^]	135 (67-271)
NIV gas to mask	42 (19-75.5)

*Median (IQR) [^]In patients who had respiratory acidaemia at admission.

The timing of the development of acidaemia had a significant impact on both inpatient and 90-day mortality (Table 38). The later in an admission that a patient developed their first respiratory acidosis, the more likely they were to die. There was a statistically significantly higher IP mortality for later acidosis in all groups (IP mortality >4 hrs 34%, <12 hrs 14.8%, <24 hrs 15.4%, <48 hrs 16.7%, <72 hrs 16.7%; all $\chi^2 p<0.001$).

Table 38. Timing of acidosis and mortality rates

Timing of acidosis from admission	Number (%)	Inpatient Mortality	90-day mortality
Under 4hrs	539 (73.5%)	15.0%	28.2%
Over 12hrs	185 (25.2%)	35.7%	41.6%

Timing of acidosis from admission	Number (%)	Inpatient Mortality	90-day mortality
Over 24hrs	131 (17.9%)	41.2%	49.6%
Over 48hrs	74 (10.1%)	50.0%	60.8%
Over 72hrs	55 (7.5%)	61.8%	69.1%

A similar pattern was seen in the 90 day mortality results (90-day mortality >4hrs 43.3% $p<0.001$, <12hrs 29.0% $p=0.002$, <24hrs 28.4% $p<0.001$, <48hrs 29.0% $p<0.001$, <72hrs 29.2% $p<0.001$).

6.5.2.1 Population with and without late acidosis

Patients who developed acidosis over 12 hours into their admission were older, with more consolidation and higher rates of AF (Table 39). Other comorbidities listed in section 6.3.2 were similar. Patients with late acidemia had less severe airflow obstruction, were more likely to be eosinopenic on admission, had lower admission blood pressure, and showed a trend towards higher admission c-reactive protein and temperature. Respiratory rate at admission was statistically significantly lower in patients who developed late acidemia, although this significance did not persist when assessing respiratory rates in the 24hrs prior to the start of ventilation; lower systolic and diastolic BP differences did, however, persist in the 24hr time period. White cell count at ventilation showed no statistical difference, although a difference did develop in the CRP count at ventilation (Table 39). It may be that patients who develop late acidosis have higher rates of sepsis than those who have early acidemia. NIV decision gases were similar between both groups.

Table 39. Descriptors of patients with and without late acidemia

Descriptor	Acidaemia <12hrs	Acidaemia >12hrs	P value
Age [*]	70.0 (9.3)	72.2 (9.2)	0.005
Female %	59.7%	54.1%	0.180
eMRCD [†]	5a (4-5a)	5a (4-5a)	0.813
BMI [*]	25.8 (8.2)	24.7 (7.1)	0.100
FEV1 [*]	36.0% (15.1)	40.7% (15.9)	<0.001
GCS [†]	15 (14-15)	15 (13-15)	0.112

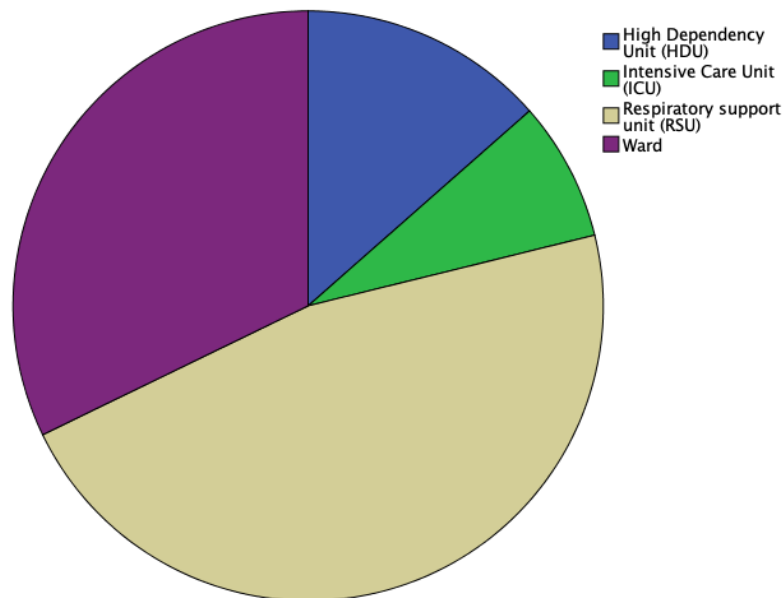
Descriptor	Acidaemia <12hrs	Acidaemia >12hrs	P value
Consolidation	34.9%	47.6%	0.002
Atrial Fibrillation	16.1%	29.7%	<0.001
pH at ventilation [†]	7.27 (7.21-7.30)	7.27 (7.23-7.30)	0.426
PaCO ₂ at ventilation [†]	9.71 (8.23- 11.70)	9.51 (8.00- 11.44)	0.340
PaO ₂ at ventilation [†]	8.03 (6.72-9.94)	8.45 (6.72-9.18)	0.174
White cell count (admission)*	13.0 (6.3)	12.5 (7.9)	0.409
White cell count (at ventilation)*	13.0 (6.4)	13.2 (8.0)	0.682
C-reactive protein (admission) [†]	36 (12-105)	42 (15-122)	0.061
C-reactive protein (at ventilation) [†]	36 (11-103)	63 (19-149)	0.001
Eosinophils (admission) [†]	0.05 (0.00-0.10)	0.00 (0.00-0.10)	0.029
Systolic blood pressure, mmHg* (admission)	137 (34.9)	127 (29.7)	<0.001
Systolic blood pressure, mmHg (at ventilation)*	136 (35.0)	126 (30.6)	0.001
Diastolic blood pressure, mmHg* (admission)	77 (21.6)	71 (16.0)	<0.001
Diastolic blood pressure, mmHg (at ventilation)*	77 (21.7)	72 (17.1)	0.001
Heart rate, bpm* (admission)	109 (21.5)	106 (21.8)	0.127
Heart rate, bpm (at ventilation)*	109 (21.1)	112 (22.2)	0.232
Respiratory rate, bpm* (admission)	28 (7.6)	25 (5.6)	<0.001
Respiratory rate, bpm (at ventilation)*	29 (7.6)	28 (6.6)	0.203
Temperature, Celsius* (admission)	36.6 (0.95)	36.8 (0.98)	0.064
Temperature, Celsius (at ventilation)*	36.6 (0.96)	36.8 (1.03)	0.107

*Mean (SD) with comparisons by t-test. †Median (IQR) with comparisons by Mann-Whitney-U. Other comparisons by Chi Squared.

6.5.3 Location of care

The majority of patients were looked after either in a respiratory support unit (RSU) or in a ward based setting (Figure 16), with only 21.1% being cared for in critical care.

Figure 16. Pie chart showing the location of care for the whole NIVO population



There is substantial variation between individual sites on where NIV was delivered (see Table 40). This is largely due to the differences in individual institution's NIV pathways. For example, at the Lane Fox Unit (London) it is routine for patients to be admitted to critical care for the delivery of acute NIV. This is different from Leeds or Plymouth where the NIV pathway is delivered almost wholly in the RSU. Mortality by location of care is therefore very likely to be biased by individual site setup and results should be interpreted with caution. However, without adjusting for baseline risk of mortality, there was no statistically significant difference between mortality by location of care across the whole NIVO population (Table 40).

Table 40. Location of delivery of NIV at each site.

Site	Percentage of patients looked after in each location			
	RSU	Ward	HDU	ITU
Northumbria	75.5%	16.5%	5.5%	2.5%
Nottingham	37.7%	13.0%	41.6%	7.8%
Plymouth	94.6%	-	2.7%	2.7%
London	5.0%	-	58.3%	36.7%

Site	Percentage of patients looked after in each location				
	RSU	Ward	HDU	ITU	
Leeds	97.4%	-	-	2.6%	
Oxford	78.6%	14.3%	-	7.1%	
Llanelli	-	59.1%	27.3%	13.6%	
Gateshead	-	78.3%	11.6%	10.1%	
South Tyneside	-	92.5%	-	7.5%	
Taunton	100%	-	-	-	
Total	46.7%	32.2%	13.5%	7.6%	
IP mortality	17.3%	22.5%	20.2%	26.8%	p=0.250*
90-day mortality	31.0%	33.5%	34.3%	30.4%	p=0.873*

*Chi-Squared test

6.5.4 Ventilation settings

6.5.4.1 Ventilation pressures

Ventilation pressures were recorded after one hour of ventilation. Additionally, the maximal pressure delivered throughout the ventilatory episode was recorded (Table 41). There was a significant increase in IPAP, EPAP and Backup rate (BUR) between 1 hour and max for each variable (paired t-tests all $p < 0.001$) in keeping with standard practice of increasing pressures over the first period of NIV as tolerated. The maximal IPAP pressures, however, remain on the lower end of those recommended in the BTS guidelines (IPAP 20-30)⁽³¹⁶⁾ and 240 (32.7%) NIVO patients had ventilation with maximal IPAP $< 20 \text{ cmH}_2\text{O}$.

Table 41. Ventilation pressures in NIVO.

After one hour of ventilation*			Maximal delivered*		
IPAP	EPAP	BUR	IPAP	EPAP	BUR
18 (5)	5 (1)	14 (3)	21 (5)	5 (2)	14 (3)

*All presented as Mean (SD)

6.5.4.2 Duration of ventilation

Ventilation was delivered for a median (IQR) of 62.5 (25-109) hours. This is a crude measure as it includes all patients including those with short ventilation times (such as

those who do not tolerate NIV, or deteriorate and die quickly) and those who take a long time to wean. There was variation between sites in the duration of ventilation, shown in Table 47, page 142.

6.5.5 NIV success

6.5.5.1 pH correction

The pH was not confirmed as normalising (pH ≥ 7.35) in 83 (11.3%) patients following the commencement of ventilation. The inpatient mortality rate in this group was 68.7% (vs. 13.8% in those in which pH was confirmed as normalising; χ^2 $p < 0.001$) and 90-day mortality was 75.9% (vs. 26.6%; χ^2 $p < 0.001$). In the 650 patients whose pH did normalise, median (IQR) time to this occurring was 9 (3-25) hours. If patients refused or did not have repeated ABGs following the commencement of ventilation they were recorded as not having normalised, despite the fact they may have done so.

Univariate associations with failure to normalise pH are shown in Table 42. These patients were older, with worse baseline dyspnoea. They were more likely to have cognitive impairment, AF, and presented with a lower conscious level. pH at NIV decision was lower with higher PaCO₂ reflecting more severe respiratory failure. These patients were more likely to have consolidation on their CXR, and higher CRP, in keeping with pneumonia.

Table 42. Univariate associations with pH normalising

Variable	pH normalised	pH did not normalise	P value
Age	70.3 (9.4)	72.8 (8.4)	0.021[^]
eMRCD Score	5a (4-5a)	5a (4-5b)	<0.001[†]
On LTOT	28.5%	30.1%	0.797 [*]
Previous NIV	36.3%	32.5%	0.545 [*]
FEV ₁ % predicted	37.2 (15.4)	37.4 (15.4)	0.922 [^]
Atrial fibrillation	18.2%	30.1%	0.012[*]
Ischaemic heart disease	22.0%	26.5%	0.402 [*]
Depression	23.8%	21.7%	0.784 [*]
Cerebrovascular disease	9.4%	12.0%	0.432 [*]
Cor Pulmonale	22.2%	25.3%	0.577 [*]

Variable	pH normalised	pH did not normalise	P value
Cognitive Impairment	6.9%	14.5%	0.027*
Systolic blood pressure	133.6 (34.8)	131.3 (29.3)	0.568 [^]
Heart rate	110.0 (21.3)	109.2 (22.3)	0.748 [^]
Respiratory rate	28.5 (7.4)	28.2 (7.4)	0.774 [^]
Peripheral SpO2	84.2% (9.8)	83.9% (9.9)	0.744 [^]
Glasgow coma score	15 (14-15)	14 (12-15)	<0.001[†]
pH (NIV decision)	7.27 (7.22-7.31)	7.24 (7.16-7.27)	<0.001[†]
PaCO2 (NIV decision)	9.54 (8.19-11.57)	10.50 (8.82-12.50)	0.026[†]
Chest x-ray consolidation	36.5%	50.6%	0.016*
White cell count	11.7 (8.8-15.8)	11.5 (8.7-15.7)	0.973 [†]
C-Reactive protein	39 (13-106)	67 (27-136)	0.010[†]
Serum creatinine	72.8 (56.7-98.0)	77.0 (61.0-115.0)	0.156 [†]

*Chi-Squared Test (data for these variables presented as percentages); [^]Students t-test (data for these variables are presented as Mean (SD)); [†]Mann-Whitney-U (with data for these variables presented as Median (IQR)). Observations used were the worst in the 24hours prior to ventilation. Blood and gas results are at the time of NIV decision.

6.5.5.2 Timing of pH correction and mortality

Patients who took longer to normalise their pH did not have a higher inpatient mortality than patients who took less time (Table 43; p=0.645); suggesting time to pH correction should not be used in isolation as a measure to withdraw ventilation. In clinical practice it would be challenging to distinguish between those who have not yet normalised their pH and those who will not do so. Even so, at 72 hours or more, around one third of acidotic patients will still normalise their pH.

Table 43. Timing of pH correction and outcome.

Time to correct pH	N	IP mortality
≤4hrs	191	12.0%
>4hrs to 12hrs	168	13.1%
>12hrs to 24hrs	119	17.6%
>24hrs to 48hrs	87	12.6%
>48hrs to 72hrs	36	8.3%
>72hrs	42	16.7%

Seven patients were recorded as normalising their pH, but the time of this is missing.

6.5.5.3 Cessation of ventilation

The primary reason for the cessation of ventilatory support was that the patient had been adequately weaned in the opinion the treating team (Table 44). Twenty two patients died whilst actively receiving ventilation. Of the patients with 'Other' recorded the reasons were unclear (17 patients), pneumothorax (1), self-discharge (2), refusal of further ventilation (1) and commencement of extracorporeal membrane oxygenation (1). No reason for cessation was documented in 5 patients.

Table 44. Reasons documented for the cessation of ventilatory support.

Reason for cessation	Percentage of patients
Weaned	70.3%
Poor tolerance	14.0%
Palliative care initiated	9.6%
Died receiving ventilation	3.0%
Other	3.0%

6.5.5.4 Invasive mechanical ventilation

Only a minority of patients, 21 (2.9%), were invasively ventilated. Of these, 15 had NIV prior to invasive ventilation and 6 proceeded straight to invasive ventilation. 5 patients were weaned from IMV onto NIV. The mean (SD) duration of IMV was 7.9 (8.5) days. Inpatient mortality for invasively ventilated patients was 42.9% (vs 19.4% for solely non-invasively ventilated; Fisher's exact $p=0.022$) and 90-day mortality was 47.6% (vs 31.7%; $p=0.154$).

6.5.5.5 Length of stay

Overall length of stay (LoS) was 8 days (see Table 45). If patients were invasively ventilated their LoS was expectedly longer. The 2017/18 national COPD audit describes longer LoS in patients with a DTMT >120minutes.⁽²¹¹⁾ These findings were replicated in the whole NIVO population, though with a weak signal (DTMT <120min 8 (5-13) days vs. >120min 8.5 (6-15) days; Mann-Whitney-U $p=0.048$). If restricted to only patients who were acidotic on admission there was no difference in LoS (DTMT <120min 8 (5-13) days vs. >120min 8.0 (5-14.5) days; Mann-Whitney-U $p=0.725$).

Table 45. Length of stay in NIVO.

Group examined	Length of stay*
Survived to discharge	8 (6-14) days
Died as inpatient	7 (4-15) days
Died within 90 days	8 (4.25-16) days
Invasively ventilated	11 (7.5-25) days
All patients	8 (5-14) days

*Median (IQR)

6.6 Site by site demographic summaries

Table 46 and Table 47 provide a summary of various demographics, investigation findings and ventilatory parameters split by site. There was variability between sites in a number of fields – this is advantageous as the data is more generalisable when using it to validate the derived clinical prediction tool.

Table 46. Summary of selected demographics and admission related factors by site.

Site	Age*	Female	eMRCD†	Current smoker	At home^	BMI†	FEV1% predicted*	LTOT	Previous NIV	WCC*	LoS†	Consolidation
Northumbria	71.9 (9.2)	56.5%	5a (4-5a)	39.0%	75.0%	24.5 (20.2-30.1)	40.5% (16.6)	25.0%	40.0%	14.4 (8.7)	8 (5-14.75)	41.5%
Nottingham	70.2 (10.1)	62.3%	5a (4-5b)	87.0%	74.0%	25.4 (20.8-31.8)	38.6% (13.3)	26.0%	28.6%	14.1 (7.3)	8 (5-15)	24.7%
Plymouth	68.9 (8.3)	56.8%	5a (4-5b)	70.3%	73.0%	21.4 (19.4-28.4)	36.9% (16.7)	35.1%	37.8%	14.1 (7.3)	9 (5.5-14.5)	45.9%
London	67.7 (9.1)	50.0%	4 (4-5a)	65.0%	55.0%	23.9 (18.9-31.9)	30.6% (13.8)	38.3%	58.3%	12.0 (4.9)	8 (6-11.75)	31.7%
Leeds	68.8 (8.5)	62.9%	5a (4-5a)	87.1%	80.2%	21.7 (18.0-26.6)	34.5% (14.6)	30.2%	37.1%	11.5 (5.5)	8.5 (5-14)	31.9%
Oxford	68.3 (10.5)	78.6%	4 (2-4)	42.9%	92.9%	20.2 (15.9-23.9)	34.0% (13.8)	21.4%	21.4%	15.1 (5.6)	6.5 (3-16.25)	28.6%
Llanelli	70.8 (9.6)	63.6%	4 (4-5a)	77.3%	84.1%	24.9 (21.1-31.2)	36.5% (13.4)	15.9%	20.5%	13.1 (5.2)	9 (6-20)	56.8%
Gateshead	72.8 (10.1)	63.8%	4 (4-5a)	52.2%	71.0%	23.5 (18.5-30.1)	38.1% (16.2)	33.3%	29.0%	12.8 (6.4)	9 (5-14.5)	39.1%
South Tyneside	70.5 (9.6)	53.7%	5a (4-5b)	65.7%	73.1%	27.3 (20.9-32.6)	38.1% (15.5)	35.8%	34.3%	11.0 (4.1)	8 (5-13)	41.8%
Taunton	71.8 (8.6)	46.9%	4 (4-5a)	59.2%	81.6%	24.7(21-29.6)	35.8% (13.4)	24.5%	28.6%	12.6 (4.9)	8 (6-16.5)	40.8%

*Mean (SD) †Median (IQR) ^patients living in their own home without formal carers.

Table 47. Summary of selected ventilation indices by site.

Site	pH [†]	PaO2 [†]	PaCO2 [†]	IPAP [*]	EPAP [*]	DTMT (mins) [†]	1 st Acidosis >12hrs	pH correction	IMV	Duration of NIV (hrs) [†]
Northumbria	7.27 (7.23-7.31)	7.45 (6.50-9.08)	9.60 (8.00-11.30)	23.9 (3.4)	4.7 (1.1)	151 (77.3-789.3)	25.0%	95.5%	2.0%	95.5 (59.3-135)
Nottingham	7.27 (7.20-7.30)	8.10 (7.01-9.84)	10.10 (8.79-11.95)	17.4 (4.3)	5.7 (1.5)	240 (120-902.5)	26.0%	87.0%	1.3%	40 (19-91.5)
Plymouth	7.25 (7.17-7.28)	7.51 (5.84-10.02)	10.90 (9.06-13.15)	21.8 (4.24)	5.7 (1.3)	113 (48-241.5)	13.5%	86.5%	2.7%	62.5 (23-114.5)
London	7.27 (7.23-7.30)	8.00 (6.63-9.39)	9.27 (8.20-11.50)	21.4 (6.4)	6.8 (2.2)	167.5 (76.5-407.8)	18.3%	95.0%	8.3%	31.5 (7.0-63.5)
Leeds	7.26 (7.21-7.30)	8.31 (7.05-9.91)	9.10 (8.15-11.17)	19.3 (4.0)	6.0 (1.4)	244.5 (120.5-814.5)	24.1%	87.1%	1.7%	63 (40-88.8)
Oxford	7.23 (7.16-7.29)	8.45 (6.69-9.42)	11.30 (9.02-13.18)	18.4 (4.0)	6.2 (2.4)	145.5 (68.3-613)	14.3%	100%	0%	56 (17.5-109.3)
Llanelli	7.27 (7.20-7.30)	9.00 (7.03-10.48)	9.35 (8.10-12.00)	21.9 (6.0)	5.5 (1.8)	325.5 (108.8-1180.3)	27.3%	90.9%	2.3%	50 (23.5-110)
Gateshead	7.28 (7.22-7.30)	7.78 (7.10-9.25)	9.20 (8.06-11.05)	20.3 (5.5)	5.9 (1.9)	370 (179-1951.5)	39.1%	84.1%	5.8%	32 (19-62.5)
South Tyneside	7.31 (7.24-7.33)	7.85 (7.10-9.94)	9.50 (8.17-11.28)	19.1 (3.0)	5.1 (1.5)	250 (95-1230)	26.9%	86.6%	4.5%	88 (48-108)
Taunton	7.23 (7.18-7.28)	8.90 (7.27-12.40)	10.20 (9.13-12.00)	18.8 (3.1)	4.9 (1.3)	74 (30.5-791)	24.5%	65.3%	0%	46 (16-107)

*Mean (SD) [†]Median (IQR). Blood gas values taken from NIV decision. Ventilation pressures represent maximum delivered.

6.7 Existing clinical prediction tools

Data points for a number of existing clinical tools were collected to enable comparison with the novel tool. The median score results are shown below (Table 48) and their discriminatory values are shown in Figure 18 and Table 57, page 152.

Table 48. Results of existing prediction scores.

Comparator score	Result from NIVO cohort [†]
Confalonieri risk chart	5.37 (4.08-6.63)
CURB 65	2 (1-3)
DECAF	3 (2-3)
CAPS	22 (16-28)
APACHE II	19 (16-22)

*Mean (SD) [†]Median (IQR). This is equivalent to a moderate risk CURB 65 score, a high risk DECAF score, a CAPS predicted mortality of approximately 15-20%, and an APACHE II predicted mortality of approximately 25%. The Confalonieri risk score presented here allows discriminative comparison with the novel tool but is not comparable to how the Confalonieri score would categorise risk on an individual patient.

6.8 Validation of the novel prognostic tool

The derivation study (see section 5.1) proposed a predictive tool from a number of candidate variables which were significantly associated with mortality. The primary aim of the validation study is to ensure that these variables are generalisable to a temporally and geographically different population, without losing its discriminatory ability; but also to ensure that the tool is as simple and user friendly as possible whilst maintaining these characteristics.

6.8.1 Variables in the derivation tool

Nine indices were identified in the derivation study (Table 49), with all indices being 'up to the point of ventilation'.

Table 49. Variables identified in the derivation study.

eMRCD Score (split as 0-4, 5a, 5b)
Timing of acidaemia occurring >12hours from admission
Eosinopenia (<0.05x10⁹/L)

Any history of Atrial Fibrillation (up to the point of ventilation)
pH <7.25
Negative base excess (<0)
Consolidation on chest x-ray
Glasgow Coma Score <15
Long term oxygen therapy

6.8.2 Base excess and pH

Negative base excess (BE) was identified as a stronger predictor of outcome than pH in the derivation cohort. BE has not been found to be a predictor in other predictive tools (Section 3.4). There was concern, therefore, that BE's inclusion in the derivation was the result of overfitting to the derivation population. Between the derivation and validation study national NIV guidance changed from using a PaCO₂ of 6.0kPa to 6.5kPa. This is likely to have reduced the number of patients with primarily metabolic acidosis being inappropriately ventilated and may render BE less helpful. Additionally, lower pH has frequently been found to be associated with poor outcome in other studies (although this does not entitle it to be included in the model) and has higher face validity with clinicians. We had therefore pre-planned a comparative analysis of these variables in the validation study.

To assess the relative effect of pH versus BE all derivation variables were put into a single step regression model ('enter' methodology), forcing them all to remain in the final output. This method allows a direct comparison of the relative effects of pH vs BE and demonstrated BE is non-significant predictor ($p=0.624$) of mortality compared to pH ($p<0.001$). Therefore, only pH was retained with base excess removed.

6.8.3 Simplicity

When using prognostic scores in a clinical area, simplicity (whilst maintaining accuracy) is key. Whilst online calculators are increasingly common, not all scores are available on them. Consequently, many scores are calculated at the bedside from memory. The more complicated a score is the less likely it is to be utilised, therefore using the least number of variables necessary is beneficial. It is important to remember that this is validation of

an existing score: assessment of new (not previously proposed) variables should be avoided – this would result in re-derivation.

The derivation tool (using pH) candidates were entered into a stepwise, backwards logistic regression analysis using validation patient data, and with inpatient mortality as the dependent variable (Table 50). Both eosinopenia and LTOT were non-significant (using a cut-off of <0.1 , as in the derivation study) predictors and drop out of the resultant model, leaving six variables. Whilst the addition of new variables into the model would be a re-derivation, the removal of derivation predictors which are non-significant in validation is acceptable; they add no additional predictive power and their initial inclusion was likely due to overfitting to the derivation population.

Table 50. Result of backwards logistic regression using derivation predictors in the validation cohort.

Variable	B	S.E	Wald	P value	Odds ratio (95% CI)
Consolidation	0.358	0.210	2.891	0.089	1.43 (0.95-2.16)
GCS <15	0.658	0.217	9.244	0.002	1.93 (1.26-2.95)
Atrial fibrillation	0.842	0.239	12.422	<0.001	2.32 (1.45-3.71)
pH <7.25	0.961	0.222	18.729	<0.001	2.61 (1.69-4.04)
Time to acidaemia >12hrs	1.289	0.225	32.788	<0.001	3.63 (2.33-5.64)
eMRCD 5a	1.425	0.267	28.515	<0.001	4.16 (2.46-7.02)
eMRCD 5b	1.960	0.287	46.735	<0.001	7.10 (4.05-12.46)

Intercept -2.832, Cox & Snell R^2 0.181, Nagelkerke R^2 0.285, Hosmer and Lemeshow goodness-of-fit 0.130, Percentage correct following final step 81.9%. Cook's distances, Leverage values and Residuals all within acceptable limits. Atrial fibrillation at any point up to the commencement of ventilation.

6.8.3.1 Consolidation

In the final regression model chest x-ray consolidation is the weakest predictor of mortality and its 95% confidence interval crosses 1. It remains in the model moving forward to both minimise changes from derivation and because it remains statistically significant at the pre-determined p-value of <0.1 .

6.8.4 Reweighting of proposed variables

Given the removal of two indices from the derivation study, it is necessary to re-weight the original scores assigned to each variable (the original assigned weightings were part of the derivation study and are not detailed in this thesis).

The reweighting of variables is accepted practice in the external validation of predictive scores, and ensures that assigned weights accurately reflect the relative contribution of each variable to the outcome.^(471, 512) The same method for assigning weights were followed as in the derivation study: namely dividing the exponentiated beta coefficients (B_{Exp}) by the variable with the lowest score (in this case CXR consolidation, $B_{Exp} = 1.43$), see Table 51.

Table 51. Reweighting of predictors in the validation study.

Variable	B_{Exp}	$B_{Exp}/1.43$	Weighting assigned
Consolidation	1.43	1	1
GCS <15	1.93	1.35	1
Atrial fibrillation	2.32	1.62	1
pH <7.25	2.61	1.83	1
Time to acidaemia >12hrs	3.63	2.54	2
eMRCD 5a	4.16	2.91	2
eMRCD 5b	7.10	4.97	3

Atrial fibrillation at any point up to the commencement of ventilation.

6.8.5 The Non-Invasive Ventilation Outcomes (NIVO) score

The final score is shown in Table 52. This has been named the Non-Invasive Ventilation Outcomes (NIVO) score for simplicity and ease of recalling application in clinical practice. The maximum possible score is 9, as a patient cannot be both eMRCD 5a and 5b simultaneously.

Table 52. The Non-Invasive Ventilation Outcomes (NIVO) score.

	Score for variable being present
Consolidation	1
GCS under 15	1
Atrial Fibrillation	1
pH under 7.25	1
Time to acidaemia over 12 hours	2
eMRCD 5a	2
eMRCD 5b	3

Score	/9

6.9 Testing the NIVO Score

6.9.1 Inpatient and 90- day mortality

Inpatient and 90-day mortality by NIVO score is shown in Table 53, with graphical representation in Appendix K, section 14.11. Both inpatient and 90-day mortality broadly increase as the score increases. The exception to that is between a score of 1 and 2 where there is a slight fall in % mortality due to the low numbers of death at this level – this is of little consequence once NIVO is split into risk categories (section 6.9.3). NIVO was derived (and validated) with inpatient mortality as the dependent variable, so it is encouraging that 90-day mortality follows the same pattern as inpatient mortality; this reinforces that the NIVO predictors are good measures of outcome in this population.

Table 53. NIVO Score and inpatient and 90-day mortality rates

NIVO score	Total n=	Inpatient mortality		90-day mortality	
		Number	Percentage	Number	Percentage
0	67	0	0%	7	10.4%
1	79	7	8.9%	16	20.3%
2	133	7	5.3%	21	15.8%
3	152	23	15.1%	40	26.3%
4	116	22	19.0%	47	40.5%
5	97	34	35.1%	45	46.4%
6	54	29	53.7%	32	59.3%
7	26	17	65.4%	20	76.9%
8	8	7	87.5%	7	87.5%
9	1	1	100%	1	100%
Total	733	147	20.1%	236	32.2%

6.9.2 Predicted and observed mortality

An important factor in the assessment of the accuracy tool is whether there is close association between the predicted and observed mortality by site (see Table 54). The predicted mortality was calculated by assigning every patient the predicted mortality percentage from their NIVO score, adding those values at each site together, and dividing by the number of patients recruited there. There was a close alignment between sites and their predicted/observed inpatient mortality values from the score. Sites who contributed a larger number of patients tend to have a closer agreement, and whilst the absolute differences are altered the pattern seen with inpatient mortality is similar to that seen with 90-day mortality (Table 55). Given both the NIVO predicted and observed mortalities displayed here are calculated from the same population, the total mortality has to be equal.

Table 54. Predicted and observed inpatient mortality by site.

Site	Number	Inpatient mortality (%)		Difference
		Predicted	Observed	
Northumbria	200	21.4%	18.0%	-3.40%
Nottingham	77	20.5%	19.5%	-1.00%
Plymouth	37	19.5%	13.5%	-6.00%
London	60	15.6%	18.3%	2.70%
Leeds	116	19.1%	19.8%	0.70%
Oxford	14	13.6%	21.4%	7.80%
Llanelli	44	19.1%	25.0%	5.90%
Gateshead	69	21.9%	26.1%	4.20%
South Tyneside	67	21.9%	28.4%	6.50%
Taunton	49	20.0%	12.2%	-7.80%
TOTAL	733	20.1%	20.1%	0.0%

Table 55. Predicted and observed 90-day mortality by site

Site	Number	90 day mortality (%)		Difference
		Predicted	Observed	
Northumbria	200	33.1%	31.0%	-2.10%
Nottingham	77	33.2%	40.3%	7.10%
Plymouth	37	33.1%	24.3%	-8.80%
London	60	27.3%	26.7%	-0.60%
Leeds	116	31.3%	32.8%	1.50%
Oxford	14	25.6%	28.6%	3.00%
Llanelli	44	30.7%	36.4%	5.70%
Gateshead	69	34.6%	33.3%	-1.30%
South Tyneside	67	33.3%	27.3%	-6.00%
Taunton	49	32.5%	24.5%	-8.00%
TOTAL	733	32.2%	32.2%	0.0%

6.9.3 Risk categorisation

The scoring system from NIVO can be simplified down to 4 simple risk groups (Table 56). This may have utility in helping guide level of care, as well as simplifying the results for the clinicians calculating the score. The low risk group still confers a 15.8% risk of death by 90 days after discharge and should therefore receive prompt follow up and optimisation of treatment care.

Table 56. NIVO risk categories and associated mortality.

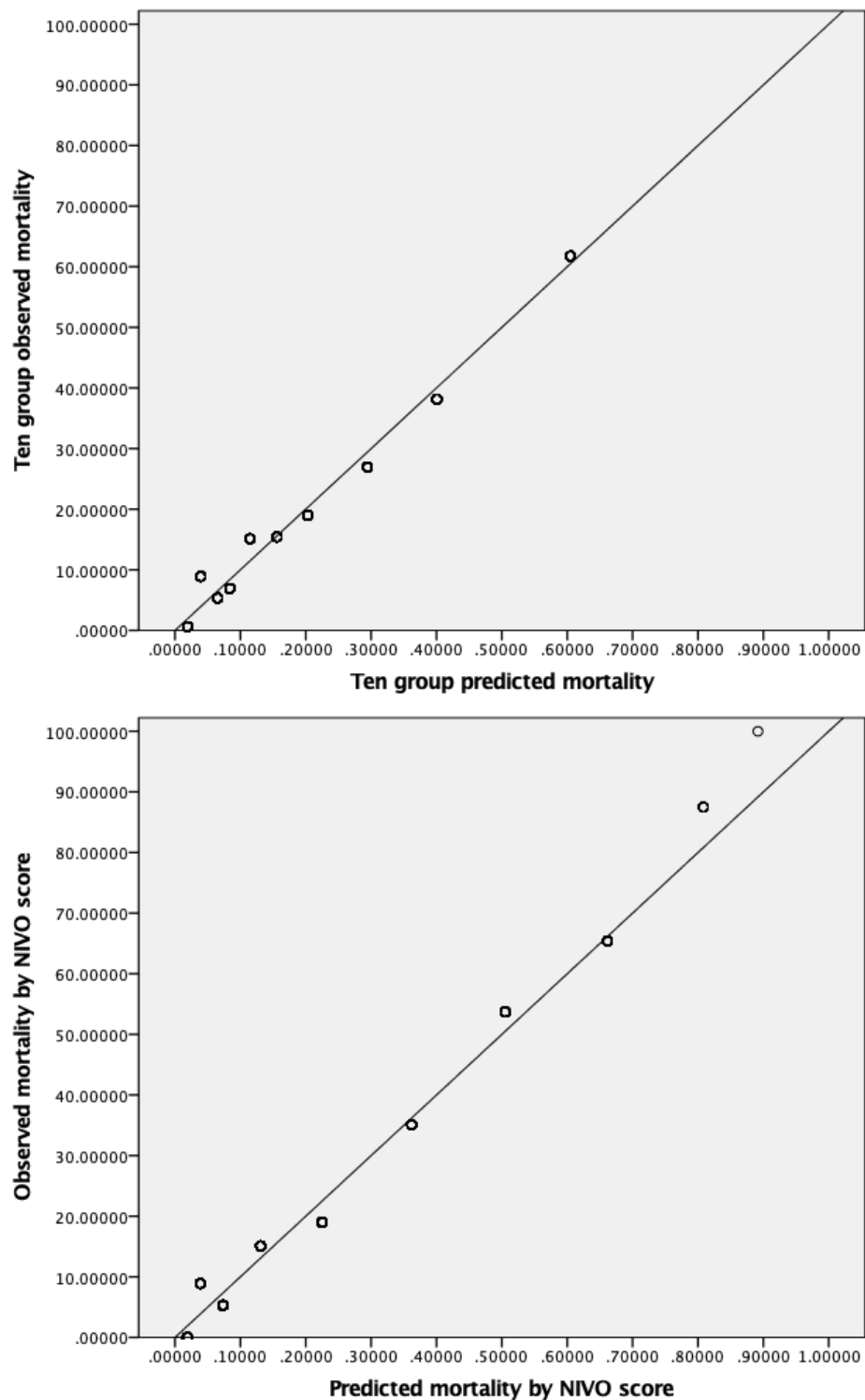
Risk Group (NIVO scores)	N=	Inpatient mortality		90-day mortality	
		N=	%	N=	%
Low Risk 0-2	279	14	5.0%	44	15.8%
Medium Risk 3-4	268	45	16.8%	87	32.5%
High Risk	151	63	41.7%	77	51.0%

5-6					
Very High Risk					
7-9	35	25	71.4%	28	80.0%

6.9.4 Model fit and calibration

The NIVO score has acceptable calibration with a Hosmer and Lemeshow goodness-of-fit result of 0.130, and a Nagelkerke R^2 of 0.285 meaning that the model itself accounts for 28.5% of the observed variance. All Cook's values were less than 1. 3.8% of cases had residual values $>\pm 1.96$, comfortably under the cut off of 5%. No cases had higher than 3 times estimated mean leverage values ($3 \times \text{estimated mean leverage} = 0.029$). A calibration plot of predicted vs. observed mortality was produced using both 10 equal groups and the NIVO score itself (Figure 17).

Figure 17. Predicted vs. observed mortality calibration plots using both ten equal groups (top panel) and the NIVO score (bottom panel).



6.9.5 Discrimination

The AUROC for NIVO is 0.79 and demonstrates the tool has better discrimination than any of the comparator scores to predict inpatient mortality in this population. The full AUROC with confidence intervals for NIVO and each comparator tool is described in

Table 57. Of note, all of the scores were calculated (where relevant) using values from the 24 hours prior to ventilation; making them a direct comparison to the suggested use and timing of the NIVO tool.

Figure 18. ROC curves for the NIVO score and its comparator scores for inpatient mortality.

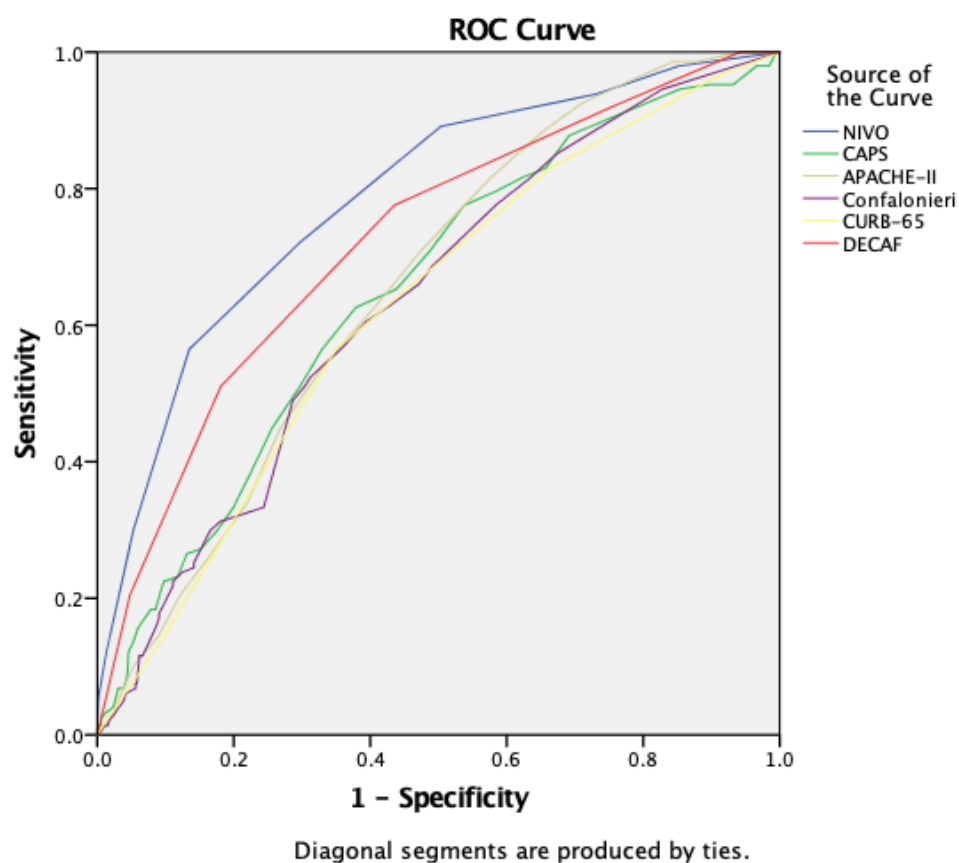


Table 57. AUROC and 95% confidence intervals for NIVO and comparator tools examining inpatient mortality.

Clinical Score	AUROC (95% confidence intervals)	AUROC difference From NIVO	P value of difference*
NIVO Score	0.79 (0.75-0.83)	n/a	n/a
CAPS Score	0.65 (0.60-0.70)	0.139	<0.0001
APACHE-II Score	0.66 (0.61-0.70)	0.133	<0.0001
Confalonieri Score	0.64 (0.59-0.68)	0.154	<0.0001
CURB-65 Score	0.63 (0.58-0.67)	0.164	<0.0001
DECAF Score	0.73 (0.68-0.77)	0.065	0.0001

*Compared using the method of DeLong

It is worth noting, however, that this is not necessarily the originally suggested timeframe for the application of these scores (DECAF or CURB-65 for instance are designed to be calculated as early as possible in an attendance, and can be used to inform discharge decisions from the ED as well as other aspects of care). Whilst the comparators displayed are not all ECOPD specific scores, the non-COPD scores are frequently used to risk categorise patients with ECOPD in clinical practice. All comparator scores had a significantly worse discriminatory ability than NIVO in this population.

6.10 Chapter Summary

The validation study has demonstrated that the accurate prediction of inpatient mortality in patients admitted with ECOPD who require assisted ventilation is not only possible, but simple to calculate with readily available clinical indices. Not only is the NIVO score simple to calculate, but it is well calibrated and more discriminative than comparator scores. Importantly, the NIVO validation population is both temporally and geographically separate from the derivation, and the demographic characteristics of the patients included reflect those of real world NIV & COPD care in hospital meaning it is convincingly generalisable. Indeed, the predictive indices make conceptual sense, increasing the face validity of the tool.

7 Analysis of pre-specified subgroups

Subgroup analyses were pre-specified in the NIVO validation study protocol and are presented in this chapter. No further exploration of variables that were independently associated with death in the NIVO score (such as consolidation), nor additional subgroups analyses, have been undertaken as to avoid over interpretation of the data.

7.1 Late failure and relapse

Late failure was defined as the recurrence of acidaemia (pH <7.35) whilst still receiving assisted ventilation, at least 24hrs after the initial correction of pH, and with a corresponding rise in CO₂ of at least 1.0kPa. Relapse was defined as the recurrence of respiratory acidaemia at least 24 hours after NIV cessation.

Of all NIVO validation study patients 41 (5.6%) experienced late failure alone, 48 (6.5%) experienced relapse alone and 4 (0.5%) had both late failure and relapse.

7.1.1 Late failure patients

The median time from NIV commencement to late failure was 67.0 (44.2-139.9) hours and the time from initial pH correction to late failure was 56.1 (36.5-87.1) hours. Of the 45 patients developing late failure, 68.9% did so >48 hours after NIV started.

7.1.1.1 Demographics

The descriptors of patients with and without late failure are shown in Table 58. Patients with late failure had broadly similar background demographics, though with lower BMI and a higher rate of left ventricular systolic dysfunction. The obvious differences come in the

Table 58. Demographic comparison of patients both with and without late failure in the validation cohort.

Descriptor	No late failure	Late failure	P value
Age*	70.4 (9.4)	72.4 (7.7)	0.163
Own home (+/- carers)	92.2%	93.3%	1.000
eMRCD [†]	5a (4-5a)	5a (4-5a)	0.235
FEV ₁ % predicted*	37.3% (15.5)	35.3% (14.5)	0.405
LTOT	28.1%	37.8%	0.175
BMI [†]	24.4 (19.7-30.0)	21.9 (17.6-26.5)	0.046

Descriptor	No late failure	Late failure	P value
Previous admissions [†]	1 (0-3)	1 (0-4)	0.603
On long term steroid	10.3%	8.9%	1.000
Had previous acute NIV	35.2%	46.7%	0.148
Comorbidities			
Cor Pulmonale	22.1%	28.9%	0.275
IHD	22.5%	22.2%	1.000
LVSD	13.4%	24.4%	0.046
AF	19.6%	17.8%	0.848
Depression	23.7%	22.2%	1.000
Cognitive impairment	8.0%	4.4%	0.568
Admission related			
CXR consolidation	38.2%	35.6%	0.754
Eosinopenia (pre NIV)	53.3%	55.6%	0.878
Not for IPPV	59.2%	71.1%	0.119
Not for CPR	55.2%	55.6%	1.000
First acidemia >12hrs	25.0%	28.9%	0.595
NIV start to pH correction (mins) [†]	529 (180-1474)	460 (100-1081)	0.366
Blood gas results at time of NIV decision			
pH [†]	7.27 (7.22-7.30)	7.26 (7.23-7.30)	0.601
PaCO ₂ [†]	9.56 (8.16-11.49)	10.50 (9.20-12.70)	0.003
PaO ₂ [†]	8.04 (6.84-9.83)	8.72 (6.26-8.98)	0.109
Base excess [*]	4.4 (6.5)	7.4 (7.8)	0.004
HCO ₃ ^{-*}	30.2 (6.7)	34.7 (7.5)	<0.001
Ventilator settings			
1 hour IPAP [*]	17.8 (5.0)	20.5 (5.3)	0.001
1 hour EPAP [*]	5.0 (1.3)	5.1 (1.4)	0.645
1 hour BUR [*]	13.9 (2.6)	15.1 (2.4)	0.004
Max IPAP [*]	20.6 (4.8)	24.3 (4.3)	<0.001
Max EPAP [*]	5.5 (1.6)	5.7 (1.7)	0.380
Max BUR [*]	14.2 (2.7)	15.9 (2.2)	<0.001

*Mean (SD) with comparisons by t-test. †Median (IQR) with comparisons by Mann-Whitney-U. Categorical comparisons Fisher's exact test.

admission blood gases, which show a significantly higher PaCO₂, base excess and bicarbonate in the late failure population. The high bicarbonate and base excess in particular suggest that patients with chronic (compensated) type two respiratory failure are the population most at risk of late failure, particularly if undernourished. Patients with late failure had significantly higher 1 hour IPAP and BUR, though there is no clear reason for this in the data.

Whilst the maximum IPAP and BUR are also higher in the late failure group this is not necessarily a fair comparison. Maximum IPAP/EPAP/BUR were taken only once during the period of ventilation, and the pressures were not specified as pre- or post-late failure. Therefore, the higher 'max' values may be representative of changes to ventilator settings occurring in response to the advent of late failure.

7.1.1.2 Late failure gases

Blood gases were recorded in all patients pre- and post- late failure (Table 59). Additionally, we captured the lowest PaCO₂ recorded after normalisation of pH; the median change in PaCO₂ was 2.58 (1.90-3.65) kPa from lowest recorded to late failure.

Table 59. Blood gas results both at late failure and the last prior to late failure.

	pH [†]	PaCO ₂ [†]	PaO ₂ [†]	Bicarbonate*	Base Excess*
Last pre-Late Failure	7.38 (7.36-7.42)	7.37 (6.45-8.45)	8.00 (7.05-9.40)	33.2 (8.5)	8.6 (7.1)
At Late Failure	7.31 (7.26-7.32)	9.35 (8.30-10.90)	7.80 (6.55-8.60)	34.4 (6.9)	8.4 (6.6)

*Mean (SD) †Median (IQR)

7.1.1.3 Actions after late failure

Changes in care in response to the advent of late failure were recorded. Patients could have more than one change recorded (64.5% did have). Only one patient (2.2%) had no changes made to their treatment as a result of late failure. Table 60 shows the proportion of patients receiving each change.

