DERIVATION AND VALIDATION OF A NOVEL SCORING TOOL TO PREDICT INPATIENT MORTALITY IN EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE REQUIRING ASSISTED VENTILATION.

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

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Submitted January 2020

Abstract

Background: Exacerbations of Chronic Obstructive Pulmonary Disease (COPD) are common and account for approximately 12% of UK hospital admissions. A significant proportion will be complicated by respiratory acidaemia which has a high mortality. Non-Invasive ventilation (NIV) confers a 2-3 fold reduction in mortality in this setting. Despite this, practice is sub-optimal; the intervention is underused, infrastructure is lacking, and complex decisions are made by a wide range of clinicians. It is feasible that pessimism contributes.

Aims: To derive and separately validate a simple, bedside, clinical tool to predict in-hospital mortality in exacerbations of COPD complicated by respiratory acidaemia requiring assisted ventilation.

Methods: The study was split into two parts with similar methods. The derivation study was a single trust (2 sites: one urban and one rural) retrospective study. In patients meeting selection criteria, data were collected, and multivariable regression analysis identified independent predictors of in-hospital death. A simple predictive model was created. The validation study captured a more limited dataset in prospectively recruited patients across 10 trusts. The predictive model's performance was assessed.

Results: 489 patients were identified in the derivation study and 733 in the validation. Independent predictors of outcome were confirmed, and a final, simple bedside model entitled the NIVO score produced. Using atrial fibrillation, chest X-ray consolidation, eMRCD score, Glasgow coma scale, timing of acidaemia relative to admission time and pH in a simple scoring system stratified risk was obtained with an area under the receiver operated curve of 0.79 in the validation cohort.

Discussion: Using only simple, readily available indices good prediction of in-hospital mortality is feasible. The NIVO score outperformed pre-identified comparator scores in both its derivation and validation studies. Potential practical applications include but are not limited to guiding level of care, setting treatment limitations and objectifying discussion with patients or family members.

Dedication

I would like to thank my wife Ellie for her unending patience in this endeavour, this is as much yours as mine. I would also like to thank my supervisory team of Professor Bourke and Dr Steer for their skill, inspiration and enthusiasm. Nick Lane has been a great colleague and I have gained a friend.

Acknowledgement

I would like to acknowledge and say thank you for the following contributions:

Professor Stephen Bourke and Dr John Steer for trial design, guidance, oversight and thesis revision suggestions.

Dr Nicholas Lane joined the research group shortly after recruitment to validation study commenced. He and I completed the validation component together including ongoing governance and site visits. Day to day running of this was split 50/50. We jointly collected and collated data and data verification and cleaning was a joint endeavour. Subsequent analysis is all my own work.

Mrs Vicky Ferguson for exceptional administrative support.

Dr Carlos Echevarria for assistance in database design and statistical problem solving.

Professor Gibson for acting as chair of the trial steering committee.

Mrs Therese Gibson for acting as patient representative on the trial steering committee.

The wider NIVO study group too numerous to list for data collection at external sites.

Declaration

I declare that this thesis is my own work. It has not been submitted in this or any other university previously. Where other sources of information have been used, they have been acknowledged.

Tom Hartley,

June 2019.

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Chapter 1. Introduction: COPD

1.1 What is Chronic Obstructive Pulmonary Disease (COPD)?

1.1.1 Description and Definition.

COPD is a complex lung disease characterised by airflow obstruction and often caused by smoking. Akin to other chronic diseases, damage is not limited to a single organ and both the pulmonary (e.g. airflow obstruction, emphysema, mucus hypersecretion) and systemic (e.g. anaemia, osteoporosis, skeletal muscle weakness) effects of COPD contribute to the symptoms and disabilities. Manifestations are heterogeneous with some individuals developing profound changes in lung architecture as seen in emphysema while others, perhaps of a similar age with similar tobacco history exposure, may have far less architectural change but instead produce copious secretions and suffer frequent flare ups, termed exacerbations. Some patients are too breathless to leave the house or need supplementary oxygen while others with similar lung function measurements can walk miles with normal oxygen levels. Rate of functional and physiological decline can differ dramatically. The psychological effects of chronic breathlessness and disability and their interplay with anxiety and depression further broaden disease manifestations.