Table 60. Changes in treatment in response to late failure.

Action	Patients
Was NIV Continued?	Yes, 43 (95.6%)
Were there changes to ventilatory pressures, back up rate, or was the target time of ventilation increased?	Yes, 27 (60.0%)
Were steps taken to improve patient-ventilator synchrony?	Yes, 14 (31.1%)
Was the patient invasively ventilated as a consequence of late failure?	Yes, 1 (2.2%)
Was palliative care commenced as a consequence of late failure?	Yes, 7 (15.6%)

The vast majority of patients had NIV continued following late failure. Of the seven patients who had palliative care commenced as a result of late failure, NIV was continued in six of them, with six of them ultimately dying in hospital.

7.1.2 Relapse patients

A similar proportion of patients had relapse (52, 7.1%) of respiratory acidaemia following the discontinuation of ventilation as had late failure, though there was little overlap between the populations.

7.1.2.1 Demographics

The population suffering with relapsed respiratory failure had very similar demographics to those without (Table 61). The only significant differences were in LTOT, NIV decision PaO₂ and the more frequent ischaemic heart disease in those with relapse; though strong trends towards lower BMI and increased LVSD were seen, in common with late failure. Whilst the majority (45, 86.5%) of patients with relapse only had one episode, 6 (11.5%) had 2 episodes and one patient had 6 episodes throughout their admission. The median number of days of ventilation following relapse was 2 (0-4.75).

Table 61. Comparisons of patients with and without the advent of relapse.

Descriptor	No relapse	Relapse	P value
Age*	70.6 (9.3)	69.7 (9.4)	0.488
Own home (+/- carers)	92.1%	94.2%	0.789

Descriptor	No relapse	Relapse	P value
eMRCD [†]	5a (4-5a)	5a (4-5a)	0.372
FEV ₁ % predicted*	37.4 (15.5)	34.3 (13.6)	0.163
LTOT	27.6%	42.3%	0.037
BMI [†]	24.4 (19.6-30.0)	22.1 (18.7-26.0)	0.073
Previous admissions [†]	1 (0-3)	1 (0.25-3)	0.766
On long term steroid	10.0%	13.5%	0.473
Had previous acute NIV	35.8%	36.5%	1.000
Comorbidities			
Cor Pulmonale	22.8%	19.2%	0.730
IHD	21.6%	34.6%	0.038
LVSD	13.4%	23.1%	0.062
AF	19.1%	25.0%	0.282
Depression	23.5%	25.5%	0.865
Cognitive impairment	7.9%	5.8%	0.789
Admission related			
CXR consolidation	37.6%	44.2%	0.375
Eosinopenia (pre NIV)	53.3%	55.8%	0.774
Not for IPPV	60.4%	53.8%	0.380
Not for CPR	55.4%	53.8%	0.885
First acidemia >12hrs	24.8%	30.8%	0.326
NIV start to pH correction (mins) [†]	521 (169-1490)	490 (244-1124)	0.750
Duration of ventilation (hrs) [†]	62 (25-109)	64 (26-101)	0.746
Blood gas results at time of NIV decision			
pH [†]	7.27 (7.21-7.30)	7.26 (7.22-7.30)	0.587
PaCO ₂ [†]	9.60 (8.18-11.60)	10.00 (8.65-12.17)	0.243
PaO ₂ [†]	7.96 (6.70-9.72)	8.86 (7.17-10.86)	0.027
Base excess*	4.5 (6.6)	5.6 (7.5)	0.244
HCO ₃ ^{-*}	30.4 (6.8)	31.4 (7.2)	0.298
Ventilator settings (initial period of ventilation only)			
1 hour IPAP*	18.0 (5.1)	17.2 (4.9)	0.247

Descriptor	No relapse	Relapse	P value
1 hour EPAP*	5.0 (1.3)	5.0 (1.3)	0.916
1 hour BUR*	14.0 (2.6)	14.3 (2.7)	0.402
Max IPAP*	20.8 (4.9)	21.3 (4.6)	0.483
Max EPAP*	5.5 (1.6)	5.7 (1.8)	0.355
Max BUR*	14.3 (2.7)	14.7 (3.1)	0.276

*Mean (SD) with comparisons by t-test. †Median (IQR) with comparisons by Mann-Whitney-U. Categorical comparisons Fisher's exact test.

7.1.3 Outcomes from late failure and relapse

Inpatient mortality was high for patients developing either late failure, or relapse.

Though numbers are small, relapse carried a higher risk of mortality than late failure (see Table 62), and the combination of both was associated with the worst outcomes, although numbers in this group are very small.

Table 62. Inpatient and inpatient + 90 day mortality rates in those with and without late failure or relapse.

	N=	Inpatient mortality	Inpatient & 90-day
None	640	17.7%	30.3%
Late Failure	41	31.7%	36.6%
Relapse	48	37.5%	50.0%
Both Late Failure & Relapse	4	75.0%	75.0%

Of the patients surviving to discharge, 7 (25%) late failure and 6 (20%) relapse patients started home ventilation within the subsequent 12 months. All relapse patients started this at discharge, whereas only 4 of the 7 late failure patients started at discharge.

7.1.3.1 Differences in the late failure and relapse populations

Late failure and relapse populations appear to be different, with different outcomes.

This is most strongly evidenced by the small amount of overlap (n=4) between the two groups. Whilst late failure patients are older than non-late failure; relapse are younger; there are similarities in the number for cardiopulmonary resuscitation, but the late failure group were less likely to be considered suitable for escalation. Comorbidities are high in all patients, though cardiac comorbidities appear to be of particular importance in both groups. The NIV decision gases in relapse patients were broadly similar to the non-relapse patients, whereas late failure patients have higher CO₂, base excess and

bicarbonate readings. Interestingly, the late failure patients are ventilated at higher pressures initially - suggesting that they are being recognised as different by clinicians, but unfortunately these data do not allow further exploration of this.

7.2 Persistent hypercapnia

As NIVO was an observational study we did not specify when arterial blood gases should be taken, but if patients had a blood gas in the period after acute ventilation had ended (but prior to discharge) this was recorded and is termed 'post-wean'. A post-wean blood gas was performed in 413 (56.3%) of patients. Median time to post-wean gas from the end of acute ventilation was 1498 (960-3417) minutes; around 25 hours. 24 patients had a post-wean gas performed but went on to die as an inpatient – these patients are not included in the analysis below; only patient surviving to discharge are included.

ABGs presented below do not include any EM values; there were sizeable differences in the rate of post-wean ABGs at each site and it's therefore unlikely that this data is truly MAR/MCAR and is more likely a result of model of care differences.

7.2.1 Post-wean arterial blood gas results

Results of post-wean gases are shown in Table 63. Of the 389 patients who had a post-wean gas and survived to discharge, 300 (77.1%) were hypercapnic (defined as $\text{PaCO}_2 \geq 6.0\text{kPa}$). Of these, 171/300 had a PaCO_2 of $>7.0\text{kPa}$.

Table 63. Results of post-wean blood gases.

pH[†]	PaO2[†]	PaCO2[†]	Base Excess[*]	Bicarbonate[*]
7.41 (7.38-7.45)	7.80 (6.99-8.85)	6.85 (6.03-8.00)	8.4 (5.7)	132.9 (5.7)

*Mean (SD) †Median (IQR).

7.2.2 Demographics

Patients who had persisting hypercapnia following the cessation of acute ventilation had worse baseline functional status, were more frequently prescribed LTOT, had more severe airflow obstruction, were more likely to have had NIV previously, and had more cor pulmonale (likely correlated with the higher level of LTOT), shown in Table 64.

Interestingly, patients with hypercapnia were less likely to have ischaemic heart disease than non-hypercapnic. Patients with hypercapnia took longer to initial pH correction, had higher PaCO_2 and HCO_3 levels, and a trend toward higher pH at the time of NIV decision, all suggesting a higher level of chronic respiratory failure.

Table 64. Demographics of patients surviving to discharge with and without post-wean hypercapnia.

Descriptor	No Hypercapnia	Hypercapnia present	P value
Age*	70.5 (8.6)	69.2 (9.2)	0.244
Own home (+/- carers)	94.4%	95.7%	0.612
eMRCD [†] % scoring 5a or 5b	4 (4-5a) 41.6%	4 (4-5a) 49.3%	0.025
FEV ₁ % predicted*	43.6% (16.5)	37.0% (15.6)	0.001
LTOT	5.6%	28.7%	<0.001
BMI [†]	25.0 (20.5-28.4)	25.5 (20.3-32.1)	0.180
Previous admissions [†]	1 (0-3)	1 (0-3)	0.934
On long term steroid	11.2%	11.3%	0.980
Had previous acute NIV	25.8%	38.7%	0.027
Comorbidities			
Cor Pulmonale	13.5%	26.7%	0.010
IHD	33.7%	17.3%	0.001
LVSD	12.4%	12.3%	0.995
AF	14.6%	14.0%	0.885
Depression	22.5%	26.3%	0.463
Cognitive impairment	6.7%	6.7%	0.980
Admission related			
CXR consolidation	29.2%	38.0%	0.129
Not for CPR	43.8%	48.0%	0.488
NIV decision pH [†]	7.23 (7.19-7.31)	7.23 (7.23-7.31)	0.086
NIV decision PaO ₂ [†]	8.0 (6.8-9.9)	7.9 (6.8-9.4)	0.567
NIV decision PaCO ₂ [†]	8.23 (7.38-10.17)	9.92 (8.50-11.78)	<0.001
NIV decision HCO ₃ [*]	27.1 (5.0)	32.4 (7.20)	<0.001
First acidaemia >12hrs	22.5%	18.3%	0.385
Time to pH correction (mins) [†]	305 (95-997)	517 (191-1513)	0.004
Duration of ventilation (hrs) [†]	60.0 (21.5-109.5)	69.5 (32.0-116.0)	0.186

*Mean (SD) with comparisons by t-test. [†]Median (IQR) with comparisons by Mann-Whitney-U. Categorical comparisons with Chi Squared test.

7.2.3 Hypercapnia and readmissions

Of the 389 patients who had a post-wean blood gas the majority, 272 (69.9%) were readmitted within the year following discharge. There was no difference in likelihood of being readmitted, nor time to readmission, whether a patient was hypercapnic or not Table 65. Similarly, there were no observed differences between type of readmission, nor the total number of days spent as an inpatient. Patients who were hypercapnic were more likely to subsequently receive acute NIV on readmission – this is not immediately clear from the median values shown in Table 65, but mean number of admissions in hypercapnic patients was 0.84 vs. 0.60 in non-hypercapnic patients.

Table 65. Readmissions between those with and without post-wean hypercapnia

Variable	No Hypercapnia	Hypercapnia	P value
Readmitted within year[^]	61 (68.5%)	211 (70.3%)	0.746
Days to first readmission^{†*}	41 (13.5-113.0)	38 (11.0-95.0)	0.709
Days as inpatient over the year^{†*}	20 (7.50-35.0)	19 (7.0-36.0)	0.936
Number of readmissions[†]	1 (0-4)	1 (0-3)	0.907
Number of respiratory readmissions[†]	1 (0-3)	1 (0-3)	0.596
Number of COPD readmissions[†]	1 (0-2.5)	1 (0-2)	0.557
Number of readmissions with NIV use[†]	0 (0-1)	0 (0-1)	0.036
[^] Absolute number (%) compared with Chi Square test. [†] Median (IQR) with comparisons made with Mann-Whitney-U test. [*] In those who were readmitted			

7.2.4 Hypercapnia and subsequent mortality

Of the 389 patients with a post-wean blood gas 138 (35.5%) died within a year of index admission. Median (IQR) time to death was 133 (47-229) days. Table 66 shows the proportion of patients dying within 1, 3, 6 and 12 months following discharge. Numbers are small below three months making comparison more challenging but there is a trend towards increased death of those with hypercapnia. By 6 months there is a clear difference, and patients with hypercapnia are almost twice as likely to die as patients without hypercapnia by 12 months.

Table 66. Comparison of death at 1, 3, 6 and 12 months in patients with and without post-wean hypercapnia.

Variable	No Hypercapnia	Hypercapnia	P value
Died by 1 month	2 (2.2%)	25 (8.3%)	0.056
Died by 3 months	8 (9.0%)	48 (16.0%)	0.098
Died by 6 months	11 (12.4%)	78 (26.0%)	0.007
Died by 12 months	20 (22.5%)	118 (39.3%)	0.004

7.2.5 Hypercapnia and home ventilation

A minority of patients, 20 (7.3%), with post-wean hypercapnia were prescribed home ventilation at discharge (excluding 27 patients already on home NIV at admission), although a larger proportion 64 (23.4%) were commenced on home ventilation at any point in the year. This leaves 209 (76.6%) patients with post-wean hypercapnia who never received home ventilation. There was a significantly higher ($p=0.010$) median (IQR) post-wean PaCO_2 in hypercapnic patients started on home ventilation (PaCO_2 7.75kPa (6.80-8.50)) than those not started on it (PaCO_2 7.16 (6.54-8.15)) in the year following discharge.

7.3 Home ventilation patients

Data were collected on the number of patients on home ventilation (HMV) both pre-admission, and who commenced following discharge. Where a patient consented into the longitudinal study and was started on home ventilation in the year following their discharge, ventilatory pressures and compliance were recorded.

7.3.1 Number of home ventilation patients

Sixty four patients (8.7%) were already receiving home ventilation at the point of their primary admission into the NIVO study. All of these patients required an increase in their usual (long-term) ventilatory settings or pattern (pressures or duration) in response to an acute respiratory acidosis secondary to ECOPD. Of these 64 patients, 8 (12.5%) died as an inpatient and 6 (9.4%) had their HMV stopped whilst an inpatient.

31 of 530 (5.9%) patients who survived to discharge started HMV at discharge from hospital. 62 patients started home ventilation at a later point, meaning in the 12 months from discharge 93 (15.8% of all surviving) patients were started on home ventilation. One patient was on HMV at admission, which was stopped at discharge, and then re-prescribed later in the follow up period.

7.3.2 Home ventilation at discharge

The population characteristics of patients started on home ventilation at discharge are shown below in Table 67. The comparisons are made with patients who survived to discharge and who were not on home ventilation at admission. There were no significant differences between most variables though, perhaps expectedly, patients started on home ventilation at discharge had more LTOT, a higher post-wean PaCO₂ and a higher BMI. There was a non-significant trend towards younger patients being started on home ventilation.

Table 67. Comparisons of patients started and not started on home ventilation at discharge.

Descriptor	No HMV at discharge (n=499)	Started HMV at discharge (n=31)	P value
Age*	70.2 (9.3)	67.1 (8.8)	0.068
Own home (+/- carers)	93.6%	96.8%	0.712
eMRCD [†]	4 (4-5a)	4 (4-5a)	0.704
FEV ₁ % predicted*	38.3% (15.4)	35.2% (14.4)	0.272
LTOT	20.2%	38.7%	0.022
BMI [†]	24.4 (19.8-29.7)	30.7 (22.9-37.2)	0.009
Previous admissions [†]	1 (0-3)	1 (1-3)	0.953
On long term steroid	9.4%	9.7%	1.000
Comorbidities			
Cor Pulmonale	21.8%	19.4%	1.000
IHD	21.2%	19.4%	1.000
LVSD	12.6%	6.5%	0.408
AF	16.0%	22.6%	0.322
Depression	24.0%	22.6%	1.000
Cognitive impairment	8.4%	6.5%	1.000
Admission related			
CXR consolidation	36.3%	29.0%	0.448
Post-wean pH [†]	7.42 (7.39-7.45)	7.41 (7.38-7.44)	0.225
Post-wean PaCO ₂ [†]	6.76 (6.00-7.80)	8.20 (7.03-9.45)	<0.001
Not for CPR	51.7%	51.6%	1.000

*Mean (SD) with comparisons by t-test. [†]Median (IQR) with comparisons by Mann-Whitney-U. Categorical comparisons with Fisher's exact test.

7.3.3 Indication for home ventilation

The indication for home ventilation was recorded and patterns were slightly different depending on whether home ventilation was started at discharge, or at a later point Table 68. Patients could have more than one indication documented. Other reasons for starting HMV were mixed OSA/COPD (4 patients), the inability to wean the patient from acute NIV (7 patients), Obesity/COPD (1 patient), to prevent readmission (1 patient) and unspecified (9 patients).

Table 68. Indications for commencing home ventilation at discharge and during follow up.

Indication for HMV	Started post discharge	Started at discharge
Recurrent admissions requiring acute NIV*	47 (75.8%)	6 (19.4%)
Symptom control	28 (45.2%)	16 (51.6%)
To facilitate LTOT	12 (19.4%)	6 (19.4%)
HOT-HMV criteria⁽²⁴⁴⁾	10 (16.1%)	2 (9.7%)
Other*	8 (12.9%)	14 (45.2%)
More than one reason	31 (50%)	10 (32.3%)

*Significant to p=0.001 or less on Fisher's exact test.

7.3.4 Longitudinal home ventilation patients

7.3.4.1 Ventilation pressures

There were 37 patients who consented into the longitudinal study (Chapter 9) and were started on home ventilation either at discharge or within the follow up year. In these patients ventilatory pressures and compliance were captured alongside other longitudinal questionnaires. Missing data rates were high in this group and are presented in italics within Table 69.

Table 69. Numbers and ventilatory pressures of patients on home ventilation in longitudinal follow up.

	On HMV	Died	w/d	Stopped	IPAP*	EPAP*	BUR*
At discharge	11	n/a	n/a	n/a	21.1 (4.2)	6.4 (1.9)	11.8 (2.2)
Missing data	-	-	-	-	27.3%	27.3%	54.5%
3 months	16	4	3	0	22.6 (3.9)	5.6 (1.8)	13.4 (2.1)

	On HMV	Died	w/d	Stopped	IPAP*	EPAP*	BUR*
Missing data	-	-	-	-	31.3%	31.3%	43.8%
6 months	23	5	3	0	23.2 (6.5)	5.1 (2.2)	14.5 (2.6)
Missing data	-	-	-	-	21.7%	21.7%	39.1%
12 months	24	9	3	1	23.7 (6.2)	5.0 (2.0)	15.0 (2.7)
Missing data	-	-	-	-	37.5%	37.5%	50.0%
*Mean (SD). On HMV= patients actively receiving home ventilation; Died= patients that died; w/d=patients who have withdrawn from longitudinal follow up; Stopped= patients on whom home ventilation was discontinued.							

7.3.4.2 Ventilator usage

Average use of the ventilator was also gathered from both the ventilator and the patient at follow appointments in during the longitudinal study (Table 70). Again, there were high levels of missing data in this cohort.

Over the whole year, verified (5.7 hours per night) and patient reported (5.8 hours per night) use was remarkably similar. These data do not capture all NIVO patients who were on home ventilation; only those who had taken part in the longitudinal study. It may be that reported vs. verified compliance varies more in the non-longitudinal cohort.

Table 70. Longitudinal verified and patient reported compliance by month.

	Verified use (mins)*	Patient reported use (mins)*
Month 3	336.7 (202.2)	330 (182.5)
Missing data	36.4%	36.4%
Month 6	372.9 (175.9)	348.1 (173.9)
Missing data	52.1%	56.5%
Month 12	312.4 (157.7)	363.9 (171.5)
Missing data	54.2%	66.7%

*Mean (SD)

7.3.5 Readmission rates in home ventilation at discharge

Readmission rates over the year following in those on (n=81) and not on (n=505) HMV at discharge were compared. There were no differences on readmission rate, number of days spent in hospital, time to readmission, or requirement for further NIV (Table 71). Additionally, there were no differences in subsequent readmission rate (p=0.559), total

number of readmissions ($p=0.745$), nor time to readmission ($p=0.668$) in patients who had hypercapnia ($\text{PaCO}_2 \geq 6.0\text{kPa}$) on post wean blood gases and who were either on ($n=45$) or not on ($n=255$) HMV at discharge.

Table 71. Readmissions in patient on, or not on, home ventilation at discharge.

Variable	Not on HMV at discharge	On HMV at discharge	P value
Readmitted*	358 (70.9%)	55 (67.9%)	0.584
If readmitted, total days in hospital[†]	17 (7-34)	22 (7-43)	0.365
If readmitted, days to readmission[†]	40 (12-97)	23 (9-94)	0.301
Number of readmissions[†]	1 (1-3)	1 (1-3)	0.749
Number of COPD admissions[†]	1 (0-2)	1 (1-3)	0.533
Number of NIV readmissions[†]	0 (0-1)	0 (0-1.5)	0.107
[†] Median (IQR) with comparisons made by Mann Whitney U. *Categorical (%) with comparisons made by Chi Squared test			

7.3.6 Mortality rates in home ventilation at discharge

Table 72 demonstrates the mortality rates between patients discharged on home ventilation ($n=81$) and those not on home ventilation at discharge ($n=505$). These data suggest that patients treated with home ventilation are more likely to die within six months than those who are not treated, although by one year this effect is lost and mortality rates are similar overall.

Table 72. Comparison of death at 1, 3, 6 and 12 months in patients on, or not on, home ventilation at discharge.

Variable	Not on HMV at discharge	On HMV at discharge	P value*
Died by 1 month	36 (7.1%)	6 (7.4%)	0.820
Died by 3 months	75 (14.9%)	14 (17.3%)	0.617

Died by 6 months	120 (18.4%)	25 (30.9%)	0.011
Died by 12 months	176 (34.9%)	32 (39.5%)	0.453
*Comparisons made by Fishers exact test			

7.4 Pre-admission long term oxygen therapy

There were 210 (28.6%) patients included in the validation study who were on LTOT at the point of admission. Of these, 53 (25.2%) died as an inpatient – higher than the mortality rate of non-LTOT patients (18.0%); $p=0.026$. Whilst LTOT had univariate association with inpatient mortality in the validation study, it was not independently associated with mortality (see section 6.8.3) and was not included in the NIVO score. In survivors, demographic differences and outcome were examined in both LTOT and non-LTOT patients.

7.4.1 Demographics

One hundred and fifty seven LTOT users survived to discharge, and demographic comparisons with non-LTOT users ($n=429$) are shown in Table 73. A number of differences were observed between the LTOT and non-LTOT population.

Surviving patients with LTOT had worse eMRCD scores, were more likely to have previously received acute NIV, and had more severe airflow obstruction. BMI was slightly higher in LTOT patients, although the difference in median values is not of clear clinical significance. It is not surprising that patients on LTOT more commonly had Cor Pulmonale as this is one of the conditions in which LTOT is indicated earlier; and it is perhaps unsurprising that there were a higher number of patients with AF in the LTOT group given the amount with Cor Pulmonale. Patients receiving LTOT were less likely to be offered escalation to invasive ventilation and were more likely to be DNACPR than those not on LTOT. Whilst their NIV decision PaCO_2 and PaO_2 were worse than non-LTOT patients, the pH and bicarbonate suggest that LTOT patients had acute-on-chronic respiratory failure to a greater extent than non-LTOT patients.

Table 73. Comparisons between patients surviving to discharge who were on and not on LTOT.

Variable	Not on LTOT	On LTOT	P value
Age*	69.5 (9.4)	70.4 (8.8)	0.339
eMRCD [†]	4 (4-5a)	5a (4-5b)	<0.001
Previous admissions [†]	1 (0-3)	2 (1-4)	0.002
Previous NIV	27.5%	61.8%	<0.001
Home (+/- carers)	94.6%	91.1%	0.127

Variable	Not on LTOT	On LTOT	P value
FEV₁ % predicted*	39.0% (15.1)	32.1% (14.9)	<0.001
BMI[†]	24.6 (19.6-30.2)	25.6 (21.1-31.5)	0.026
LVSD	11.9%	14.0%	0.490
IHD	21.2%	22.9%	0.655
Cor Pulmonale	17.9%	34.4%	<0.001
Atrial Fibrillation	14.0%	21.7%	0.025
Depression	23.1%	28.0%	0.217
Cognitive Impairment	7.9%	7.0%	0.711
Long Term Steroids	8.9%	14.0%	0.068
CXR consolidation	35.4%	34.4%	0.816
NIV pH[†]	7.27 (7.22-7.30)	7.28 (7.24-7.31)	0.024
NIV PaCO₂[†]	9.20 (7.90-10.80)	10.37 (8.91-12.66)	<0.001
NIV PaO₂[†]	8.10 (7.02-9.89)	7.54 (6.22-8.85)	0.001
NIV Bicarbonate*	29.2 (6.1)	34.4 (7.2)	<0.001
For Resus	56.6%	32.5%	<0.001
For Invasive ventilation	50.1%	30.6%	<0.001

*Mean (SD) with comparisons by t-test. †Median (IQR) with comparisons by Mann-Whitney-U. Categorical comparisons with Chi Squared.

7.4.2 Long term oxygen therapy, smoking and mortality

Every centre in NIVO allowed current smokers to have LTOT. There was no significant difference in inpatient mortality for patients on LTOT if they were current smokers (IP mortality 23.0%) or ex-smokers (IP mortality 27.8%); $p=0.422$. Of patients on LTOT who survived to discharge, 87 (55.4%) were current smokers at admission (defined as any smoking within the six weeks prior to admission).

Mortality rates in current smokers in the whole NIVO population, irrespective of LTOT use, were not different to ex-smokers at any timepoint throughout the study: inpatient mortality (ex-smoker 20.1% vs. current smoker 20.2%; $p=1.00$), 90 day mortality (ex-smoker 29.4% vs. current smoker 34.1%; $p=0.190$), one year mortality (ex-smoker 48.7% vs. current smoker 48.7%; $p=1.00$).

7.4.3 Readmission and long term oxygen therapy

The readmission rate over the year after discharge was higher in patients using LTOT than in patients not using LTOT (88.2% vs. 66.2% readmitted respectively; $p < 0.001$). Additionally, LTOT patients had a shorter time to readmission, higher frequency of admissions, and more COPD related readmissions (with more requiring NIV) than those not using LTOT (Table 74).

Table 74. Readmissions in patients on and not on LTOT at admission.

Variable	Not on LTOT	On LTOT	P value
Time to readmission, days^{†*}	40.5 (14.0-110.0)	27 (7.0-84.5)	0.023
Days as an inpatient^{†*}	16.5 (6.25-33.75)	20 (8.0-40.5)	0.206
Number of readmissions[†]	1 (0-3)	2 (1-4)	0.008
Number of COPD readmissions[†]	1 (0-2)	1 (0-3)	<0.001
Number of NIV readmissions[†]	0 (0-1)	1 (0-1.5)	<0.001
[†] Data are presented as Median (IQR) and compared with Mann-Whitney-U test. *In readmitted patients			

7.4.4 Mortality and long term oxygen therapy

As discussed above, LTOT was associated with inpatient mortality on univariate analysis and appears to retain this association throughout the year following discharge. A significantly higher proportion of patients on LTOT had died at 30, 90, 180 and 365 days. Throughout the year, mortality for LTOT was approximately double that of non LTOT patients, and by 12 months over half of the patients treated with LTOT had died (Table 75).

Table 75. Comparisons of mortality at 1, 3, 6 and 12 months in patients on and not on LTOT at admission.

Month after discharge	Died, not on LTOT	Died, on LTOT	P value*
One	23 (5.4%)	19 (12.1%)	0.010
Three	49 (11.4%)	40 (25.5%)	<0.001
Six	79 (18.4%)	66 (42.0%)	<0.0001
Twelve	124 (28.9%)	84 (53.5%)	<0.0001
*Comparison at one month with Fisher's exact test, with remaining months Chi Squared			

7.4.5 Long term oxygen therapy in COPD summary

Patients requiring treatment with LTOT in COPD constitute a particularly unwell subset of patients, both during and after admission. They have a higher number of both previous admissions and re-admissions, a more frequent requirement for assisted ventilation, worse airflow obstruction, more severe respiratory acidosis, and worse baseline dyspnoea. Following discharge they spend, on average, nearly one month back in hospital through recurrent readmissions, and over half will have died by a year.

7.5 Eosinopenia at discharge

Discharge bloods (the last available prior to discharge) were recorded; 144 of 586 (24.6%) patients were eosinopenic (defined as a count of $<0.05 \times 10^9/L$) on these. Median eosinophil count for the whole population at discharge was 0.1 (0.1-0.2).

7.5.1 Population demographics

There were no significant demographic differences between patients with and without eosinopenia at discharge, although eosinopenic patients did have a significantly shorter LoS (Table 76). It is not possible, from this data, to assess whether their eosinopenia at discharge is due to a shorter LoS (and being closer to the commencement of high dose oral corticosteroids), or an intrinsic difference in the patients' response. Given the similarity in their demographics, it seems probable that the former is the likely explanation.

Table 76. Comparisons of patients with and without Eosinopenia at discharge.

Variable	No Eosinopenia	Eosinopenia present	P value
Age*	69.5 (9.4)	70.4 (8.5)	0.305
eMRCD [†]	4 (4-5a)	5a (4-5a)	0.463
Previous admissions [†]	1 (0-3)	1 (0-3)	0.235
Previous NIV	37.6%	34.0%	0.445
LTOT	26.7%	27.1%	0.928
Home (+/- carers)	93.2%	95.1%	0.409
FEV ₁ % predicted*	37.0% (15.8)	37.8% (13.8)	0.574
BMI [†]	24.9 (20.3-30.4)	24.7 (19.2-32.2)	0.787
LVSD	12.7%	11.8%	0.785
IHD	21.5%	22.2%	0.854
Cor Pulmonale	23.1%	20.1%	0.462
Atrial Fibrillation	16.1%	16.0%	0.979
Depression	25.6%	20.8%	0.251
Cognitive Impairment	8.1%	6.3%	0.458
Long Term Steroids	10.6%	9.0%	0.581

Variable	No Eosinopenia	Eosinopenia present	P value
CXR consolidation	33.9%	38.9%	0.280
NIV pH[†]	7.28 (7.22-7.31)	7.27 (7.23-7.30)	0.698
NIV PaCO₂[†]	9.40 (8.14-11.28)	9.73 (8.22-11.68)	0.409
NIV PaO₂[†]	7.95 (6.90-9.40)	7.87 (6.52-9.84)	0.951
NIV Bicarbonate[*]	30.6 (6.9)	30.7 (6.4)	0.785
For Resus	49.3%	52.8%	0.471
For Invasive ventilation	45.7%	42.4%	0.501
Length of Stay[†]	9 (6-15.3)	7 (5-11)	<0.001

*Mean (SD) with comparisons by t-test. †Median (IQR) with comparisons by Mann-Whitney-U. Categorical comparisons with Chi Squared.

7.5.2 Eosinopenia at discharge, readmission and mortality

Patients who were eosinopenic on discharge did not have a higher rate of readmission over the following year than those who were not (70.4% vs. 70.8% respectively; $p=0.914$). There were no differences in the number of readmissions, type of readmission, time spent in hospital, or time to first readmission between groups. Additionally, there were no significant differences, at any timepoint, in the number of patients who died following discharge Table 77.

Table 77. Comparisons of death at 1, 3, 6 and 12 months in both patients with and without eosinopenia at discharge.

Month after discharge	Died, Not eosinopenic	Died, eosinopenic	P value*
One (30 days)	29 (6.6%)	13 (9.0%)	0.352
Three (60 days)	62 (14.0%)	27 (18.8%)	0.179
Six (180 days)	107 (24.2%)	38 (26.4%)	0.598
Twelve (365 days)	153 (34.6%)	55 (38.2%)	0.436
*Comparison at one month with Fisher's exact test, with remaining months Chi Squared			

7.6 Readmission and mortality following discharge

Readmission and mortality were tracked for one year in the 586 validation study patients who survived to discharge.

7.6.1 Readmissions to a year

Most NIVO patients who survived to discharge were readmitted within the following 12 months: 413 of 586 (70.5%). Readmission rates at 1, 3, 6 and 12 months are shown in Table 78 below. Readmission rates are notably higher than those reported in the national COPD audit patients requiring ventilation: 26.5% at 30 days and 46.2% at 90 days).⁽²¹¹⁾

Table 78. Readmission rates over the year following discharge.

Months from discharge	Value
One (30 days)	186 (31.7%)
Three (90 days)	300 (51.2%)
Six (180 days)	360 (61.4%)
Twelve (365 days)	413 (70.5%)

In the year following discharge, patients in NIVO had a total of 1,308 further admissions to hospital, of which the overwhelming majority, 1,091 (83.4%), were respiratory. Of these, 436 (40%) required treatment with NIV. Of respiratory readmissions 961 (88.1%) were due to COPD. The total number of inpatient days over the year was 11,755. Table 79, below, demonstrates median (IQR) results for a patient (for both NIV and non-respiratory admissions, the proportion of people with one or more readmission is also shown). The median (IQR) length of readmission was 7 (4-12) days.

Table 79. Readmission statistics in the NIVO population over the year following discharge.

Variable*	Result
If readmitted, total inpatient days	18 (7-36)
If readmitted, days to 1 st readmission	39 (11-97)
Number of readmissions	1 (1-3)
Number of respiratory admissions	1 (1-2)

Variable*	Result
Number of COPD related admissions	1 (1-2)
Number of NIV readmissions	0 (0-1)
<i>Number (%) with ≥1 readmission</i>	230 (39.3%)
Number of non-respiratory admissions	0 (0-0)
<i>Number (%) with ≥1 readmission</i>	143 (24.4%)
*All reported as Median (IQR)	

7.6.1.1 Readmitted population comparison

Most patients included in the NIVO study had at least one readmission within 12 months following discharge. Variables associated with acute admission were similar between those readmitted and not readmitted. Background demographics such as eMRCD, severity of airflow obstruction, requirement of LTOT, number of previous admissions (including previous requirement for NIV) were significantly associated with readmission. These align with known predictors of readmission in COPD. Interestingly, the only comorbidity associated with readmission was depression. Several individual comorbid conditions, including LVSD, Cor pulmonale, and the Charlson comorbidity index (a measure of overall comorbid burden) increase the chance of readmission in the overall COPD population, and have been identified as independent predictors in a number of clinical tools (Table 8). In the NIVO population, readmissions were numerically more common in patients with several comorbidities (Table 80) but failed to reach statistical significance in all except depression. Comorbidities may exert a lesser influence on the risk of readmission in patients requiring ventilation for their index admission. Compared to non-ventilated patients, they are likely to have more severe underlying COPD, which in turn may simply be a proportionally stronger or more dominant driver of readmission risk.

Table 80. Population characteristics and comparisons of patients who were and were not readmitted to hospital.

Descriptor	Not readmitted N=173	Readmitted N=413	P value
Age*	69.1 (8.9)	70.0 (9.3)	0.294
Own home (+/- carers)	96%	92.7%	0.144
eMRCD[†]	4 (3.5-5a)	5a (4-5a)	<0.001

Descriptor	Not readmitted N=173	Readmitted N=413	P value
<i>% scoring 5a or 5b</i>	34.7%	56.4%	<0.001
FEV ₁ % predicted*	39.3 (17.0)	36.3 (14.6)	0.034
LTOT	16.2%	31.2%	<0.001
BMI [†]	26.2 (20.1-33.0)	24.6 (20.2-29.8)	0.060
Previous admissions [†]	1 (0-2)	2 (0-4)	<0.001
On long term steroid	10.4%	10.2%	0.932
Had previous acute NIV	26.6%	40.9%	0.001
<i>Comorbidities</i>			
Cor Pulmonale	19.1%	23.7%	0.217
IHD	18.5%	23.0%	0.227
LVSD	9.2%	13.8%	0.128
AF	13.3%	17.2%	0.241
Depression	17.3%	27.4%	0.010
Cognitive impairment	6.4%	8.2%	0.437
<i>Admission related</i>			
CXR consolidation	35.8%	34.9%	0.822
Glasgow Come Score <15	29.5%	32.2%	0.517
Diaphragm Height (cm) [†]	2.4 (1.7-3.3)	2.4 (1.7-3.0)	0.133
NIV decision pH [†]	7.27 (7.21-7.31)	7.28 (7.23-7.31)	0.619
NIV decision PaO ₂ [†]	7.80 (6.53-9.34)	8.00 (6.92-9.75)	0.238
NIV decision PaCO ₂ [†]	9.37 (8.00-11.15)	9.53 (8.20-11.52)	0.431
NIV decision HCO ₃ [*]	30.3 (6.62)	30.8 (6.86)	0.443
First acidemia >12hrs	17.3%	21.5%	0.248

There was a non-significant trend towards higher BMI in the non-readmitted group overall. When split into BMI categories (Table 81) there was no significant difference (Kruskal Wallace p=0.094) between these; although obesity does appear to trend towards being associated with reduced readmission.

Table 81. Comparisons between BMI groups and readmission

BMI Category	Not readmitted N=173	Readmitted N=413
Underweight (<18.5)	30 (29.7%)	71 (70.3%)
Normal weight (18.5-24.9)	49 (25.1%)	146 (74.9%)
Overweight (25.0-29.5)	35 (26.9%)	95 (73.1%)
Obese (≥30.0)	59 (36.9%)	101 (63.1%)

7.6.2 Mortality at one year

In the year following discharge, there was significant mortality in the NIVO population. Over a third of patients surviving to discharge had died by one year, bringing the total mortality (including inpatient death) to almost 50% (Table 82).

Table 82. Mortality to one year in the NIVO population.

Month after discharge	Discharged, subsequently died (%)	Including IP Mortality (%)
-	N=586	N=733
One (30 days)	42 (7.2%)	189 (25.8%)
Three (60 days)	89 (15.2%)	236 (32.2%)
Six (180 days)	145 (24.7%)	292 (39.8%)
Twelve (365 days)	208 (35.5%)	355 (48.4%)

7.6.2.1 Population comparisons at one year

In the population that survived to discharge, comparisons were made between those who subsequently died within one year and those that survived (Table 83). Patients who died had worse baseline dyspnoea and were more likely to be unable to leave the house unassisted. Patients who died were marginally older, but this was not statistically significant. Patients who died had more severe airflow obstruction, were more likely to be on LTOT, have a lower BMI, and had been in hospital more frequently in the preceding year. Comorbid cor pulmonale, depression and atrial fibrillation were more common in those who died; although LVSD and IHD were similar between groups. Patients who subsequently died had a lower diaphragm height (measured in centimetres perpendicularly from a line drawn between the lateral and medial insertion points, to

the maximum height of the dome, preferentially on the right side) suggesting worse hyperinflation, than those who did not die. NIV decision pH and PaO₂ were similar, though PaCO₂ and bicarbonate were higher in those that died, suggesting background respiratory failure was more prevalent in these patients. Patients who died were less likely to have been considered for cardiopulmonary resuscitation during their index admission, suggesting that clinicians are recognising a phenotype of sick patients. Over the subsequent year, patients who died were more likely to have been readmitted to hospital, with a shorter time to readmission and a higher chance of requiring NIV again.

Table 83. Population characteristics and comparison between patients who survived or had died by one year.

Descriptor	Survived one year N=378	Died by one year N= 208	P value
Age*	69.3 (9.3)	70.7 (9.1)	0.074
Own home (+/- carers)	95.0%	91.3%	0.084
eMRCD [†]	4 (4-5a)	5a (4-5b)	<0.001
% scoring 5a or 5b	43.4%	62.0%	<0.001
FEV ₁ % predicted*	38.2% (15.7)	35.3% (14.6)	0.029
LTOT	19.3%	40.4%	<0.001
BMI [†]	25.3 (20.7-31.4)	23.4 (18.4-29.6)	0.005
Previous admissions [†]	1 (0-3)	2 (1-4)	<0.001
On long term steroid	10.6%	9.6%	0.712
Had previous acute NIV	33.6%	42.3%	0.036
<i>Comorbidities</i>			
Cor Pulmonale	19.3%	27.9%	0.017
IHD	20.1%	24.5%	0.215
LVSD	11.6%	13.9%	0.419
AF	13.5%	20.7%	0.023
Depression	22.0%	28.8%	0.063
Cognitive impairment	6.3%	10.1%	0.103
<i>Admission related</i>			
CXR consolidation	33.9%	37.5%	0.378
Glasgow Come Score <15	29.4%	35.1%	0.153

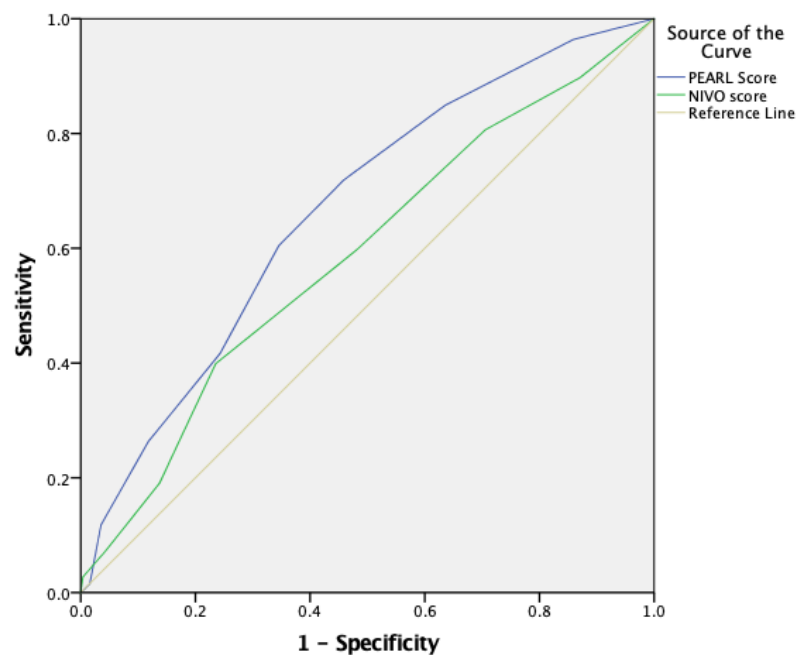
Descriptor	Survived one year N=378	Died by one year N= 208	P value
Diaphragm Height (cm) [†]	2.4 (1.7-3.1)	2.1 (1.7-2.9)	<0.036
Not for CPR	43.7%	61.1%	<0.001
NIV decision pH [†]	7.27 (7.22-7.31)	7.28 (7.23-7.31)	0.940
NIV decision PaO ₂ [†]	7.91 (6.80-9.50)	7.88 (6.65-9.50)	0.999
NIV decision PaCO ₂ [†]	9.14 (8.00-11.03)	10.30 (8.60-11.80)	<0.001
NIV decision HCO ₃ [*]	30.0 (6.3)	31.8 (7.5)	0.003
First acidemia >12hrs	21.2%	18.8%	0.487
<i>Readmissions</i>			
Readmission rate	65.3%	79.8%	<0.001
Time as inpatient, days [†]	18 (7-33)	19.5 (7-41)	0.836
Time to first readmission, days [†]	45 (17-119)	29 (8-68)	<0.001
Number of readmissions [†]	1 (0-3)	2 (1-3)	0.043
Number of COPD readmissions [†]	1 (0-2)	1 (0-2)	0.019
Number of NIV readmissions [†]	0 (0-1)	0 (0-1)	<0.001

*Mean (SD) with comparisons by t-test. †Median (IQR) with comparisons by Mann-Whitney-U. Categorical comparisons with Chi Squared.

7.6.3 The PEARL score in the NIVO population

The PEARL Score was developed to predict readmission or death at 90 days following severe COPD exacerbation.⁽¹⁶³⁾ Patients receiving treatment with NIV made up a minority of patients (14.8%) within the PEARL development cohorts. In the NIVO population who survive to discharge, PEARL performs moderately well for prediction of readmission or death within 90 days, with an AUROC of 0.667. In comparison, the NIVO Score is a weaker predictor of readmission or death (AUROC= 0.587; p=0.0014) (Figure 19). Accepting the difference in measured time periods displayed in the tables (1 year in tables vs. 90 days here), this outperformance is unsurprising; predictors of acute in-hospital mortality differ from predictors of subsequent risk of readmission or mortality.

Figure 19. ROC curves for the NIVO and PEARL score in predicting readmission or death within 90 days



7.6.4 Readmission and mortality summary

Readmission and mortality rates in NIVO patients were high. Overlaps between demographic variables associated with readmission and death were seen, particularly in relation to indices present prior to admission. Stable state breathlessness, lung function, requirement for long term oxygen therapy, previous admissions/NIV, and comorbid depression all featured strongly. Regardless of any given univariate association between those who were readmitted or died, 70% were readmitted and 50% died within a year of their index admission. This population clearly has extensive healthcare needs, suggesting that particular attention to careful assessment, follow up and treatment planning should be afforded to any patient who requires assisted ventilation for ECOPD. Clinicians should have a low threshold for instituting discussions around advance care planning, emergency healthcare planning, and consideration of referral to palliative care teams.

8 Clinical diagnosis patients

It is not uncommon for patients to be admitted to hospital with (or who later develop) respiratory acidaemia and a clinical history, examination and investigations in keeping with ECOPD, but who have never had confirmatory pre-admission spirometry. In many cases the patient may be clinically diagnosed with an exacerbation of COPD and ventilated for respiratory acidaemia, whilst awaiting confirmatory spirometry. It is pertinent to see if the NIVO score works in this patient population.

A significantly reduced dataset was collected on patients who met all other inclusion criteria but had never undertaken pre-admission spirometry – termed ‘clinical diagnosis’ (CD) patients, with the aim to assess the performance of the NIVO score in this group. Given the reduced dataset collected comparison of NIVO to the APACHE-II, Confalonieri risk chart and CAPS scores is not possible.

8.1 Number recruited

One hundred and eleven patients were recruited to the clinical diagnosis cohort over the same time period as the full validation study. A site by site breakdown is shown on Table 11 (Page 112).

8.2 Demographics

Compared to the validation cohort, clinical diagnosis patients were of a similar age, gender and ethnicity, had a similar comorbidity burden, and similar blood & ABG results. Population characteristics are shown in Table 84.

Table 84. Population characteristics and comparisons of the clinical diagnosis and validation cohorts.

Value	Clinical Diagnosis	Validation	P value
Number	111	733	-
Age*	69.6 (10.9)	70.5 (9.3)	0.341
Female %	52.3%	58.3%	0.257
Caucasian %	97.3%	98%	0.720
eMRCD[†]	4 (4-5a)	5a (4-5a)	0.002
LTOT	15 (13.5%)	210 (28.6%)	0.001

Value	Clinical Diagnosis	Validation	P value
BMI[†]	26.8 (21-31.9)	24.1 (19.6-29.7)	0.016
BMI ≥35.0 (%)	16 (14.4%)	92 (12.6%)	0.545
Comorbidities			
LVSD (%)	19 (17.4%)	103 (14.1%)	0.381
Depression (%)	25 (22.5%)	173 (23.6%)	0.904
AF (%)	18 (16.2%)	143 (19.5%)	0.517
Observations			
Consolidation (%)	41 (37.3%)	279 (38.1%)	0.916
Effective Cough (%)	22 (19.8%)	111 (15.1%)	0.210
Confusion (%)	44 (44.0%)	181 (25.4%)	0.002
GCS[†]	15 (13-15)	15 (14-15)	0.080
Systolic BP*	127.0 (29.2)	133.3 (34.2)	0.068
Diastolic BP*	71.2 (17.4)	75.4 (20.7)	0.041
RR*	26.3 (7.4)	28.4 (7.4)	0.006
Blood results at admission and NIV decision gas			
Hb*	13.6 (2.4)	13.7 (2.1)	0.595
Hct*	0.43 (0.07)	0.43 (0.06)	0.592
WCC*	12.5 (6.5)	13.1 (6.8)	0.426
Eosin[†]	0.0 (0.0-0.1)	0.0 (0.0-0.1)	0.184
CRP[†]	37 (20-105)	40 (13-110)	0.782
Urea[†]	8.2 (4.9-11.9)	7.0 (5.1-10.3)	0.292
Potassium*	4.7 (0.7)	4.6 (0.6)	0.354
Albumin*	37.2 (5.2)	37.7 (5.2)	0.358
pH[†]	7.26 (7.20-7.29)	7.27 (7.22-7.30)	0.175
BE*	4.5 (7.1)	4.6 (6.6)	0.948
Admission to NIV gas in mins	126 (34-587)	137 (41-767)	0.601
Time to NIV gas >12hrs (%)	25 (22.5%)	185 (25.2%)	0.558

*Mean (SD) with comparisons by t-test. [†]Median (IQR) with comparisons by Mann-Whitney-U. Categorical comparisons with chi-squared test.

CD patients had less severe baseline dyspnoea, less LTOT, higher BMI and more confusion. Despite higher median BMI in the CD group, the proportion of patients with a BMI of ≥ 35.0 was similar to the validation. Although RR and Diastolic blood pressure were significantly different, the clinical significance in their difference is minimal (Table 84). It is interesting that 13.5% of CD patients were prescribed LTOT but had no available spirometry. It may be that these patients did have a historic diagnosis with spirometry, but records of this could not be found despite searching of hospital, lung function and primary care records.

Less severe baseline eMRCD is perhaps unsurprising as these patients could be earlier in the natural history of their disease, meaning they may not have had as much contact with healthcare services in order to be formally diagnosed.

8.3 The NIVO score in clinical diagnosis patients

8.3.1 Inpatient mortality

Despite their lower eMRCD scores, CD inpatient mortality is similar to validation patients (Table 85). eMRCD was the strongest predictor of outcome in NIVO; this suggests CD patients may have worse outcomes than validation patients – potentially due to under optimisation of pre-hospital treatment or mis-diagnosis of ECOPD in hospital. Whilst none of the other univariate comparators were significantly different, GCS had a clear trend towards being lower in CD patients.

Table 85. Comparison of clinical diagnosis and validation inpatient mortality

	Clinical Diagnosis	Validation	P value*
Inpatient Mortality	22 (19.8%)	147 (20.1%)	1.000

*Chi Squared

Table 86 shows the breakdown of NIVO score with inpatient mortality in CD patients, with validation patients as a comparator. CD patients have a higher mortality than validation for 2/3 of the individual NIVO scores.

Table 86. NIVO score and inpatient mortality in clinical diagnosis patients

NIVO Score	Number of CD patients	CD inpatient mortality	Validation IP mortality
0	9	1 (11.1%)	0%
1	21	1 (4.8%)	8.9%
2	23	3 (13.0%)	5.3%
3	18	5 (27.8%)	15.1%
4	19	2 (10.5%)	19.0%
5	11	2 (18.2%)	35.1%
6	8	6 (75.0%)	53.7%
7	1	1 (100%)	65.4%
8	1	1 (100%)	87.5%
9	0	n/a	100%

Clinical diagnosis mortality shown as number (percentage with this outcome). Validation percentage mortality shown for comparison.

The pattern of increased mortality with progressively higher NIVO scores is similar, but not as clear cut as in validation patients. In higher scores patient numbers are exceptionally low, making conclusions difficult to draw. One possibility for similar outcomes despite less severe dyspnoea is a more severe acute insult in the CD group, though the data does not support this – the median NIVO score in CD patients was 3 (1-4) and in validation patients was 3 (2-5) $p=0.075$, with a similar pattern seen in the DECAF score (CD 2 (2-3) vs. Validation 3 (2-3); $p=0.49$). If removing dyspnoea from the NIVO score (as this is a non-acute measurement), median NIVO scores in both groups are 2 (1-3), $p=0.952$; again, suggesting that the acute insult was not worse in the CD group. The NIVO risk groups clearly stratify mortality risk in the CD population, shown in Table 87.

Table 87. Risk groups by NIVO score in the clinical diagnosis population

Risk Group (NIVO Score)	N	Inpatient mortality
Low (0-2)	53	9.4%
Medium (3-4)	37	18.9%
High (5-6)	19	42.1%
Very High (7-9)	2	100%

8.3.2 ROC analysis

The NIVO score has weaker discrimination in clinical diagnosis patients as in the validation study (Figure 20). There is no statistically significant difference between the AUROCs of NIVO, DECAF or CURB-65 in this population, although the NIVO score has the highest numerical value (0.724) and still offers moderate prediction of outcome (Table 88).

Figure 20. ROC curve analysis for NIVO and comparator tools examining inpatient mortality in clinical diagnosis patients.

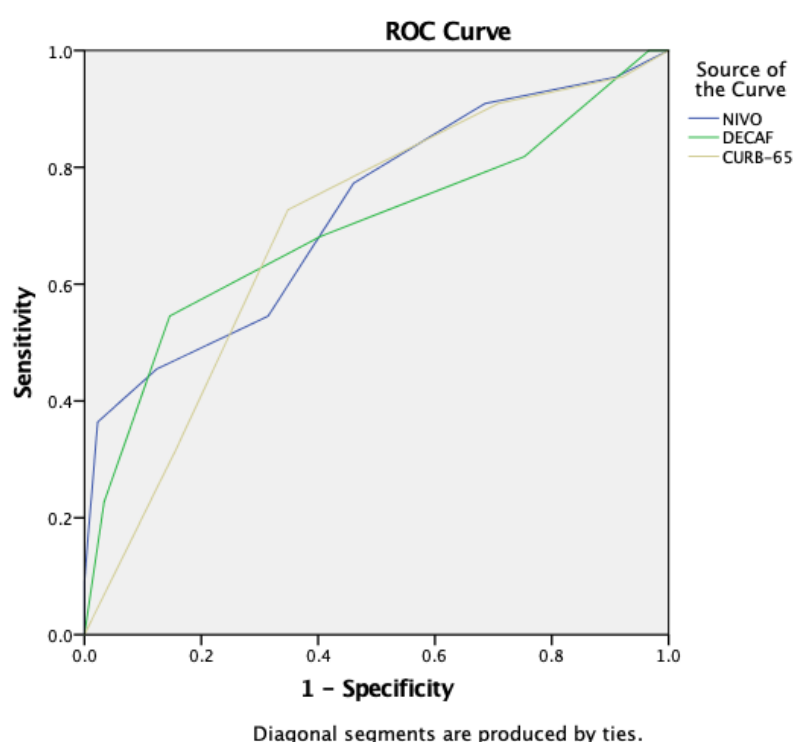


Table 88. Comparisons of the NIVO AUROC in the clinical diagnosis group.

Clinical Score	AUROC (95% confidence intervals)	AUROC difference From NIVO	P value of difference*
NIVO Score	0.724 (0.598-0.851)	n/a	n/a
CURB-65 Score	0.695 (0.575-0.815)	0.029	0.69
DECAF Score	0.695 (0.554-0.836)	0.029	0.54

*Compared using the method of DeLong

8.4 Follow up lung function tests

A year post admission, searches were performed to see if CD patients had undertaken diagnostic lung function testing (defined as both an FEV₁ and (F)VC value recorded). Eighty-nine CD patients survived to discharge and 41 (46.1%) had diagnostic spirometry. Of those, 33 patients (80.5%) had an FEV₁/FVC ratio <70%. Two patients only had FEV₁ and are classed as not having 'diagnostic spirometry'. Mean time to spirometry in those who did have it was 2.5 months. Post-admission spirometry and BMI results from CD patients are compared with validation patients in Table 89.

The CD patients who went on to have obstructive diagnostic spirometry had a significantly higher FEV₁ (t-test p=0.006) and better eMRCD scores (CD subsequent obstructive spirometry 4 (3-4) vs. validation 5a (4-5a); Mann-Whitney-U p=<0.001) than the validation patients. Whilst there was no significant difference in the BMI of CD patients with either subsequent obstructive or non-obstructive spirometry (p=0.201), there is a trend towards higher BMI in the non-obstructive group, though numbers are very small. It is worth acknowledging that patients could have airflow obstruction, but this may have been misreported if they had a submaximal FVC. Even if a slow VC was recorded and larger than the FVC, the FEV₁/FVC may have been reported as this is more commonly understood.

Table 89. Spirometry and BMI in validation patients, and CD patients both with and without subsequent obstructive spirometry.

Measurement	CD: subsequent obstructive spirometry	CD: subsequent non-obstructive spirometry	Validation patients [†]
N=	33	8	733
Days to Spirometry	59 (76)	141 (147)	N/A
FEV ₁ (L)	1.02 (0.49)	1.23 (0.39)	0.84 (0.36)
FVC (L)	2.15 (0.76)	1.63 (0.55)	1.96 (0.71)
FEV ₁ /FVC Ratio	0.47 (0.10)	0.75 (0.05)	0.44 (0.13)
FEV ₁ % predicted	41.5 (14.4)	61.3 (20.8)	37.2 (15.4)
FVC % predicted	70.0 (19.7)	69.8 (25.0)	67.4 (21.9)
BMI	26.7 (7.1)	30.5 (8.9)	25.5 (8.0)
Data are presented as mean (SD) unless otherwise stated. *Data presented as median (IQR) [†] Pre-admission results			

Disappointingly, in a group of patients who suffered a life threatening medical event, at 12 months 62.9% (56/89) of patients either did not have confirmation of COPD (no spirometry) or did not have COPD (no airflow obstruction). When spirometry was completed, the diagnosis of COPD was incorrect in 19.5% of cases.

9 Results of the longitudinal study

9.1 Headline data

Nine of the 10 NIVO sites performed the full, 'type b', longitudinal study. One site, Prince Philip Hospital in Llanelli, was designated as a 'type a' site and therefore only collected a reduced dataset. All patients surviving to discharge from the validation study (excluding clinical diagnosis patients) were screened to enter the longitudinal study.

For reference, 'baseline' data refers to data collected from patients once medically stable, but prior to discharge during their index admission. Patients could be consented into the longitudinal up to 48 hours following discharge (primarily to facilitate inclusion of patients discharged at the weekend) and were followed up for a year from their discharge.

9.2 Missing data

Missing data for variables also included in the validation study and for each longitudinal questionnaire by month is detailed in Appendix B, section 14.2. Month-to-month, the missing data rate from questionnaires was around 23.3%. Remaining missing data rates are detailed throughout.

9.3 Recruitment data

Of the 586 patients who survived to discharge in the validation study, 272 (including 19 type a site patients) were consented into the longitudinal study, representing 46.4% of patients.

9.3.1 Ineligible and declining patients

137 patients were deemed to be ineligible for entry into the longitudinal study by the research teams. A further 172 (29.4%) patients were approached for inclusion but declined to consent. The reasons provided for ineligibility are listed in Table 90. For patients who had 'another' cause of inability to be able to provide informed consent, the reasons were either mental health diagnoses (4/6) or learning difficulties (2/6).

Table 90. Reasons listed for ineligibility for the longitudinal study

Reason for ineligibility	N (%)
Unexpected or sudden discharge	41 (29.9%)
Inability to give informed consent due to dementia, delirium, cognitive impairment	32 (23.4%)
Inability to give informed consent reason unspecified	3 (2.2%)
Inability to give informed consent for another reason	6 (4.4%)
Other reason for ineligibility	25 (18.2%)
No reason provided	30 (21.9%)

For the 25 patients with 'other reason' for ineligibility listed the reasons listed were the following: social difficulties (e.g. safeguarding) prohibiting inclusion (5 patients); significant ongoing morbidity, or palliative care involvement (5 patients); aggressive, abusive or uncooperative behaviour (5 patients); staffing difficulties (4 patients); bereavement, significant distress or other personal factor (3 patients); alcohol or drug misuse (2 patients); nursing home refusal to facilitate visits (1 patient). There were 5 patients who initially consented but then provided no longitudinal data; they have been recoded as ineligible, but have not been included above, thus bringing the total ineligible patients to 142.

9.3.2 Recruitment by site

No formal target for conversion into the longitudinal study was set, however sites were encouraged to aim for a rate of $\geq 50\%$ of those recruited to validation; Northumbria Healthcare achieved this target (Table 91).

Table 91. Site by site recruitment into the longitudinal study.

Site	Number in longitudinal	% of total validation recruitment	% of those surviving to discharge
Northumbria	100	50%	61%
Nottingham	20	26%	32%

Site	Number in longitudinal	% of total validation recruitment	% of those surviving to discharge
Plymouth	10	27%	31%
London	27	45%	55%
Leeds	50	43%	54%
Oxford	5	36%	46%
Gateshead	8	12%	16%
South Tyneside	22	33%	46%
Taunton	11	22%	26%
Llanelli (<i>'type a' site</i>)	19	43%	58%
Total	272	37%	46%

9.4 Population description

Descriptors below compare the consented longitudinal population to the population who survived to discharge that either did not consent or were ineligible for the longitudinal study.

9.4.1 Background descriptors

Patients who entered the longitudinal study were marginally younger and had had fewer hospital admissions during the preceding year than patients who did not. Smoking history, gender and ethnicity were all similar. Whilst the number of previous admissions and age do reach statistical significance difference, in clinical terms the difference is small (Table 92).

Table 92. Population characteristics of patients who did and did not participate in the longitudinal study.

Variable	In longitudinal	Not in longitudinal	P value
Age*	68.9 (9.1)	70.5 (9.3)	0.046
Female	60.7%	57.0%	0.400
Caucasian	97.8%	97.8%	0.985
Current Smoker	61.4%	64.5%	0.440

Variable	In longitudinal	Not in longitudinal	P value
Cigarette Pack Years*	46.3 (22.1)	46.0 (24.4)	0.860
≥1 admission in the last 12 months	65.8%	71.7%	0.127
Number of admissions in last 12 months†	1 (0-3)	1 (0-4)	0.046

*Mean (SD) with comparisons by t-test. †Median (IQR) with comparisons by Mann-Whitney-U. Categorical comparisons with chi-squared test.

9.4.2 Home circumstances

In the longitudinal study, 97.1% of patients lived in their own home either with or without carers (Table 93), versus 90.8% (Chi Squared $p=0.002$) in patients not in the longitudinal.

Table 93. Descriptors of longitudinal patients' residential background at admission.

Admitted from	% of longitudinal patients
Home	222 (81.6%)
Home (with carers)	42 (15.4%)
Sheltered accommodation	2 (0.7%)
Sheltered accommodation (with carers)	n/a
Residential care	2 (0.7%)
Nursing care	2 (0.7%)
Community hospital	1 (0.4%)
Homeless	1 (0.4%)

9.4.3 Comorbidity

The comorbidity burden was high (Table 94), though is broadly similar between patients in and not in the longitudinal study. Longitudinal patients had a higher level of comorbid LVSD and, as expected, there was a significantly higher level of cognitive impairment in non-longitudinal patients reflecting the difficulty in undertaking informed consent in these patients.

Table 94. Comorbidity burden in longitudinal and non-longitudinal patients.

Condition	Patients in longitudinal	Patients not in longitudinal	P value
Cor Pulmonale	58 (21.3%)	73 (23.2%)	0.577
LVSD	44 (16.2%)	29 (9.2%)	0.011
NYHA Class[†]	3 (2-3)	3 (2-3)	
Atrial Fibrillation	40 (14.7%)	53 (16.9%)	0.473
Ischaemic Heart disease	64 (23.5%)	63 (20.1%)	0.310
Cerebrovascular disease	30 (11.1%)	27 (8.6%)	0.315
Cognitive impairment	6 (2.2%)	39 (12.4%)	<0.001
Depression	67 (24.6%)	76 (24.2%)	0.904
Liver failure*	n/a	4 (1.3%)	0.128**
Renal failure*	1 (0.4%)	n/a	0.464**
Immunocompromise*	4 (1.5%)	3 (1.0%)	0.710**

*as defined in the APACHE-II score. [†]Median (IQR) in patients with Left ventricular systolic dysfunction (LVSD).

**Fisher's exact test

9.4.4 Medication

The proportion of patients on captured medications is shown in Table 95. There were no significant differences in prescription rates in patients not taking part in the longitudinal, save ACEi/ARB's. Non-longitudinal patients had a lower rate of prescription (23.9%; p=0.010) than longitudinal patients. This is unsurprising, given the higher rates of LVSD seen in the longitudinal patients (shown in Table 94).

Table 95. Proportions of longitudinal patients on various medications at admission.

Medication	% of longitudinal patients prescribed
Long term oral steroids	10.3%
Diuretic	37.1%
Beta blocker	23.9%
ACEi or ARB	33.5%
Statin	45.2%
Long acting beta-2-agonist	91.9%

Medication	% of longitudinal patients prescribed
Long acting muscarinic antagonist	81.6%
Inhaled corticosteroid	80.1%
Oral Carbocisteine	43.0%
Maintenance Azithromycin	12.5%
Oral Theophylline	7.7%

ACEi = Angiotensin converting enzyme inhibitor; ARB= Angiotensin receptor blocker.

9.4.5 COPD severity and eMRCD scores

Median (IQR) eMRCD dyspnoea scores in the longitudinal group were 4 (4-5a) vs. 5a (4-5a) in the non-longitudinal group (p=0.020). Despite this difference, the overall proportion of patients unable to leave their house unassisted was similar at 47.1% and 52.5% respectively (p=0.185). There were no differences in the severity of airflow obstruction, BMI, LTOT prescription or previous/domiciliary NIV usage (Table 96).

Table 96. Lung function, BMI, LTOT and NIV comparisons in patients both in, and not in, the longitudinal study.

Variable	In longitudinal	Not in longitudinal	P value
FEV ₁ [*]	0.84L (0.35)	0.86L (0.36)	0.688
Percentage predicted FEV ₁ [*]	36.8% (14.7)	37.4% (15.4)	0.610
FVC [*]	1.98 (0.71)	1.98 (0.69)	0.936
FEV ₁ /FVC [*]	0.44 (0.13)	0.44 (0.12)	0.957
Body mass index [†]	25.2 (20.3-32.3)	24.7 (19.7-29.7)	0.126
On LTOT at admission	67 (24.6%)	90 (28.7%)	0.272
Previous NIV treatment	93 (34.2%)	122 (38.9%)	0.243
On home NIV at admission	30 (11.0%)	26 (8.3%)	0.259

*Mean (SD); †Median (IQR)

9.5 Admission specific descriptors

9.5.1 Observations at ventilation

The observations preceding ventilation were again, broadly similar with the exception of those most related to conscious level (Table 97). The longitudinal cohort had higher GCS scores, less confusion and more effective cough at the time of ventilation. The higher underlying level of cognitive dysfunction, contributing to acute delirium, may explain these results.

Table 97. Comparison of worst pre-ventilation observations in patients both in and not in the longitudinal study.

Variable	Longitudinal	Non-longitudinal	P value
Systolic blood pressure* (mmHg)	136.8 (35.7)	132.5 (34.6)	0.141
Diastolic blood pressure* (mmHg)	77.1 (21.5)	74.5 (21.2)	0.139
Heart rate* (bpm)	109.3 (21.5)	108.6 (20.9)	0.669
Respiratory rate* (bpm)	29 (7.3)	28 (7.6)	0.461
Temperature* (°C)	36.7 (1.00)	36.7 (0.9)	0.825
Oxygen Saturations† (%)	87 (81-90)	87 (81-90)	0.883
Glasgow Coma Score†	15 (15-15)	15 (14-15)	<0.001
Confusion present	15.3%	27.9%	<0.001
Effective cough	90.8%	84.4%	0.020

*Mean (SD); †Median (IQR)

9.5.2 Chest x-ray & blood results

There was no difference in rates of consolidation on CXR between longitudinal (35.3%) and non-longitudinal (35.0%; p=0.947) patients. The only difference in NIV decision blood tests was in eosinophil level, in which longitudinal patients had higher eosinophil counts; this carried through to discharge bloods. At discharge, longitudinal patients had statistically higher creatinine and lower CRP levels. None of these differences appear to be of any substantial clinical significance (Table 100, page 201), suggesting the longitudinal and non-longitudinal populations were similar.

There were high rates of missing data for discharge albumin (52.7%), bilirubin (55.8%) and glucose (63.7%) therefore these results have not been analysed.

9.5.3 Blood gas results

Table 101 (page 202) shows the blood gas results in both the longitudinal and non-longitudinal cohort at ventilation and post-wean. There were no significant differences in the blood gases at ventilation. In post-wean gases there was a higher proportion of patients with persistent hypercapnia in the longitudinal group, although non-longitudinal patients had evidence of worse chronic respiratory failure (with higher PaCO₂, base excess and bicarbonate). The proportion of non-longitudinal and longitudinal patients having a post-wean blood gas was different and could potentially be exerting an influence over these findings.

9.5.4 NIVO score

The median (IQR) NIVO score for the longitudinal group was lower 3 (1-3.75) than for the non-longitudinal group was 3 (2-4); p=0.006. Risk category grouping is shown in Table 98.

Table 98. NIVO risk group categories for longitudinal and non-longitudinal patients.

Risk group	Longitudinal	Non-longitudinal
Low Risk (NIVO Score 0-2)	49.3%	41.7%
Medium Risk (NIVO score 3-4)	37.5%	38.5%
High Risk (NIVO score 5-6)	12.5%	17.2%
Very High Risk (NIVO Score 7-9)	0.7%	2.5%

9.5.5 Ventilation modality and location

Of patients consented into the longitudinal study, 3 (1.1%) were invasively ventilated during their admission; 16 (5.9%) had late failure (section 7.1.1) and 13 (4.8%) had

relapse (section 7.1.2). 52.6% were considered for IMV and 55.9% for cardiopulmonary resuscitation – each around 10% higher than for the full validation cohort. Location of care was 55% RSU, 25% ward based, 13% in HDU and 7% in ITU.

9.6 Readmission and mortality

There was no difference in the readmission rate or LoS at any timepoint between those participating or not participating in the longitudinal study (Table 99, below). There was no difference in time to readmission between groups (Figure 21, log rank test $p=0.280$). Mortality over the study was lower in patients in the longitudinal study. A significant difference appears after 30 days, but before 90, and can be seen in the Kaplan-Meier curve (Figure 22), with lines separating. Whilst chi square assessment had become non-significant at one year, the log rank test ($p=0.042$) was significant, suggesting there is a cumulative difference in mortality between the longitudinal and non-longitudinal patients, with longitudinal living longer.

Table 99. Comparisons of readmission and mortality in longitudinal and non-longitudinal patients

Variable	In longitudinal N=272	Not in longitudinal N=314	P value
Readmissions			
One month (30 days)	77 (28.3%)	109 (34.7%)	0.097
Three months (90 days)	130 (47.8%)	170 (54.1%)	0.125
Six Months (180 days)	160 (58.8%)	200 (63.7%)	0.227
One Year (365 days)	190 (69.9%)	314 (71.0%)	0.758
Total inpatient days[†]	18.5 (7-38.3)	18 (7-34)	0.616
Number of readmissions[†]	1 (1-3)	1 (1-3)	0.484
Average LoS[†]	7.3 (4.5-13.0)	6.1 (3.6-11.3)	0.072
COPD readmissions[†]	1 (0-2)	1 (0-2)	0.802
NIV readmissions[†]	0 (0-1)	0 (0-1)	0.894
Mortality			
One month (30 days)	15 (5.5%)	27 (8.6%)	0.149

Variable	In longitudinal N=272	Not in longitudinal N=314	P value
Three months (90 days)	30 (11.0%)	59 (18.8%)	0.009
Six Months (180 days)	54 (19.9%)	91 (29.0%)	0.011
One Year (365 days)	86 (31.6%)	122 (38.9%)	0.068
†Data presented as Median (IQR) with comparisons by Mann-Whitney-U test. Remaining variables presented as categorical (%) with comparisons by Chi Squared			

Figure 21. Time to readmission for longitudinal and non-longitudinal study patients.

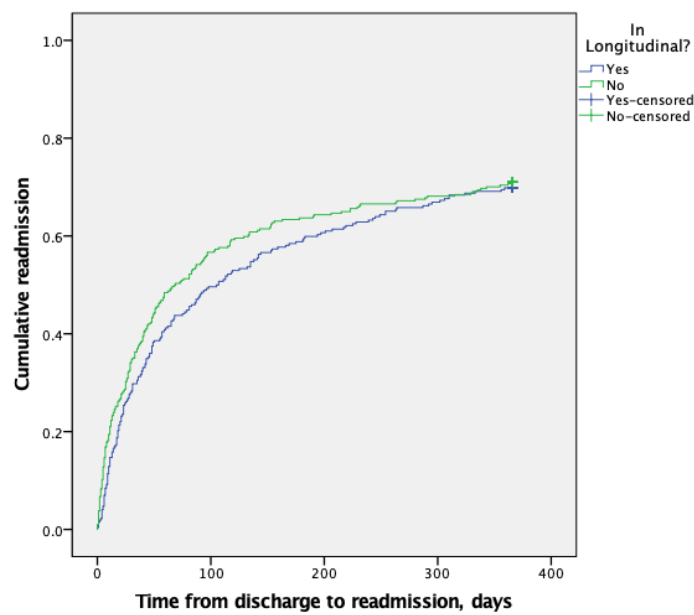


Figure 22. Time to death for longitudinal and non-longitudinal study patients.

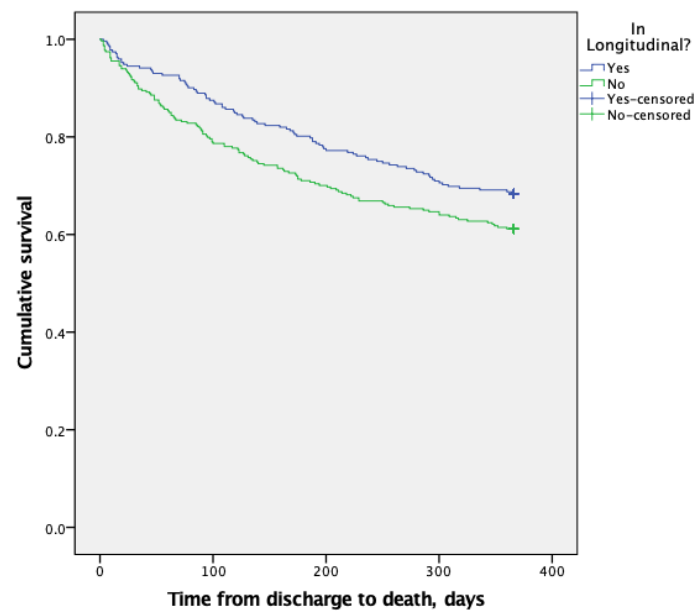


Table 100. Blood results of patients in and not in the longitudinal study.

Result	At time of NIV decision			At Discharge		
	Longitudinal	Non-Longitudinal	P value	Longitudinal	Non-Longitudinal	P value
Haemoglobin (g/dL)*	14.0 (2.0)	13.7 (2.1)	0.070	13.2 (1.8)	12.9 (1.8)	0.119
Haematocrit (L/L)*	0.44 (0.06)	0.43 (0.06)	0.314	0.41 (0.06)	0.41 (0.05)	0.721
Platelets (x10⁹/L)*	269 (96)	271 (112)	0.836	278 (97)	283 (106)	0.538
White Cell Count (x10⁹/L)*	12.9 (6.2)	12.7 (6.8)	0.623	9.9 (3.0)	9.9 (3.2)	0.860
Eosinophil Count (x10⁹/L)[†]	0.1 (0-0.2)	0.0 (0-0.1)	0.025	0.1 (0.1-0.2)	0.1 (0.0-0.2)	0.027
Eosinophil count <0.05 (%)	46.0%	57.0%	0.008	20.2%	28.3%	0.023
Sodium (mmol/L)*	136.1 (5.4)	137.0 (5.4)	0.267	138.8 (3.5)	138.8 (3.6)	0.988
Potassium (x10⁹/L)*	4.6 (0.6)	4.6 (0.6)	0.782	4.2 (0.4)	4.2 (0.5)	0.317
Urea (x10⁹/L)[†]	6.7 (4.7-9.7)	6.6 (5.0-9.8)	0.758	6.2 (4.2-7.6)	6.3 (4.4-7.9)	0.453
Creatinine (x10⁹/L)[†]	74.5 (58.0-95.0)	71.0 (54.8-97.5)	0.329	70.4 (58.0-83.0)	66 (52-77)	0.006
Albumin (g/L)*	38.0 (4.9)	37.8 (5.0)	0.605	-	-	-
Bilirubin[†] (μmol/L)	8.0 (6-12)	8 (5-12)	0.773	-	-	-
Glucose (mmol/L)*	8.5 (3.3)	8.1 (3.4)	0.115	-	-	-
CRP (mg/L)[†]	32 (11-103)	44 (13-109)	0.205	11 (5-28)	16 (5-37)	0.003

*Mean (SD); [†]Median (IQR).

Table 101. Blood gas results at NIV decision and discharge in both longitudinal and non-longitudinal patients.

Result	At time of NIV decision			Post-wean **		
	Longitudinal	Non-Longitudinal	P value	Longitudinal	Non-Longitudinal	P value
Missing data	0%	0%	n/a	29.0% (79/272)	40.4% (127/314)	n/a
pH [†]	7.28 (7.23-7.31)	7.27 (7.22-7.30)	0.141	7.41 (7.39-7.45)	7.41 (7.38-7.45)	0.600
PaO ₂ [†]	7.90 (6.90-9.37)	7.96 (6.63-9.80)	0.651	7.80 (7.10-8.60)	7.75 (6.80-9.01)	0.810
PaCO ₂ [†]	9.32 (8.13-11.17)	9.70 (8.20-11.70)	0.133	6.70 (6.10-7.60)	7.14 (6.00-8.30)	0.026
Base Excess*	4.3 (6.6)	5.1 (6.5)	0.138	7.8 (5.2)	9.0 (6.2)	0.036
Bicarbonate*	30.4 (6.7)	30.8 (6.9)	0.504	32.3 (5.1)	33.4 (6.1)	0.047
Persistent PaCO ₂ ≥6.0kPa post ventilation	-	-	-	56.6%	46.5%	0.015

*Mean (SD); [†]Median (IQR). **These data do not include imputed values for the reasons discussed in Section 7.2

Table 102. Comparison of key patient characteristics of the longitudinal cohort, with both eligible non-longitudinal and ineligible patients.

Variable	Longitudinal (n=272)	Eligible non- longitudinal (n=172)	Non-eligible non- longitudinal (n=142)	Comparisons, p value	
				Longitudinal and eligible patients	Longitudinal and ineligible patients
Age*	68.9 (9.1)	70.7 (8.2)	70.3 (10.5)	0.046	0.209
Female (%)	165 (60.7%)	105 (61%)	74 (52.1%)	1.000	0.116
Smoker (%)	167 (61.4%)	109 (64.9%)	91 (64.1%)	0.479	0.592
Number of admissions in the last 12 months[†]	1 (0-3)	1 (0-4)	2 (0-4)	0.096	0.103
Living in own home (%)	264 (97.1%)	162 (94.2%)	123 (86.6%)	0.338	0.002
eMRCD score[†]	4 (4-5a)	5a (4-5a)	4 (4-5a)	0.001	0.856
LTOT (%)	67 (24.6%)	61 (35.5%)	29 (20.4%)	0.018	0.335
Cor Pulmonale (%)	58 (21.3%)	42 (24.4%)	31 (21.8%)	0.485	0.905
Atrial fibrillation (%)	40 (14.7%)	21 (12.2%)	32 (22.5%)	0.483	0.046
Cognitive impairment (%)	6 (2.2%)	6 (3.5%)	33 (23.2%)	0.550	<0.001
LVSD (%)	44 (16.2%)	17 (9.9%)	12 (8.5%)	0.067	0.034
FEV₁ % predicted*	36.8% (14.7)	36.3% (15.4%)	39.1% (16.5)	0.729	0.165

Variable	Longitudinal (n=272)	Eligible non- longitudinal (n=172)	Non-eligible non- longitudinal (n=142)	Comparisons, p value	
				Longitudinal and eligible patients	Longitudinal and ineligible patients
Body mass index[†]	25.2 (20.3- 32.3)	24.6 (20.2-29.7)	24.7 (19.0-29.7)	0.242	0.171
Previous NIV (%)	93 (34.2%)	72 (41.9%)	50 (35.2%)	0.103	0.836
Home NIV (%)	30 (11.0%)	20 (11.6%)	6 (4.2%)	0.878	0.026
Glasgow Coma Score[†]	15 (15-15)	15 (14-15)	15 (13-15)	0.057	<0.001
Post-wean PaCO₂[†]	6.70 (6.10- 7.60)	7.3 (6.18-8.40)	7.00 (5.86-8.20)	0.003	0.175
Chest X-ray consolidation (%)	96 (35.3%)	53 (30.8%)	57 (40.1%)	0.354	0.332
NIVO Score[†]	3(1-3.75)	3 (2-4)	3 (2-4)	0.082	0.003

*Mean (SD); [†]Median (IQR). LTOT= long term oxygen therapy; LVSD= Left ventricular systolic dysfunction; FEV1%= Percent predicted of forced expiratory volume in one second; NIV= Non-invasive ventilation; NIVO Score= Non-invasive ventilation outcomes score.

9.7 Comparison with eligible non-longitudinal patients

Comparisons of key descriptors between patients participating in the longitudinal study with both ineligible, and eligible but non-consenting, patients are shown in Table 102 (page 203). Whilst a number of differences are seen between longitudinal and ineligible patients, fewer differences are noted between longitudinal and eligible non-longitudinal patients. Overall, the majority of indices show no difference, suggesting these groups are broadly similar.

9.8 Longitudinal background summary

The average longitudinal patient was overall slightly younger and more likely to live at home, having had fewer admissions within the last year, a lower eMRCD score and lower post-wean PaCO₂ than the average non-longitudinal patient. However, they were still in their late 60's, have significant multimorbidity burden, a heavy smoking history, significantly impaired lung function, and almost half were unable to leave the house unassisted. Whilst there were some differences in admission related factors, such as eosinopenia, pre-ventilation GCS and confusion rates, the majority of findings during their acute admission were similar to non-longitudinal patients. The longitudinal cohort, much like the validation cohort, appears to reasonably reflect the 'real life' patients with COPD seen in day-to-day clinical practice. The results of subsequent longitudinal outcomes below, therefore, are likely to be readily generalisable to the wider population.

9.9 Attitudes toward ventilation

Patients attitude towards ventilation was explored at both baseline (pre-discharge, stable state) and 3 months following discharge (Table 103). The following data include results from both 'a' and 'b' sites. Baseline questions were asked following the cessation of acute ventilation, when the patient was medically stable as an inpatient, or up to a maximum of 48hrs following discharge. At three months, 19 (7.0%) patients had withdrawn from follow up, 29 (10.7%) had died and 50 (18.4%) were not contactable. Therefore, in eligible patients there is a 22.3% missing data rate at 3 months.

Table 103. Longitudinal patient reported attitudes towards ventilation at baseline and three months.

	At baseline	At three months	P value*
Response rate	261/272 (96%)	174/224 (78%)	n/a
Considering your recent experience on ventilation, and how you feel at present and about the future, are you glad that you received ventilation?	255 (97.7%)	168 (96.6%)	1.000
If faced with a similar severe exacerbation in the future, would you choose to receive ventilation again?	249 (95.4%)	164 (94.3%)	0.267
Are you satisfied with your current overall Quality of Life?	189 (72.4%)	126 (72.8%)	0.256

*p values calculated by McNemars test

The overwhelming majority of patients were glad they received ventilation, both immediately following the episode and at three months post discharge. A similar proportion of patients would choose to have ventilation again if the need arose; suggesting that despite the potential discomfort and intrusiveness of acute NIV, this is an acceptable trade-off for patients to make. Nearly three quarters of patients were happy with their overall quality of life (with no further qualification of what QoL was/meant to them), both at baseline and at three months. Importantly, there were no significant changes in attitude in any domain at three months; a time period after which patients may have had reflected on their illness, admission and treatment burden.

9.10 Type 'b' site outcomes

From this point forward, all results pertain to the 253 patients consented into the full longitudinal study (type 'b' sites) with the 19 patients in type 'a' sites excluded. Two or more questionnaire responses were completed by 239 patients: 13 patients only completed baseline (pre discharge, post-weaning) questionnaires. Change cannot be measured in these patients and have therefore been excluded from the quality of life analysis. One patient refused to complete baseline questionnaires and has therefore been excluded from QoL analysis despite completing later questionnaires.

In total, there were 1981 assessments of longitudinal QoL made at type b sites, with 9903 quality of life questionnaires being completed by patients at these (excluding the attitudes towards ventilation questions in section 9.9).

9.10.1 Mortality and withdrawal by month

The overall mortality of non-withdrawn longitudinal patients was 28.5% at one year. 29 patients withdrew during the course of the study, predominantly in the first 6 months. Of the 29 patients who were withdrawn, 2 were lost to follow up, 2 were clinician decisions and the remaining 25 were patient decisions. Table 104 shows the month-by-month breakdown of participation in the longitudinal study.

Table 104. Number of patients participating in the NIVO longitudinal study by month.

Month	Patients in study	Died	Withdrawn
Baseline (pre-discharge)	253 (100%)	n/a	n/a
One	233	14 (5.5%)	6 (2.4%)
Two	219	18 (7.1%)	16 (6.3%)
Three	207	27 (10.7%)	19 (7.5%)
Four	197	36 (14.2%)	20 (7.9%)
Five	191	41 (16.2%)	21 (8.3%)
Six	181	46 (18.2%)	26 (10.3%)
Seven	172	54 (21.3%)	27 (10.7%)
Eight	170	56 (22.1%)	27 (10.7%)

Month	Patients in study	Died	Withdrawn
Nine	166	60 (23.7%)	27 (10.7%)
Ten	158	67 (26.5%)	28 (11.1%)
Eleven	155	69 (27.3%)	29 (11.5%)
Twelve	152 (60%)	72 (28.5%)	29 (11.5%)

In the withdrawn patients, a further 9 deaths occurred following withdrawal, bringing the one year mortality of all patients consented into the longitudinal study to 32.0% (81 patients).

9.11 Baseline quality of life and functional status

Quality of life (by CAT, EQ-5D-5L, HADS) and functional status (by eMRCD and NEADL) were assessed after the cessation of ventilation but prior to discharge. The tools used are discussed further in section 2.3.2. Table 105 shows results of these ‘baseline’ (pre-discharge) assessments.

The mean CAT score demonstrates a high burden (score ≥ 21) of COPD symptoms, with significant limitations demonstrated in both the EQ-5D-5L UI & VAS. Participants reported substantial breathlessness shown by eMRCD scores and reduced independence in completing ADLs demonstrated by NEADL score. Anxiety and depression is suggested with a score of ≥ 8 for either domain; baseline results show evidence of mild but clinically significant anxiety symptoms across the NIVO population with depression scores at the upper limit of normal.

Table 105. Baseline quality of life and functional status results.

Baseline quality of life measurement	Results (all patients)
eMRCD score, median (IQR) [†]	4(4-5a)
NEADL Score, mean (SD) [‡]	33.0 (16.0)
CAT Score, mean (SD) [†]	24.0 (7.4)
EQ-5D-5L UI, median (IQR) [‡]	0.600 (0.300-0.800)
EQ-5D-5L VAS, mean (SD) [‡]	48.7 (21.2)
HADS – Anxiety, mean (SD) [†]	8.6 (5.3)
HADS – Depression, mean (SD) [†]	7.3 (4.4)
[†] Lower scores indicate better quality of life. [‡] Higher scores indicate better quality of life. CAT score= Chronic obstructive pulmonary disease assessment tool; eMRCD= Extended medical research council dyspnoea score; EQ-5D-5L= EuroQol five domain, five level score; UI = Utility index; VAS= visual analogue scale; NEADL= Nottingham extended activities of daily living score; HADS= Hospital anxiety and depression scale.	

9.11.1 Baseline associations with overall satisfaction with overall quality of life

At baseline, all patients were asked about their overall satisfaction with their quality of life (see section 9.9), with 72.4% stating that it was satisfactory. Compared to patients who were satisfied with their QoL, patients who were not satisfied had a significantly and clinically higher COPD symptom burden (CAT score), higher anxiety and depression levels (HADS scores) and worse overall health status (EQ-5D-5L), see Table 106. There

was no statistically or clinically significant difference in functional status either in ability to perform ADLs (NEADL) or breathlessness (eMRCD), although both these tools trend towards being worse in unsatisfied patients.

Table 106. Comparison of baseline scores in patients either satisfied or unsatisfied with their overall quality of life at baseline.

Quality of life measurement	Satisfied with QoL at baseline (n=169)	Unsatisfied with QoL at baseline (n=67)	P value
eMRCD score, median (IQR) [†]	4 (4-5a)	5a (4-5a)	0.093
CAT Score, mean (SD) [†]	22.8 (7.7)	27.1 (5.9)	<0.001
EQ-5D-5L UI, median (IQR) [‡]	0.700 (0.400-0.800)	0.400 (0.200-0.700)	<0.001
EQ-5D-5L VAS, mean (SD) [‡]	52.1 (20.3)	40.3 (21.2)	<0.001
NEADL, mean (SD) [‡]	33.8 (16.6)	30.1 (13.7)	0.081
HADS – Anxiety, mean (SD) [†]	7.8 (5.1)	10.7 (5.1)	<0.001
HADS – Depression, mean (SD) [†]	6.3 (4.1)	9.9 (4.3)	<0.001
[†] Lower scores indicate better quality of life. [‡] Higher scores indicate better quality of life. Means compared by t-test, medians compared by Mann-Whitney-U test. 3 missing patients. CAT score= Chronic obstructive pulmonary disease assessment tool; EQ-5D-5L= EuroQol five domain, five level score; UI = Utility index; VAS= visual analogue scale; NEADL= Nottingham extended activities of daily living score; HADS= Hospital anxiety and depression scale. MCID values (+/-): eMRCD =1; CAT score =2; EQ-5D-5L UI =0.051; EQ-5D-5L VAS =6.7; NEADL =5; HADS A/D =1.5			

9.11.2 Baseline associations with exacerbation, readmission and mortality

Univariate associations between both readmission and mortality were presented in the full validation cohort (section 7.6) and are not re-evaluated here. The following three subsections assess only baseline functional status and quality of life scores with exacerbation, readmission and mortality at one year.

9.11.2.1 Community treated exacerbation

During the follow up period 182/239 (76.2%) patients provided data about episodes of community managed COPD exacerbation, separate to hospital admission. Patients who reported community managed exacerbation(s) during follow up had no significant differences observed in any baseline score compared to those who did not report further exacerbations (Table 107).

Table 107. Comparison of baseline scores in patients who had further community managed exacerbation(s) or not

Baseline quality of life measurement	At least one exacerbation (=117)	No exacerbations (n=65)	P value
eMRCD score, median (IQR) [†]	4 (4-5a)	4 (4-5a)	0.620
CAT Score, mean (SD) [†]	23.3 (7.9)	24.1 (7.2)	0.509
EQ-5D-5L UI, median (IQR) [‡]	0.700 (0.400-0.800)	0.600 (0.350-0.850)	0.948
EQ-5D-5L VAS, mean (SD) [‡]	48.4 (21.9)	50.9 (20.3)	0.467
NEADL, mean (SD) [‡]	34.0 (14.3)	35.8 (16.9)	0.447
HADS – Anxiety, mean (SD) [†]	8.4 (5.1)	8.0 (5.7)	0.624
HADS – Depression, mean (SD) [†]	6.9 (4.4)	7.2 (4.4)	0.614
[†] Lower scores indicate better quality of life. [‡] Higher scores indicate better quality of life. Means compared by t-test, medians compared by Mann-Whitney-U test. CAT score= Chronic obstructive pulmonary disease assessment tool; EQ-5D-5L= EuroQol five domain, five level score; UI = Utility index; VAS= visual analogue scale; NEADL= Nottingham extended activities of daily living score; HADS= Hospital anxiety and depression scale. MCID values (+/-): eMRCD =1; CAT score =2; EQ-5D-5L UI =0.051; EQ-5D-5L VAS =6.7; NEADL =5; HADS A/D =1.5			

9.11.2.2 Readmission to hospital

In contrast to community managed exacerbation, patients who were subsequently readmitted to hospital had, at baseline, lower overall health status according to the EQ-5D-5L utility index, as well as worse depression scores and worse functional status (more dependent for ADLs and worse dyspnoea). COPD symptoms, anxiety and the EQ-5D-5L visual analogue scale were similar. Comparisons are shown in Table 108.

Table 108. Comparison of baseline scores in patients who were or were not readmitted.

Baseline quality of life measurement	Readmitted (n=170)	Not readmitted (n=69)	P value
eMRCD score, median (IQR) [†]	5a (4-5a)	4 (3-5a)	<0.001
CAT Score, mean (SD) [†]	24.5 (7.6)	22.8 (6.8)	0.115

Baseline quality of life measurement	Readmitted (n=170)	Not readmitted (n=69)	P value
EQ-5D-5L UI, median (IQR) [‡]	0.600 (0.300-0.800)	0.700 (0.450-0.900)	0.020
EQ-5D-5L VAS, mean (SD) [‡]	48.6 (20.9)	49.0 (22.3)	0.911
NEADL, mean (SD) [‡]	31.4 (14.7)	36.9 (18.4)	0.030
HADS – Anxiety, mean (SD) [†]	9.0 (5.1)	7.8 (5.6)	0.128
HADS – Depression, mean (SD) [†]	7.7 (4.4)	6.2 (4.3)	0.015

[†]Lower scores indicate better quality of life. [‡]Higher scores indicate better quality of life. Means compared by t-test, medians compared by Mann-Whitney-U test. CAT score= Chronic obstructive pulmonary disease assessment tool; EQ-5D-5L= EuroQol five domain, five level score; UI = Utility index; VAS= visual analogue scale; NEADL= Nottingham extended activities of daily living score; HADS= Hospital anxiety and depression scale. MCID values (+/-): eMRCD =1; CAT score =2; EQ-5D-5L UI =0.051; EQ-5D-5L VAS =6.7; NEADL =5; HADS A/D =1.5

9.11.2.3 Mortality

Patients who died during follow up had worse baseline functional status (worse NEADL and eMRCD scores) and poorer overall health status (EQ-5D-5L UI) than those who survived. Other measures, including the EQ-5D-5L VAS, were similar (Table 109). A non-significant trend toward a higher symptom baseline symptom burden (CAT) was observed in those who subsequently died. Interestingly, there was no significant difference between patients who were satisfied or dissatisfied with their quality of life at baseline, and who subsequently died (Chi square; p= 0.120).

Table 109. Comparison of baseline scores in patients who did or did not die during follow up.