The Global Initiative for Chronic Obstructive Lung Disease's (GOLD) states that *'Chronic obstructive pulmonary disease is a common, preventable and treatable disease that is characterised by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.'*[1]

This broad definition emphasises that articulating COPD in a single concise definition requires simplification but the persistent presence of respiratory symptoms is cardinal. COPD is however, a very useful label to communicate that this patient has one of a myriad of interlinked phenotypes some of which are well described and long observed but which overall, we poorly understand. Certainly, predicting the future disease state (if any) beyond 'COPD' of a young, heavy smoker is currently difficult. Some treatments such as guiding inhaled corticosteroids by peripheral eosinophil count or targeting Roflumilast at those producing daily sputum who are frequent exacerbators are clearly in recognition of differing response by phenotype.[1]

Secondly as the definition states there is usually (but not necessarily) chronic exposure to an identifiable airborne irritant. In the UK and worldwide the majority of COPD is caused by tobacco smoking. In some societies smoke from indoor biomass fires for heating or cooking may be a significant contributor.[2] Occupational dusts or chemicals may also be causative.[3]

Overall, despite heterogeneity COPD does describe a group of patients with more similarities than differences and remains a useful diagnostic term.

1.1.2 Spirometry.

'There is no single diagnostic test for COPD. Making a diagnosis relies on clinical judgement based on a combination of history, physical examination and confirmation of the presence of airflow obstruction using spirometry'.[4] In common with other international standards [3,5] the National Institute for Health and Care Excellence (NICE) recommends that airflow obstruction as demonstrated by spirometry forms the cornerstone of the objective criteria by which COPD is diagnosed.

Spirometry is performed from maximal inspiration. The amount of air expelled from the lung in a single forced expiration in the first second is termed the forced expiratory volume in one second (FEV_1). The total amount of air expelled from a forced expiration is termed forced vital capacity (FVC) or vital capacity (VC) if from a relaxed manoeuvre. In COPD, due to dynamic collapse of airways during a forced manoeuvre, the FVC may be significantly lower than the VC and consequently underestimate the total air expelled.[6] The largest recorded FEV_1 divided by the largest FVC or VC forms the FEV_1/(F)VC ratio. Current practice is to diagnose airflow obstruction when this value is <0.7. Having established airflow obstruction further categorisation is possible using the percentage predicted FEV_1.[1,4]

1.1.3 Spirometry Staging.

Recorded values can be compared to reference values derived from healthy populations. These predicted values vary dependent on various factors notably gender, height, age and ethnicity.[7-9] A percentage predicted value is the actual recorded value relative to the reference value and may be greater than, equal to, or less than 100%. Using a lower limit of normal value (i.e. recognising standard deviations) may increase diagnostic accuracy especially in older people.[10]

A simple way of grading the severity of airflow obstruction in COPD is by spirometry: International guideline bodies have adopted the gradation shown in Table 1. In recent years there has been recognition that this approach is poorly predictive on an individual patient level.

Table 1 COPD staging by spirometry values.

	FEV_1 (percent predicted)	**Stage/Grade**
FEV_1/(F)VC <0.7	≥80%	Mild
	50-79%	Moderate
	30-49%	Severe
	<30%	Very Severe

These sections represent an acknowledged oversimplification of spirometry and lung function testing in COPD. As discussed, COPD is not a single entity and patients with chronic bronchitis or emphysema may not have airflow obstruction. Similarly, there is momentum toward the use of lower limit of normal in diagnosis and this method may well take over from the simple 70% cut off in the future.