Baseline quality of life measurement	Survived (n=159)	Died (n=80)	P value
eMRCD score, median (IQR) [†]	4 (4-5a)	5a (4-5a)	0.002
CAT Score, mean (SD) [†]	23.5 (7.60)	25.2 (6.9)	0.087
EQ-5D-5L UI, median (IQR) [‡]	0.700 (0.400-0.800)	0.500 (0.200-0.800)	0.015
EQ-5D-5L VAS, mean (SD) [‡]	49.0 (22.2)	48.1 (19.2)	0.751
NEADL, mean (SD) [‡]	35.5 (15.4)	28.0 (16.1)	<0.001

Baseline quality of life measurement	Survived (n=159)	Died (n=80)	P value
HADS – Anxiety, mean (SD) [†]	8.5 (5.4)	9.0 (5.0)	0.528
HADS – Depression, mean (SD) [†]	7.0 (4.4)	7.9 (4.5)	0.163
[†] Lower scores indicate better quality of life. [‡] Higher scores indicate better quality of life. Means compared by t-test, medians compared by Mann-Whitney-U test. CAT score= Chronic obstructive pulmonary disease assessment tool; EQ-5D-5L= EuroQol five domain, five level score; UI = Utility index; VAS= visual analogue scale; NEADL= Nottingham extended activities of daily living score; HADS= Hospital anxiety and depression scale. MCID values (+/-): eMRCD =1; CAT score =2; EQ-5D-5L UI =0.051; EQ-5D-5L VAS =6.7; NEADL =5; HADS A/D =1.5			

9.11.3 Summary of baseline status and its associations

Substantial morbidity was seen in longitudinal patients prior to discharge, with poor functional status (measured by high levels of dyspnoea and dependence in ADLs) and substantial impairments in other quality of life scores. Clinically significant anxiety was common, and patients suffered a high burden of COPD symptoms. Whilst no individual baseline score was associated with recurrent community managed exacerbations, poorer functional status (eMRCD and NEADL) and a worse EQ-5D-5L utility index was associated with both readmission and one year mortality. In contrast, functional status measures were the only tools not associated with worse baseline satisfaction with overall quality of life, though worse functional status trended heavily towards this.

9.12 Longitudinal change in functional status and quality of life following discharge

The median follow-up time was 359 days. In the total population, when compared to baseline scores, there was no overall clinically important change (improvement nor deterioration) in any of the quality of life tools used in this study over the follow up period (see Table 110).

On average, over the year following discharge, functional status (eMRCD and NEADL) deteriorated, but not by a clinically important amount. Whilst anxiety scores improved a little (HADS-A), COPD symptoms and generic health scores (CAT Score, EQ-5D-5L) worsened, as did symptoms of depression (HADS-D). However, in similarity to functional status measurements, no mean change value crossed the threshold of minimally important clinical difference.

Time to recovery (i.e., time to best score) was approximately two months for symptom based scores (CAT, EQ-5D-5L and HADS), and shorter (approx. 1 month) for activities of daily living as measured by NEADL. eMRCD scores were largely stable over follow up (discussed further in section 9.14.1). However, excluding the 144 (60.3%) patients who had their best eMRCD score at baseline, the median (IQR) time to best eMRCD was around three months (91 (37-158) days) following discharge. In the other scores, a quarter of patients progressively deteriorated from the point of discharge.

There was variability between scores in the slowest recovering quarter of patients with CAT, EQ-5D-5L VAS and HADS-Depression taking approximately 6 months, EQ-5D-5L UI and HADS-Anxiety taking 5 months, NEADL at 4 months and eMRCD at 2 months to recover.

With the exception of HADS-Anxiety and eMRCD, in which over two thirds of follow up was spent with a score equal to or better than baseline, all of the remaining scores measured in NIVO were spent at a worse level than baseline for more than half of the follow up period; albeit not crossing the MCID.

Table 110. Longitudinal changes in functional status and quality of life for the whole population.

Quality of life measurement	Result
Duration of follow up, in days (median (IQR))	359 (171-367)
Mean change in quality of life (mean(SD))*	
eMRCD score	-0.174 (0.716)
CAT Score	-1.060 (7.140)
EQ-5D-5L UI	-0.029 (0.231)
EQ-5D-5L VAS	-1.783 (22.300)
NEADL Score	-2.745 (10.754)
HADS – Anxiety	0.284 (4.356)
HADS – Depression	-1.148 (4.088)
Time taken to achieve best quality of life in days (median(IQR))	
eMRCD Score	0 (0-65)
CAT Score	67 (0-183)
EQ-5D-5L UI	65 (0-159)
EQ-5D-5L VAS	61 (0-187)
NEADL Score	33 (0-119)
HADS – Anxiety	62 (0-148)
HADS – Depression	63 (0-184)
Time spent equal to or better than baseline as a percentage, (median (IQR))	
eMRCD Score	67.4 (10-100)
CAT Score	35.8 (0.0-84.2)
EQ-5D-5L UI	43.8 (0.0-85.9)
EQ-5D-5L VAS	45.6 (0.0-90.7)
NEADL Score	35.4 (0.0-82.4)
HADS – Anxiety	69.7 (9.3-96.7)
HADS – Depression	45.9 (0.0-84.2)
*Negative values indicate worsening of QoL score, positive values indicate improvement in QoL score. eMRCD= extended medical research council dyspnoea score; CAT score= Chronic obstructive pulmonary disease assessment tool; EQ-5D-5L= EuroQol five domain, five level score; UI = Utility index; VAS= visual analogue scale; NEADL= Nottingham extended activities of daily living score; HADS= Hospital anxiety and depression scale. MCID values (+/-): eMRCD =1; CAT score =2; EQ-5D-5L UI =0.051; EQ-5D-5L VAS =6.7; NEADL =5; HADS A/D =1.5	

9.12.1 The NIVO score and longitudinal change

Table 111 shows mean change in quality of life over the year, broken down by the NIVO risk category during index admission (see section 6.9.3). Two comparative p-values are present, one including and one excluding 'very high risk' NIVO scores. The two 'very high risk' patients report an improvement in QoL much greater than the other risk groups and, in some cases (e.g., CAT score), reverse the trend entirely; this group may be overly influencing the comparisons. Excluding 'very high risk' patients (NIVO 7-9), the trend demonstrates that QoL scores were more likely to deteriorate if the patient had a higher NIVO risk category during their index admission. eMRCD, EQ-5D-5L and HADS-Anxiety reach statistically significant differences, although clinically significant changes are also seen in other tools. With the exception of eMRCD, the low risk group is the only group with results showing any improvement (in both HADS-Anxiety and VAS), although these were marginal and did not pass the MCID. Despite statistical significance between groups, no clinically significant improvement nor deterioration was observed in any QoL score for low or medium risk NIVO groups.

Results of the eMRCD score row here should be interpreted carefully: it is a component of the NIVO score. Of the 32 NIVO high or very high risk patients, 31 had an eMRCD score of 5a (n=20) or 5b (n=11). Therefore, some of the improvement in eMRCD demonstrated in these patients may be a result of a ceiling effect.

Table 111. NIVO score risk category and mean change in functional status and quality of life.

Mean change in quality of life*	Low (n=114)	Medium (n=93)	High (n=30)	Very high (n=2)	P value (all patients)	P value (excl. very high)
eMRCD Score	-0.286 (0.757)	-0.135 (0.650)	0.063 (0.668)	0.800 (0.566)	0.017	0.040
CAT Score	-0.166 (7.696)	-1.875 (5.981)	<u>-2.673 (7.593)</u>	<u>10.050 (0.495)</u>	0.024	0.103
EQ-5D-5L UI	-0.011 (0.227)	-0.020 (0.218)	<u>-0.140 (0.247)</u>	<u>0.200 (0.424)</u>	0.020	0.019
EQ-5D-5L VAS	1.948 (22.825)	-3.284 (21.960)	<u>-11.193 (19.171)</u>	-3.550 (1.485)	0.029	0.011
NEADL Score	-2.123 (11.365)	-2.399 (10.042)	<u>-6.853 (9.926)</u>	<u>7.300 (5.657)</u>	0.085	0.088
HADS – Anxiety	0.975 (4.486)	-0.134 (3.944)	-1.137 (4.615)	<u>1.650 (7.707)</u>	0.068	0.030
HADS – Depression	-0.673 (3.918)	-1.484 (3.791)	<u>-2.280 (5.090)</u>	<u>4.350 (5.728)</u>	0.043	0.105
*Negative results indicate worsening of QoL score, positive results indicate improvement in QoL score. Underlined results are those which indicate a change greater than the minimum clinically important difference. eMRCD= extended medical research council dyspnoea score; CAT score= Chronic obstructive pulmonary disease assessment tool; EQ-5D-5L= EuroQol five domain, five level score; UI = Utility index; VAS= visual analogue scale; NEADL= Nottingham extended activities of daily living score; HADS= Hospital anxiety and depression scale. P values calculated by one way ANOVA. MCID values (+/-): eMRCD =1; CAT score =2; EQ-5D-5L UI =0.051; EQ-5D-5L VAS =6.7; NEADL =5; HADS A/D =1.5						

9.12.2 Relationship between change in quality of life and baseline satisfaction, exacerbation rates and readmission

Differences in longitudinal change in overall functional status and quality of life was compared in patients with and without baseline satisfaction with QoL, further exacerbation, and readmission. Death within a year is not compared as death was equated to the worst possible score in each survey, making useful comparison difficult.

9.12.2.1 Satisfaction with overall quality of life at baseline

With the exception of EQ-5D-5L UI, there were no important differences in subsequent mean change of quality of life between patients who were either 'satisfied' or 'not satisfied' with their overall quality of life at baseline (Table 112). For the EQ-5D-5L UI, patients satisfied with their QoL at baseline experienced a statistically significant, and marginally clinically important, improvement during follow up.

Table 112. Comparisons of mean change in scores between patients who were or were not satisfied with their overall quality of life at baseline.

Mean change in quality of life	Satisfied with QoL at baseline (n=169)	Unsatisfied with QoL at baseline (n=67)	P value
eMRCD Score	-0.149 (0.762)	-0.215 (0.580)	0.521
CAT Score	-1.101 (7.489)	-1.140 (6.22)	0.969
EQ-5D-5L UI	<u>-0.053 (0.224)</u>	0.033 (0.241)	0.010
EQ-5D-5L VAS	-2.045 (23.089)	-1.631 (20.174)	0.898
NEADL Score	-2.572 (11.415)	-2.915 (9.021)	0.826
HADS – Anxiety	0.0722 (4.461)	0.737 (4.143)	0.293
HADS – Depression	-1.400 (4.035)	-0.536 (4.246)	0.145
Negative results indicate worsening of QoL score, positive results indicate improvement in QoL score. Means compared by t-test. Underlined results are those which indicate a change greater than the minimum clinically important difference. 3 missing patients. CAT score= Chronic obstructive pulmonary disease assessment tool; EQ-5D-5L= EuroQol five domain, five level score; UI = Utility index; VAS= visual analogue scale; NEADL= Nottingham extended activities of daily living score; HADS= Hospital anxiety and depression scale. MCID values (+/-): eMRCD =1; CAT score =2; EQ-5D-5L UI =0.051; EQ-5D-5L VAS =6.7; NEADL =5; HADS A/D =1.5			

9.12.2.2 Community treated exacerbation

Surprisingly, anxiety improved most markedly in those patients who reported a community managed exacerbation during follow up (Table 113). No other QoL scores pass the MCID, nor reach statistical significance between exacerbators or non-exacerbators.

Table 113. Comparisons of mean change in scores between patients who did or did not have further community managed exacerbation(s).

Mean change in quality of life	At least one exacerbation (=117)	No exacerbations (n=65)	P value
eMRCD Score	-0.097 (0.725)	-0.112 (0.770)	0.897
CAT Score	0.234 (7.879)	-0.251 (6.099)	0.668
EQ-5D-5L UI	0.026 (0.226)	-0.025 (0.207)	0.141
EQ-5D-5L VAS	4.026 (19.700)	-0.975 (22.639)	0.122
NEADL Score	-0.720 (9.853)	-1.391 (11.403)	0.678
HADS – Anxiety	<u>1.678 (4.037)</u>	0.402 (3.690)	0.037
HADS – Depression	-0.122 (3.762)	-0.509 (3.631)	0.502
Negative results indicate worsening of QoL score, positive results indicate improvement in QoL score. Means compared by t-test. Underlined results are those which indicate a change greater than the minimum clinically important difference. CAT score= Chronic obstructive pulmonary disease assessment tool; EQ-5D-5L= EuroQol five domain, five level score; UI = Utility index; VAS= visual analogue scale; NEADL= Nottingham extended activities of daily living score; HADS= Hospital anxiety and depression scale. MCID values (+/-): eMRCD =1; CAT score =2; EQ-5D-5L UI =0.051; EQ-5D-5L VAS =6.7; NEADL =5; HADS A/D =1.5			

9.12.2.3 Readmission to hospital

Although there were no clinically important differences between readmitted and non-readmitted patients (suggesting that both populations' QoL remains stable overall, Table 114) there are statistically significant divergences in the CAT score, EQ-5D-5L-VAS and NEADL scores, which all trend towards improvement in non-readmitted patients, and towards deterioration in those readmitted.

Table 114. Comparisons of mean change in scores between patients who were or were not readmitted to hospital.

Mean change in quality of life	Readmitted (=170)	No readmissions (n=69)	P value
eMRCD score	-0.204 (0.669)	-0.103 (0.821)	0.326
CAT Score	-1.888 (6.779)	0.978 (7.636)	0.005
EQ-5D-5L UI	-0.047 (0.219)	0.016 (0.255)	0.056
EQ-5D-5L VAS	-4.499 (20.222)	4.907 (25.697)	0.008
NEADL Score	-4.217 (9.314)	0.880 (13.055)	0.001
HADS – Anxiety	0.118 (4.121)	0.954 (4.855)	0.130
HADS – Depression	-1.365 (3.909)	-0.615 (4.482)	0.199
Negative results indicate worsening of QoL score, positive results indicate improvement in QoL score. Means compared by t-test. Underlined results are those which indicate a change greater than the minimum clinically important difference. CAT score= Chronic obstructive pulmonary disease assessment tool; EQ-5D-5L= EuroQoL five domain, five level score; UI = Utility index; VAS= visual analogue scale; NEADL= Nottingham extended activities of daily living score; HADS= Hospital anxiety and depression scale. MCID values (+/-): eMRCD =1; CAT score =2; EQ-5D-5L UI =0.051; EQ-5D-5L VAS =6.7; NEADL =5; HADS A/D =1.5			

9.12.3 Summary of change in quality of life

In the longitudinal NIVO population, most patients spent more than half of the follow up period experiencing a QoL worse than their baseline status. Only eMRCD and anxiety scores had over 50% of time equal to or better than that measured at baseline. Despite this, across the longitudinal population, no change (in any score) passed the minimum clinically important difference threshold. Overall, both functional status and quality of life remained stable in the year following ventilation. Time to recovery (best recorded scores) was around two months for most patients.

Higher NIVO scores may suggest an increased likelihood of deterioration in QoL scores and functional status, but the numbers in these groups in the longitudinal cohort were too low to be conclusive. Baseline satisfaction with overall quality of life is not clearly associated with changes over the year following discharge. The occurrence of community treated exacerbations of COPD post discharge did not demonstrate an appreciable effect on the quality of life experienced by patients, save being associated with a clinically significant improvement in anxiety scores.

9.13 Anxiety and depression and their association with readmission or death

Rates of anxiety and depression and subsequent readmission or death were examined. Baseline HADS scores suggested clinically important (score of ≥ 8) anxiety in 130 (54.4%) patients, and for depression in 104 (43.5%) patients.

9.13.1 Readmission

Baseline depression scores were significantly higher in those who had subsequent readmission, although both scores were under the diagnostic threshold of 8. Anxiety at baseline was higher (and clinically relevant) in readmitted patients, though not significantly more so than in those who were not readmitted (shown in Table 108, page 211). Both anxiety and depression remained stable throughout the year however there was a trend towards higher levels of depression in those who were readmitted, Table 115.

During the follow up period, patients who were readmitted spent less time with anxiety scores equal to or better than their baseline compared to those not readmitted; depression was similar between these groups. There were no significant differences in time to best score: depression levels recovered at around 2 months in both groups, and while anxiety took slightly longer (3 months) to recover in patients who were not readmitted than those who were (2 months), this was not a significant difference.

Table 115. Comparison of longitudinal changes in anxiety and depression in both readmitted and non-readmitted patients.

Metric	Readmitted (n=170)	Not readmitted (n=69)	P value
Mean change over follow up (mean (SD))^{†§}			
HADS Anxiety	0.118 (4.121)	0.954 (4.855)	0.130
HADS Depression	-1.365 (3.909)	-0.615 (4.482)	0.199
Time spent equal to or better than baseline as a percentage of total follow-up time (Median (IQR))[^]			
HADS Anxiety	65.6 (6.9-87.6)	80.5 (19.3-100)	0.022
HADS Depression	45.7 (0-79.9)	49.1 (0-100)	0.438

Metric	Readmitted (n=170)	Not readmitted (n=69)	P value
Time to achieve best score in days (Median (IQR))^			
HADS Anxiety	56.5 (0-133.3)	90 (0-198.5)	0.152
HADS Depression	63 (0-159.3)	69 (0-212.5)	0.840
^Compared with Mann-Whitney-U test; †Compared with two-tailed t-test. ‡Negative values signal a worsening of QoL. HADS= Hospital anxiety and depression scale. MCID values +/- 1.5			

Patients with a clinically relevant baseline HADS Score (≥ 8 in either the anxiety or depression domain) were more likely to be admitted than those without – 80% of ‘baseline anxious’ and 78% of ‘baseline depressed’ patients were readmitted over the year. Table 116 below shows the proportion of patients with baseline anxiety or depression as a proportion of the readmitted or non-readmitted cohort, suggesting significant anxiety and/or depression may play a role in patients being subsequently readmitted.

Table 116. Prevalence of clinically relevant baseline anxiety and depression in both readmitted and non-readmitted patients.

	Readmitted n=170	Not readmitted n=69	
Significant baseline anxiety	104 (61.2%)	26 (37.7%)	0.001
Not anxious at baseline	66 (38.8%)	43 (62.3%)	
Significant baseline depression	81 (47.6%)	23 (33.3%)	0.043
Not depressed at baseline	89 (52.4%)	46 (66.7%)	
Comparisons made by chi-squared test. Significant anxiety or depression defined as a score of ≥8 for the respective domain.			

9.13.2 Death

Anxiety and depression scores at baseline were similar between patients who died or those that did not (shown in Table 109, page 212). In patients who died during follow up, there was clinically and statistically significant worsening in both anxiety and depression scores, compared to survivors (who had improvements in anxiety and stable depression scores). Additionally, patients who died spent significantly less time at or

better than their baseline HADS scores, and in the majority of patients (anxiety 62.5%, depression 57.5%) these results peaked at baseline; see Table 117 below.

Table 117. Comparison of longitudinal changes in anxiety and depression between patients who died or survived over follow up.

Metric	Survived (n=159)	Died (n=80)	P value
Mean change over follow up (mean (SD))^{†§}			
HADS Anxiety	<u>1.814 (3.686)</u>	<u>-2.758 (3.990)</u>	<0.001
HADS Depression	0.176 (3.467)	<u>-3.780 (3.968)</u>	<0.001
Time spent equal to or better than baseline as a percentage of total follow-up time (Median (IQR))[^]			
HADS Anxiety	83.5 (59.4-100)	4.7 (0-60)	<0.001
HADS Depression	63.1 (21.5-100)	0 (0-45.9)	<0.001
Time to achieve best score in days (Median (IQR))[^]			
HADS Anxiety	103 (36-217)	0 (0-36)	<0.001
HADS Depression	122 (36-218)	0 (0-63.5)	<0.001
[^] Compared with Mann-Whitney-U test; [†] Compared with two-tailed t-test. [§] Negative values signal a worsening of QoL. HADS= Hospital anxiety and depression scale. Underlined cells represent a change greater than the minimum clinically important difference. MCID values +/- 1.5			

There was no association between clinically important baseline anxiety or depression (a HADS score of ≥ 8 for each domain) and death during follow up (Table 118, page 225). Survival curves comparing patients with and without both anxiety and depression are shown below (Figure 23). Whilst the curves do separate, there is no significant difference observed between these for anxiety (log-rank $p=0.180$) or depression (log-rank $p=0.092$).

Figure 23. Survival curves showing time to death in patients with and without clinically significant baseline anxiety (top panel) and depression (bottom panel).

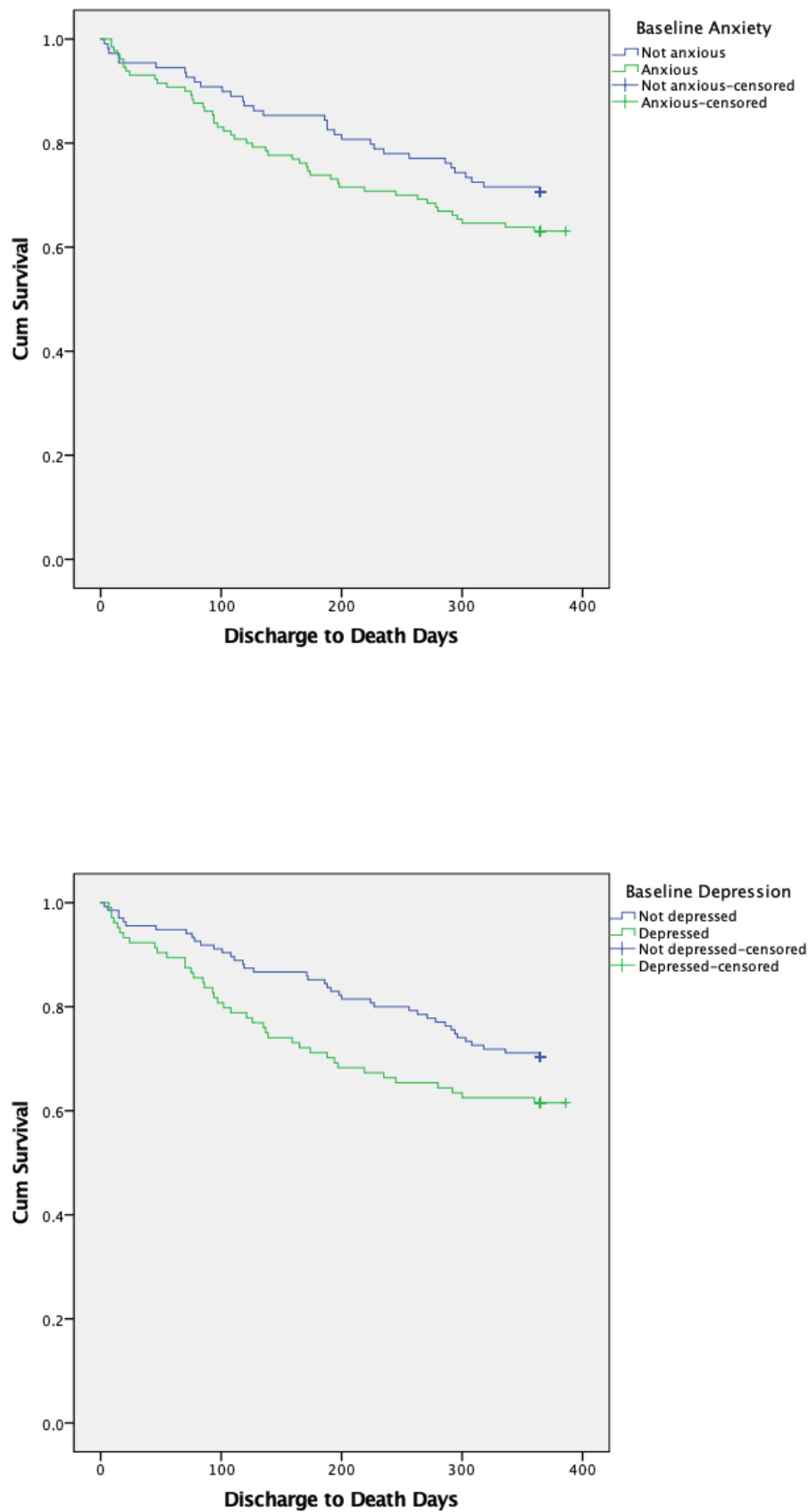


Table 118. Prevalence of clinically relevant baseline anxiety and depression in patients who did or did not die during follow up.

	Survived (n=159)	Died (n=80)	P value
Significant baseline anxiety	82 (51.6%)	48 (60.0%)	0.217
Not anxious at baseline	77 (48.4%)	32 (40.0%)	
Significant baseline depression	64 (40.3%)	40 (50.0%)	0.151
Not depressed at baseline	95 (59.7%)	40 (50.0%)	
Comparisons made by chi-squared test. Significant anxiety or depression defined as a score of ≥8 for the respective domain.			

9.13.3 Baseline anxiety and depression summary

Anxiety and depression are common in this population, affecting around 50% of patients at baseline, and are associated with worse outcomes. Patients with clinically important anxiety or depression at baseline experienced an increased risk of readmission over the following year, though no statistical significance was demonstrated between these and increased mortality.

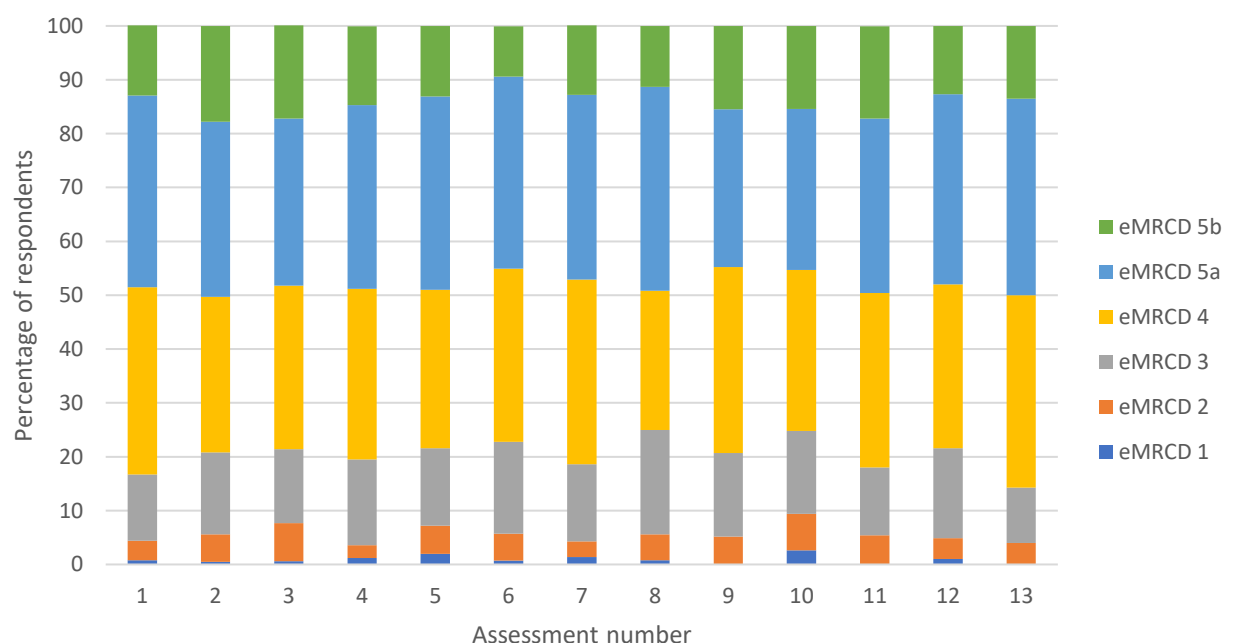
In patients that survived the year, overall anxiety levels improved beyond the MCID. Depression remained stable, albeit tending towards worsening in patients who were readmitted. The role of anxiety and depression in the prediction of poor outcome will be discussed in section 9.16.

9.14 Secondary longitudinal analyses

9.14.1 Stability of the eMRCD score

The eMRCD score was recorded monthly throughout the longitudinal study, with the distribution at each month shown in Figure 24. Patients demonstrated significant levels of breathlessness throughout, with approximately half unable to leave their house unassisted throughout the year, and a further 30% only able to walk up to 100m at best. There was no significant variation between eMRCD distribution from baseline to month 12 (Friedman ANOVA: chi-square 17.343; $p=0.137$).

Figure 24. eMRCD score distribution by month in the longitudinal study (assessment number 1=baseline and 13=month twelve).



Despite no clinically significant longitudinal change in eMRCD across the whole population during follow up, fifty individual patients did demonstrate clinically significant mean change in their eMRCD scores: thirty two (13.4%) demonstrated a reduction of greater than -1.0 over their follow up (signalling a worsening of breathlessness), and eighteen (7.5%) demonstrated a rise of greater than +1.0 (signalling an improvement in breathlessness). There were no significant differences in any population descriptor between those that improved or deteriorated beyond the MCID. However, patients who had a clinically significant deterioration in dyspnoea over the year had better median (IQR) admission eMRCD scores compared to those who had

improvement (deteriorating patients 3(2.25-4) vs. improving patients 5a(4-5.25); $p<0.001$). Median NIVO scores were also lower in those who had a deterioration in breathlessness (deteriorating patients 1(1-2.75) vs. improving patients 3(1.75-4.25); $p=0.014$). This may, in part, be representative of a ceiling effect of the eMRCD score.

9.14.2 Patient reported health resource utilisation

At three, six and twelve months following discharge, patients were asked how many times they had either been readmitted to hospital, or had needed to use oral corticosteroids and/or antibiotics for an exacerbation of COPD in the community, since the last assessment. The majority of patients reported a further exacerbation in the community following discharge, with a sizable minority having multiple exacerbations (Table 119). The pattern was similar for readmission to hospital with exacerbation of COPD. By three months after discharge, 42% of patients reported being readmitted for a further exacerbation, data in keeping with national COPD audit readmission findings.⁽²⁹⁹⁾

Table 119. Patient reported health resource utilisation during follow up.

	0-3 months	3-6 months	6-12 months	Within year
Eligible	207	181	152	253
Missing	26.6%	27.6%	17.8%	28.1%
Patient reported community treated exacerbations				
Median (IQR) exacerbations	0 (0-1)	1 (0-2)	1 (0-2)	1 (0-3)
Any exacerbation	62 (40.7%)	70 (53.4%)	73 (58.4%)	117 (64.3%)
>1 exacerbation	19 (12.5%)	34 (26.0%)	43 (34.4%)	85 (46.7%)
Patient reported readmissions for ECOPD				
Median (IQR) readmissions	0 (0-1)	0 (0-1)	0 (0-1)	1 (0-2)
Any readmission	64 (42.1%)	40 (30.5%)	37 (29.6%)	99 (54.4%)
>1 readmission	20 (13.2%)	15 (11.4%)	21 (16.8%)	55 (30.2%)

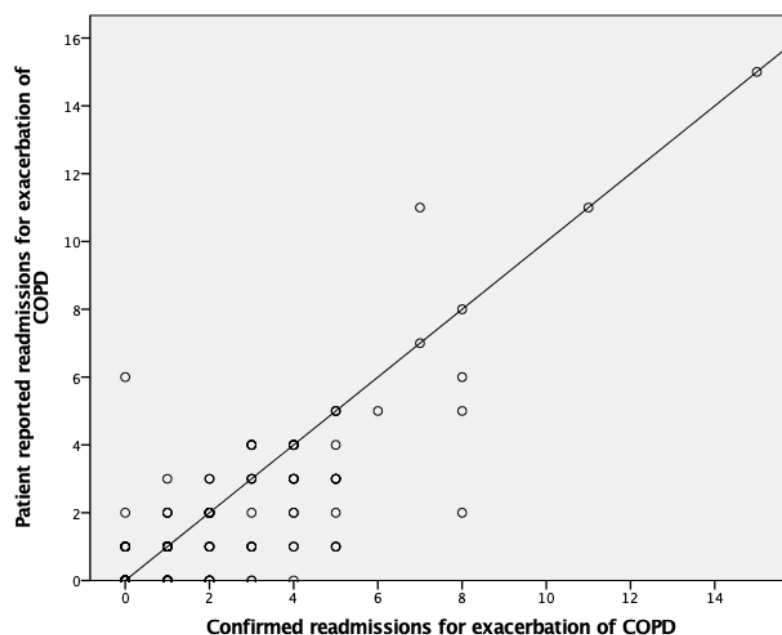
If a patient completed at least one of the 3, 6 or 12 month visits throughout the year they are included in the 'within year' column in Table 119. Seventy one patients (28.1%) of those consented did not answer any of these assessments and as such are reported as missing data in the table. Following discharge, two thirds of patients had at least one

further exacerbation managed within the community, and just over half of patients had at least one further admission to hospital for ECOPD. A significant proportion of patients described multiple exacerbations with 18 (9.9%) having 6 or more over the year.

9.14.2.1 Correlation with recorded readmissions

Of the 182 patients that provided patient reported readmission information, correlation between patient reported readmissions (for exacerbations of COPD) and confirmed readmissions was moderate (Spearman's correlation coefficient 0.737).⁽⁵¹³⁾ Whilst the majority (n=102) recalled readmissions accurately, 58 patients under reported readmissions and 22 over reported, with a significant difference between reported and recorded readmissions (Wilcoxon signed ranks $p < 0.0001$). Figure 25 shows reported vs. recorded admissions along with a perfect correlation reference line. One patient had 15 readmissions within the year, with five requiring NIV. This patient spent 194 days in hospital and their first readmission was three days after their index discharge. Their eMRCD score was 5a, FEV₁ was 24% predicted, NIVO score was 2 (index admission) and were started on HMV at discharge. They had clinically significant baseline anxiety and depression, and a significant deterioration in their CAT over follow up; though their HADS scores improved beyond the MCID this may have contributed to their readmission frequency. They survived beyond the year-long follow up.

Figure 25. Correlation between reported and confirmed readmissions for ECOPD.



9.14.3 Spirometry, oxygen saturation and body mass index

At the baseline, three, six and twelve month assessment, patients were asked to perform spirometry, be weighed and have peripheral oxygen saturations measured.

9.14.3.1 Oxygen saturation and BMI

Peripheral oxygen saturation and BMI were performed at study visits are shown in Table 120. Between these assessments there are no clear clinically significant variations.

Table 120. Peripheral pulse oximetry and body mass index results over follow up.

	Baseline	3 months	6 months	12 months
Eligible	253	207	181	152
SpO2	91.4% (3.0)	91.7% (3.2)	92.3% (4.14)	92.2 (4.12)
Missing	3.2%	28.0%	32.6%	24.3%
BMI	25.2 (20.4-32.2)	24.6 (21.0-30.9)	25.6 (21.6-33.1)	25.1 (21.2-32.2)
Missing	5.1%	30.4%	35.4%	30.9%

9.14.3.2 Spirometry results

One in four patients did not have spirometry performed pre-discharge, with follow up visits having higher missing data rates. The most common reason for this was patient refusal to undertake spirometry or non-completion of the visit. Spirometry results during the follow up period are shown in Table 121. When comparing patients completing both baseline and three months (n=107) the absolute values for FEV₁, FEV₁ percentage predicted, and FVC all significantly improved (paired t-test p= <0.001, 0.001 and <0.001 respectively), whilst the FEV₁/FVC ratio remained stable (p=0.655). Recovery of absolute values occurred by three months and then remained stable for the remainder of the year.

At one year, compared to baseline (n=81), the change in absolute FEV₁ had become non-significant, albeit with an appreciable upward trend (p=0.074). FEV₁ percent predicted (p=0.028) and FVC (p=0.020) remained significantly higher. Again, there was no change in the ratio (p=0.379).

Table 121. Spirometry over the longitudinal study.

Variable	Baseline	3 months	6 months	12 months
Eligible patients	253	207	181	152
FEV ₁ Litres	0.68 (0.30)	0.75 (0.36)	0.75 (0.37)	0.74 (0.35)
FEV ₁ % predicted	30.8% (13.2)	34.0% (16.0)	34.1% (15.7)	33.9% (15.4)
FVC Litres	1.60 (0.59)	1.80 (0.73)	1.81 (0.72)	1.82 (0.63)
FEV ₁ /FVC Ratio	44.0% (15.0)	42.4% (15.4)	42.5% (14.6)	41.4% (14.4)
Missing	25.3%	41.1%	47.5%	38.8%

9.15 Correlation between longitudinal tools

The mean change over the year was significantly correlated between all tools, bar between the eMRCD and EQ-5D-5L VAS. Similarly, there were significant correlations between the percentage of time spent equal to or better than baseline between all tools with the exceptions of the eMRCD with both the EQ-5D-5L UI and VAS. All tools had a significant correlation with each other for time to best score. Overall, the CAT score demonstrated the strongest correlation significance with other tools (Pearson's all $p < 0.001$) in all three methods of measurement.

The correlation matrices between the mean change over time, percentage of time equal to or better than baseline, and time to best score respectively are all shown in Appendix D (section 14.4). Graphical representation of the correlation of mean change over time between individual tools are shown in Appendix E (section 14.5).

9.16 Identifying individuals with a poor outcome following discharge

9.16.1 Defining “poor outcome”

The CAT score was chosen as the quality of life tool to identify poor outcome; this is the most widely validated tool in COPD plus it had the most significant correlations (Appendix D, section 14.4) with change in other QoL scores measured over the longitudinal study. A patient was said to have experienced poor outcome if they had either of the following:

1. They were in the worst 50% of CAT scores at baseline and had a clinically significant deterioration in **their** quality of life over the follow up period (i.e., their mean change over follow up was ≥ -2); or
2. They died within six months of discharge

The remaining patients were considered to have an acceptable outcome. The cut point for the worst 50% of CAT scores was a baseline score of ≥ 24 out of 40. Using the above criteria, 67 (28%) patients experienced a poor outcome following discharge and 172 had an acceptable quality of life.

9.16.2 Univariate associations between poor and acceptable outcome

The following tables (Table 122 through Table 124) show the univariate comparisons between patients who had acceptable or poor outcome. Markedly asymmetric categorical variables (those with fewer than 5% of the population in either group) are not shown.

On univariate analysis patients who had subsequent poor outcome were more less likely to be living in their own home; more likely to have had a hospital admission within the preceding year, have worse baseline dyspnoea (higher eMRCd); more likely to be on LTOT therapy prior to admission; have more severe airflow obstruction; have a lower BMI; more likely to have LVSD and depression; have a higher PaCO₂ at ventilation and post-ventilation; were more likely to be confused preceding admission; have a lower haemoglobin and haematocrit (at admission and pre-discharge) and a higher white cell count at admission and have a higher PEARL and NIVO score. Patients with subsequent

poor outcome had significantly worse quality of life scores at baseline in all domains, bar the EQ-5D-5L VAS in which scores were similar.

Table 122. Background characteristics and comparison of patients with acceptable and poor outcome.

Variable	Acceptable outcome n=172	Poor Outcome n=67	p value
Demographics			
Age*	69.3 (8.7)	68.3 (8.7)	0.410
Female (%)	105 (61.0%)	39 (58.2%)	0.687
Independent in own home (%)	146 (84.9%)	47 (70.1%)	0.0095
Current smoker (%)	107 (62.2%)	38 (56.7)	0.435
Pack years*	48.5 (23.0)	46.0 (21.5)	0.454
Any admission in previous year (%)	106 (61.6%)	54 (80.6%)	0.0051
Markers of underlying disease severity			
eMRCD [†]	4 (4-5a)	5a (4-5a)	0.0003
LTOT (%)	34 (19.8%)	30 (44.8%)	<0.0001
FEV ₁ in litres*	0.85 (0.37)	0.80 (0.33)	0.267
FEV ₁ % predicted*	37.5% (14.7)	33.6% (14.9)	0.068
FVC in litres*	2.03 (0.73)	1.90 (0.73)	0.210
FEV ₁ /FVC Ratio*	0.43 (0.12)	0.44 (0.13)	0.857
BMI [†]	25.6 (20.9-32.5)	22.4 (18.4-30.9)	0.045
Previous acute NIV (%)	62 (36.0%)	26 (38.8%)	0.691
On HMV at admission (%)	18 (10.5%)	11 (16.4%)	0.206
Comorbidities			
Cor pulmonale (%)	33 (19.2%)	17 (25.4%)	0.291
Left ventricular systolic dysfunction (%)	21 (12.2%)	18 (26.9%)	0.0059
Depression (%)	35 (20.3%)	23 (34.3%)	0.024
Atrial fibrillation (%)	26 (15.1%)	10 (14.9%)	0.970

Variable	Acceptable outcome n=172	Poor Outcome n=67	p value
Ischaemic heart disease (%)	40 (23.3%)	16 (23.9%)	0.918
Cerebrovascular disease (%)	17 (9.9%)	10 (14.9%)	0.276
Admission medication			
Long term steroid (%)	20 (11.6%)	6 (9.0%)	0.551
*Data are presented as Mean (SD) and compared by t-test. †Data are presented as Median (IQR) and compared by Mann-Whitney U test. Other data are presented as absolute number (%) and compared with Chi Squared test. Definitions: Independent in own home means living without formal carers; eMRCD= extended medical research dyspnoea score; LTOT= long term oxygen therapy; HMV= home mechanical ventilation; FEV₁= forced expiratory volume in one second; FVC= forced vital capacity; BMI= body mass index; NIV= non-invasive ventilation.			

Table 123. Admission and ventilation related indices and comparison of patients with acceptable and poor outcome.

Variable	Acceptable outcome n=172	Poor Outcome n=67	p value
Investigations			
CXR consolidation (%)	52 (30.2%)	28 (41.8%)	0.089
Diaphragm height (cm)*	2.6 (1.0)	2.3 (0.9)	0.030
Blood gas results[^]			
pH[†]	7.28 (7.23-7.31)	7.28 (7.22-7.31)	0.779
PaCO₂[†]	9.23 (7.93-10.94)	10.10 (8.30-11.30)	0.040
PaO₂[†]	7.93 (7.00-9.28)	7.51 (6.47-9.35)	0.349
HCO₃[*]	30.4 (6.6)	31.1 (7.3)	0.438
Base Excess[*]	4.37 (6.53)	5.31 (7.35)	0.336
pH <7.25 (%)	63 (36.6%)	22 (32.8%)	0.582
Observations[^]			
Confusion (%)	23 (13.4%)	17 (25.4%)	0.026
GCS[†]	15 (15-15)	15 (14-15)	0.108
Blood results[^]			
Haemoglobin (g/dL)*	14.4 (2.0)	13.2 (2.0)	0.0001
Haematocrit (L/L)*	0.45 (0.06)	0.42 (0.06)	0.0028
Platelets (x10⁹/L)*	267.8 (90.8)	284.9 (120.6)	0.296
White Cell Count (x10⁹/L)*	12.4 (5.2)	14.6 (8.6)	0.053
Eosinophil Count (x10⁹/L)[†]	0.10 (0.0-0.2)	0.10 (0.0-0.2)	0.944
Sodium (mmol/L)*	136.4 (5.0)	135.4 (6.5)	0.256
Potassium (x10⁹/L)*	4.6 (0.6)	4.7 (0.6)	0.215
Urea (x10⁹/L)[†]	6.5 (4.7-9.1)	6.8 (4.3-10.0)	0.830
Creatinine (x10⁹/L)[†]	75 (60.3-95.8)	70 (55.0-90.0)	0.347
Albumin (g/L)*	37.7 (5.1)	37.6 (4.6)	0.832
Glucose (mmol/L)*	8.4 (3.4)	8.8 (3.8)	0.419
CRP (mg/L)[†]	31.0 (10.0-90.5)	37.0 (15.0-110.0)	0.289
Ventilation settings[^]			

Variable	Acceptable outcome n=172	Poor Outcome n=67	p value
Time to pH correction, hours [†]	7.0 (2.0-17.8)	6.0 (3.0-30.5)	0.298
Duration of NIV, hours [†]	77 (37.5-115.8)	70 (42-109)	0.842
Disease severity tool scores			
PEARL Score[†]	2 (1-5)	4 (2-6)	0.0002
NIVO Score[†]	2 (1-3)	3 (2-4)	0.0071
*Data are presented as Mean (SD) and compared by t-test. [†]Data are presented as Median (IQR) and compared by Mann-Whitney U test. Other data are presented as absolute number (%) and compared with Chi Squared test. [^]Blood gas results and blood tests results were the final taken prior to ventilation; observations were the worst individual recorded in the 24 hours prior to ventilation. Ventilation settings were the maximum achieved during the period of ventilation. DTMT= door to mask time; pH= potential of hydrogen; PaCO₂= partial pressure of carbon dioxide; PaO₂= partial pressure of oxygen; HCO₃= bicarbonate; CXR= chest x-ray; GCS= Glasgow coma score; CRP= C-reactive protein; PEARL Score= Previous admissions, dyspnoea measured by Extended medical research council dyspnoea score, Age, Right heart failure, Left hearth failure score; NIVO= Non-invasive ventilation outcome score.			

Table 124. Post-wean indices, quality of life scores and comparison of patients with acceptable and poor outcome.

Variable	Acceptable outcome n=172	Poor Outcome n=67	p value
Post ventilation blood gas results			
pH [†]	7.41 (7.40-7.44)	7.41 (7.38-7.43)	0.204
PaCO ₂ [†]	6.87 (6.30-7.46)	7.10 (6.50-7.69)	0.083
PaO ₂ [†]	7.92 (7.40-8.38)	8.10 (7.54-8.53)	0.320
HCO ₃ [*]	32.5 (4.4)	33.2 (5.0)	0.337
Base Excess [*]	8.03 (4.38)	8.84 (4.99)	0.217
Hypercapnia (%)	94 (54.7%)	43 (64.2%)	0.181
Discharge medications			
Diuretic (%)	82 (48.0%)	35 (52.2%)	0.552
Beta blocker (%)	46 (26.9%)	23 (34.3%)	0.256
ACEi/ARB (%)	49 (28.7%)	22 (32.8%)	0.526
Statin (%)	77 (45.0%)	31 (46.3%)	0.863
LABA (%)	165 (96.5%)	65 (97.0%)	0.840
LAMA (%)	150 (87.7%)	56 (83.6%)	0.400
Inhaled Corticosteroid (%)	144 (84.2%)	52 (77.6%)	0.230
Carbocisteine (%)	80 (47.1%)	39 (58.2%)	0.122
Azithromycin (%)	22 (12.9%)	12 (17.9%)	0.317
Blood tests prior to discharge			
Haemoglobin (g/dL) [*]	13.4 (1.8)	12.5 (1.7)	0.0005
Haematocrit (L/L) [*]	0.42 (0.06)	0.40 (0.05)	0.0071
Platelets (x10 ⁹ /L) [*]	273.6 (91.8)	289.9 (111.0)	0.287
White Cell Count (x10 ⁹ /L) [*]	10.1 (2.9)	9.7 (3.5)	0.416
Eosinophil Count (x10 ⁹ /L) [†]	0.1 (0.1-0.2)	0.12 (0.1-0.2)	0.193
Sodium (mmol/L) [*]	138.6 (3.4)	138.7 (3.7)	0.817
Potassium (x10 ⁹ /L) [*]	4.2 (0.5)	4.2 (0.4)	0.840
Urea (x10 ⁹ /L) [†]	6.2 (4.3-7.5)	6.1 (4.2-7.5)	0.959
Creatinine (x10 ⁹ /L) [†]	71.5 (59.3-83.0)	67.1 (53.0-76.0)	0.122

Variable	Acceptable outcome n=172	Poor Outcome n=67	p value
Albumin (g/L)*	34.8 (4.0)	35.2 (3.3)	0.566
Bilirubin (μmol/L) [†]	9.0 (7.0-10.3)	8.0 (6.0-9.4)	0.020
Glucose (mmol/L)*	7.8 (2.3)	7.7 (1.8)	0.790
CRP (mg/L) [†]	11.5 (5.0-28.2)	12 (5.0-32.0)	0.609
Findings at discharge			
Discharged on HMV (%)	24 (14.0%)	15 (22.4%)	0.113
Length of stay, days [†]	8 (6-13)	8 (6-15)	0.299
Quality of life scores at discharge			
Happy with QoL (%)	131 (76.2%)	39 (58.2%)	0.0059
HADS-Anxiety*	8.0 (5.3)	10.4 (5.0)	0.0011
HADS-Depression*	6.6 (4.2)	9.1 (4.6)	<0.0001
NEADL Score*	35.9 (15.3)	25.6 (15.6)	<0.0001
EQ-5D-5L UI [†]	0.70 (0.4-0.8)	0.40 (0.2-0.7)	<0.0001
EQ-5D-5L VAS*	49.6 (21.7)	46.4 (20.1)	0.285
CAT Score*	23.0 (7.8)	26.7 (5.4)	<0.0001
*Data are presented as Mean (SD) and compared by t-test. [†]Data are presented as Median (IQR) and compared by Mann-Whitney U test. Other data are presented as absolute number (%) and compared with Chi Squared test. pH= potential of hydrogen; PaCO₂= partial pressure of carbon dioxide; PaO₂= partial pressure of oxygen; HCO₃= bicarbonate; Hypercapnia= a post ventilation PaCO₂ of ≥6.0 kPa; ACEi= angiotensin converting enzyme inhibitor; ARB= angiotensin receptor blocker; LABA= long acting beta-two agonist; LAMA=long acting muscarinic antagonist; CRP= C-reactive protein; QoL= quality of life; HADS= Hospital Anxiety and Depression Score; NEADL= Nottingham Extended Activities of Daily Living score (0-66 scoring); EQ-5D-5L= EuroQol 5 Domain 5 Level score; UI= Utility Index; VAS= Visual Analogue Scale; CAT= Chronic Obstructive Pulmonary Disease Assessment Tool score.			

9.17 Predicting poor outcome

9.17.1 Candidate predictors of poor outcome

A cut off of $p < 0.1$ was used as for the significance level for a univariate predictor moving forward as a potential candidate for multivariate analysis. Following univariate analysis, the following decisions were made about potential candidate variables prior to further examination.

- Discharge medications were chosen over admission as they are more likely to influence QoL following admission (with the exception of long term steroid, which was not captured at discharge).
- PaCO₂ recorded at the time the decision for NIV was made was favoured over the value recorded following NIV wean as the rate of missing data was lower (0% vs. 44%).
- Admission white cell count was excluded due to its dynamic relationship and confounding factors (for example severity of acute insult or timing of corticosteroid use). Of note, WCC recorded at discharge was not related to outcome.
- Admission haemoglobin and haematocrit were used as they both had lower missing data rates than discharge (haemoglobin, 0.3% vs 7.3%), (haematocrit, 0.5% vs 7.5%).
- Discharge Bilirubin was excluded as it had 55.8% missing data rate
- EQ-5D-5L was excluded as only one half of the assessment demonstrated univariate significance.
- CAT score was excluded given its role in the dependent variable.

9.17.2 Correlation and multicollinearity

Correlation between candidate variables was assessed and where this was >0.7 only one was taken forward to the logistic regression. This only occurred in one case with haemoglobin and haematocrit (Pearson correlation coefficient= 0.932). Haematocrit was dropped and haemoglobin carried forward. The candidate variables are shown in Table 125.

Table 125. Candidate variables for 'poor outcome' tool following univariate analysis.

Variable
Independent in own home vs. not
Previous admission within the last year
eMRCD score
On long term oxygen therapy at admission
FEV1 as % predicted
Body Mass Index
Diagnosis of left ventricular systolic dysfunction
Diagnosis of depression
Chest x-ray consolidation at ventilation
Diaphragm height
PaCO ₂ at ventilation
Confusion prior to ventilation
Admission haemoglobin
PEARL Score
NIVO Score
Baseline satisfaction with overall quality of life ('Yes' or 'No')
Baseline HADS Anxiety score
Baseline HADS Depression score
Baseline NEADL Score

9.17.3 Enter regression analysis and variance inflation scores

All variables were forced into a an 'enter' regression model and variance inflation factors (VIF) were examined. Variables with a VIF of >3 demonstrate possible multicollinearity and were further assessed. Mean VIF for the model was 1.703. The only candidate predictors with VIF >3 were the PEARL score (VIF=3.385) and the eMRCD (VIF=3.118); this makes conceptual sense as LVSD, eMRCD and previous admission are all components of the PEARL score. The NIVO score (VIF=2.538) had the next the highest VIF, though was under the threshold of 3. Whilst the NIVO score VIF result did not demonstrate the need to correct for multicollinearity, the NIVO score does comprise of

two other univariate associations with poor outcome (eMRCD and CXR consolidation) and therefore both the NIVO and PEARL scores were removed from the model. Following their removal, whilst there was evidence of mild residual collinearity (mean VIF=1.382 and largest individual VIF=2.193), there was no need to remove other candidates from the model.

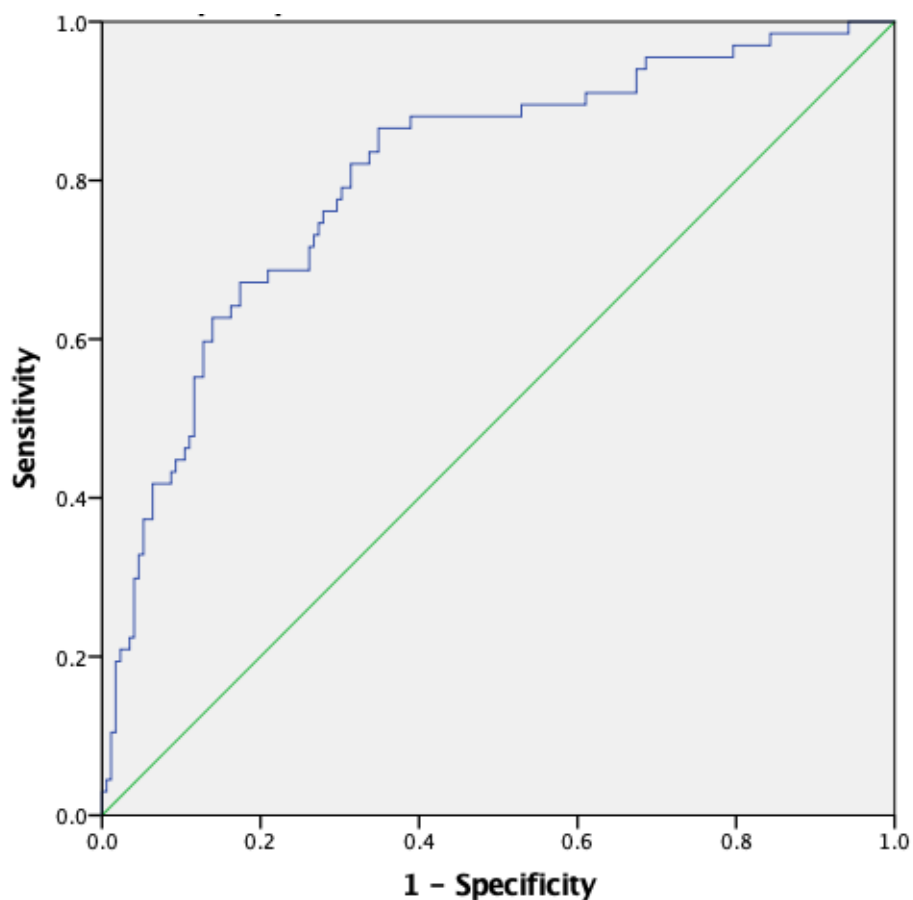
9.17.4 Independent predictors of poor outcome and model building

The remaining variables were entered into a backwards stepwise multivariate regression analysis; independent predictors of poor outcome are shown in Table 126. This model shows good discrimination with an AUROC of 0.806 (Figure 26) and is well calibrated (see footnotes of Table 126).

Table 126. Multivariate regression analysis result for 'poor outcome' model with continuous variables.

VARIABLE	B	S.E	Wald	P value	Odds Ratio (95% CI)
Long term oxygen therapy	1.119	.362	9.544	.002	3.062 (1.505-6.226)
Left Ventricular Systolic Dysfunction	1.034	.433	5.691	.017	2.812 (1.203-6.574)
Diaphragm height (cm)	-0.378	.178	4.517	.034	0.686 (0.484-0.971)
Confusion pre ventilation	1.096	.423	6.711	.010	2.991 (1.306-6.852)
Admission Haemoglobin	-0.223	.086	6.753	.009	0.800 (0.677-0.947)
Baseline HADS depression score	0.091	.042	4.766	.029	1.095 (1.009-1.188)
Baseline NEADL score	-0.025	.012	4.237	.040	0.975 (0.952-0.999)
Intercept 3.992, Cox & Snell R ² 0.224, Nagelkerke R ² 0.323, Hosmer and Lemeshow goodness-of-fit test 0.599, Percentage correct following final step 77.4%. Cook's distances, leverage Values, and residual values all within acceptable limits.					

Figure 26. ROC analysis of 'poor outcome' model using continuous variables.



9.17.5 Categorisation of indices predictive of poor outcome.

The model above uses continuous variables to calculate outcome and it would require significant computation thus rendering it less likely to be integrated into clinical practice. Therefore, in a similar manner to the NIVO score, continuous variables were dichotomised. The ROC curve of each continuous variable (diaphragm height, haemoglobin, NEADL, HADS depression score) was analysed with the dependent variable as poor outcome; the shoulder of the ROC curve was used to identify the most appropriate cut point for that variable. If there was no clear shoulder, then median split or a clinically meaningful threshold was used instead. The resultant cut points were:

- Diaphragm height $\leq 2.3\text{cm}$
- Haemoglobin $\leq 14\text{ g/dL}$
- NEADL Score ≤ 30
- HADS depression score ≥ 8

9.17.6 Regression analysis using categorical variables

These dichotomised variables were re-run through backwards stepwise regression analysis (Table 127). Haemoglobin loses statistical significance at a 0.05 level, though is still below the prespecified $p=0.1$ removal significance level and did not drop out of the model.

Table 127. Multivariate regression analysis result for 'poor outcome' model with dichotomised variables.

VARIABLE	B	S.E	Wald	P value	Odds Ratio (95% CI)
Long term oxygen therapy	1.069	.369	8.412	.004	2.913 (1.414-5.999)
Left ventricular systolic dysfunction	1.017	.425	5.721	.017	2.764 (1.201-6.358)
Diaphragm height $\leq 2.3\text{cm}$	.730	.341	4.571	.033	2.074 (1.063-4.048)
Confusion pre ventilation	1.045	.424	6.072	.014	2.843 (1.238-6.525)
Haemoglobin $\leq 14\text{g/dL}$	.684	.350	3.813	.051	1.981 (0.997-3.934)
Baseline HADS Depression ≥ 8	.856	.352	5.902	.015	2.354 (1.180-4.695)
Baseline NEADL ≤ 30	1.162	.353	10.814	.001	3.197 (1.599-6.393)
Intercept -2.707, Cox & Snell R^2 0.232, Nagelkerke R^2 0.333, Hosmer and Lemeshow goodness-of-fit 0.060, Percentage correct following final step 78.7%. Cook's distances all <1 , no cases $>3\times$ mean leverage value (0.1004), and residual values all within acceptable limits (2.93% of cases larger than ± 1.96).					

9.17.7 Variable weighting

The model was weighted as per the NIVO score derivation and validation tools. The B_{exp} value for each variable was divided by the lowest B_{exp} and then weighting applied based on the result. The lowest B_{exp} was 1.981 (see Table 128).

Table 128. Weighting of variables in 'poor outcome' model.

Variable	B _{exp}	B _{exp} /1.981	Weighting assigned
Long term oxygen therapy	2.913	1.470	1
Left ventricular systolic dysfunction	2.764	1.395	1
Diaphragm height ≤2.3cm	2.074	1.047	1
Confusion pre ventilation	2.843	1.435	1
Haemoglobin ≤14g/dL	1.981	1.435	1
Baseline HADS Depression ≥8	2.354	1.188	1
Baseline NEADL ≤30	3.197	1.614	1

9.17.8 Performance of novel 'poor outcome' tool

The assigned weighting results in a novel, seven variable, clinical tool. The predicted and observed 'poor outcome' results of this are shown in Table 129 below. The maximum score recorded from the longitudinal patient cohort was 6, therefore it was not possible to perform prediction/observation on a score of seven. There was a marked increase in the proportion of patients experiencing a poor outcome with a score of three or more (score ≥3 patients with poor outcome= 51.8%, compared to 7.8% with a score of 0-2; $p<0.0001$), which could prove to be a useful clinical bedside cut point.

Table 129. Observed vs. predicted occurrence of poor outcome by the novel 'poor outcome' score.

Score	N=	'Poor outcome'	
		Predicted	Observed
0	20	3.2%	10%
1	46	7.3%	4.3%
2	63	16.6%	9.5%
3	63	33.5%	41.3%
4	26	57.1%	61.5%
5	16	76.2%	75.0%
6	5	89.2%	60%

Score	N=	'Poor outcome'	
		Predicted	Observed
7	0	-	-
Overall	239	28.0%	28.0%

9.17.9 Calibration and discrimination

Calibration was acceptable with Cook's values, Hosmer and Lemeshow goodness-of-fit, residual values, and leverage values all within acceptable limits (see footnotes of Table 127, page 242). A ten equal group calibration curve of predicted vs. observed probability of poor outcome was plotted (Figure 27). The discrimination of the dichotomised regression model was excellent (AUROC 0.818; 95% CI's 0.758-0.879) as was the weighted novel poor outcome tool (AUROC 0.809; 95% CI's 0.747-0.871), both shown below in Figure 28. There was no significant difference between the area under the curves using the method of DeLonge ($p=0.238$).

Figure 27. Calibration curve of predicted vs. observed mortality for the 'poor outcome' score using ten equal groups.

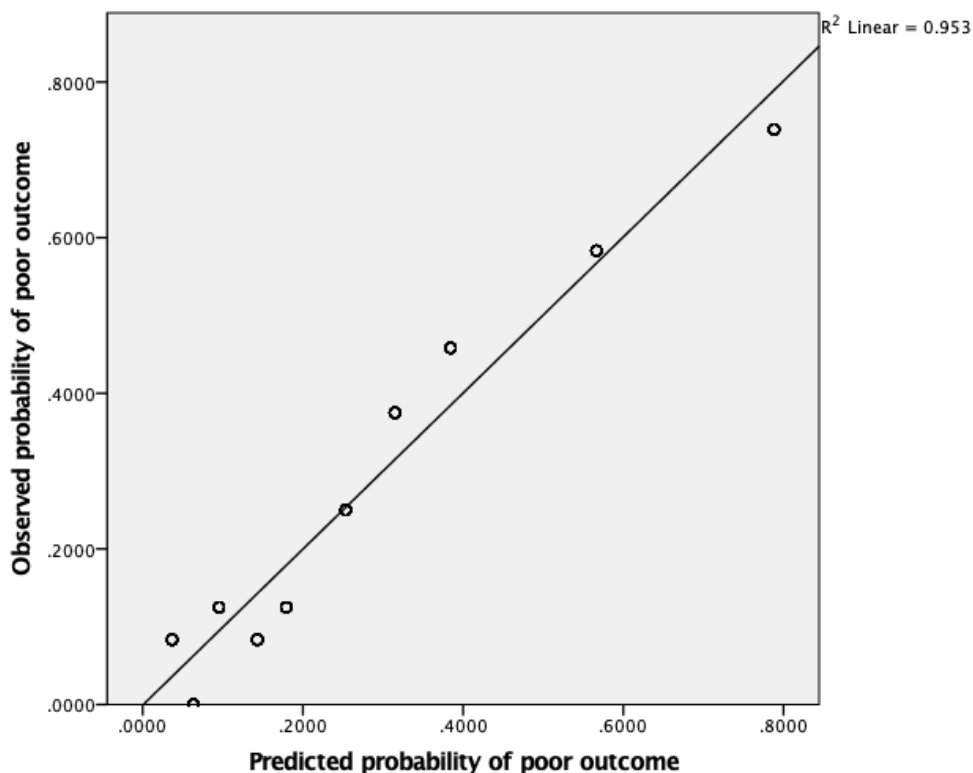
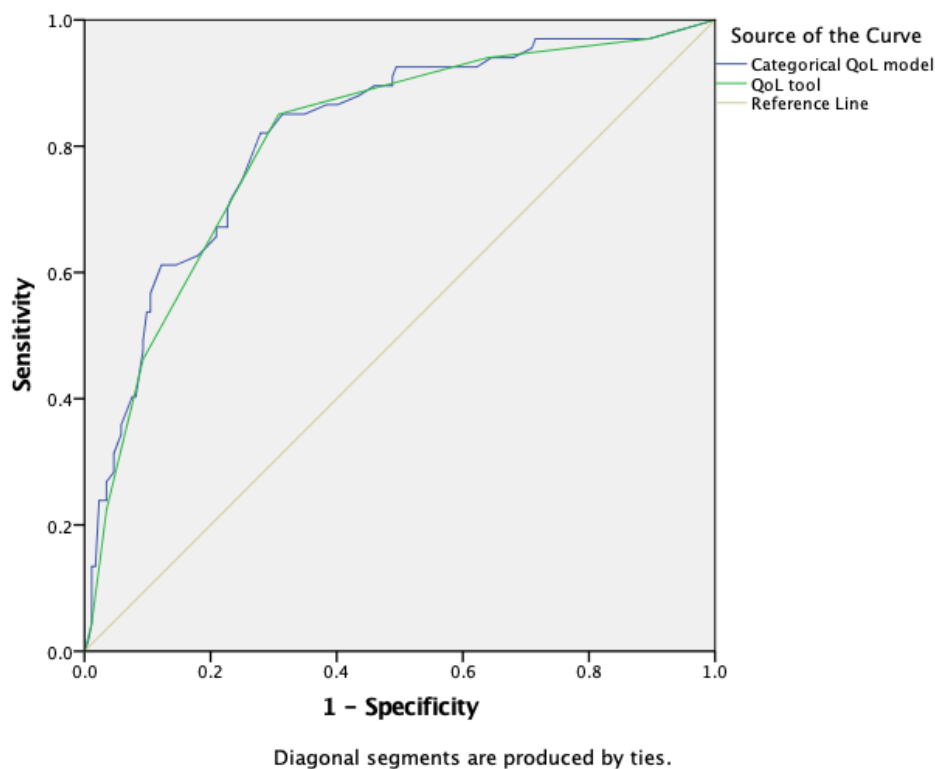


Figure 28. ROC analysis of the categorical 'poor outcome' model and the weighted 'poor outcome' prediction tool.



9.17.10 Comparison with NIVO and PEARL

The novel 'poor outcome' tool had stronger discrimination than the NIVO score (AUROC 0.610, 95% CI 0.533-0.687) or PEARL score (AUROC 0.653, 95% CI 0.577-0.729) for the prediction of poor outcome in this population. This should be interpreted with caution as the novel poor outcome tool is being assessed within its derivation cohort; predictive tools perform better in their derivation than validation cohorts. However, the NIVO score is made up of primarily acute indices, the PEARL score includes indices not associated with poor outcome on univariate analysis in this population, with other indices that dropped out in regression analysis. Additionally, neither the NIVO nor PEARL score have a specific QoL component included. External validation of the novel tool would need to be performed in order to make a truly fair comparison.

9.18 Chapter summary

The results of the longitudinal study are the largest described, over a one year time period, in a population of patients surviving assisted ventilation for ECOPD; with 272 patients consenting. The longitudinal population have slightly less severe disease than

those who survived but who did not consent, but substantial multimorbidity is present; the median eMRCD is 4 and patients have significant lung function impairment, with mean FEV₁ of 36.7% predicted. Moreover, almost 75% are readmitted and one third died within the year. These are not highly selected patients, and accurately represent the 'real life' patients with COPD admitted to UK hospitals. Whilst significant QoL impairments were present in both baseline and follow up quality of life questionnaires, the overall quality of life remained stable over the following year. Nearly all patients were happy with their ventilatory treatment and would accept it again, and three quarters were happy with their overall QoL; no attrition in these attitudes was seen in the 3 months following discharge. In this population, time to recovery was around 2 months for most measures, although activities of daily living were quicker at 1 month.

As in the validation population, readmission rates were high and were associated with clinically relevant anxiety and depression. A potential clinical prediction score, that requires external validation, could accurately predict poor outcome within 6 months of hospital discharge. This score uses simple bedside indices combined with two simple-to-score, patient completed, questionnaires. Importantly, this tool appears to have a step at which outcomes substantially worsen (score ≥ 3), which may provide additional clinical utility.

10 Discussion of results

10.1 NIVO study summary

Between October 2016 and February 2018 the NIVO validation study recruited 733 unique, consecutive patients with spirometry confirmed COPD in 10 UK centres. The primary aim of the validation study was to provide external validation of a predictive clinical tool which had been derived within one hospital trust in North East England. In addition to validation of the tool, various subgroups (late failure, relapse, home ventilation, eosinopenia, LTOT prescription), the utility of the NIVO score in patients without spirometry confirmed COPD but who were treated as such, and readmission and mortality rates post discharge were examined. In addition to this, we recruited 272 patients to the longitudinal arm of the study which tracked quality of life, measured by various questionnaires, over the year following discharge and derived a model for prediction of poor outcome in these patients.

10.2 Validation study summary

The derivation study (the detailed results of which are presented in a previous doctoral thesis) identified independent predictors of mortality and produced a clinical tool from these which was brought forward for external validation in this study. Importantly, throughout the validation study, the TRIPOD recommendations for prognostic research were strictly adhered to.⁽⁴⁶⁷⁾ In the validation of the novel tool, two of the variables (LTOT and eosinopenia) lost their independent predictive value. This was a pre-planned analysis to ensure the simplest possible final model. The loss of independent predictive value of these indices was likely as a result of overfitting of the original model to the derivation population, and in the validation study were dropped from the predictive model. The resultant model was reweighted in the same manner as the derivation study had been and with this scoring a simple clinical score was created and named the NIVO score (Table 130). Importantly, the removal of indices from the tool does not constitute a 're-derivation' as adding new variables to the model would do.

Table 130. The NIVO score.

	Score for variable being present
Consolidation	1
GCS under 15	1
Atrial Fibrillation	1
pH under 7.25	1
Time to acidaemia over 12 hours	2
eMRCD 5a	2
eMRCD 5b	3
NIVO Score	/9

The NIVO score was well calibrated and it significantly outperformed all pre-specified comparator scores in this study. There was stepwise increase in both inpatient and 90-day mortality observed with increase in the NIVO score. This provides potential clinical utility by affording clinicians the opportunity to identify patients at particularly high or low risk of inpatient death: 38% of patients were in the low risk category (inpatient mortality 5%), with fewer than 5% of patients were in the very high risk category (NIVO score 7-9, inpatient mortality 71.4% and the only category with over 50% mortality).

The NIVO Score predictors have face validity and a number are already included in other COPD related scores (see Table 8 and Table 9, pages 76-82). The identification of the time to acidaemia as an important predictor of inpatient mortality is not novel – its role in inpatient mortality was described in both the DECAF derivation cohort⁽³⁶⁷⁾ and the 2011 NCROP data⁽³¹⁸⁾ – although it has not been widely studied since. It was the second strongest predictor in this study, and its inclusion as a variable in a clinical tool is new. The delayed development of acidaemia post admission makes conceptual sense as a poor prognostic maker. If a patient deteriorates or ‘fails medical treatment’ after a number of hours into hospital admission, it would suggest they either are more frail with less physiological reserve, or they have a more severe acute illness that has not responded to medical intervention, and their outcome is likely to be worse. In the NIVO

validation study, inpatient mortality progressively increased the further from admission that the initial respiratory acidosis occurred.

The outcome measure of the NIVO score is inpatient mortality, which differs from the Confalonieri risk chart or Anton's model which stratify risk of 'NIV failure' (requirement of intubation or death).^(492, 493) NIV failure may be of interest to clinicians but it is arguably more difficult to explain to patients than mortality alone. Discussions about intubation are often laced with prognostic pessimism and may inappropriately dissuade a patient from accepting treatment; survival in the sickest patients is actually up to 10 times higher than clinicians' estimate, and most patients are happy to have received and would accept such treatments again.⁽⁴⁴⁸⁾ Moreover, the most robust estimates of outcome from both the Confalonieri and Anton tools come after treatment with NIV has already begun and a physiological response to NIV has been measured (in the form of repeat blood gases). This substantially limits their use in informed decision making and discussions around prognosis which would generally occur prior to the decision to start a treatment. It also seems highly unlikely that having commenced NIV only one to two hours prior, any clinician would remove it based solely on the recalculation of a clinical tool; though understanding risk of NIV failure may play a role in some clinicians' consideration of early referral for invasive ventilation. The NIV failure rate in the Confalonieri study was 22.8%, with 17.9% of the total population being intubated in contrast to a rate of only 2.9% in the NIVO validation study.

An important feature of the NIVO score is that all six variables included in the tool are routinely available as part of usual clinical care, the variables are dichotomous and therefore no complex computation is required, and the tool can be scored prior to the commencement of NIV. This facilitates pre-treatment discussions with patients and their families, the wider clinical team, and increases the likelihood of the NIVO score being used by clinicians, as well as lending itself to incorporation into NIV care records and documentation.

10.2.1 Potential uses of the NIVO tool

The NIVO tool has several potential applications, most of which have been touched upon earlier in this thesis, but which have been expanded upon and linked to validation results below.

a) **Informed discussions with patients and shared decision making.**

This is perhaps the most important potential benefit of the NIVO score. The accurate understanding of possible outcome prior to the commencement of treatment is key to providing patients with the information required to give truly informed consent. The NIVO score provides objective stratification of the risk of death, which is likely to outperform clinician estimates. This could work both ways – patients may be motivated to persevere with NIV when presented with a mortality risk of, say, 49% (high risk NIVO score) where they otherwise may have asked for it to be removed. Conversely, some patients with a very high risk of death may decide on balance that they do not want to receive NIV and would prefer conservative care and a more palliative approach.

b) **Challenging prognostic pessimism and improving clinician confidence around NIV decisions.**

This aspect is particularly important as the overwhelming majority of doctors who make decisions to initiate treatment with NIV are non-consultant and non-respiratory or critical care specialists, and may not frequently look after patients with COPD or respiratory failure.⁽³³⁹⁾ Following on from point a, it is important to realise the numbers of patients in the very high risk group is small (n=35) at only 4.8% of the NIVO population. A lack of research into selecting the right patients for treatment with NIV was highlighted in a 2017 Cochrane review.⁽³¹⁷⁾ The majority (75%) of patients in NIVO fall into a group with a relatively low inpatient mortality; there is arguably almost no reason not to offer this population treatment with NIV (setting aside highly specific individual circumstances). This should provide clinicians with reassurance they are ‘doing the right thing’ by commencing NIV, even if this contradicts their own internal prognostic assessment. This could increase the number of patients commenced on NIV and reduce use of defensive pessimism (see section 3.1.2). Given prognostic pessimism can often be institutionalised or learned from role models, the

empirical evidence on outcome in NIVO may empower more junior members of a team to challenge incorrect assumptions about outcome by its more senior members.

Another way of challenging a decision not to treat with ventilation is to highlight that the outcomes demonstrated in NIVO are in patients already treated with NIV, which is known to reduce mortality rates by 50%.⁽³²⁰⁾ Therefore, the decision not to offer NIV will reduce the chance of survival, perhaps substantially. This would need to be understood by the clinical team and the patient.

c) Facilitating audit.

Increasingly regional and national audit programs are collecting data and analysing outcomes. Indeed, the BTS NIV and National COPD secondary care audit programs already collect data on patients with ECOPD treated with NIV. Using the NIVO score to adjust results for case mix would facilitate fairer comparison of units and both identify outlying trusts (good or bad) and could also highlight hospitals who are unduly selective (e.g., they may have no NIVO 5-9 scores). Results of such audit and comparisons with expected vs. observed mortality is likely to create specific areas of improvement that institutions can make.

d) Improving equity of care.

The NCEPOD 'inspiring change' report and British Thoracic Society NIV audit report 2019 demonstrate substantial and worrying variability in delivery of NIV care between hospitals.^(339, 510) Even within the 10 NIVO sites this was observed to some extent. For example, substantial variation between the number of patients considered for IMV or CPR was demonstrated, as well as differences in door-to-mask times and duration of NIV treatment. The NIVO score could improve equity of care and access to NIV as a result of all of its other potential advantages combined. By challenging pessimism, improving confidence that NIV is the right course of treatment, facilitating internal and inter-unit audit, and improving communication between the various stakeholders, it is possible that provision of NIV will increase and that (currently) subjective decisions may be more objectively reached. It is, of course, inevitable that some variation will

persist, but discrepancies between ~60% of patients being considered for IMV in one trust vs. ~15% in another as seen in NIVO will hopefully reduce.

e) **Contribute to decisions on level of care.**

The NIVO score may have a role in helping decide levels of care given the resource limited environment in which assisted ventilation occurs. Targeting patients in high or very high risk groups (41.7% and 71.4% inpatient mortality respectively) with higher levels of care, for example in an RSU or critical care environment, may lower the high mortality in this group and reduce overall mortality. Similarly, the NIVO score may identify patients of a low risk of death who may be safely treated in a ward based environment. In many respects, this would hopefully be only a short lived use of NIVO. The BTS quality standards for NIV clearly state that all patients should be managed in an area designated for ventilation with appropriate staffing.⁽⁵¹¹⁾ Currently, however, this may not be practicable in many hospitals: in NIVO, three trusts did not have an RSU; 1 in 3 patients were treated on the ward as the highest levels of care; and in some trusts with an RSU around 15% of patients were treated on the ward – suggesting RSU bed pressures.

f) **Increasing rapid follow up.**

90-day mortality rates amongst NIVO patients are substantial. Even a score of zero is associated with a 10% three month mortality; recognition of such outcomes may help service planning and facilitate creation of space for 'rapid access' outpatient clinics within the first couple of weeks following discharge. These could result in quicker optimisation and titration of medications, increased referrals to pulmonary rehabilitation, dietetics and psychology (including allied health professional or nurse-led CBT), increase referrals for home ventilation (such as used in HOT-HMV⁽²⁴⁴⁾), improve patient education, and in some cases expedite palliative care.

10.3 Pre-specified subgroups, readmission, and mortality

10.3.1 Late failure and relapse

Late failure was defined as the recurrence of respiratory acidaemia >24hrs after initial pH correction, with a corresponding rise in PaCO₂. Relapse was defined as the recurrence of respiratory acidaemia at least 24hours after the cessation of ventilation (see section 7.1).

Late failure has previously been shown to be associated with frailer patients and confer very poor outcome.⁽³⁵⁶⁾ Moretti *et al* demonstrated a prevalence of late failure of around 23%, with a worrying inpatient mortality rate of 67.7% (rising to 92% if NIV was continued after occurrence, rather than switching to invasive ventilation).⁽³⁵⁹⁾ In the UK, the prevalence and outcome of late failure or relapse is unknown. In the NIVO derivation study, 7.2% of patients developed late failure, none were intubated, and overall mortality was 34.3%; all significantly lower than Moretti found. The NIVO validation study reveals similar findings to the derivation study. 41 (5.6%) patients developed late failure after an average of 2.8 days from the commencement of NIV (2.3 days from pH correction).

The demographics of late failure patients were broadly similar to those who did not develop late failure, save a higher rate of left ventricular systolic dysfunction, lower BMI and evidence of more longstanding respiratory failure (higher PaCO₂, base excess and bicarbonate despite similar pH) in the late failure group. Conversely, Moretti found a higher PaCO₂ in those not experiencing late failure, though base excess, bicarbonate, BMI, nor prevalence of comorbidities were reported, making comparisons challenging.⁽³⁵⁹⁾ The findings regarding relapse were similar to late failure, though few patients (n=4) experienced both, suggesting different underlying mechanisms. The prevalence of relapse was slightly higher than late failure, at 7.1%, and the occurrence of relapse was associated with a 38% inpatient mortality.

In contrast to Moretti's study, where 61% of patients were intubated following late failure, only one of the NIVO validation patients proceeded to intubation. In 95.6% of cases, NIV was continued with changes to either ventilatory settings, or with steps to improve patient-ventilator synchrony; overall mortality was 35.6% - around one third of the mortality rate of the NIV-continued Moretti cohort. This difference may reflect

improvement in the clinical application of NIV over time (interfaces, settings, ventilators, synchrony), as well as possible population differences. As discussed in section 1.10.3.1, it may be that in patients who have optimised NIV (ventilator settings and synchrony), failure to improve is not due to a failure of the ventilatory interface itself (NIV rather than invasive ventilation), but rather an intrinsic failure of the patient's lungs due to the severity of their underlying disease, physiological reserve and acute insult.

Unfortunately, the NIVO study cannot answer this question. Whilst the occurrence of either late failure or relapse is clearly associated with worse outcome, given that 60-70% of patients still survive to discharge, neither would appear to justify the withdrawal of ventilation in and of themselves.

10.3.2 Persistent post ventilation hypercapnia and home ventilation

Hypercapnia was defined as a PaCO₂ of ≥ 6.0 kPa in keeping with the physiologically normal definition of hypercapnia.^(395, 514) This is not the same definition currently used to commence NIV for acute hypercapnic respiratory failure, nor the same threshold as used in some home ventilation trials, but was used to explore factors associated with physiological abnormality; home ventilation was further explored as a separate subgroup analysis.

Unfortunately, there was a high level of missing data in the recording of post ventilation blood gases, due in part to the observational nature of the study – the taking of such ABGs was not mandated. Nonetheless, 413 (56%) patients had post ventilation gas, and of these 389 (94.2%) patients survived to discharge with 300 (77%) demonstrating persistent hypercapnia. Patients with persistent hypercapnia had worse stable-state dyspnoea, were more frequently prescribed LTOT and had more severe airflow obstruction. The presence of hypercapnia was not associated with more frequent readmissions, nor longer readmissions, although patients were more likely to require NIV again when readmitted. By 6 months, however, patients with persistent hypercapnia were twice as likely to die as those without. Persistent hypercapnia appears to identify a poor prognostic marker that is potentially modifiable; particularly in light of the HOT-HMV trial results which demonstrated a 51% reduction in discharge or death with home ventilation treatment.⁽²⁴⁴⁾ Despite this, only 1/3 of persistently hypercapnic patients had home ventilation started at any point in the following year. Patients who

commenced on HMV in NIVO had a higher median post-ventilation PaCO₂ (7.75kPa) than those who did not (7.16kPa). Both of these values are above the inclusion criteria used in HOT-HMV (PaCO₂ 7.0kPa) suggesting that HMV could potentially have been of benefit to more patients and was underutilised in the NIVO population. We do not have data on how many patients were offered HMV but declined it.

Leaving persistent hypercapnia aside, over the year following discharge, HMV treatment was provided in 93 of 586 (15.8%) NIVO patients surviving to discharge. Demographics were similar to non-users, though home ventilation patients were more likely to be on LTOT. The BMI of patients on home ventilation at discharge was higher, suggesting some overlap with obesity hypoventilation related respiratory failure. The most common reason for starting home ventilation was recurrent admissions with respiratory failure; only 12 patients were started due to HOT-HMV criteria. Throughout the follow up period (in patients taking part in the longitudinal study) the reported and ventilator-verified usage times of HMV were remarkably similar; overall reported rates were 347 minutes per night with ventilator-confirmed usage of 340 minutes per night. This is better than is reported in CPAP treatment for obstructive sleep apnoea patients, in which adherence is thought to be around 60-70% with average nightly usage of 280 minutes.^(515, 516) Given CPAP treatment non-adherence is seen most commonly in mildly or asymptomatic OSA patients, it may be that the severity of symptoms experienced by patients with COPD requiring ventilation improves adherence to treatment.

10.3.3 Long term oxygen therapy at admission

Rates of LTOT prescription were similar between the derivation study (29.2%) and the validation study (28.6%). LTOT prescription was identified as an independent predictor (albeit the weakest one) of mortality in the derivation study, and in the validation cohort was again associated with significantly higher inpatient mortality (25.2%) than in those not requiring it (18%). Despite this, in the validation of the predictive model, LTOT was not retained, suggesting overfitting of the data to the derivation population and risk being captured by other NIVO indices. Patients prescribed LTOT are an unwell group with significantly worse dyspnoea, airflow obstruction, more frequent readmissions, more cor pulmonale and atrial fibrillation as well as significantly higher mortality (approximately double) over the following year, than patients not prescribed LTOT.

Mortality in this group was higher (53.5%) in the validation study than in the derivation (43.8%). LTOT prescription was additionally identified as an independent predictor of poor outcome in the longitudinal study.

Of interest, over half of patients using LTOT recruited to the NIVO validation study were current smokers at admission. The median PaO₂ of LTOT users in NIVO was 7.54kPa. Since the NIVO validation study opened to recruitment, the NICE guidelines on COPD have been updated with the recommendation that LTOT should only be considered “for people with COPD who do not smoke”.⁽¹⁸²⁾ This raises interesting ethical questions about the initiation or withdrawal of LTOT in our population. Under circumstances in which a patient is told their continued smoking precludes receiving LTOT, it is likely that some will continue to smoke whilst telling healthcare professionals they are not doing so. This phenomenon has been demonstrated in a study exploring rates of smoking in UK lung transplant referral patients; all believed to be ex-smokers and 44% of whom had COPD. Examination of urinary cotinine levels at transplant assessment demonstrated results in keeping with active smoking in 21% of patients.⁽⁵¹⁷⁾ NICE currently already recommend undertaking a structured risk assessment and education with every patient needing LTOT.⁽¹⁸²⁾ LTOT is a life prolonging treatment, and burns are rare even in populations with high known smoking rates on LTOT. Therefore, it seems that in patients with the ability to understand how to ‘smoke safely’ and who engage with healthcare services, withholding of LTOT treatment in smokers may be difficult to justify.^(518, 519) Furthermore if we are only providing education and performing risk assessments to ‘non-smokers’ the ‘actually-smoking-non-smokers’ will not get tailored safety advice and education around the use of cigarettes and oxygen, potentially making LTOT more dangerous.

10.3.4 Eosinopenia at discharge

In keeping with the findings in the NIVO derivation study, there were no demographic differences observed between eosinopenic and non-eosinopenic patients in the validation study. The proportion of eosinopenic patients was smaller in the validation (24.6%) than the derivation (32.3%) study. Index admission length of stay was 2 days shorter in eosinopenic patients; but the reason for this is unclear and not discernible from the NIVO data.

Following discharge, no difference in the total number of days in hospital over the following year, the number of admissions, nor time to first readmission was seen. Similarly, eosinopenia did not show any evidence as a marker of increased mortality post discharge.

10.3.5 Readmission and long term mortality

The readmission burden in the year following discharge was substantial; 413/586 patients with a total of 1308 readmissions were experienced. The vast majority of such admissions were further exacerbations of COPD and a third of readmissions required treatment with NIV. The rates observed in NIVO are around 10% higher at both 30 and 90 days than recorded in the national COPD audit.⁽²¹¹⁾ However, the national audit includes patients both treated with and not with NIV, and NIV patients are known to have higher readmissions. Nevertheless, this readmission burden is worrisome with nearly 12,000 bed days used by NIVO participants. According to the websites of the various NHS trusts participating in NIVO, a population of approximately 6,930,000 people were covered by the NIVO study; approximately 10% of the UK population. A very simple extrapolation of this number suggests that UK hospitals may look after around 120,000 bed days in readmissions following acute NIV for ECOPD alone. This readmission burden is not only challenging and costly for healthcare systems; readmission in NIVO was associated with increased anxiety and depression levels compared to non-readmitted patients (see section 9.13) and was associated with significantly increased mortality rates at one year (section 7.6.2).

Whilst the NIVO score was not designed to predict risk of readmission, the strongest independent predictor of mortality was the eMRCD, which was also the strongest predictor of mortality or death at 90-days in the PEARL score and mMRCD was the strongest predictor in the CODEX score; highlighting commonality amongst adverse predictors in COPD.^(163, 481) These scores may help us identify patients or highlight potentially treatable traits, such as dyspnoea, heart failure, or significant anxiety and/or depression. Targeting such patients with increased healthcare input (for example specialist nursing home visits, rapid access to pulmonary rehabilitation and optimisation of medication) may help reduce the readmission burden. Implementation studies examining this would be worthy of future study. Whilst reducing readmissions is a

priority, it is important to recognise that readmission may not be a universally adverse event for patients. Data published examining ventilated patients at Northumbria Healthcare has previously shown a reduction in 30-day post discharge mortality which corresponded with an increase in readmission rates.⁽²⁹⁸⁾ It may be that in some patients, early rehospitalisation is protective.

10.4 Clinical diagnosis patients

Clinical diagnosis patients (those without previous spirometry, but who were treated as presumed ECOPD and met other inclusion criteria) were captured separately in NIVO. Whilst missing diagnoses in patients who have COPD is a well-recognised phenomenon (see section 1.5.5), the proportion of patients in NIVO (i.e., those unwell enough to develop respiratory failure) was startlingly high at 13.2% of all patients included. Clinical diagnosis patients had better stable state dyspnoea and broadly similar other demographics, yet suffered similar inpatient mortality to validation patients suggesting outcomes in these patients are worse than may initially be expected. NIVO scores are statistically similar, but trend toward being lower in CD patients ($p=0.075$), and when removing eMRCD the other variables in NIVO are similar ($p=0.952$). Marik demonstrated that misdiagnosis of COPD is common in patients who actually have OHS; this is a likely factor in the CD group as they had significantly higher BMI than validation patients.⁽⁵²⁰⁾ It is likely that the NIVO score will be calculated in this population if it is adopted into clinical practice, therefore it is necessary to ensure it is still valid and accurate.

The NIVO score demonstrated a stepwise increase in mortality in CD patients, and NIVO risk groups identified approximately 50% of patients as low risk and 81% with low-moderate risk, conferring potential clinical utility. The NIVO score offers moderate prediction of inpatient mortality in clinical diagnosis patients. The AUROC of NIVO (0.724) was numerically higher than either the DECAF (0.695) or CURB-65 (0.695) scores, although no statistical difference between these values was shown, and it was not as discriminative as in the validation cohort (AUROC 0.79). Misdiagnosis of ECOPD, as discussed above, and thus inclusion of patients who did not have COPD may explain the reduced AUROC of the NIVO score. It is important to note that the number of CD

patients is small and 'CD validation' of the NIVO score is therefore underpowered; further examination in such a population is required to confirm its validity.

Disappointingly, of the 89 patients who survived to discharge less than half had diagnostic spirometry performed over the subsequent year. In those that did, 4/5 patients demonstrated airflow obstruction. Overall, by one year, 63% of clinical diagnosis patients treated as ECOPD with ventilation had not had COPD confirmed. One potential mechanism for improving this is to perform inpatient spirometry in all patients admitted as 'ECOPD' who have no previous spirometry available. Fernández-Villar demonstrated that, whilst absolute FEV₁ changes around admission, the FEV₁/FVC ratio remained similar between admission and 2 months post discharge.⁽⁵²¹⁾ In patients in the longitudinal component of the NIVO study (all spirometry confirmed COPD), we performed spirometry prior to discharge and at three, six and twelve months following discharge. Similar to the findings by Fernández-Villar, whilst the absolute FEV₁ and FVC improved in the NIVO longitudinal cohort, the ratio remained stable from inpatient to 3-month follow up. Whilst our findings were in spirometry confirmed patients, it may be that performing inpatient spirometry in all patients treated as 'ECOPD' but where spirometry results are unavailable could help reduce misdiagnosis and would be worthy of future research. Of course, stable state spirometry ideally should be performed to confirm diagnosis; but given the current poor completion of this demonstrated in NIVO, it seems performing inpatient spirometry may be a reasonable measure to institute. Ruling out airway obstruction in some patients could potentially reduce misdiagnosis and inappropriate treatment of OHS, amongst other conditions, with treatments such as systemic corticosteroid or bronchodilators.

10.5 Validation study strengths

To our knowledge this is the largest study which attempts to prospectively validate a prognostic score in this population, with 733 patients included (the Confalonieri risk chart was validated in a population of 145 patients⁽⁴⁹³⁾). Added to the derivation study there were 1222 patients included in the whole NIVO project. Unlike other large studies which have used existing datasets, the NIVO derivation study had bespoke dataset including all known and suspected predictors, therefore maximising the ability to collect

variables which may be associated with morality to bring forward to the validation study. The validation of the NIVO tool was robust; performed prospectively with temporal and geographical differentiation from derivation, and adhered to the TRIPOD guidelines published for prognostic modelling research.⁽⁴⁶⁷⁾ The spread of the 10 recruiting centres across urban, suburban and rural populations in the UK, coupled with the number of patients included is a significant additional strength. A daily search of areas providing NIV or IMV in the hospital was conducted in each centre to maximise recruitment of consecutive, unique patients thus minimising survivor bias.

Good research practice was followed from the inception of the study. Patients were included in the trial design, protocols including outcomes and an analysis plan were published prior to the commencement of recruitment and good research governance was practiced throughout. Multiple trial steering committee meetings were held throughout the period the trial was open, with all research staff at each site invited (not just principal investigators), an independent chair, and a patient representative.

Electronic data monitoring and verification was performed continuously throughout the study, with additional physical visits performed after recruitment at each site had ended.

External centres (and clinicians outside of the immediate research team at the primary centre) were not made aware of the indices in the tool as not to influence their usual practice and introduce bias into the study. There were very low missing data rates in the indices included in the score; minimal imputation was required to complete the dataset. This adds credence to the argument that the variables included are routinely available to the treating clinician and which in themselves do not require complex calculation.

A common criticism of many research studies is that the studied population is not representative of the population seen in day to day clinical practice. It was therefore of the utmost importance that the population included in NIVO did represent a generalisable population. If the study is not representative of real life patients, the utility of the score in clinical practice would be vastly reduced. With this in mind, the exclusion criteria were minimal and inclusion criteria broad. This helped ensure inclusion of patients who represent those treated as ECOPD with NIV in normal clinical practice.