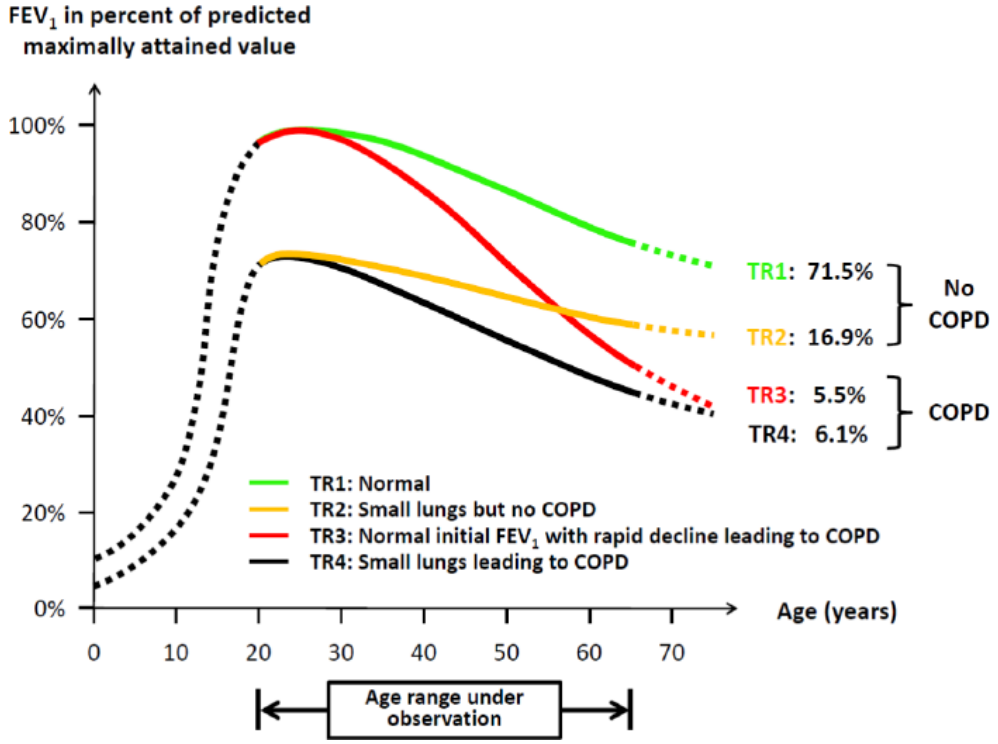
1.2 COPD Epidemiology.

1.2.1 Genetic Predisposition to Development of Airflow Obstruction.

Not everyone with chronic inhaled irritant exposure will develop COPD. The Copenhagen City Heart Study followed a general population for 25 years and recorded serial investigation results including spirometry. After adjusting for tobacco burden, they conclude that 30-40% of smokers without initial disease will develop COPD. People who smoked throughout the timeframe had a greater risk than intermittent smokers or those that stopped but the development of COPD was not universal in smokers. Total tobacco burden was modest whether an early quitter or a continuous smoker (mean 14.8-19.1 cigarette pack years).[11] Therefore, there are other factors beyond tobacco burden that determine whether a smoker will develop COPD or not. Fletcher and Peto proposed a classic representation of lung function decline developed from a random population of London men in the 1970s. This schematic model reinforces that genetic susceptibility is important with some individuals being prone to more rapid lung function decline when exposed to tobacco smoke and others seemingly protected from development of airflow obstruction.[12] The rate of decline,

particularly the accelerated decline in late disease have been questioned and other schema proposed. Figure 1 illustrates this alternate view: the maximum achieved FEV_1 in early adulthood as determined by genetic and environmental factors in early life is an important influence on the likelihood of developing COPD. In this model airflow obstruction can develop from normal maximum FEV_1 with rapid decline or from a low maximum FEV_1 with normal rate of decline in FEV_1.[13]

Figure 1 Lung function trajectories leading to chronic obstructive pulmonary disease.[13]



COPD is a global disease found irrespective of race or ethnicity. Small studies inconsistently report significantly differing susceptibility between ethnic groups, however, a large meta-analysis found pacific islanders to be the only outlying group (less COPD than expected).[14] Another large study found no relationship between genetic ancestry and COPD rates after adjusting for confounders.[15]