Whilst an argument can be made against using a static $FEV_1/[F]VC$ (rather than using the lower limit of normal) to help diagnose COPD, anecdotally, the majority of patients seen

on the acute take don't have documented standardised residuals reported on spirometry in clinic letters or in primary care. As such, using a strict LLN may have over-defined the population and reduced the generalisability, so the decision was made to use a static cut off. Besides, the current NICE guidance for diagnosis in the UK and the GOLD guide both state a static cut-off of <0.70 , therefore this most closely represents UK practice.^(1, 182)

We believe our aim of recruiting a population representative of real world medicine has been achieved. The population in NIVO is not highly selected; patients had significant morbidity, and compare similarly to those in NCEPOD, NRCOP and NACAP reports, all of which represent sizable national audits of 'real life' patients treated for ECOPD in the UK. Amongst other variables, NIVO inpatient mortality (20.1%) was similar to that described in the ECOPD NIV population seen in the NCEPOD report (25.1%), median age was similar between NCROP, NACAP and NIVO (73, 71, 70.5 respectively), FEV1% predicted was 37.1% in NIVO and 34% in NRCOP, similar proportions lived at home in NIVO (92.3%) and NCROP (90%), an MRCD score of 5 made up 41% in NCROP and 56% in NIVO, 40% had cardiovascular comorbidity reported in NACAP with 52.9% having ≥ 1 cardiovascular multimorbidity in NIVO, and 40% were not for cardiopulmonary resuscitation in NCROP with 56.3% not for resuscitation in NIVO.^(211, 318, 339) The vast majority of patients in NIVO were treated in the RSU or ward environment, reflecting real life practice within the UK.

In addition to the predictive ability of the NIVO score, the validation study has shed further light on subgroups in this population which were previously under investigated and described. Most notably, the data on late failure and relapse is the first we are aware of describing the UK prevalence and outcomes. This data shows prevalence is lower and outcomes are better than previously thought; this may help challenge pessimism and change practice in this subgroup.

The biggest strength of the NIVO score is its high predictive ability. The aim of the NIVO project was to create a simple to use bedside tool, using routinely available clinical indices, and which did not require complex computation yet still retained predictive ability, and then to perform robust external validation to ensure validity. This has been achieved. The NIVO score outperformed all pre-specified comparator scores, provided risk categorisation, and is validated at gold standards.

10.6 Validation study weaknesses

Given the observational nature of the NIVO study, the 'intervention' (i.e., how NIV was delivered) was not controlled by the study protocol. This was intentional and necessary, but nonetheless could introduce a weakness to the study as treatment was not standardised across the study population. Different hospitals could have, for example, different weaning protocols, may have ventilated at different pressures, or ventilated patients in different settings (ward based vs. RSU vs. critical care). There are national guidelines and quality standards for the provision of NIV in COPD; however, not controlling the intervention increases the risk of deviation from such guidelines which may assert a direct effect on patient outcome. Nonetheless, to have controlled the intervention would have required individual patient consent as this would have been a departure from usual clinical practice. Should this have occurred, the study population would have only been reflective of those who were able to give informed consent, substantially limiting recruitment of those who may have been sickest and at the highest risk of the primary outcome measure. Additionally, given the time critical nature of NIV treatment, it is likely anyone admitted or requiring NIV outside the working hours of research staff would not have been included. This would have led to a smaller study population with much reduced generalisability, and ultimately would have rendered the tool less likely to be used in clinical practice. So, whilst in part a potential weakness, the fact that the NIVO study accommodated these natural variations in practice, is representative of the real life patient population, and yet still performs excellently is a significant strength.

It is important to consider those who were not treated with NIV despite meeting criteria for NIV initiation, as such patients were not included in NIVO. This could have occurred as a result of, among other reasons, prognostic pessimism (e.g., in elderly patients or those with significant baseline dyspnoea) or patient wishes. We were only able to mitigate for this potential bias rather than eliminate it altogether. It is impossible to quantify the amount of 'NIV selection' that occurred, but it is possible that it did. Efforts were made to reduce this; prior to site selection, each site provided internal audit data to the chief investigator to be examined for signs of NIV selection bias. Sites

demonstrating a highly selective NIV service (e.g., a low proportion of patients with an eMRCd score of 5a or b) were not selected as a participating site, with all selected sites having streamlined and well-established ventilation services. Despite the potential selection bias introduced through NIVO study site selection, the severity of disease seen in the population characteristics and how they compare with large national audits is reassuring that there was no substantial selection. Another concern in prognostic research is that of interobserver bias in recognising the study outcome; in NIVO this was not too much of a concern as death is difficult to misinterpret.

In discussion of the coronary disease specific GRACE prognostic score, its authors succinctly remarked “How generalizable are prediction tools? They are as generalizable as the population from which they are derived”.⁽⁵²²⁾ The NIVO study was conducted within the United Kingdom and the National Health Service model of care, and therefore claims of generalisability are potentially limited to ventilatory practices in ECOPD and the UK population. Unlike some other countries with different models of care, such as the United States, NIV in the UK is predominantly delivered outside of the critical care setting and there are low rates of invasive ventilation. Such differences in models of care may render these findings less relevant to a non-UK population. Of course, validating the NIVO score in another population or country would overcome this limitation.

The aim from the outset was to develop the simplest possible model. The dropping of two variables (eosinophils and LTOT) from the originally derived predictive model could raise the question of whether the validation of NIVO was actually rederivation. This is not the case. In contrast to the addition of new variables, which is clearly defined as rederivation, the removal of existing indices that do not confer independent prognostic value in the validation cohort is not rederivation; this was confirmed by independent statistical advice. Also of importance, the weighting of the final NIVO score was the same in derivation and validation populations. Validating an unchanged derivation model could have been undertaken, though this did not seem sensible as it would have added further complexity to the scoring of the tool without providing additional prognostic performance. None of the remaining variables were altered between derivation and validation, and those that were dropped are likely a result of overfitting to the derivation population. This process is, of course, one of the main objectives of undertaking the validation of a prognostic score.

A potential criticism of the NIVO score is the use of dichotomous variables in the tool, rather than continuous, and the potential loss of predictive value. This argument has been levelled on a number of occasions including a recent high profile article, specifically examining prognostic tools for COPD, published in the British Medical Journal.⁽⁴⁷²⁾ Firstly, a number of predictors used in NIVO score are dichotomous in their purest form: a patient either has or has not got consolidation or atrial fibrillation, so for these variables the point is moot. The argument for the use of continuous variables is the loss of prediction by dichotomising.^(472, 523) Whilst it seems sensible to reason that using a larger number of divisions for a variable retains its predictive power better within a model, this is only true if there is linear change in risk across that variable. It is often the case that risk is non-linear and if there is highly skewed data then dichotomising the variable can give very similar, or better, performance to maintaining continuous variables. The AUROC using continuous variables in the NIVO validation study was 0.80 (0.76-0.84) vs 0.79 (0.75-0.83) in the validated (dichotomous) model. The methodology in NIVO has been used in previous prognostic research and was chosen intentionally, despite being at odds with some recommendations. The use of continuous variables in the prognostic model would potentially require the end user to have to undertake complex calculation of a score to get an end result. Whilst arguably statistically pure, the end result would be much more difficult and time consuming for a busy clinician to use and therefore the translation into routine clinical use would be much less likely. Ultimately, if a prognostic score is not used because it is too complex, or because it is not able to accurately predict outcome, there was no benefit to having undertaken the research in the first place. We believe that NIVO has struck the right balance: the inclusion of dichotomous variables has provided a simple to use tool, whilst maintaining predictive ability with clinically meaningful results.

Furthermore, and whilst not exactly a weakness but more of a challenge, integrating the NIVO score into usual clinical care may be difficult. The score may be of most use at the centres with the greatest prognostic pessimism. Prognostic pessimism is unlikely to be a purposeful trait in a clinician, and these centres may not recognise their need to challenge their practice. One potential mechanism of overcoming this would be inclusion in the national audit, discussed in section 10.2.1, as this would facilitate open comparison between often siloed centres, or national averages.

10.7 Longitudinal study discussion

Whilst inpatient death is clearly an important outcome marker and is highly relevant to patients, families and healthcare teams, the majority of patients (79% in NIVO) did not die in hospital and were discharged home. An important, yet often ignored outcome, is the patient's quality of life following hospital discharge. The Cochrane consortium highlighted that patients with potential low quality of life are often excluded from inclusion in trials, and in their review of NIV treatment for ECOPD there is no discussion of quality of life outcomes.⁽³¹⁷⁾ From conception of the NIVO study we sought to monitor QoL following discharge, given the paucity of data available and the importance of these outcomes. As previously mentioned, the NIVO study was intentionally designed to include the most unwell patients (those most likely to die) who Cochrane state are often excluded. Only a minority of patients were deemed ineligible to enter the longitudinal study due to underlying health problems (primarily resulting in the inability to give informed consent), and nearly 50% of validation patients were included in the longitudinal. Whilst some demographic differences were suggestive of lower morbidity in the longitudinal group (lower age, fewer previous admissions, lower NIVO score and better median eMRCD), the majority (including lung function tests, most comorbidities, LTOT or HMV prescription, the percentage of housebound patients) were similar. The longitudinal study population remains a representative cohort of the population which receives NIV for ECOPD in the UK and demonstrates what happens to patients' quality of life over the year following admission for this. We have also identified independent predictors and derived a candidate score to predict poor outcome over the following months in those surviving to discharge.

10.7.1 Quality of life outcomes

Comparison with other research in this area is challenging, as so little has been previously undertaken. The primary comparators are with the DECAF derivation cohort and the CAOS study.^(376, 394, 448) Arguably the most important three questions asked in the longitudinal study were those in section 9.9, exploring attitudes towards ventilation and overall satisfaction with quality of life. They are remarkably simple, and the question "are you satisfied with your current overall quality of life?" in particular allowed the

patient to entirely judge what their quality of life is with no further qualification or prompting by the researcher. Nearly all NIVO patients (~94-98%) were glad they received ventilation and would want it again; findings nearly identical to the CAOS study where 96% agreed.⁽³⁹⁴⁾ Almost three quarters in NIVO were happy with their quality of life both at discharge (72.4%) and three months (72.8%), with no attrition between these time points. Perhaps every other consideration of quality of life in the study should be prefaced with the overarching context that, on the whole, patients are glad to be treated with NIV and are generally satisfied with their quality of life.

The burden of symptoms prior to discharge was expectedly high. Levels of breathlessness, COPD symptoms, and experiences of anxiety and depression were all significant and clinically relevant. The ability of patients to undertake their ADLs was also substantially limited. Generic health questions asked in the EQ-5D-5L score revealed similar findings. Clinically relevant baseline anxiety levels were similar to those reported by Dowson et al,⁽²⁶⁹⁾ at around 50% though depression levels were substantially higher in NIVO (43.5% vs. 28%). Over the following months, the quantity of time spent equal to, or better than, baseline scores was under 50% for most tools; suggesting a slight worsening of symptom burden in each score. Anxiety and eMRCD were more favourable, with more than 50% of time spent equal or better. Despite the deterioration noted in the time spend equal to or better than baseline for most indices, the mean change in the population did not cross the minimum clinically important difference for any individual score over the follow up period. This means that, overall, the quality of life of the NIVO population remained stable over the follow up period. These findings emulate those seen in the DECAF derivation cohort, and are in keeping with the CAOS results that patients felt at least as good as their preadmission period at six months after discharge.^(376, 394) Low or medium NIVO risk groups did not appear to be associated with subsequent clinically significant change in quality of life. Higher risk groups may be associated with a deterioration in quality of life, though patient numbers are small. The NIVO score is principally composed of acute indices, save the eMRCD, therefore it is not surprising that its predictive ability is less robust in longer term QoL outcomes. Prediction of change in life with poor outcome was better with the novel predictive QoL score derived in this population.

Time to recovery, measured by the median time to best score, was around two months for most of the QoL tools with the exception of the NEADL (around one month) and eMRCD (best at baseline). The upper quartiles for time to recovery were all around or less than six months, in keeping with the findings of a recent metanalysis examining time to recovery following exacerbations of COPD.⁽⁵²⁴⁾ The time to recovery observed in NIVO is shorter than that reported in the DECAF derivation cohort, though this could be due to the less frequent follow up visits performed in that study influencing their results.⁽³⁷⁶⁾

10.7.2 Re-exacerbation and quality of life

The majority of patients (64.3%) had community treated exacerbations in addition to hospital treated exacerbations, with almost half (46.7%) having multiple exacerbations over the year following discharge. Approximately 40% of patients experienced a further exacerbation or hospital readmission by 90 days, in keeping with the pattern of temporal clustering of exacerbations of COPD.⁽³⁰⁶⁾ Interestingly, whilst most patients reported their readmissions accurately, there were more who ‘under’ rather than ‘over’ reported these. This has been a well-known phenomenon for some time; Seemungal *et al* found only 51% of exacerbations were reported, and a larger study by Langsetmo *et al* was even worse with only 31% reported, with more recent data showing this trend has continued.^(206, 525, 526) Extrapolating this to NIVO paints a particularly bleak picture of exacerbation burden. However, the effect of exacerbation and readmission on QoL in NIVO was interesting. Patients who reported at least one community treated exacerbation in NIVO had a clinically significant improvement in their anxiety levels over follow up, whilst other domains remained stable. The reasons for this are not immediately clear, and the literature does not appear to replicate this finding; it may be related to increased input and reassurance from contact from primary care teams. Regression to the mean (i.e., these patients having worse baseline anxiety and just got better as the year went on) is unlikely as there was no difference between exacerbators and non-exacerbators’ baseline anxiety levels, or other QoL scores, prior to discharge. Patients experiencing readmission, however, were different. There were statistically worse scores at baseline found in the ability to perform ADLs (NEADL), self-reported wellness (EQ-5D-5L) and depression rates (HADS-D) in those who subsequently experienced a readmission. Over the follow up period, whilst no score crossed the MCID

for either group, there were statistically significant differences in the CAT, EQ-5D-5L VAS and NEADL scores between those who were readmitted and those who were not. The mean change in these scores were universally worse for those readmitted, and better for the non-readmitted patients suggesting that, whilst not meeting the MCID, readmission has a negative impact on QoL. The prevalence of both clinically significant baseline anxiety and depression was higher in patients who were subsequently readmitted than those who were not, in keeping with many previous studies showing these symptoms are risk factors for readmission.^(527, 528)

10.7.3 Prediction of poor outcome

Poor outcome was defined as patients with a CAT score in the lowest 50% at baseline and who personally suffered a reduction in their CAT score over the MCID, or who died within six months. A predictive model for this outcome was derived (Table 131), using similar methodology to that used in the NIVO score. The 'poor outcome' tool has face validity, and importantly included the patient completed measures of the NEADL and HADS (depression) which have been found to be predictive of quality of life and mortality in other COPD cohorts.^(275, 529, 530) Both the HADS and NEADL are simple scores for a patient to complete and print outs could easily be given to patients during their recovery prior to discharge; there is already a strong argument for the assessing both of these scores to aide optimising treatment, outside of their role in the novel poor outcome tool. One of the more novel indices in the poor outcome tool is diaphragm height measurement, acting as a surrogate marker for the severity of hyperinflation; with increasing hyperinflation resulting in more flattened diaphragms, worsening breathlessness, reduced exercise tolerance and more discomfort. Although the diaphragm height does require some additional calculation on the part of the clinician, in practice this is relatively easy with digital radiology systems.

Table 131. The 'poor outcome' tool.

Variable	Weighting assigned
Long term oxygen therapy	1
Left ventricular systolic dysfunction	1
Diaphragm height $\leq 2.3\text{cm}$	1
Confusion pre ventilation	1
Haemoglobin $\leq 14\text{g/dL}$	1
Baseline HADS Depression ≥ 8	1
Baseline NEADL ≤ 30	1
Total Score	/ 7

The predictive tool was well calibrated and provided excellent discriminatory ability with a ROC curve of 0.809. Of course, as this was derived in the NIVO population a good ROC curve would be expected, and external geographic and temporal validation would need to be undertaken prior to the use of this tool in clinical practice. Nonetheless, using the derived tool in the NIVO population, there appeared to be a clinically useful cut point with a score of three or more ($n=110/239$); equating to an 51.8% chance of experiencing poor outcome compared to a score of 0-2 ($n=129/239$) which was associated with a 7.8% chance of poor outcome. It may be that this tool could be helpful in terms of expediting earlier referrals to specialist services such as palliative care, occupational therapy, physiotherapy and psychological support services, as well as highlighting patients to primary and integrated care teams to ensure appropriate ongoing follow up.

10.8 Longitudinal study strengths

Data collection was robust with a huge amount of longitudinal quality of life data being prospectively collected monthly. Nearly 10,000 questionnaires were completed across the study with a median follow up time of 359 days. Whilst missing data rates are substantial, around 23% each month, patients still completed a median of 8 months' worth of questionnaires. As far as we are aware, this is the largest study examining

quality of life outcomes in this population that has been undertaken and has produced clinically meaningful results. The mode of administration of QoL questionnaires undertaken in NIVO was predominantly with interviewers either face-to-face or on the telephone. As described by Guyatt et al, these two methods in particular likely helped maximise our response rate and reduce individual missing items within each questionnaire.⁽³⁸³⁾ Similarly to the validation study, substantial geographical spread in the patients helps increase the generalisability of the results.

Findings were broadly in agreement with the, admittedly limited, previous research undertaken in this population of patients, increasing confidence in our results. The frequency of follow up in NIVO was substantially higher than in DECAF derivation (baseline, then at 3, 6 and 12 months) or CAOS (baseline and 6 months) and will have helped increase the accuracy of QoL findings and reduced both recall bias and reconceptualization by patients. This will have been particularly important in mean change, time to recovery and time spent equal to or better than baseline with NIVO being able to identify month-to-month changes. Indices identified as independently predictive of poor outcome were in keeping with those previous described following exacerbations of COPD (albeit not in the ventilated cohorts) and a simple predictive tool was created with strong predictive ability and potential clinically useful risk levels.

10.9 Longitudinal study weaknesses

Missing data is inevitable in a large observational study and, in the present study, monthly QoL scores were missing in around 23% per month (Appendix B, section 14.2); the calculation of mean change helps to compensate for this. Additionally, the NIVO study was powered for prediction of inpatient mortality, and not for the prediction or measurement of post-discharge quality of life. One consideration which must be taken into account is that the missing data potentially represents times in which patients' quality of life had dropped and when they may not have wanted to, or felt able to, respond to questions about their COPD; resulting in a more positive summation of quality of life data in the study than occurred in reality.

Along a similar theme, the longitudinal study demographics represented a proportion of patients with potentially less severe disease than the validation cohort and excluded patients who were not able to give consent. This is a common problem in research that was discussed in validation study summary and highlighted by the Cochrane consortium.⁽³¹⁷⁾ The result may be that those at highest likelihood of poor outcome were not included in the first place; findings may have been different if they were. Despite this, the longitudinal population does still reflect a population with substantial respiratory impairment and comorbidity; 47% were unable to get out of their house unassisted and a number of other descriptors such as BMI and lung function were similar to those not participating. The largest individual group excluded were likely to have been those with dementia, learning difficulties or prolonged delirium.

Study participation may have had a direct, though unquantifiable, effect on the results. Patients' responses and QoL may have been changed by virtue of the fact they were included in the study and were having monthly follow up with the hospital respiratory team. Of course, this could have had either positive (e.g., *'I'm getting really close follow up from an expert, which I find comforting'*), or negative (e.g., *'I hate having to discuss my symptoms every month'*) effects. Anecdotally, a number of patients commented that they found the monthly follow up reassuring and felt happier due to this, which may have contributed to the findings in improving anxiety over follow up in certain cohorts.

The use of the COPD assessment test (CAT) to assess quality of life makes the NIVO study more challenging to directly compare to the DECAF derivation cohort, which used the St Georges Respiratory Questionnaire (SGRQ) to define poor outcome.⁽³⁷⁶⁾ The reason for the use of the CAT score was that in the design of the study, a patient focus group had lent favour to CAT over the more difficult to complete SGRQ. We additionally did not capture whether patients had interventions such as cognitive behavioural therapy and/or pulmonary rehabilitation either prior to admission or in the longitudinal follow up period. These interventions could have an effect on any of the longitudinal scores (including baseline) and therefore may have influenced outcomes. The NIVO longitudinal study was principally a quantitative piece of work. Undertaking qualitative research methods, such as employing the use of semi-structured interviews with patients, may have facilitated a more in depth assessment of the effect of their disease and brought to light a number of common themes around their lived experience. Whilst

this would have been undoubtedly fascinating, it was not our principal aim. Undertaking qualitative research in this population would be potentially challenging to complete but is worthy of future study.

Whilst not strictly a weakness, the poor outcome prediction model has simply been derived in the NIVO cohort and would require external validation prior to any clinical use.

11 Future research questions from this work

The NIVO study has flagged a number of potential further questions which could potentially be addressed in future research.

From the validation study:

- Does the NIVO score maintain its predictive ability in other populations such as non-UK or non-Caucasian groups?
- Does the NIVO score have utility in other diseases causing respiratory failure, such as obesity hypoventilation syndrome, asthma with fixed airflow obstruction, or COVID-19?
- An implementation study in which NIVO was used to guide clinical care in some centres compared to centres where it was not used.
 - Within this, do patients find objective information provided by NIVO helpful when communicated with them, and if such information has effects on their experience of healthcare? (For example, increasing their confidence in treatment, increasing or decreasing anxiety). Similarly, whether healthcare teams find the tool helpful to aid decision making and have confidence in it.
- Is there an optimal weaning time from NIV?
- Correlation with external databases with cause(s) of emergency department attendance, readmission to hospital, and cause of death (as documented on death certificates); such as those held by NHS digital and the Office of National Statistics.

From the clinical diagnosis cohort group:

- A more detailed study of this patient group aiming to establish why mortality is equivalent to patients with confirmed COPD, even though baseline prognostic variables more favourable in the clinical diagnosis group.
- Given the prevalence of such patients within the NIVO cohort, can we establish a way to better identify such patients and confirm a COPD diagnosis, prior to a presentation with respiratory failure?
- Can [peri-exacerbation] inpatient spirometry confidently diagnose non-reversible airways disease in a trial specifically designed to look at this?

- Validating the NIVO score in this cohort of patients in an appropriately powered study.

From the longitudinal study:

- What happens to patients over a longer period of time, for example, 5 years?
- External validation of the poor outcome clinical score.
- An implementation study of the poor outcome score, perhaps examining its utility in facilitating referral to specialist services.
- Qualitative analysis of quality of life, establishing themes emerging from post-acute NIV treatment

12 Final conclusions

Exacerbations of COPD complicated by acute respiratory failure are common.

Unfortunately, there remains inadequate treatment within the UK with inequitable delivery of NIV around the country. Additionally, quality of life outcomes following ventilation for ECOPD have been understudied. Prognostic pessimism remains a problem in patients with COPD, on both individual and institutional levels. There are no prognostic tools in routine use that have been designed in this population and predict outcomes for ECOPD requiring NIV.

This study has successfully validated a simple prognostic score for patients with ECOPD requiring assisted ventilation and in a large population of patients reflective of those seen in real life practice. NIVO score validation has been performed to gold standards: in line with TRIPOD guidance, with temporal and geographic variation and transparent methodology. In addition, there have been a number of other important findings:

- Demonstrated that 4 out of 5 patients survive to discharge and 65% of these patients survive beyond one year.
- Description of late failure and relapse in a UK population, with substantially more favourable outcomes to that described in the only previous research.
- Exploration of outcomes in groups including those with long term oxygen, home ventilation and eosinopenia.
- Characterisation of a significant minority of patients who present de novo with respiratory failure and are treated as COPD. Identification of failings in their formal diagnosis and follow up were also noted.
- The significant burden of readmission, re-exacerbation and mortality over the year following discharge, plus their effects on quality of life.
- Reconfirmed that, on the whole, patients are pleased to have been ventilated, would accept it again if required and are happy with their quality of life.
- Examination of quality of life outcomes and demonstration of stability of quality of life measures over the year following discharge.
- Identification of both patients with, and the predictors of, poor outcome in the population surviving to discharge.

13 Abstracts, presentations, prizes and publications from this work

A number of abstracts and presentations have been accepted or undertaken as part of this body of work. All abstracts below are in relation to the validation or longitudinal study. An additional five abstracts have been presented from the NIVO derivation study at the British thoracic society winter meetings 2017 and 2018 on which I am a co-author, but these are not included here. Presenters names are underlined.

13.1 2018

European Respiratory Society international congress

1. The NIVO study: attitudes to ventilation following acute NIV.

N Lane, T Hartley, V Ferguson, J Steer, S Bourke

Poster presentation

- Awarded an ERS young scientist award for this abstract

13.2 2019

European Respiratory Society international congress

1. Escalation decisions in ECOPD patients receiving acute NIV.

N Lane, T Hartley, J Steer et al

Oral presentation

2. Acute NIV in presumed ECOPD without previous spirometry.

N Lane, T Hartley, J Steer et al

Poster discussion

3. Cardiovascular disease in patients requiring NIV for ECOPD.

N Lane, T Hartley, J Steer et al

Poster presentation

- Awarded a British Lung Foundation travel award for this abstract

British Thoracic Society winter scientific meeting

1. Predicting outcome from exacerbations of COPD requiring assisted ventilation: results from the NIV Outcome (NIVO) study.

TM Hartley, ND Lane, J Steer et al

Oral presentation

Royal College of Physicians of London and Clinical Research Network research award

In September 2019 I was awarded a registrar prize jointly by the Royal College of Physicians of London and National Institute of Health Research Clinical Research Network (CRN). This was awarded for my involvement in and contribution to CRN portfolio studies, of which NIVO was the primary study.

13.3 2020

American Thoracic Society international congress (virtual)

1. The NIVO Score: Admission and 90-day mortality following acute NIV for exacerbations of COPD.

ND Lane, TM Hartley, J Steer et al

Poster Discussion

Cancellation of the physical conference due to COVID-19 pandemic

The Worcester college sleep and ventilation meeting, Oxford University

1. Objective risk stratification to inform ventilation decisions [results from the NIVO study].

ND Lane

Invited speaker but cancellation of the conference due to COVID-19 pandemic.

(Rearranged for 2022)

European respiratory society international congress (virtual)

1. The Non-Invasive Ventilation Outcomes (NIVO) score in presumed COPD exacerbation without prior spirometry.

ND Lane, TM Hartley, J Steer et al

Cancellation of the physical conference due to COVID-19 pandemic

British Thoracic Society winter scientific meeting

1. Predicting poor outcome at six months following exacerbations of COPD requiring assisted ventilation.

Oral presentation

ND Lane, TM Hartley, J Steer et al

2. Late failure and relapse in patients receiving non-invasive ventilation for exacerbations of COPD: A UK prospective study.

Oral presentation

ND Lane, TM Hartley, J Steer et al

Royal College of Physicians of London, Turner Warwick lecture series

1. Predicting outcome in exacerbations of COPD requiring assisted ventilation.

ND Lane

Northern Turner Warwick Lecturer 2020.

13.4 2021

The European Respiratory Journal

1. The NIV Outcomes (NIVO) Score: prediction of in-hospital mortality in exacerbations of COPD requiring assisted ventilation.

T Hartley, ND Lane, J Steer et al

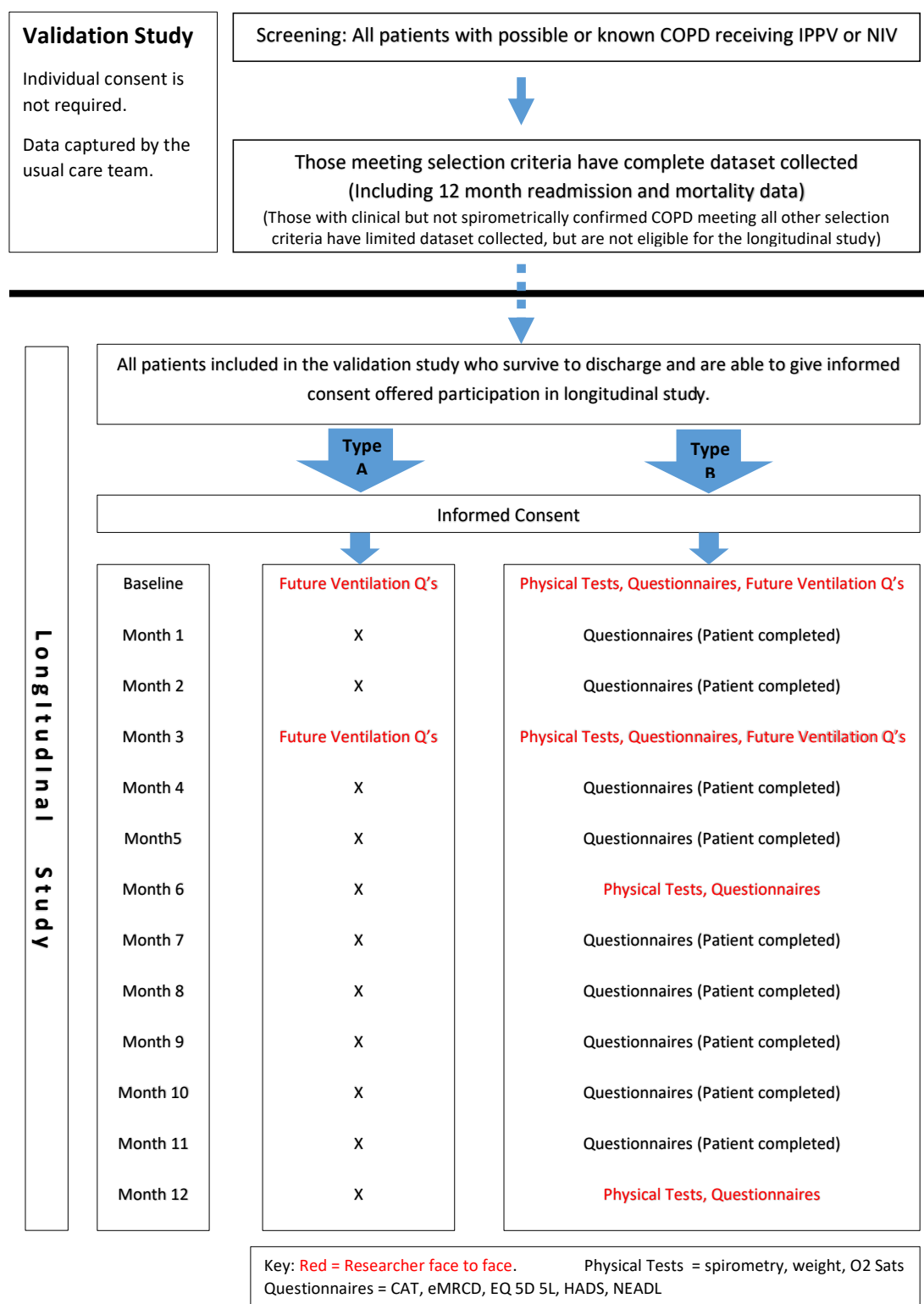
Manuscript in press.

14 Appendices

14.1 Appendix A: Study flow diagram

NIV OUTCOMES STUDY, Participant Schedule by Site Overview.

V1.0 10/5/16



14.2 Appendix B: Missing data and EM imputation results

Table 132. Details of missing data and EM imputed values

Variable	% missing	Original dataset			Complete dataset*		
		Mean	SE Mean	SD	Mean	SE Mean	SD
GCS at ventilation	2.6%	13.81	0.092	2.469	13.82	0.090	2.442
Eosinophils at ventilation	2.9%	0.119	0.009	0.238	0.12191	0.008812	0.238583
FEV1	3.4%	0.843	0.014	0.359	0.8427	0.01304	0.35304
FEV1 % predicted	4.2%	37.2	0.581	15.4	37.2	0.557	15.093
FVC	4.9%	1.96	0.027	0.705	1.96	0.02546	0.68938
BMI	4.2%	25.5	0.304	8.042	25.5	0.294	7.96
Diaphragm Height	1.8%	2.40	0.039	1.033	2.40	0.038	1.03
IPAP 1hr	1.6%	18.0	0.190	5.097	18.0	0.188	5.095
EPAP 1hr	1.6%	5.01	0.050	1.344	5.02	0.050	1.342
BUR 1hr	5.3%	14.0	0.100	2.642	14.01	0.097	2.614
IPAP Max	1.4%	20.79	0.180	4.828	20.8	0.179	4.839
EPAP Max	1.2%	5.45	0.060	1.611	5.47	0.060	1.634
BUR Max	4.1%	14.28	0.103	2.719	14.3	0.100	2.699
Systolic BP 24hrs pre-ventilation	2.2%	133.4	1.286	34.329	133.3	1.263	34.203
Diastolic BP 24hrs pre-ventilation	2.2%	75.56	0.776	20.787	75.40	0.766	20.733

Variable	% missing	Original dataset			Complete dataset*		
		Mean	SE Mean	SD	Mean	SE Mean	SD
Heart rate 24hrs pre-ventilation	1.9%	110	0.799	21.436	109.87	0.790	21.381
Respiratory rate 24hrs pre-ventilation	2.2%	28.42	0.277	7.416	28.43	0.273	7.404
Temp 24hrs pre-ventilation	2.3%	36.665	0.0367	0.9809	36.664	0.0360	0.9759
Sats 24hrs pre-ventilation	2.2%	84.19	0.369	9.892	84.10	0.363	9.816
Admission pH	2.7%	7.2855	0.00366	0.09779	7.2870	0.00361	0.09764
Admission PaO2	3.1%	8.7767	0.20283	5.40447	8.7730	0.19822	5.36655
Admission PaCO2	2.6%	9.6348	0.10715	2.86306	9.3530	0.10530	2.85092
Admission BE	3.8%	4.897	0.2466	6.5486	4.986	0.2475	6.7002
Admission HCO3	4.2%	30.299	0.02526	6.6921	30.362	0.2518	6.8163
1 st acidaemia BE	1.4%	4.813	0.2446	6.5780	4.758	0.2454	6.6434
1 st acidaemia HCO3	1.5%	30.567	0.2493	6.6979	30.497	0.2483	6.7238
NIV decision BE	1.1%	4.607	0.2460	6.6224	4.541	0.2454	6.6432
NIV decision HCO3	1.5%	30.505	0.2542	6.8300	30.468	0.2522	6.8291
Admission K	5.6%	4.590	0.0237	0.6237	4.593	0.228	0.6186
Admission urea	2.9%	8.396	0.1953	5.2104	8.434	0.1943	5.2595
Admission creatinine	1.0%	87.81	1.935	52.144	87.94	1.926	52.134
Baseline creatinine	7.8%	71.0	1.119	29.087	70.63	1.064	28.811
Admission albumin	13.0%	38.04	0.204	5.146	37.93	0.188	5.083

Variable	% missing	Original dataset			Complete dataset*		
		Mean	SE Mean	SD	Mean	SE Mean	SD
Admission Bilirubin	17.9%	10.09	0.353	8.650	10.53	0.361	9.779
Admission CRP	3.7%	78.39	3.916	104.051	78.60	3.796	102.770
Admission Glucose	9.1%	8.326	0.1300	3.3537	8.264	0.1212	3.2803
Admission Eosinophils	1.8%	0.126	0.0100	0.2688	0.129	0.0099	0.2688
NIV decision Na	1.5%	136.91	0.205	5.512	136.92	0.204	5.516
NIV decision K	6.5%	4.613	0.0246	0.6437	4.615	0.0236	0.6398
NIV decision urea	3.1%	8.494	0.1996	5.3196	8.486	0.1943	5.2598
NIV decision creatinine	1.8%	87.13	1.1839	49.358	87.18	1.815	49.129
NIV decision albumin	15.0%	37.76	0.210	5.245	37.67	0.192	5.198
NIV decision Bilirubin	19.8%	9.90	0.347	8.404	10.46	0.356	9.650
NIV decision CRP	4.6%	80.22	3.941	104.204	80.52	3.801	102.909
NIV decision glucose	14.1%	8.361	0.1335	3.3511	8.180	0.1241	3.3611
NIV decision haemoglobin	1.4%	13.747	0.0791	2.1264	13.723	0.0787	2.1320
NIV decision platelets	1.5%	271.57	4.023	108.085	271.89	3.971	107.498
NIV decision haematocrit	1.6%	0.43319	0.002396	0.064346	0.43277	0.002379	0.064396
NIV decision white cell count	1.4%	13.007	0.2505	6.7356	13.060	0.2513	6.8041
Discharge Na	6.8%	138.83	0.158	3.703	138.83	0.148	3.575
Discharge K	7.5%	4.212	0.2017	0.5048	4.216	0.0201	0.4873

Variable	% missing	Original dataset			Complete dataset*		
		Mean	SE Mean	SD	Mean	SE Mean	SD
Discharge urea	8.0%	6.689	0.1561	3.6234	6.697	0.1438	3.4818
Discharge creatinine	6.8%	72.69	1.303	30.450	72.69	1.215	29.414
Discharge albumin	52.7%	34.74	0.341	5.683	35.00	0.172	4.176
Discharge bilirubin	55.8%	8.51	0.463	7.450	8.51	0.215	5.195
Discharge CRP	12.1%	25.05	1.817	41.238	25.68	1.609	38.938
Discharge glucose	63.7%	8.025	0.2288	3.3389	7.804	0.0894	2.1639
Discharge Hb	7.3%	13.044	0.0795	1.8517	13.038	0.0737	1.7835
Discharge platelets	7.2%	279.97	4.522	105.481	280.27	4.201	101.700
Discharge haematocrit	7.5%	0.41272	0.002487	.057897	0.41250	0.002303	0.055744
Discharge white cells	7.2%	9.885	0.1384	3.2290	9.892	0.1286	3.1132
Discharge eosinophils	8.2%	0.148	0.0082	0.1897	0.1482	0.00751	0.18179

*Includes original and imputed data. Only variables with >1% missing data are included. Discharge values only include patients who survived to discharge.

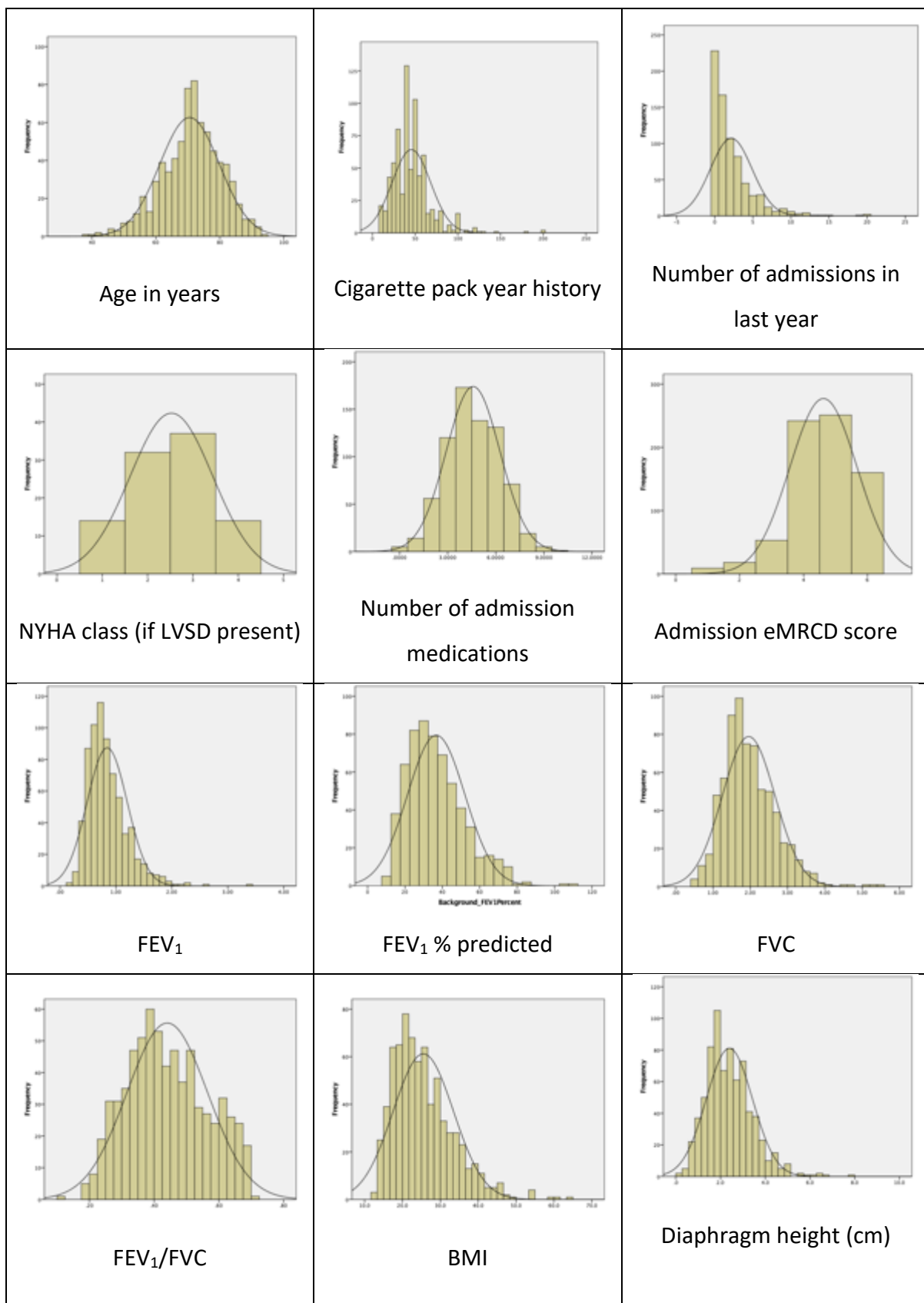
Variables with <1% missing were: Smoking status (0.5%); Date of first ever episode of NIV (0.1%); Number of episodes of NIV in the previous 12months (0.3%); Domiciliary ventilation at discharge (0.7%); Reason for NIV cessation (0.7%); Systolic BP at admission (0.3%); Diastolic BP at admission (0.3%); Admission respiratory rate (0.3%); Admission temperature (0.7%); Admission SpO₂ (0.3%); GCS at admission (0.5%); First Respiratory Acidaemia PaO₂ (0.5%); NIV decision PaO₂ (0.3%); Admission sodium (0.7%); Admission Haemoglobin (0.3%); Admission platelets (0.4%); Admission haematocrit (0.5%); Admission white cell count (0.3%).

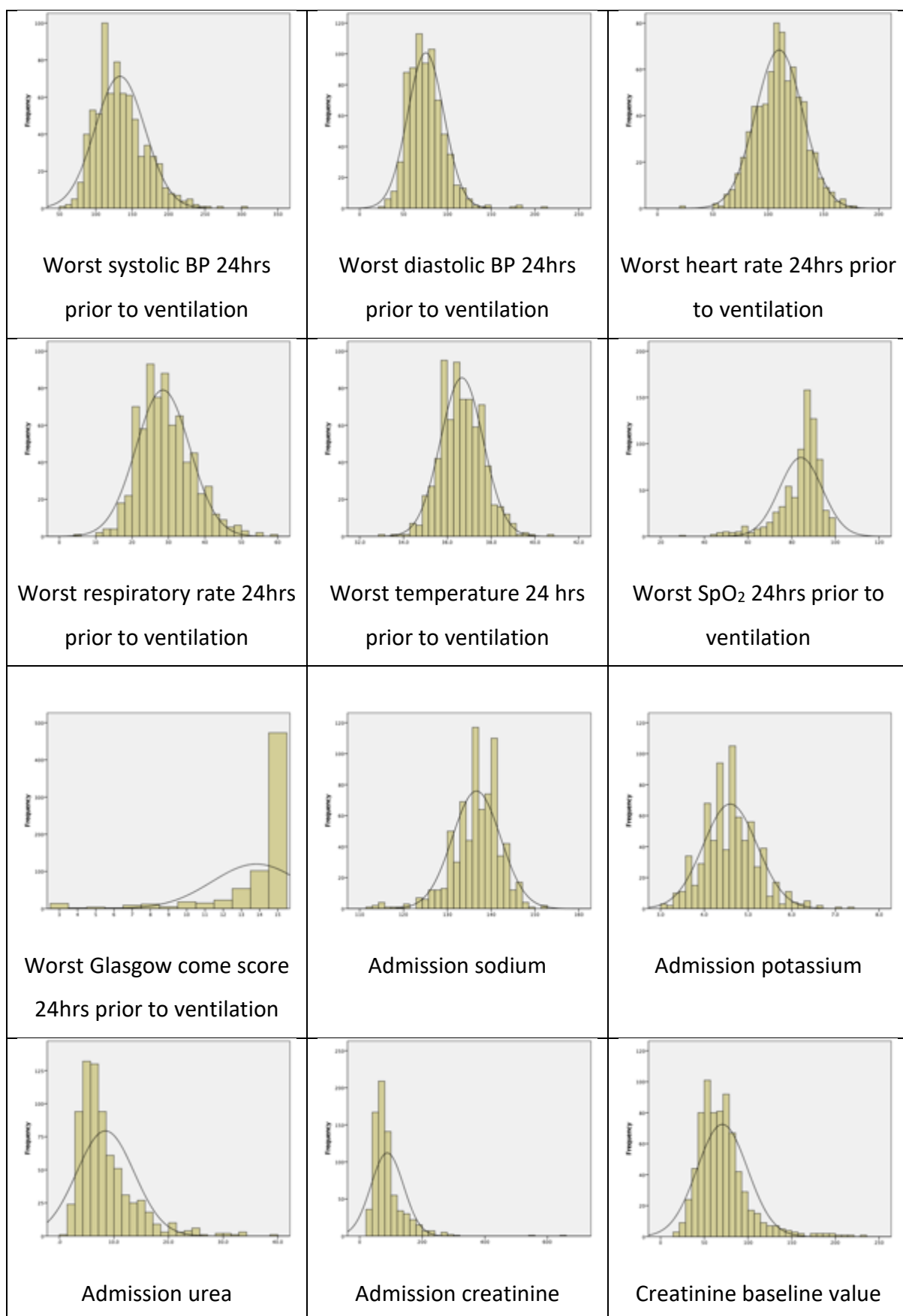
Definitions: NIV= non-invasive ventilation. SD= standard deviation; SE=standard error. Hb= Haemoglobin; CRP= C-reactive protein; K= potassium; Na= Sodium; pre-ventilation= prior to commencement of ventilation; pH= potential of hydrogen; PaO₂ = Partial pressure of oxygen; PaCO₂= partial pressure of carbon dioxide; BE= base excess; HCO₃= Bicarbonate; BMI= body mass index; FVC=Forced vital capacity; FEV₁= Forced expiratory volume in 1 second; GCS= Glasgow coma scale; IPAP= inspiratory pressure; EPAP= expiratory pressure; BUR= back up rate of ventilation; BP= blood pressure.