In 1963 the strongest genetic determinant of COPD was identified when the association between alpha 1 antitrypsin deficiency and premature emphysema was discovered and subsequently linked to a mutation in the SPERINA1 gene.[16] In recent years since the development and data-sharing of large genome-wide association studies several loci have been shown to be associated with heritability of accelerated lung function decline. A meta-analysis of nearly 21,000 European patients identified 8 gene loci of significance.[17] Many

further gene loci have been identified but reproducibility has bedevilled the field so validation in large population datasets is essential.[18]

1.2.2 COPD Burden.

COPD is thought to affect 210 million people worldwide but due to variation in diagnosis rate the actual number may be much higher.[3] Worldwide COPD is expected to be one of the major health burdens in coming decades and prevalence will continue rising.[19] Increasing life expectancy is a major contributor; those with the disease live longer and more people survive long enough to develop it.[20]

United Kingdom (UK) smoking rates are now falling, but COPD prevalence is still rising due to historical smoking rates, active case finding, improved disease specific survival and, as mentioned, an aging population. There is evidence of a plateauing in new diagnosis rates.[21]

In support of a continued rise in prevalence is a Dutch model of COPD in an aging population developed in the early 2000s. This complex, dynamic population model projects the incidence and prevalence of COPD based on annualised adjustment of demographics, births, deaths, migration and smoking rates. Historical data and spirometry data from nearly 6000 individuals is incorporated. The model predicted increase across all severity classes in both men and women until the end of the modelled period in 2025. Domestic adult smoking rates between the UK and the Netherlands at its inception were comparable.[22]

The burden of COPD in the UK is substantial: there are an estimated 1.2 million people living with diagnosed COPD representing 2% of the total population, 4.5% of the population aged over 40 and 9% aged over 70. COPD was estimated to be the second commonest reason for hospital admission [23] and it accounts for 1.7% of the total National Health Service (NHS) bed days.[21] The burden to an individual patient is also substantial with COPD being associated with a high symptom burden which will be discussed in more detail.

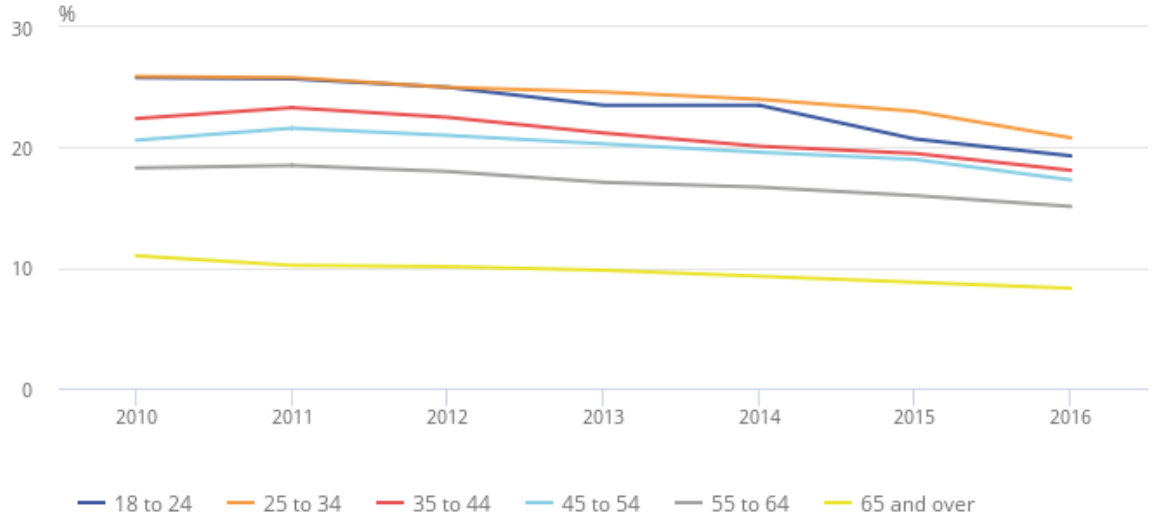
1.2.3 Smoking Habits and Health Inequality in the UK.

Development of COPD is strongly linked to tobacco smoking. In patients with air flow obstruction benefit is derived from smoking cessation with the greatest benefit seen in those with the worst lung function.[24] Thankfully as shown in Figure 2 rates of smoking have been

consistently falling for several years across all age groups and those smoking consume fewer cigarettes.[25]

Changes in smoking habits are not however symmetrical across the population, in the UK smoking and COPD are contributors to health inequality. Men aged 20-64 employed in unskilled occupations are 14 times more likely to die from COPD than those in professional roles.[26] Between 2014 and 2016 10.9% of people in managerial and professional occupations smoked versus 24.9% of those in routine and manual occupations. Overall 15.9% of those in employment smoke versus 29.8% of those unemployed. Profound regional variations also exist.[25] Similarly, smoking habits have differed between men and women meaning projected COPD rates are not equal for men and women. Globally unemployment is a risk factor for COPD.[27]

Figure 2 Proportion of current smokers, all persons by age group. UK 2010 to 2016. [25]



Impaired lung function in adulthood is associated with childhood poverty. In one study 3641 British women aged 60-79 were interviewed and had spirometry recorded. After adjustment for important confounders such as age, height, adult social class, lifetime smoking status, BMI, respiratory medications and physical activity markers of childhood poverty remain associated with impaired lung function in late adulthood, particularly paternal manual work and no access to a car in childhood. Findings were preserved irrespective of passive smoking burden.[28] English data from a national audit shows one third of patients come from the quintile of most deprived postcodes.[29]

A number of factors explain these observations including lower birth weight, childhood infections, childhood asthma, exposure to air pollution, maternal smoking in pregnancy, and occupational exposure to dusts and fumes. All are associated with deprivation and largely independent of individual control.[30-33] One large study found childhood factors to be as important as lifetime heavy smoking in the development of adult COPD.[33] While it is undeniably extremely important COPD should not just be considered a disease of smoking but more a complex combination of social, genetic, developmental and biological factors. This is important to prevent COPD being viewed as a self-inflicted illness.

1.3 COPD Manifestations.

1.3.1 Pulmonary Manifestations and Symptoms of COPD.

The direct pulmonary symptoms of COPD are easily described: Dyspnoea, wheeze, chronic cough and chronic sputum production are cardinal. Dyspnoea is usually progressive, persistent and typically exertional.

Broadly speaking, airflow obstruction develops as a consequence of loss of elastic recoil due to emphysema, increased small airway resistance due to luminal narrowing or both. Inflammation caused by cigarette smoke or other irritants leads to over-production of elastases as compared to their inhibitors (alpha 1 antitrypsin is an inhibitor whose absence leads to emphysema). Elastases, particularly neutrophilic elastase break down tissue and lead to airspace enlargement, i.e. emphysema.[34,35] A similar immune response leads to airway mucosal infiltration with inflammatory cells, interruption of muco-ciliary clearance and connective tissue deposition ultimately leading to a narrowed airway lumen.[36]