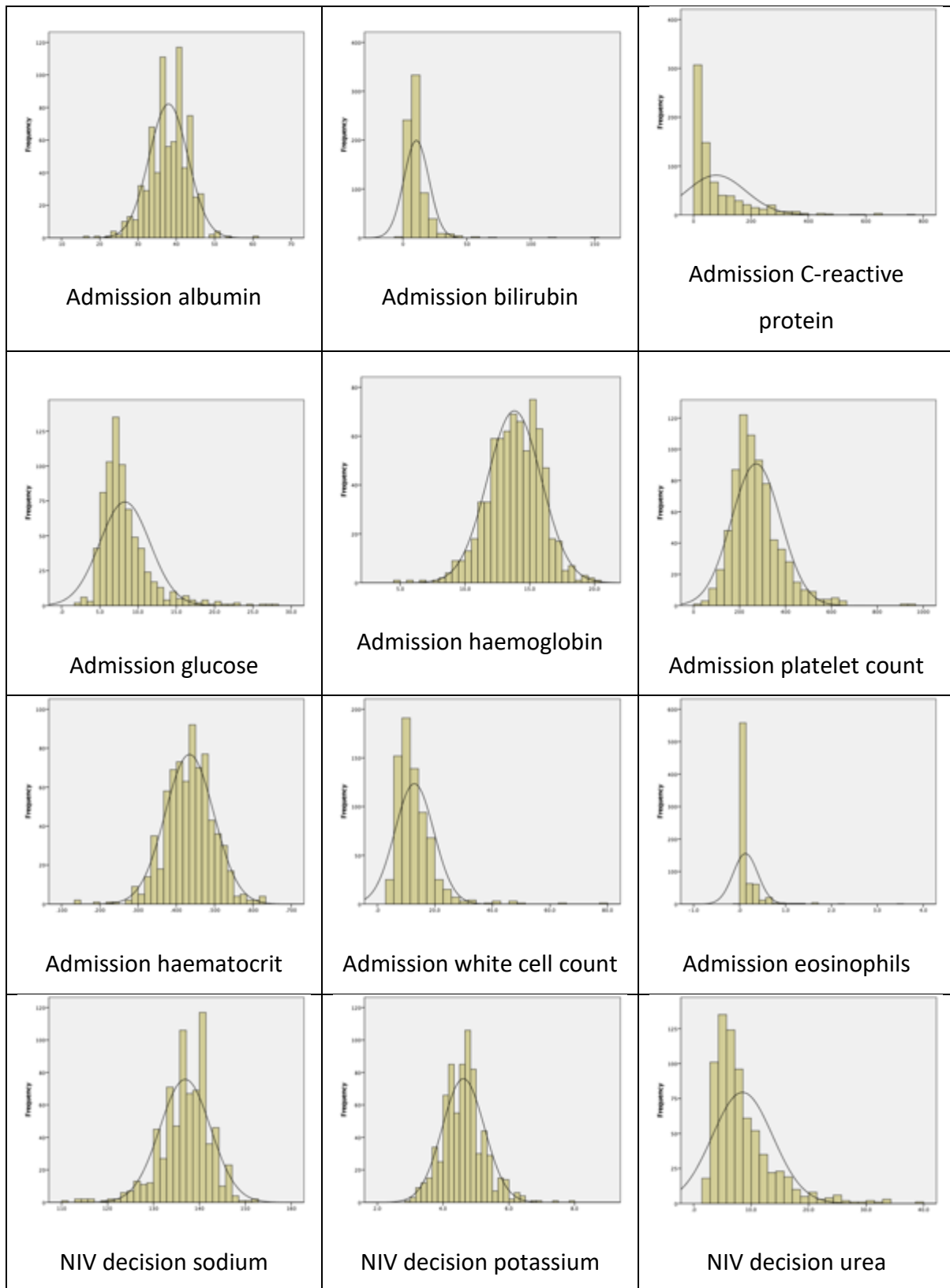
Table 133. Missing data rates for each assessment in the longitudinal study (type b sites) by month

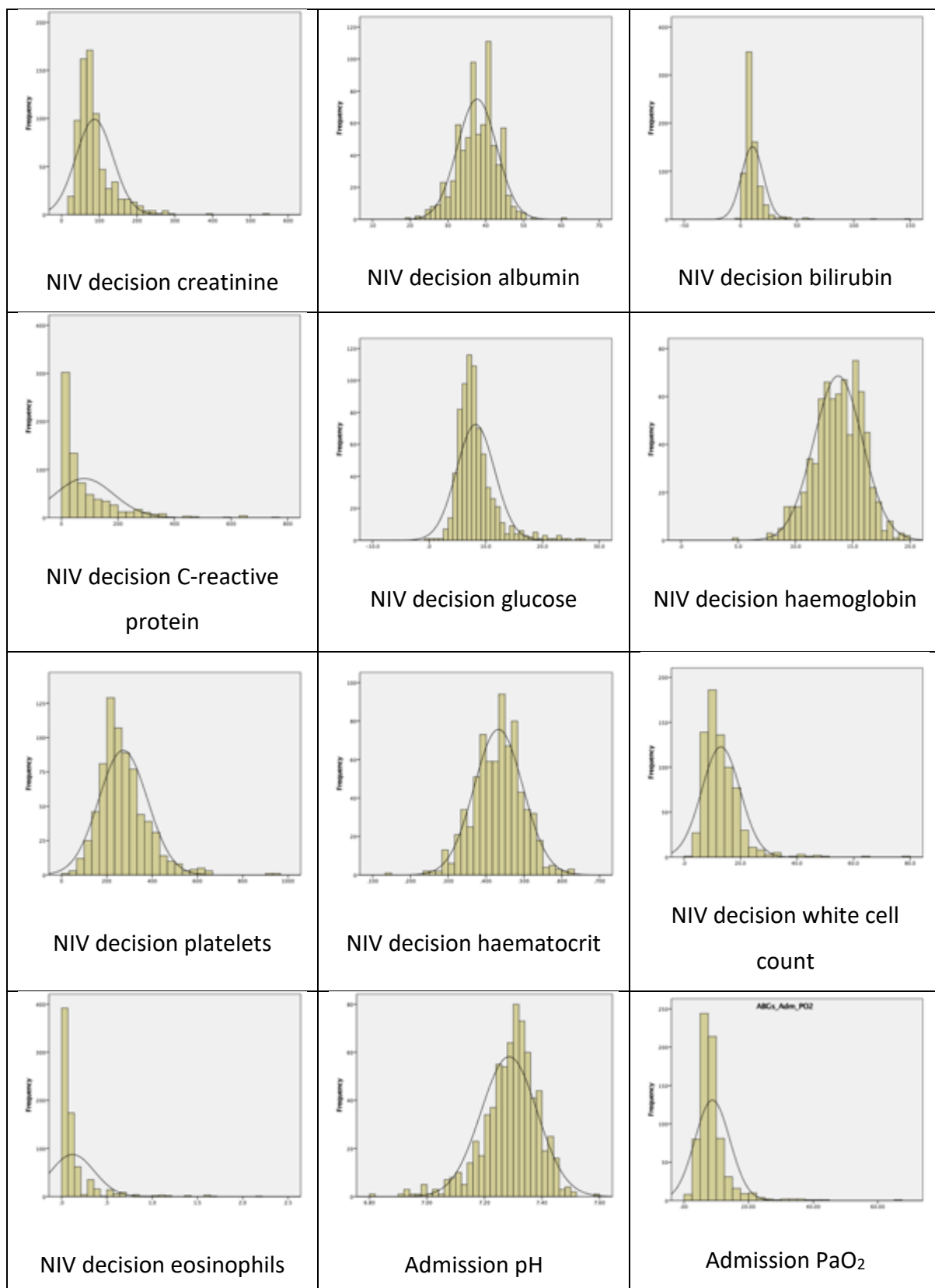
Month	Number in study	eMRCD Score	HADS	NEADL	EQ-5D-5L	CAT Score
Baseline	253	1 (0.4%)	1 (0.4%)	1 (0.4%)	1 (0.4%)	1 (0.4%)
One	233	36 (15.5%)	37 (15.9%)	37 (15.9%)	36 (15.5%)	37 (15.9%)
Two	219	51 (23.3%)	51 (23.3%)	52 (23.7%)	51 (23.3%)	51 (23.3%)
Three	207	43 (20.8%)	42 (20.3%)	41 (19.8%)	44 (21.3%)	43 (20.8%)
Four	197	44 (22.3%)	45 (22.8%)	45 (22.8%)	45 (22.8%)	44 (22.3%)
Five	191	51 (26.7%)	51 (26.7%)	51 (26.7%)	52 (27.2%)	51 (26.7%)
Six	181	41 (22.7%)	41 (22.7%)	41 (22.7%)	42 (23.2%)	42 (23.2%)
Seven	172	47 (27.3%)	48 (27.9%)	48 (27.9%)	49 (28.5%)	48 (27.9%)
Eight	170	54 (31.8%)	54 (31.8%)	54 (31.8%)	54 (31.8%)	54 (31.8%)
Nine	166	49 (29.5%)	49 (29.5%)	49 (29.5%)	49 (29.5%)	49 (29.5%)
Ten	158	47 (29.7%)	47 (29.7%)	47 (29.7%)	47 (29.7%)	48 (30.4%)
Eleven	155	53 (34.2%)	53 (34.2%)	52 (35.5%)	53 (34.2%)	53 (34.2%)
Twelve	152	26 (17.1%)	26 (17.1%)	26 (17.1%)	26 (17.1%)	26 (17.1%)
Mean missing data rate		23.2%	23.3%	23.3%	23.4%	23.3%
eMRCD= Extended medical research council dyspnoea score; HADS= Hospital anxiety and depression score; NEADL= Nottingham extended activities of daily living scale; EQ-5D-5L= EuroQoL five domain five level tool; CAT Score= COPD assessment test score.						

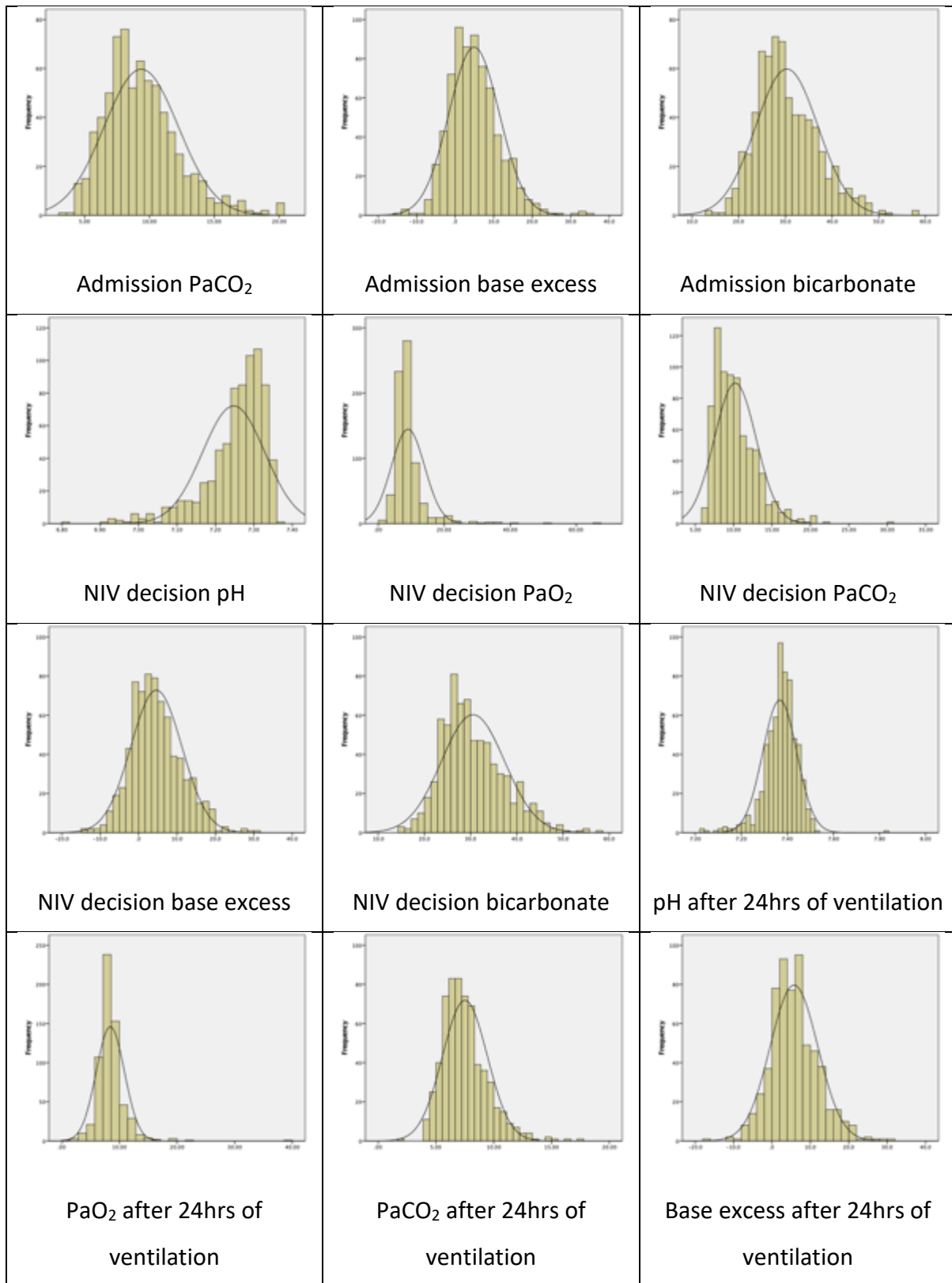
14.3 Appendix C: Histograms of population descriptors

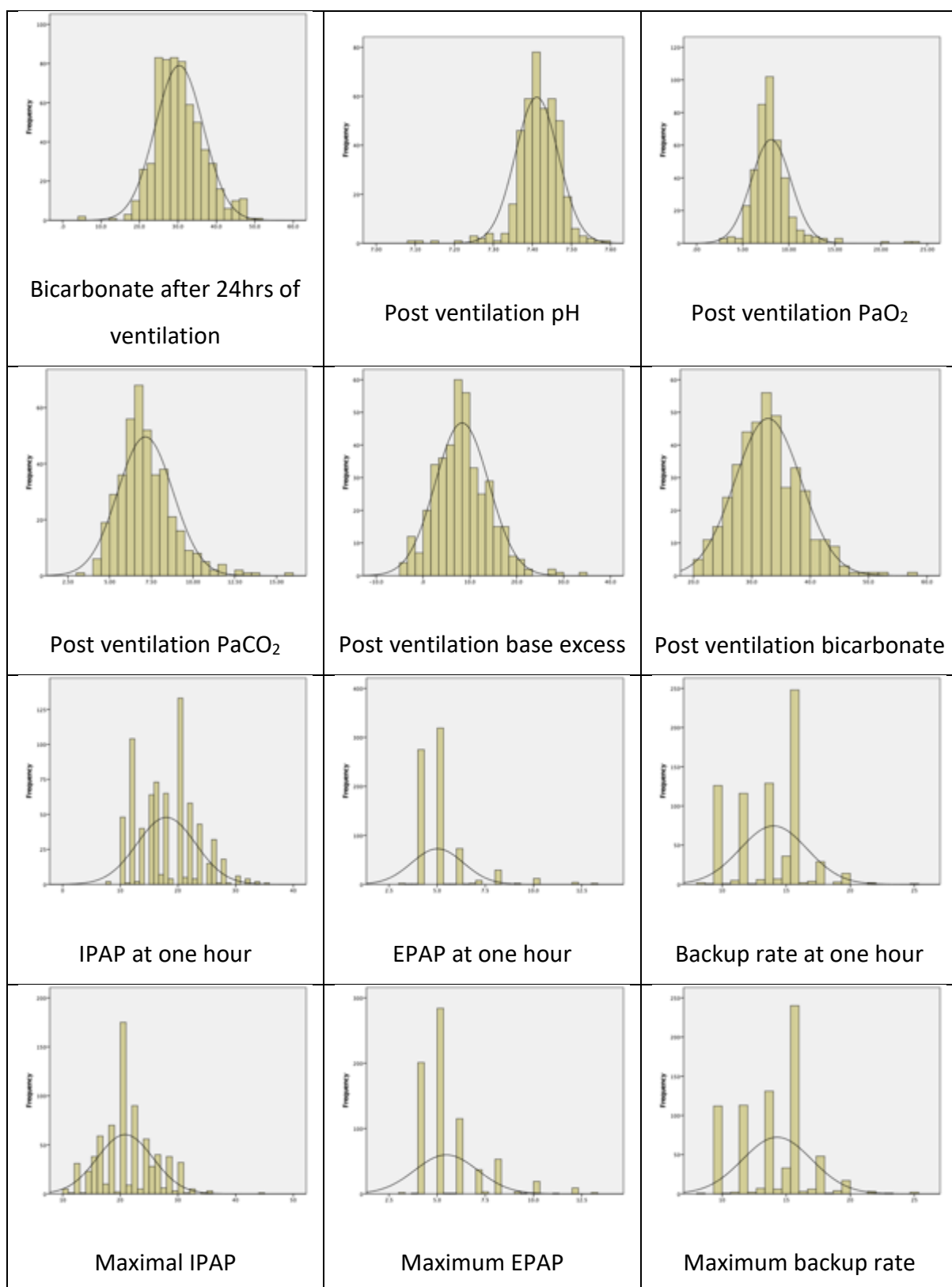


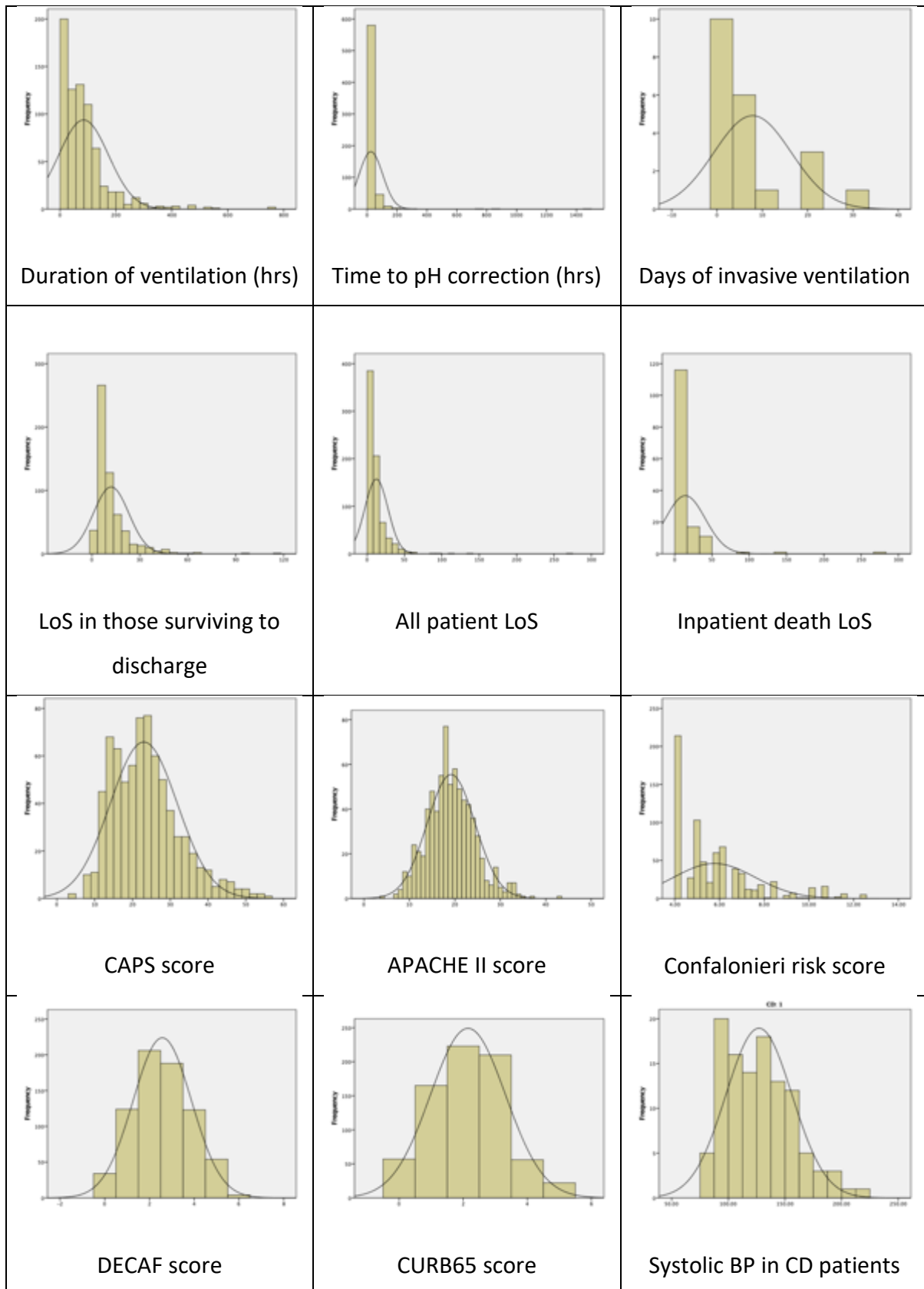


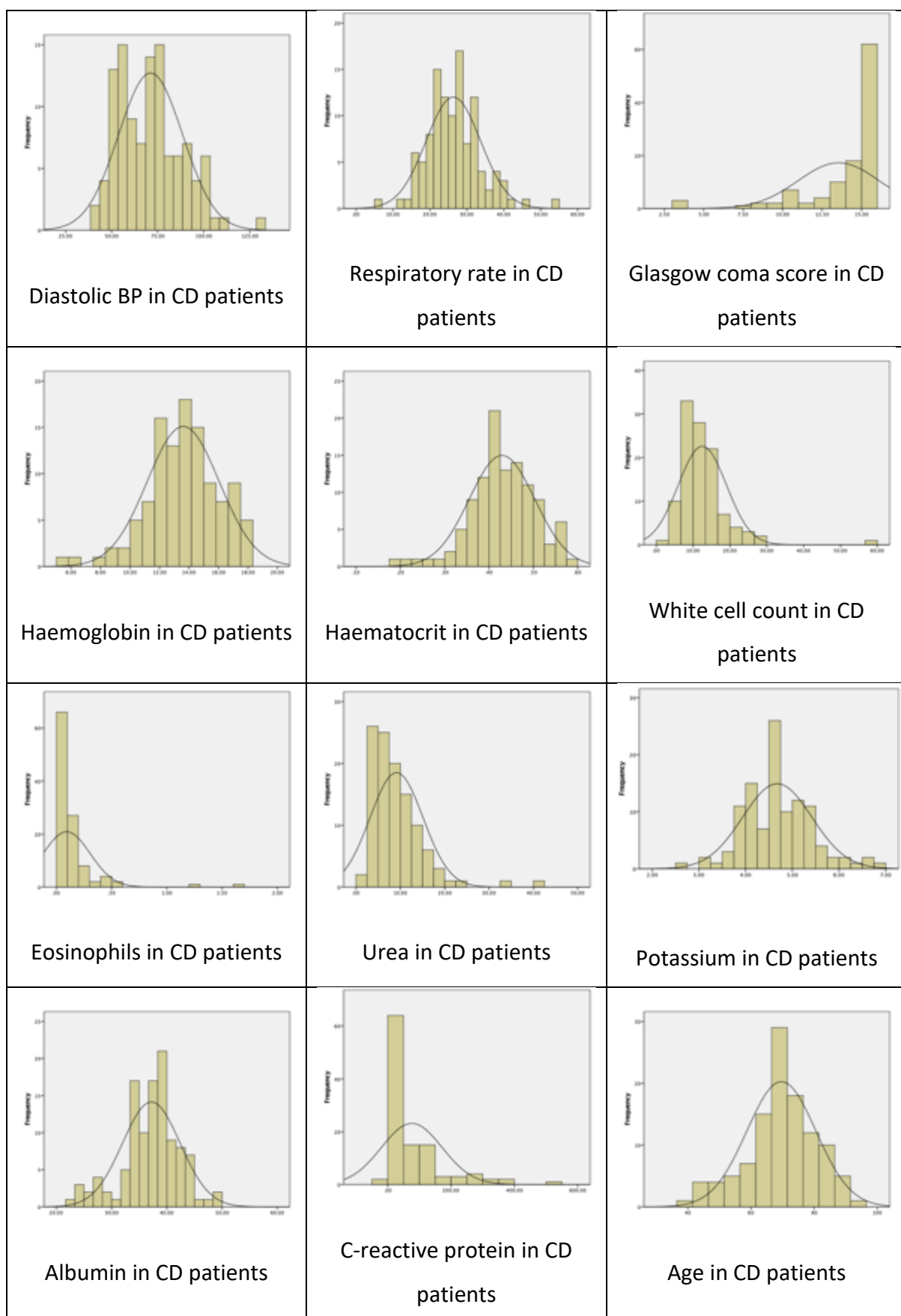


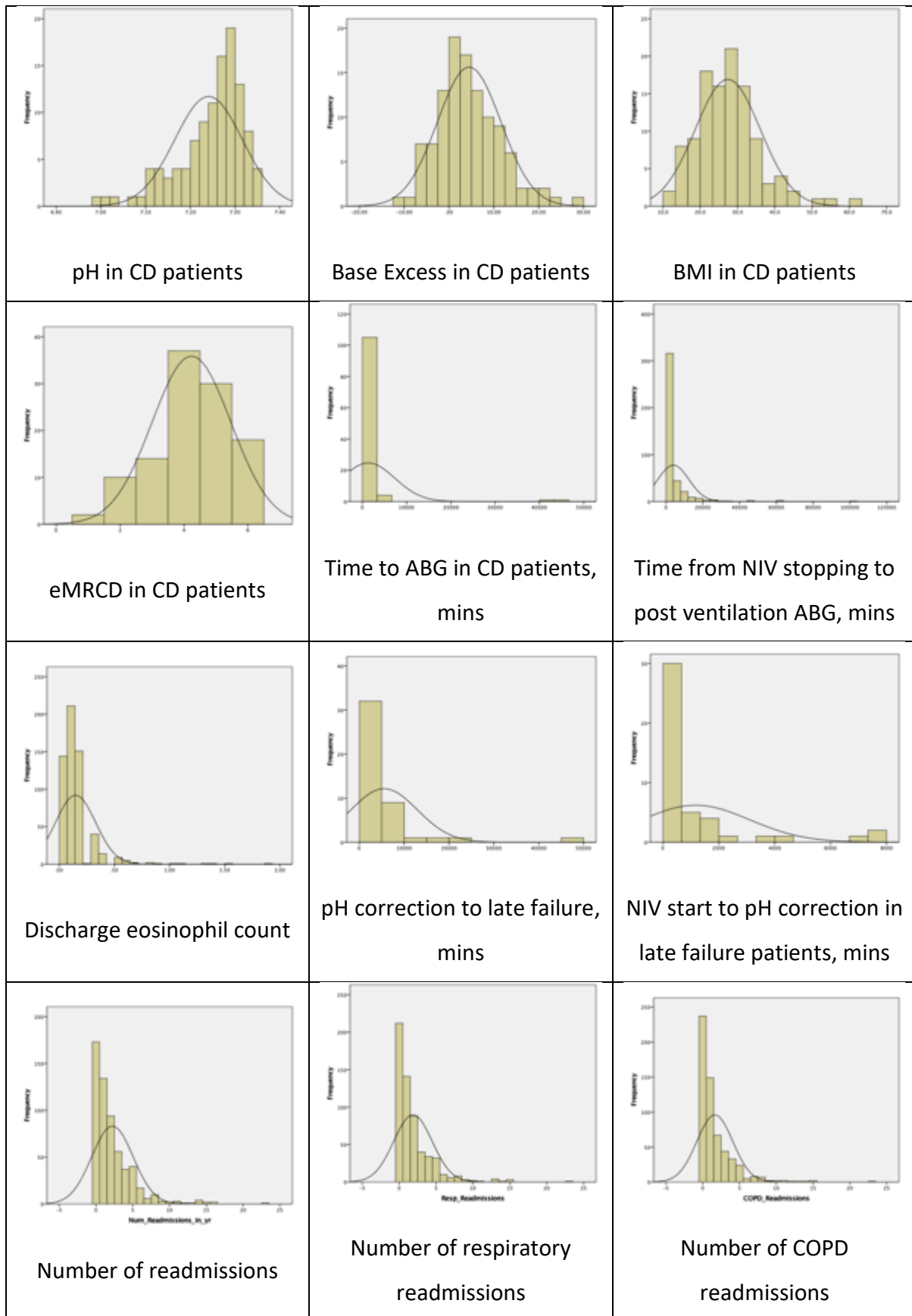


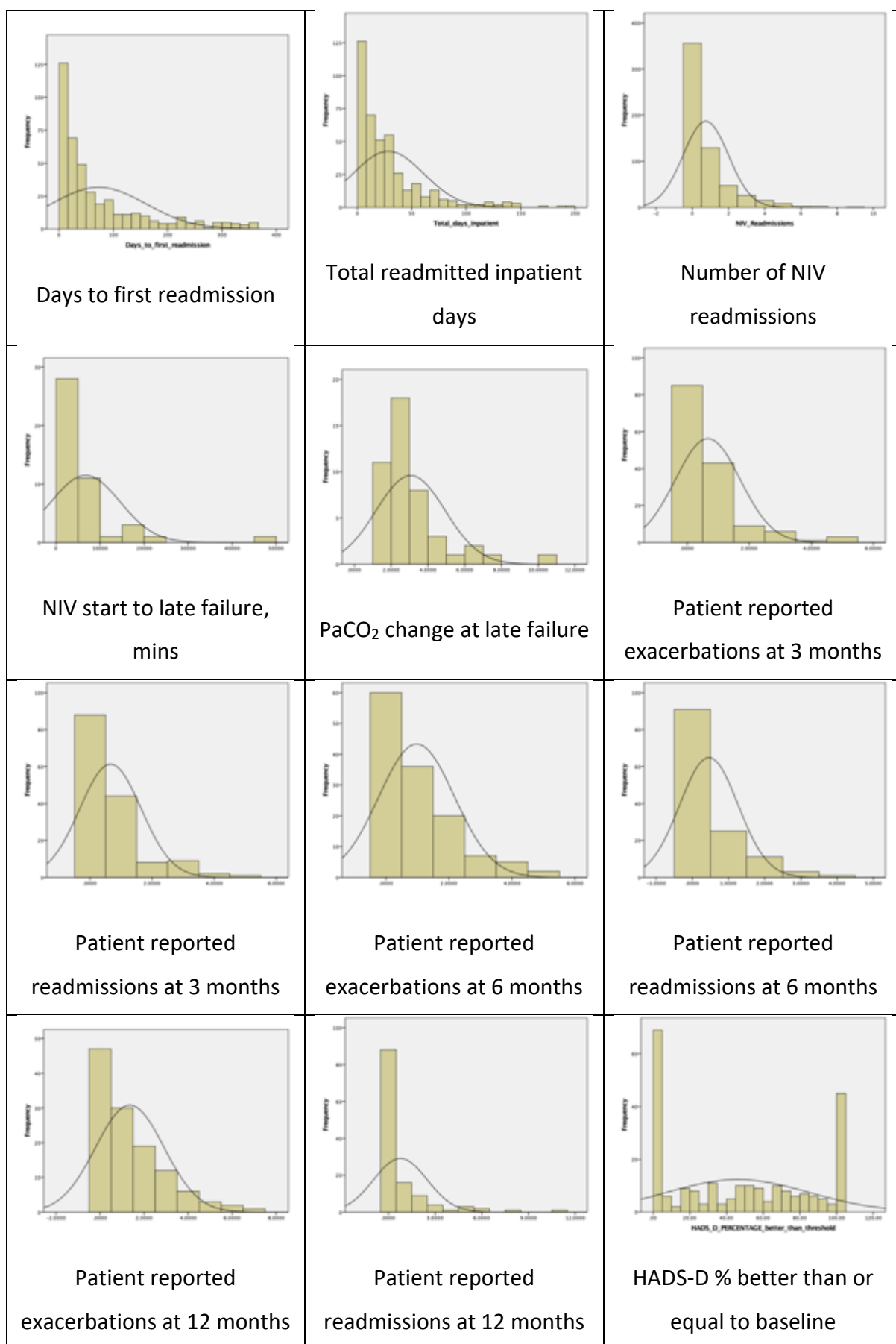


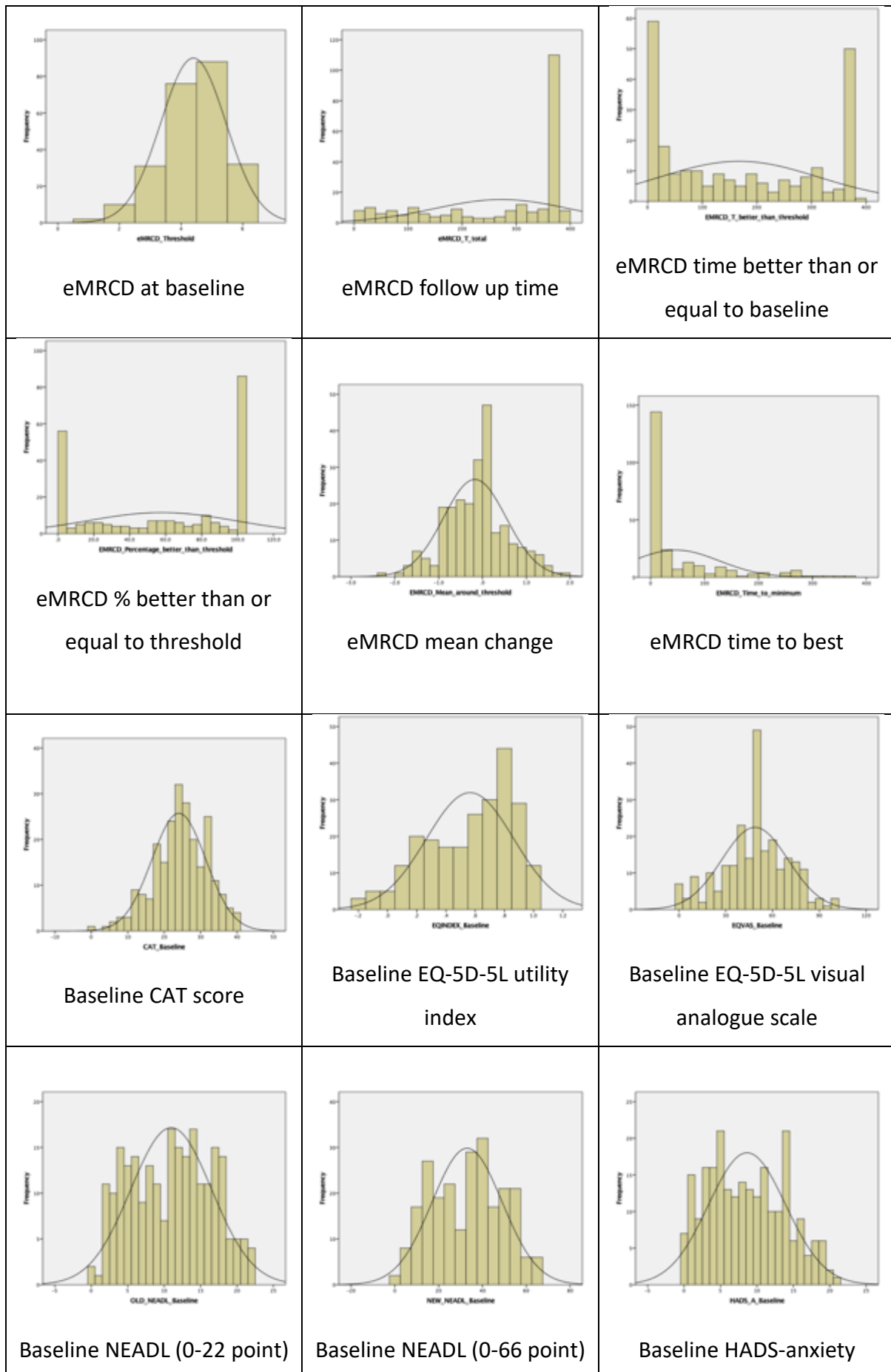


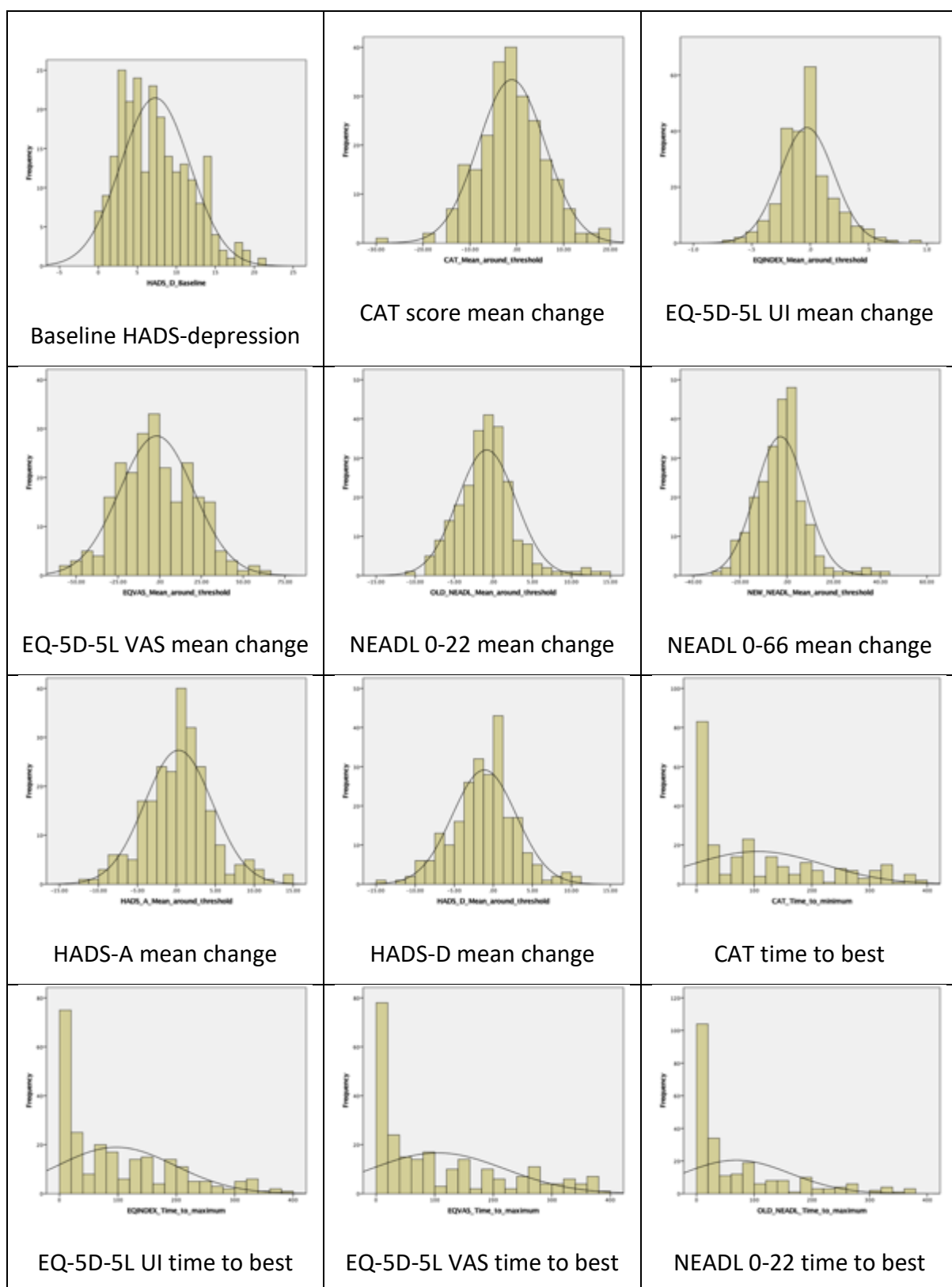


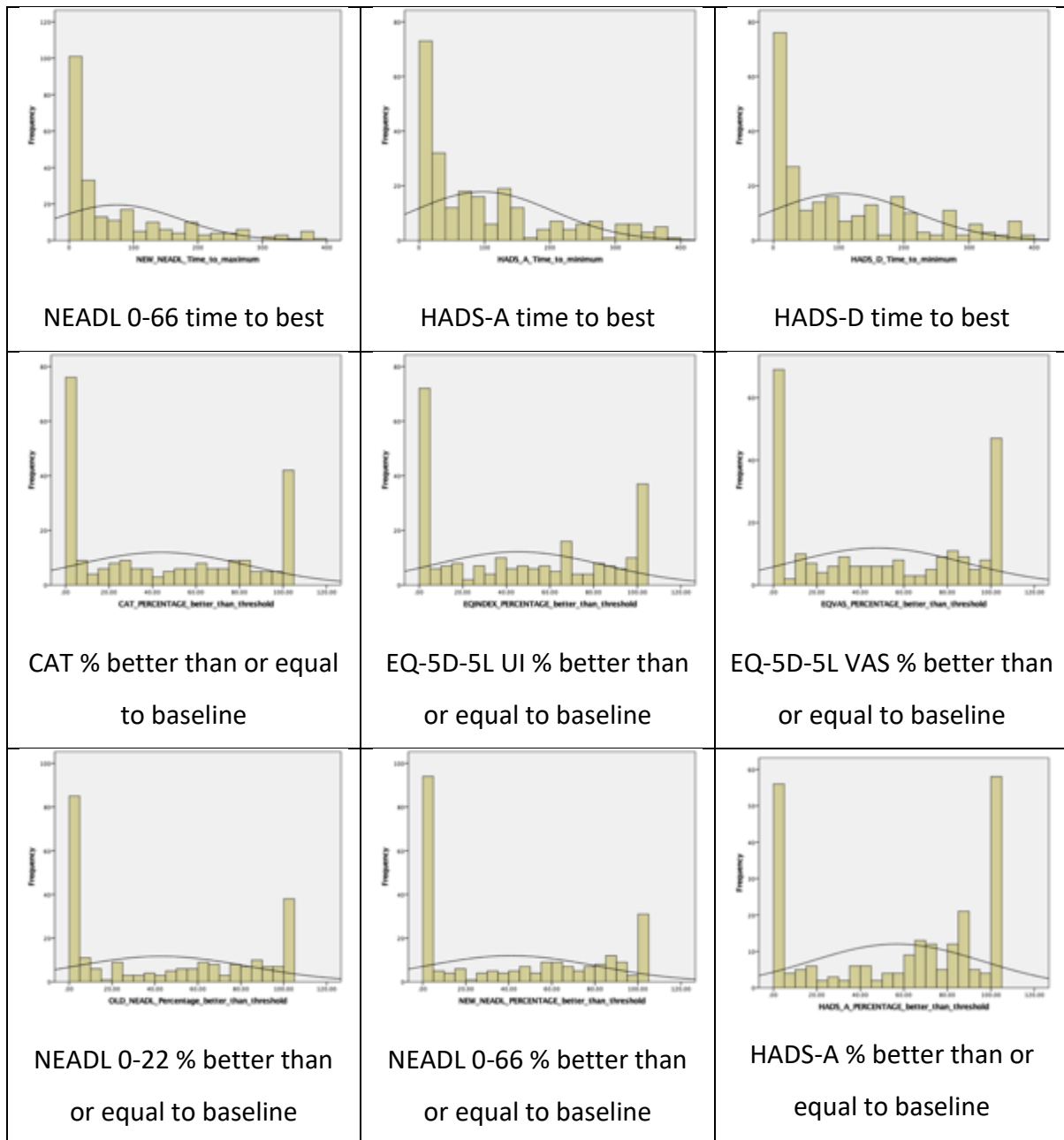












14.4 Appendix D: Correlation matrices between quality of life tools

Table 134. Correlation matrix of mean change between longitudinal quality of life tools.

Correlation of mean change	eMRCD	CAT	HADS Anxiety	HADS Depression	NEADL (0-22)	NEADL (0-66)	EQ5D5L UI	EQ5D5L VAS
eMRCD	1	.251 [†]	.149*	.207**	.223**	.236 [†]	.127*	.099
CAT		1	.543 [†]	.544 [†]	.341 [†]	.376 [†]	.508 [†]	.450 [†]
HADS Anxiety			1	.707 [†]	.374 [†]	.419 [†]	.598 [†]	.473 [†]
HADS Depression				1	.423 [†]	.463 [†]	.649 [†]	.486 [†]
NEADL (0-22)					1	.980 [†]	.423 [†]	.230 [†]
NEADL (0-66)						1	.467 [†]	.248 [†]
EQ5D5L UI							1	.458 [†]
EQ5D5L VAS								1

Pearson's correlation coefficient significance: *p<0.05; **p<0.01; [†]p<0.001. eMRCD= extended medical research council dyspnoea score. CAT score= Chronic obstructive pulmonary disease assessment tool; EQ-5D-5L= EuroQol five domain, five level score; UI = Utility index; VAS= visual analogue scale; NEADL= Nottingham extended activities of daily living score; HADS= Hospital anxiety and depression scale

Table 135. Correlation matrix of percentage of time spent equal to or better than baseline between longitudinal quality of life tools

Correlation of percentage equal to or better than baseline	eMRCD	CAT	HADS Anxiety	HADS Depression	NEADL (0-22)	NEADL (0-66)	EQ5D5L UI	EQ5D5L VAS
eMRCD	1	.240 [†]	.207 ^{**}	.183 ^{**}	.270 [†]	.268 [†]	.094	.124
CAT		1	.485 [†]	.441 [†]	.298 [†]	.356 [†]	.436 [†]	.499 [†]
HADS Anxiety			1	.541 [†]	.280 [†]	.287 [†]	.396 [†]	.496 [†]
HADS Depression				1	.292 [†]	.263 [†]	.477 [†]	.404 [†]
NEADL (0-22)					1	.893 [†]	.281 [†]	.186 ^{**}
NEADL (0-66)						1	.322 [†]	.210 ^{**}
EQ5D5L UI							1	.389 [†]
EQ5D5L VAS								1

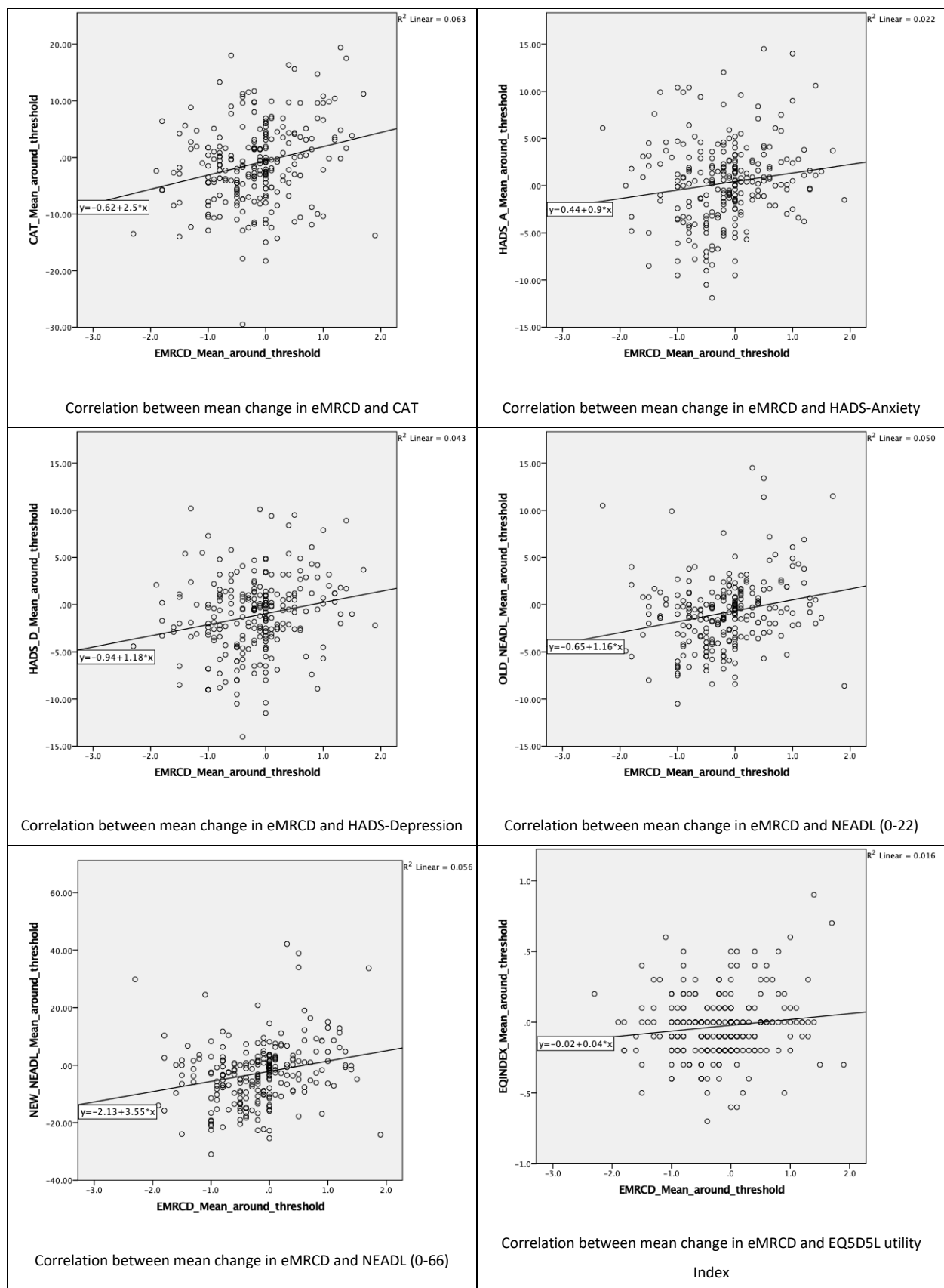
Pearson's correlation coefficient significance: *p<0.05; **p<0.01; †p<0.001. eMRCD= extended medical research council dyspnoea score. CAT score= Chronic obstructive pulmonary disease assessment tool; EQ-5D-5L= EuroQol five domain, five level score; UI = Utility index; VAS= visual analogue scale; NEADL= Nottingham extended activities of daily living score; HADS= Hospital anxiety and depression scale

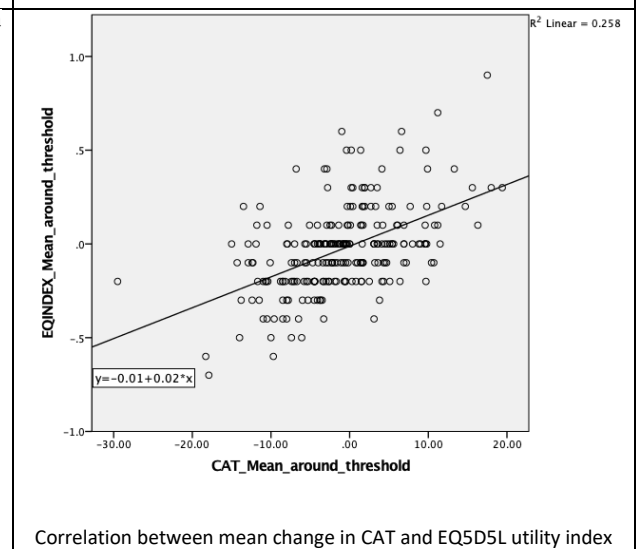
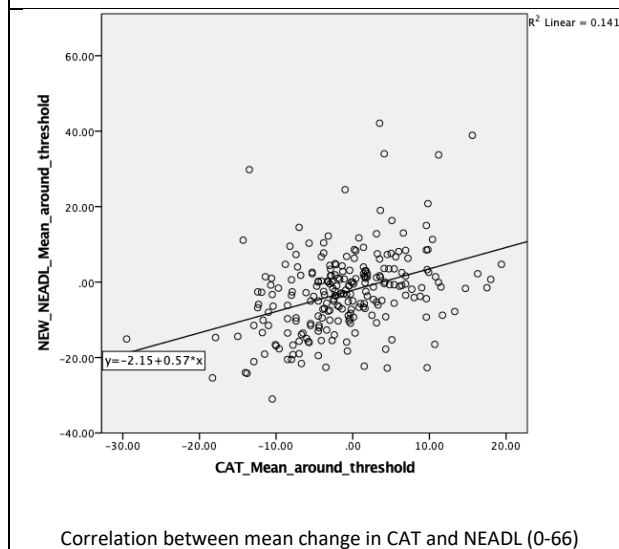
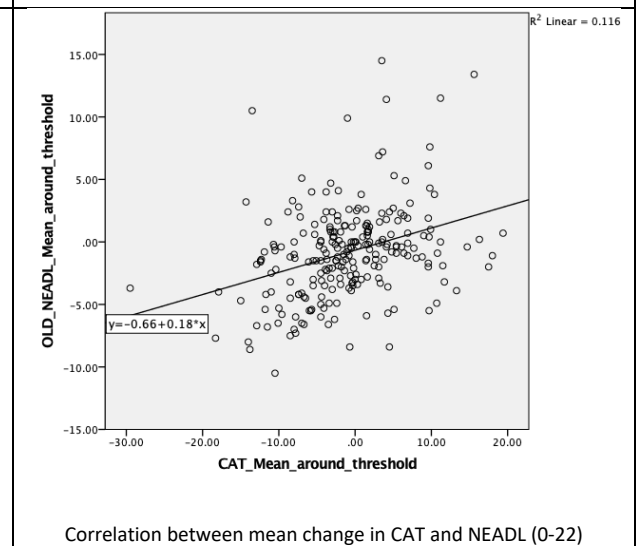
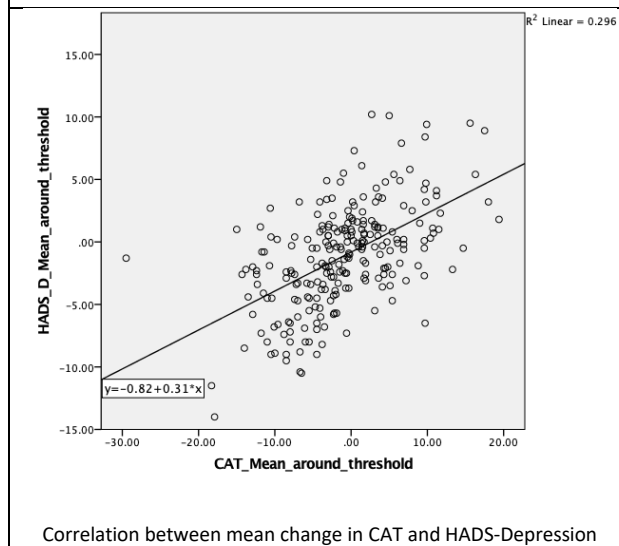
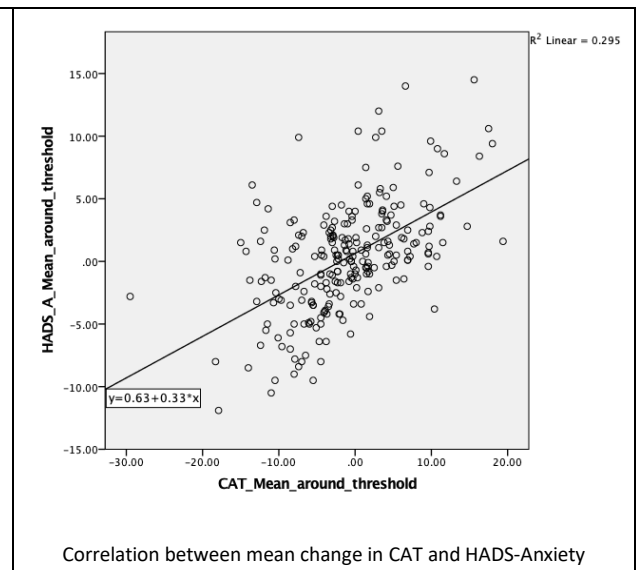
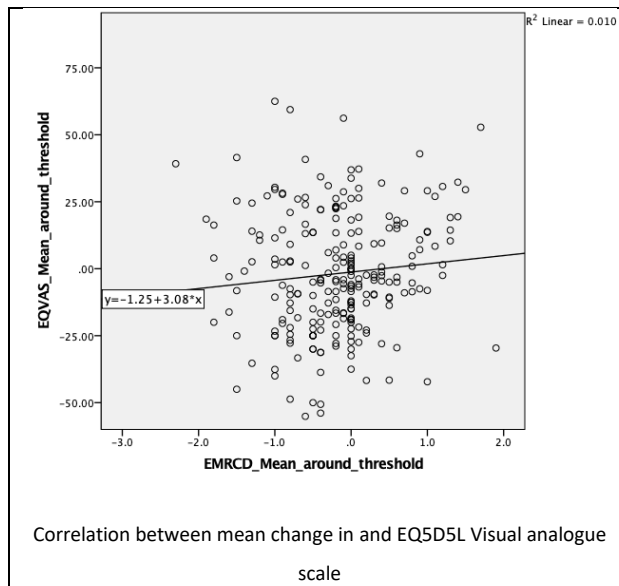
Table 136. Correlation matrix of time to best score between longitudinal quality of life tools

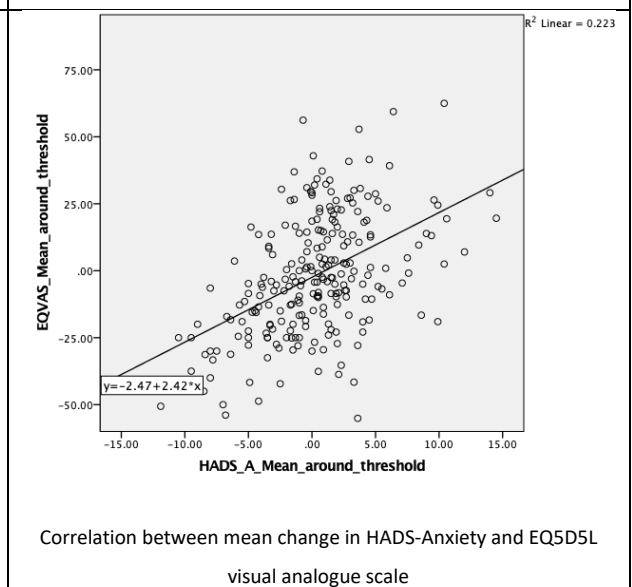
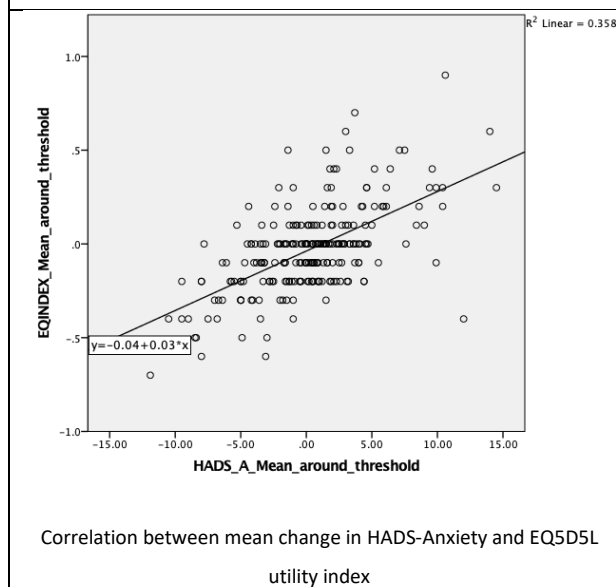
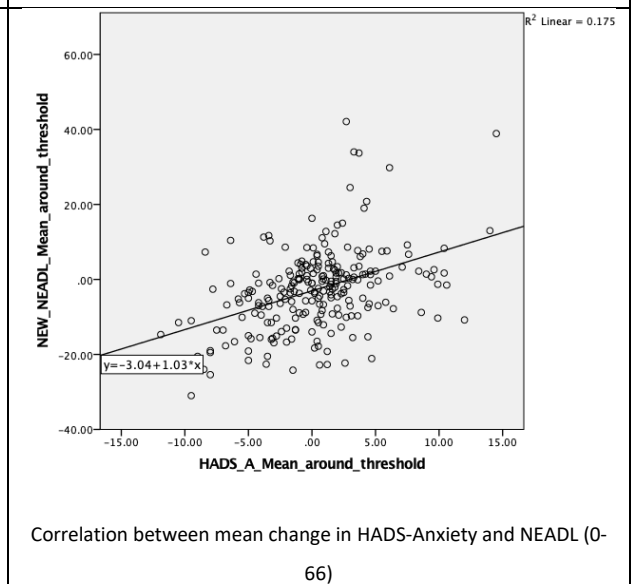
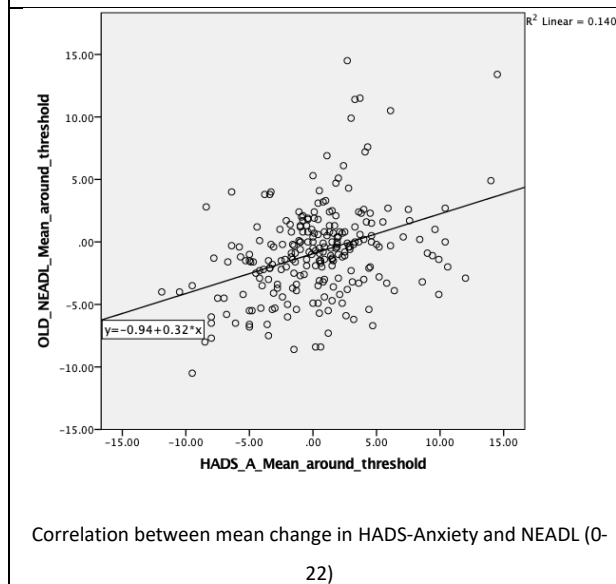
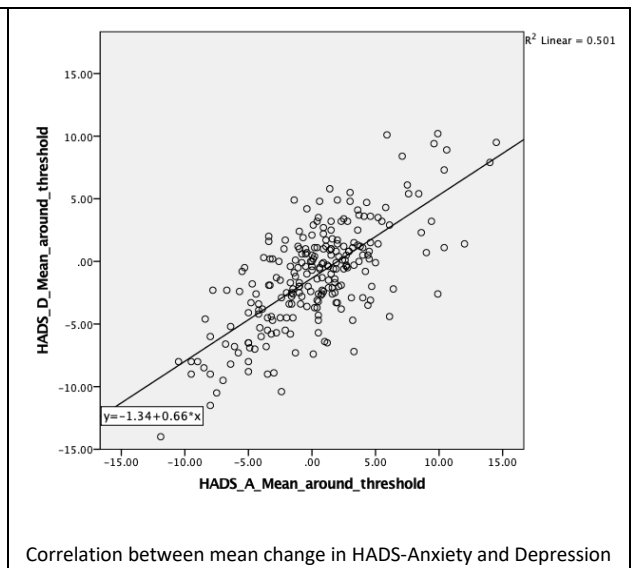
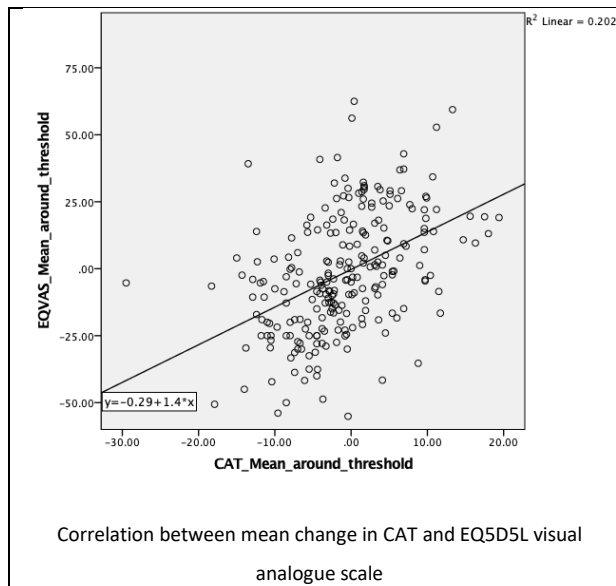
Correlation of time to best	eMRCD	CAT	HADS Anxiety	HADS Depression	NEADL (0-22)	NEADL (0-66)	EQ5D5L UI	EQ5D5L VAS
eMRCD	1	.303 [†]	.199 ^{**}	.181 ^{**}	.192 ^{**}	.165 [*]	.187 ^{**}	.230 [†]
CAT		1	.400 [†]	.349 [†]	.298 [†]	.286 [†]	.422 [†]	.348 [†]
HADS Anxiety			1	.438 [†]	.400 [†]	.517 [†]	.448 [†]	.378 [†]
HADS Depression				1	.322 [†]	.388 [†]	.479 [†]	.383 [†]
NEADL (0-22)					1	.774 [†]	.329 [†]	.331 [†]
NEADL (0-66)						1	.349 [†]	.350 [†]
EQ5D5L UI							1	.241 [†]
EQ5D5L VAS								1

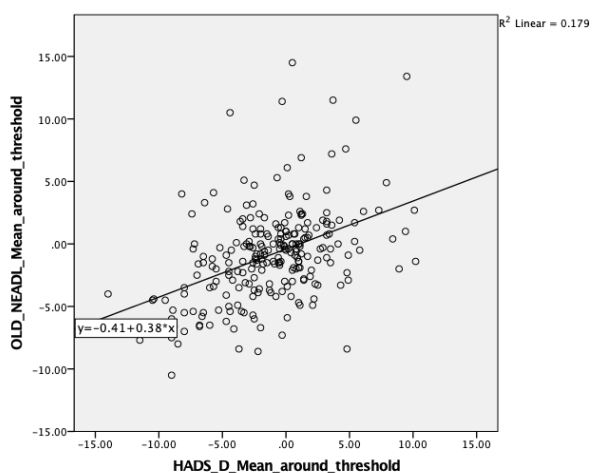
Pearson's correlation coefficient significance: *p<0.05; **p<0.01; †p<0.001. eMRCD= extended medical research council dyspnoea score. CAT score= Chronic obstructive pulmonary disease assessment tool; EQ-5D-5L= EuroQol five domain, five level score; UI = Utility index; VAS= visual analogue scale; NEADL= Nottingham extended activities of daily living score; HADS= Hospital anxiety and depression scale

14.5 Appendix E: Correlation charts of mean change in quality of life

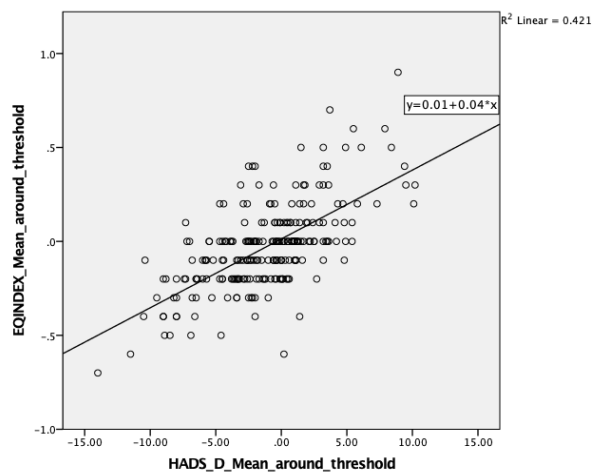




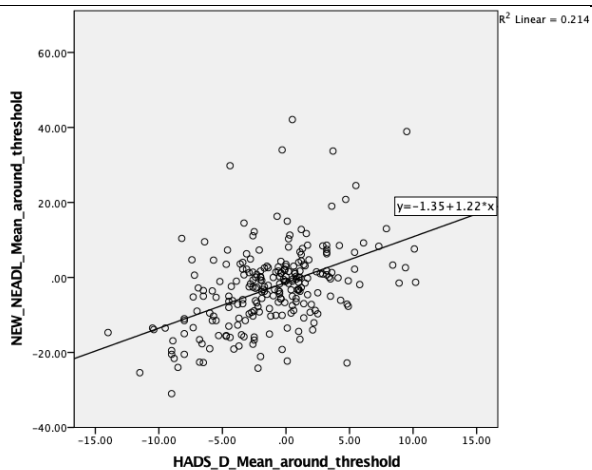




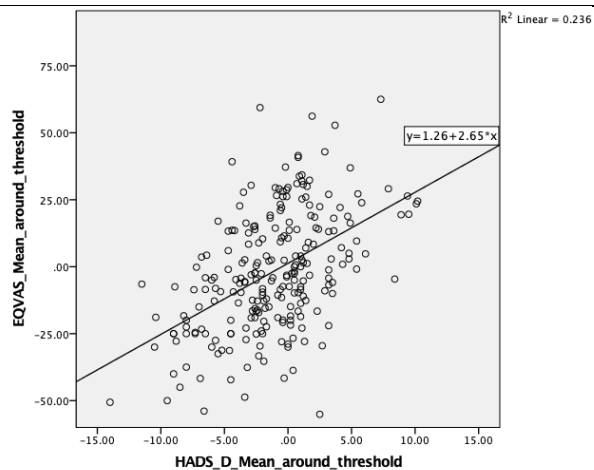
Correlation between mean change in HADS-Depression and NEADL
(0-22)



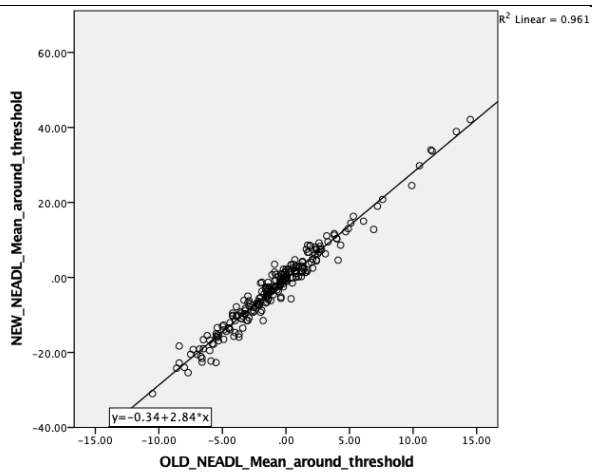
Correlation between mean change in HADS-Depression and EQ5D5L
utility index



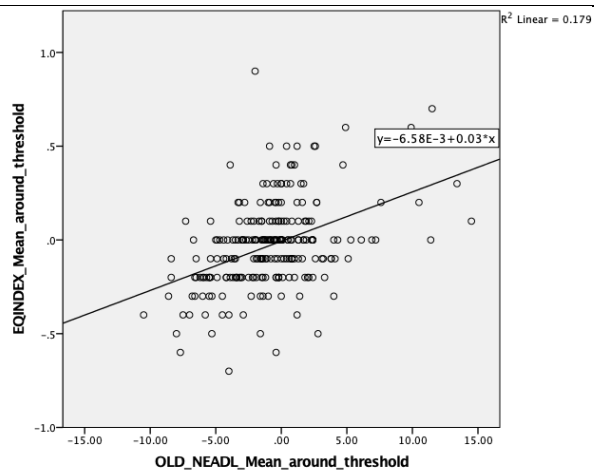
Correlation between mean change in HADS-Depression and NEADL
(0-66)



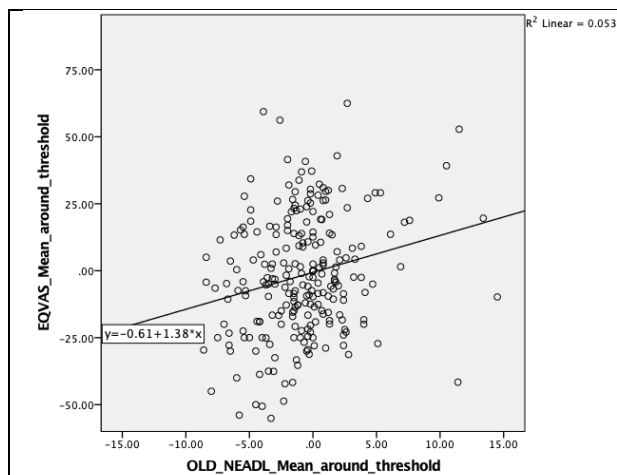
Correlation between mean change in HADS-Depression and EQ5D5L
visual analogue scale



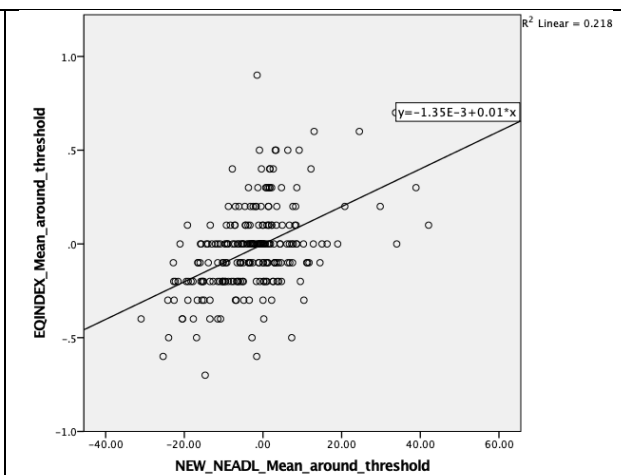
Correlation between mean change in NEADL (0-22) and NEADL (0-
66)



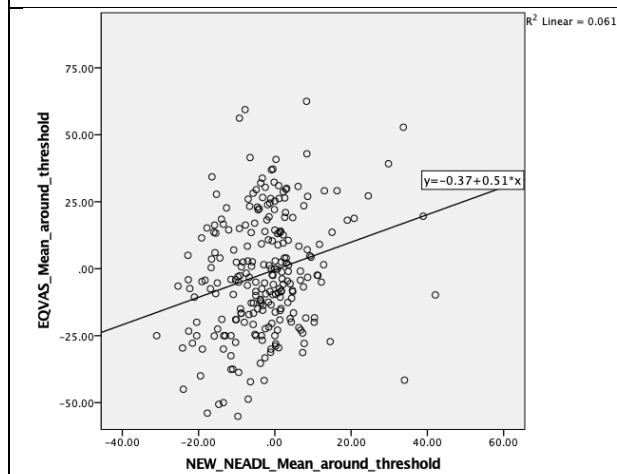
Correlation between mean change in NEADL (0-22) and EQ5D5L
utility index



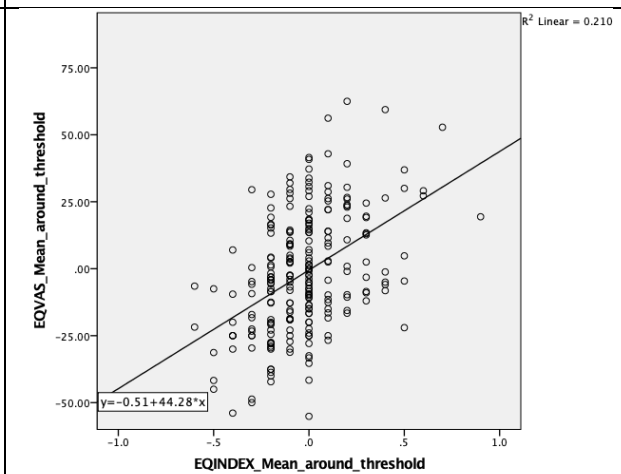
Correlation between mean change in NEADL (0-22) and EQ5D5L
visual analogue scale



Correlation between mean change in NEADL (0-66) and EQ5D5L
utility index



Correlation between mean change in NEADL (0-66) and EQ5D5L
visual analogue scale



Correlation between mean change in EQ5D5L index and visual
analogue scale

14.6 Appendix F: Validation Study and late failure or relapse CRF

NIVO Study.

Validation CRF v1.2

Northumbria Healthcare
NHS Foundation Trust



Name:		NHS number:		Hospital number:	

Admitting Hospital:		M F	Contact number:		
Ethnicity:		DOB:	PATIENT ID: _____		
Inclusion Criteria: Primary diagnosis AECOPD: ☐			Respiratory Acidaemia (pH <7.35, CO2 ≥6.5) treated NIV or IV: ☐		
Smoking ≥10 pack years: ☐			Spirometry FEV1/FVC <0.7: ☐		Age>35: ☐
Exclusion Criteria: Previous inclusion in study: ☐			Other illness limiting life <1 year: ☐		
Arrival A&E Date:		Senior RV date:		Admission to Ward Date:	
Arrival A&E Time:		Senior RV time:		Admission to Ward Time:	
Home Circumstances Home: ☐ Home + Carers: ☐ Sheltered: ☐ Sheltered + carers: ☐ Residential: ☐ Nursing: ☐ Community Hospital: ☐ Prison: ☐					
Smoking Status:		Pack Years:		Number of Admissions in last year:	
eMRCD (see guidance and ensure scored accurately) _____					
Most recent obstructive spirometry date: _____		FEV1:	(L)	FEV1% Predicted	(%)
		FVC:	(L)	FVC% Predicted	(%)
Obstructive spirometry confirmed but values unavailable: ☐ (only if all sources of spirometry eg GP/lab/notes exhausted)					
LVSD ☐		if yes- NYHA class		Cor Pulmonale ☐	
APACHE II Liver Failure ☐		APACHE II Renal Failure ☐		APACHE II Immunocompromise ☐	
AF: Any AF (including chronic/historical paroxysmal or new): up to 4 hours ☐				up to ventilation ☐	
Effective Cough ☐		Ineffective Cough ☐		Medication	Admission
Height: (m)		Weight (kg)		Discharge	
CXR Consolidation on admission ☐		CXR Consolidation at ventilation ☐		Long term Steroid	xxx
Diaphragm height: (cm)		LTOT on admission ☐		Diuretic	
Previous episode of NIV prior to this admission? Yes No				Beta Blocker	
Date first episode of NIV _____		Total episodes in last year		ACE/ARB	
Domiciliary NIV admission ☐		Domiciliary NIV discharge ☐		Statin	
Resolved acidaemia pre NIV? ☐		Date resolved acidaemia _____		LABA	
Ventilation initiated: Date Time				LAMA	
Ventilation discontinued: Date Time				ICS	
pH Correction: Date Time				Carbocysteine	
	IPAP	EPAP	BUR	Azithromycin	
1 hour				Theophylline	
Max				At time ventilation initiated was patient: For intubation ☐ For Resuscitation ☐	
Reason for cessation: Weaned ☐ Poor tolerance ☐ Palliative care initiated ☐				Highest Level of care received: Ward ☐ RSU ☐ HDU ☐ ICU ☐	
Died receiving ventilation ☐ Other ☐ (specify)				Patient invasively ventilated? ☐	
				If yes: NIV pre ☐ NIV post ☐	
				Duration invasively ventilated: (days)	

Confusion 24hr pre NIV ☐

Record pH correction!

Did patient survive to discharge? Yes No

Date of Discharge _____

Date of Death _____

Place of death: Usual residence ☐ Hospital ☐
Hospice ☐ Other _____

Cause of Death: 1a
1b
1c
2

**(commonly did not survive to discharge or unable to consent)*

PATIENT ID: _____

Late Failure (LF) is **recurrence** of respiratory acidemia while **still receiving ventilation** at least **24 hours after pH correction** with a pCO₂ rise of at least **1kPa** from **lowest recorded** after pH correction. (It is not simply delayed development of initial respiratory acidemia). Only capture LF occurring during primary episode of ventilation not during any subsequent episodes (ie relapses)

Relapse is recurrence of respiratory acidemia 24 hours after NIV cessation.

Late Failure: ☐Relapse: ☐**Late failure**Was NIV continued after late failure? Yes ☐ No ☐Was the level of pressure support, back up rate or target duration of use of NIV increased after late failure? Yes ☐ No ☐Were changes made to improve patient-ventilator synchrony or comfort after late failure (settings or interface)? Yes ☐ No ☐Was patient invasively ventilated after late Failure? Yes ☐ No ☐Was ventilation withdrawn and alternative palliative (end of life) care commenced? Yes ☐ No ☐Lowest CO₂ recorded between initial pH correction and late failure: _____

ABGs	Last Pre LF	At LF
Date/Time		
FIO ₂ *		
pH		
PCO ₂		
PO ₂		
BE		
Bicarb		
A/V		
Tosca (if app)		

Relapse

Number of episodes of relapse: _____

Total duration of ventilation post relapse? (days)

n.b. if has more than one relapse include total days for all. If established on domiciliary NIV use day nocturnal NIV only established as last day of acute ventilation.

14.7 Appendix G: Clinical Diagnosis CRF

NIVO Study.

'Clinical Diagnosis' CRF v1.1

Northumbria Healthcare **NHS**
NHS Foundation Trust

Name:		NHS number:		Hospital number:	

Admitting Hospital:		M	F	Ethnicity:	DOB:
Admission Date:		Time:		PATIENT ID:	

Inclusion Criteria: Clinical diagnosis AECOPD*: ☐		Resp Acidosis treated NIV or IV: ☐	
Smoking ≥10 pack years: ☐		Age>35: ☐	
Exclusion Criteria: Previous inclusion in study: ☐		Other illness limiting life <1 year: ☐	

*Clinical diagnosis is for use in patients without a prior firm diagnosis of COPD (ie not confirmed by spirometry) in whom a respiratory clinician has made a clinical diagnosis of COPD and the cause of their respiratory acidaemia is thought to relate to **primarily** to an exacerbation of COPD.

eMRCD _____	BMI: _____	LTOT: ☐

LVSD ☐	Depression ☐	AF up to point of ventilation ☐

CXR Consolidation at ventilation ☐	Effective Cough: ☐

In 24 hours prior to ventilation record the worst: BP: RR: GCS: Confusion: Yes No <table border="1" style="width: 100%; border-collapse: collapse;"> <tr><td>Hb</td><td></td></tr> <tr><td>Hct</td><td></td></tr> <tr><td>WCC</td><td></td></tr> <tr><td>Eosinophil</td><td></td></tr> <tr><td>Urea</td><td></td></tr> <tr><td>K</td><td></td></tr> <tr><td>Albumin</td><td></td></tr> <tr><td>CRP</td><td></td></tr> </table>	Hb		Hct		WCC		Eosinophil		Urea		K		Albumin		CRP		Ventilation decision ABG: Date: Time: pH BE
Hb																	
Hct																	
WCC																	
Eosinophil																	
Urea																	
K																	
Albumin																	
CRP																	

DID PATIENT SURVIVE TO DISCHARGE?	YES	NO

N.b. Patients with a clinical diagnosis of COPD are NOT eligible for inclusion in the longitudinal study

14.8 Appendix H: Consent form for longitudinal study

Version 1.2

23/3/16

1 year longitudinal follow up after non-invasive ventilation. Consent for patients.

PARTICIPANT NAME
NHS NUMBER
DATE OF BIRTH
ADDRESS

Chief investigator: Dr Stephen Bourke.
(Northumbria Healthcare NHS Foundation Trust)
INSERT ETHICS NUMBER
Recruiting Hospital:

Please initial each box

1) I have read the information sheet for the above study, and have had the opportunity to ask questions. I consent to take part.	
2) I understand that I do not have to take part, and I am free to withdraw at any time, without giving a reason if I do not want to. My legal rights and medical care will not be affected.	
3) I understand that if I withdraw, the information I have provided will still be used up to the time I withdraw.	
4) I understand that my medical notes and electronic data will be looked at by members of the research team and potentially by regulatory authorities. I give consent for these people to have access to my records.	
5) I understand that all information gathered will be anonymous. No identifiable data will be included in reports, articles or presentations.	
6) I give permission for information to be sent to the GP about my participation in the study, and for the study team to obtain relevant medical information from my GP if required.	

		DD	MM	YYYY
Participant name (PRINT)	Signature	Date		
		DD	MM	YYYY
Researcher taking consent (PRINT)	Signature	Date		

14.9 Appendix I: Letter sent to general practitioners

GP letter, type B site

V1.0

18/4/16

Insert GP Address

Insert Hospital site and PI

Insert Patient details

Dear General practitioner

One of your patients has agreed to take part in our research study entitled:

1 year longitudinal follow up after non-invasive ventilation.

This study has been approved by ethics review; Ref: 16/NE/0213, IRAS ID 206694

The aim of the study is to further evaluate the outcomes following an exacerbation of COPD requiring treatment with non-invasive ventilation. This study is a multi-centre UK study, the lead trust being Northumbria healthcare.

Your patient will meet with a researcher 4 times over the course of a year; at discharge, 3, 6 and 12 months at which time they will complete a short series of questionnaires assessing quality of life, functional status and anxiety and depression. Oxygen saturations, weight and spirometry will also be measured at these visits. Each month between visits the patients will be asked to complete these questionnaires themselves (approx. 30 mins/month). We are also investigating patients' attitudes to future NIV should it be required and they will be asked if they would want NIV again in the future. They will be reminded that this question is for research purposes only (however if they wish to pursue future care planning we may facilitate this by contacting you).

We may contact you for additional information however your patient's participation in the study should not otherwise impact upon you.

If you would like any further information your local PI is listed above. Otherwise do not hesitate to contact the chief investigator Dr Stephen Bourke or research fellow Dr Tom Hartley both based at North Tyneside hospital and contactable via the hospital switchboard on 0344 8118111.

Kind regards

14.10 Appendix J: Longitudinal study CRF

NIVO Study.

Longitudinal Study CRF Type B site v1.1

Northumbria Healthcare 
NHS Foundation Trust

BASELINE ASSESSMENT (Pre Discharge)

PATIENT ID	DOB	Mobile number:

Consent Gained	y ☐ n ☐	Date	Time
Discharge from hospital		Date	

Height	Weight
Oxygen saturations	FiO2

Today's Spirometry:	
FEV1	FVC

Future Ventilation With regard to the episode of ventilation you received at the beginning of this study (please remind patient of dates) and considering this treatment reduces the chance of dying 2-3 times: 1) <i>Considering your recent experience on ventilation and how you feel at present and about the future, are you glad that you received ventilation?</i> 2) <i>Based on your recent experience, if faced with a similar severe exacerbation in the future would you choose to receive ventilation again?</i> 3) <i>Are you satisfied with your current overall Quality of Life?.</i>	y ☐ n ☐ y ☐ n ☐ y ☐ n ☐

Please record any patient comments regarding future ventilation here:

Patient ID:



This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy 0 1 2 3 4 5 I am very sad

						SCORE		
I never cough	0	1	2	3	4	5	I cough all the time	
I have no phlegm (mucus) in my chest at all	0	1	2	3	4	5	My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	0	1	2	3	4	5	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	0	1	2	3	4	5	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	0	1	2	3	4	5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	0	1	2	3	4	5	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	0	1	2	3	4	5	I don't sleep soundly because of my lung condition	
I have lots of energy	0	1	2	3	4	5	I have no energy at all	
TOTAL SCORE								

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about ☐
- I have slight problems in walking about ☐
- I have moderate problems in walking about ☐
- I have severe problems in walking about ☐
- I am unable to walk about ☐

SELF-CARE

- I have no problems washing or dressing myself ☐
- I have slight problems washing or dressing myself ☐
- I have moderate problems washing or dressing myself ☐
- I have severe problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities ☐
- I have slight problems doing my usual activities ☐
- I have moderate problems doing my usual activities ☐
- I have severe problems doing my usual activities ☐
- I am unable to do my usual activities ☐

PAIN / DISCOMFORT

- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

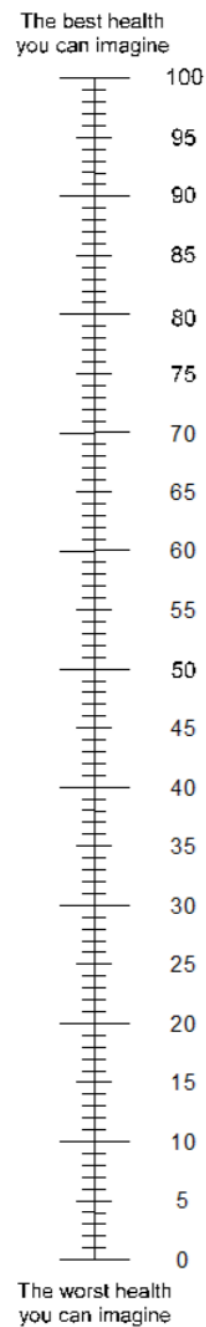
ANXIETY / DEPRESSION

- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

Patient ID:

- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is **TODAY**.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =



Patient ID:

eMRCD Score

5. Extended MRC Dyspnoea (eMRCD) Score

"In the past 3 months, when you were feeling at your best, which of the following statements best describes your level of breathlessness?" (please circle)

Breathless only with strenuous exertion	1
Breathless when hurrying on the level or walking up a slight hill	2
Walks slower than peers, or stops when walking on the flat at own pace	3
Stops after 100m, or for a few minutes, on the level	4
Unable to leave the house unaided but independent in washing and/ or dressing	5a
Unable to leave the house unaided and requires assistance in both washing and dressing	5b

Patient ID:

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			I feel as if I am slowed down:
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			I get a sort of frightened feeling like 'butterflies' in the stomach:
0		Definitely as much	0		Not at all
1		Not quite so much	1		Occasionally
2		Only a little	2		Quite Often
3		Hardly at all	3		Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			I have lost interest in my appearance:
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			I feel restless as I have to be on the move:
0		As much as I always could	3		Very much indeed
1		Not quite so much now	2		Quite a lot
2		Definitely not so much now	1		Not very much
3		Not at all	0		Not at all
		Worrying thoughts go through my mind:			I look forward with enjoyment to things:
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			I get sudden feelings of panic:
3		Not at all	3		Very often indeed
2		Not often	2		Quite often
1		Sometimes	1		Not very often
0		Most of the time	0		Not at all
		I can sit at ease and feel relaxed:			I can enjoy a good book or radio or TV program:
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:

Total score: Depression (D) _____

Anxiety (A) _____

Patient ID:

Nottingham Extended ADL Scale

The following questions are about everyday activities. Please answer by ticking ONE box for each question. Please record what you have ACTUALLY done in the last few weeks.

DID YOU.....	Not at all	with help	on your own with difficulty	on your own
1. Walk around outside?	☐	☐	☐	☐
2. Climb stairs?	☐	☐	☐	☐
3. Get in and out of a car?	☐	☐	☐	☐
4. Walk over uneven ground?	☐	☐	☐	☐
5. Cross roads?	☐	☐	☐	☐
6. Travel on public transport?	☐	☐	☐	☐
7. Manage to feed yourself?	☐	☐	☐	☐
8. Manage to make yourself a hot drink?	☐	☐	☐	☐
9. Take hot drinks from one room to another?	☐	☐	☐	☐
10. Do the washing up?	☐	☐	☐	☐
11. Make yourself a hot	☐	☐	☐	☐

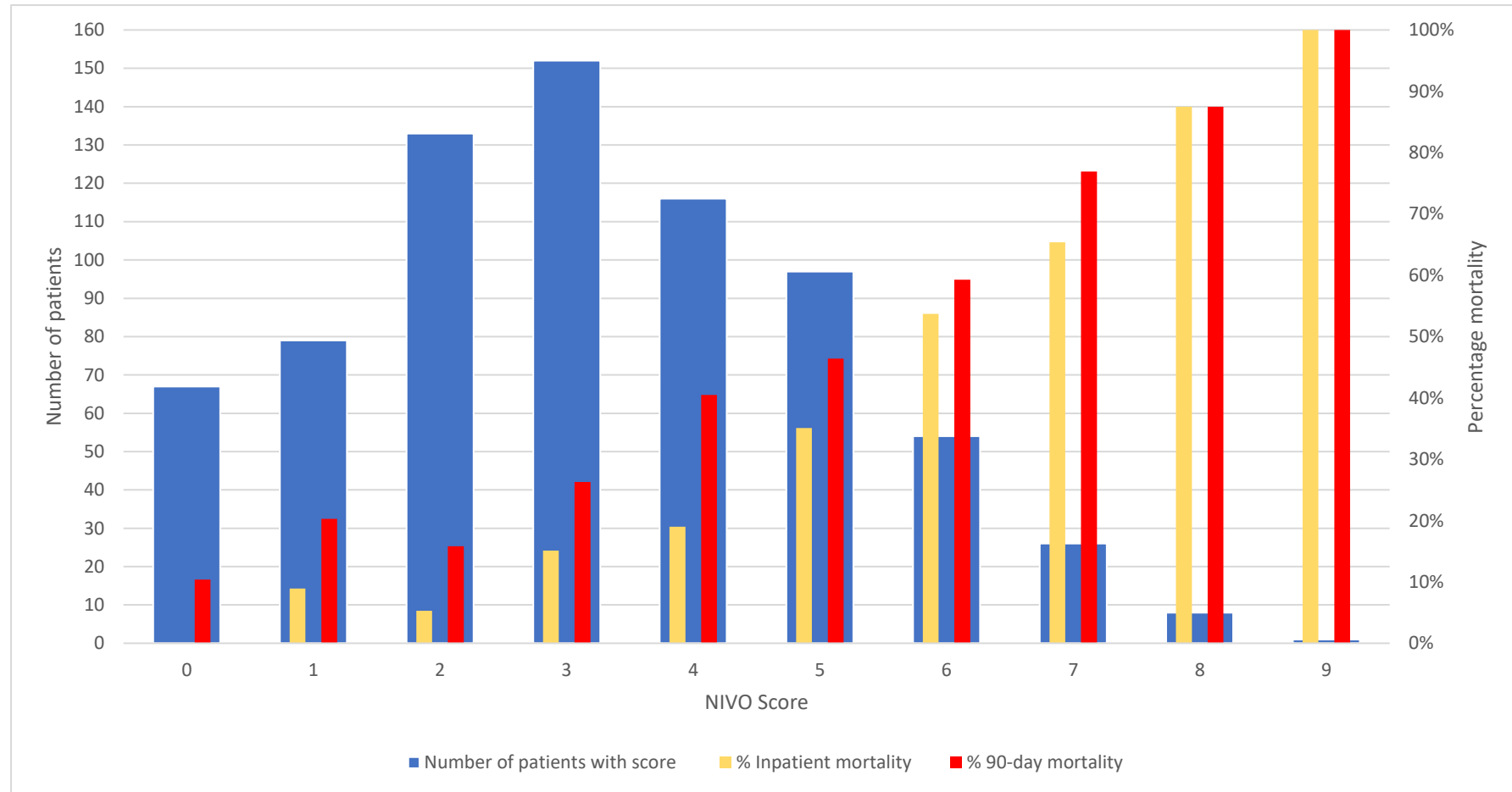
Patient ID:

	No	With help	On your own with difficulty	On your own
12. Manage your own money when out?	☐	☐	☐	☐
13. Wash small items of clothing?	☐	☐	☐	☐
14. Do your own housework?	☐	☐	☐	☐
15. Do your own shopping?	☐	☐	☐	☐
16. Do a full clothes wash?	☐	☐	☐	☐
17. Read newspapers or books?	☐	☐	☐	☐
18. Use the telephone?	☐	☐	☐	☐
19. Write letters?	☐	☐	☐	☐
20. Go out socially?	☐	☐	☐	☐
21. Manage your own garden?	☐	☐	☐	☐
22. Drive a car?	☐	☐	☐	☐

Patient ID:

14.11 Appendix K: Graphical distribution of NIVO Score and mortality

Figure 29. NIVO Score distribution with inpatient and 90-day mortality overlay.



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