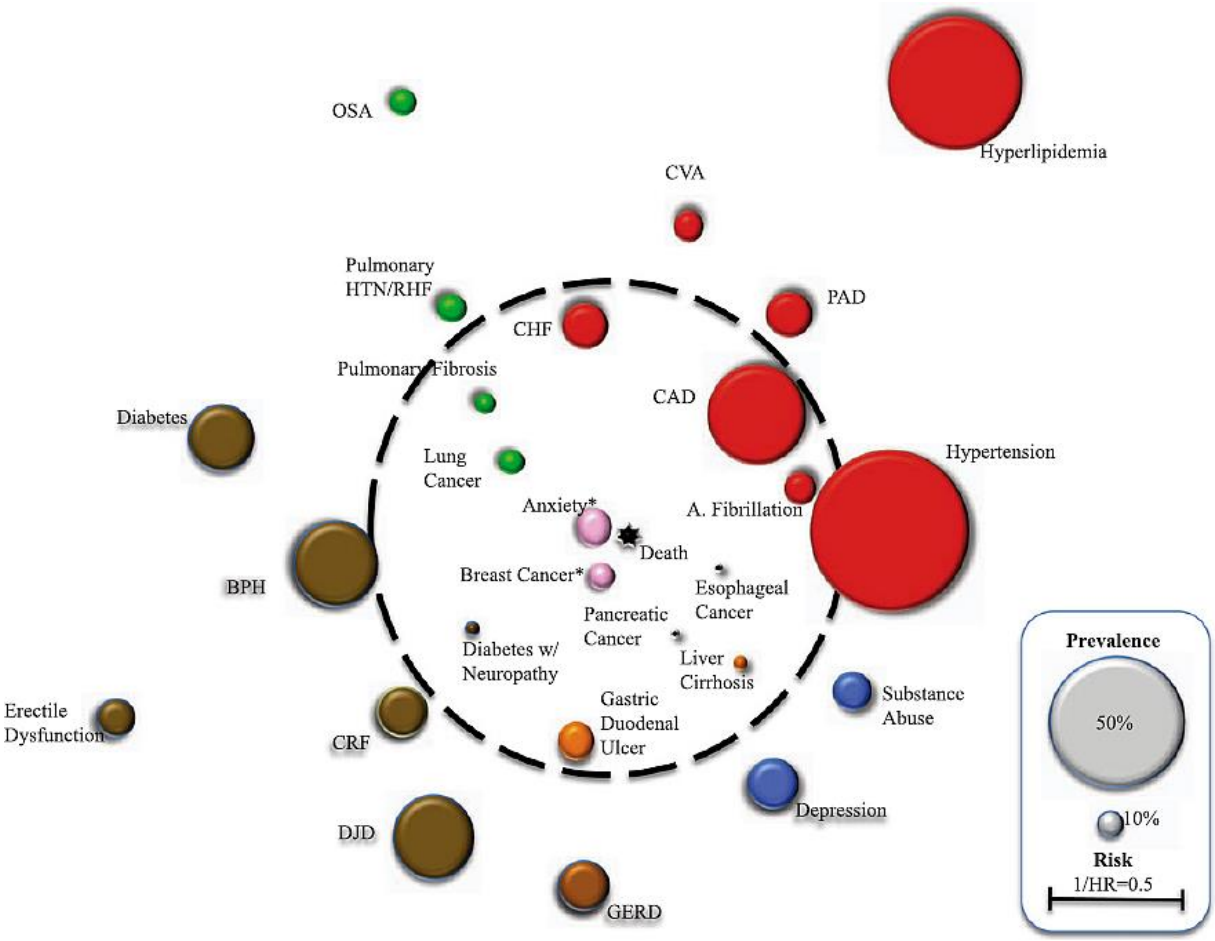
Inflammation is not just found in the small airways, throughout the lungs the airways are inflamed, airway defences are impaired and muco-ciliary clearance is impaired. These factors lead to the chronic mucus production, pre-disposition towards infection and cough that constitute major symptoms. Emphysema reduces the available surface area for gas exchange and combined with airflow obstruction leads to dyspnoea and wheeze. High lung volumes (hyper-expansion) seen in emphysema particularly lead to inefficient, effortful ventilation; exertional dyspnoea is often related to the added effects of dynamic hyperinflation, further discussed later.[37,38]

1.3.2 Extra-pulmonary Manifestations and Comorbidities Associated with COPD.

COPD is not simply a disease of the lungs, systemic inflammation may play an important role in the development of extra pulmonary manifestations of COPD. One theory contends a pro-inflammatory environment in the lungs 'spills out' systemically with downstream effects.[39] Compared to controls increased levels of a long list of circulating pro-inflammatory mediators have been demonstrated in COPD. C-Reactive protein (CRP), interleukins, fibrinogen, leucocytes and tissue necrosis factor alpha (TNFα) are perhaps the most reliably described. [39-43] Platelets may also play a role in systemic inflammation and there is suggestion that elevated platelet level (thrombocytosis) during exacerbation is associated with increased mortality.[44] The proinflammatory environment of COPD has been hypothesised as the cause of a host of associated comorbidities. It is difficult to ascribe causality to the inflammatory environment over correlation with shared environmental risk factors such as smoking, other aspects of COPD such as hypoxaemia or genetic predisposition, but it is likely to be at least in part the case. For example elevated Interleukin-6 and CRP as may be seen in COPD have both been implicated in accelerated ischaemic heart disease (IHD).[45] Irrespective of the precise mechanistic pathway there are strong correlations between COPD and other comorbidities that impact significantly upon disease progression and mortality.[46-49] The particularly strong association between COPD and accelerated ischaemic heart disease is a potential target for mortality reduction.

Divo et al. recruited 1664 patients across 5 centres, all comorbidities were recorded (79 in total). After a median of 51 months follow-up associations with mortality were reported. The authors created a 'comorbidome' (Figure 3) of those comorbidities present in at least 10% of the study population. 12 were significantly associated with increased mortality and are depicted inside a dotted line. Increasing circle size represents increasing prevalence, proximity to the centre strength of association with increased mortality and colour grouped by organ system. These results are not wholly generalisable and an associated comorbidity score is not validated. 89% of participants were male which goes some way to explaining the strong mortality association of breast cancer and anxiety which were only mortality associates in the smaller cohort of females. Nevertheless, it is a powerful reminder that COPD does not exist in isolation and multiple comorbidities are the norm.[46]

Figure 3 COPD comorbidome*.[46]



*Acronyms listed in list of abbreviations

Skeletal muscle wasting and dysfunction is not a discreet comorbidity as such but is well recognised and highly correlated with functional decline and poor outcomes. A combination of disuse, catabolism, inflammation and exogenous corticosteroid administration in COPD are likely to explain, some or all of the reason why this should be the case.[50,51] The physical training aspects of pulmonary rehabilitation have been developed to counteract the effects of myopathy. The recent Cochrane review concluded no further randomised controlled trials were required to support the efficacy of pulmonary rehabilitation in COPD.[52] In addition to those studied by Divo et.al. a long list of diverse conditions have been associated with COPD including (but not limited to) anaemia,[53] osteoporosis,[54,55] and cataracts.[56]

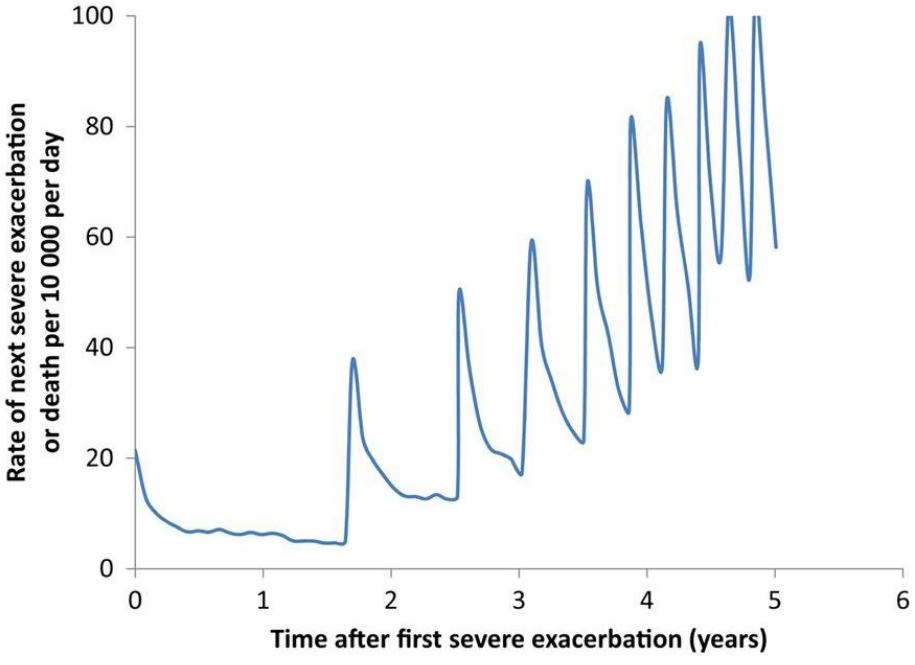
1.3.3 Exacerbations of COPD (ECOPD).

The course of COPD will be punctuated by flare ups where symptoms worsen. These episodes are more often than not associated with bacterial or viral infection.[57,58] Three bacteria (Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis) and

one virus (Rhinovirus) are implicated in a majority of infective exacerbations, with a series of other bacteria and viruses less commonly involved.[59] In one study, Haemophilus influenzae was identified from mucosal biopsy in 87% of patients intubated for ECOPD, 33% with non-exacerbated COPD and 0% of healthy controls.[60]

While some debate surrounds the precise definition of an exacerbation of COPD there is reasonable consensus. One aspect of the debate perhaps less pertinent to the UK, which has universal healthcare, is whether treatment escalation should form part of the criteria as this approach inherently incorporates access to healthcare.[61] This aside, the following definition is from the 2010 NICE guideline: *'An exacerbation is a sustained worsening of the patient's symptoms from their usual stable state which is beyond normal day-to-day variations, and is acute in onset. Commonly reported symptoms are worsening breathlessness, cough, increased sputum production and change in sputum colour. The change in these symptoms often necessitates a change in medication.'* It is generally accepted that exacerbations can be categorised into mild (treated using bronchodilators only), moderate, using oral glucocorticoids and/or antibiotics) or severe (requiring hospital admission). During an exacerbation lung function frequently deteriorates and full recovery may not occur.[62] Respiratory failure as a consequence of an exacerbation will be discussed later.

Figure 4 Median time to next exacerbation or death after first ECOPD [63]



Exacerbations are important to the natural history of COPD. From a large database in Quebec, researchers selected patients hospitalised for the first time with ECOPD and recorded further hospitalisations for ECOPD or death between 1990 and 2007. 73,106 patients were included. As can be seen in Figure 4 risk of exacerbation or death remains high in the weeks following a severe (hospitalised) exacerbation and an increasing risk was observed particularly after the second severe exacerbation.[63]

1.3.4 Does the Presence of Pneumonia Invalidate a Diagnosis of ECOPD?

This question can divide opinion and is pertinent to this thesis. It is predominately a question of interpretation and opinion rather than of evidence. There are, however, consequences for patient selection, treatment algorithms and interpretation of clinical trials. The argument is whether pneumonia is an organised, parenchymal process and ECOPD is an isolated airways process or whether they can coexist? If clinical presentations conformed to binary distinctions then there would be little debate and while there are situations where one pathology predominates, it is rarely clear-cut. The alternate position is that the conditions frequently occur together, interact along a continuum and separation adds little value. There are several cogent points to support this second opinion:

- This is predominately an academic debate, national audits consistently show a large number of patients with ECOPD have complicating pneumonia [29] (18% in UK's most recent audit). This implies that many UK physicians do not separate the two diagnoses.
- Sensitivity and specificity of computerised tomography CT is greater than chest x-ray (CXR) to diagnose pneumonia.[64-66] If the distinction were paramount then logically one must also insist upon gold standard imaging techniques yet the necessity for CT has not been incorporated into national guidance [67] as little extra value is added and normal practice is not to CT all. Furthermore, development of radiographic consolidation can lag behind symptoms and signs. Imagine a patient presents breathless and with clinical signs of consolidation. Imaging on day one is clear but on day 2 consolidation is present. Did this patient have pneumonia on day 1, must ECOPD treatment now stop? The point is moot but serves to illustrate the fallacy of binary thinking.

- There is no obvious treatment variation that separation naturally dictates. Bronchodilators or corticosteroids should not be withheld to treat bronchospasm if present, nor broad spectrum antibiotics, intravenous fluids or inotropes to treat sepsis.
- There are recognised differences between pneumonia in COPD and the simple community acquired pneumonia. Notably there is probably a reduced rate of empyema in COPD and the lung microbiome and acute microbiology differs, specifically, the rate of Pseudomonas Aeruginosa is much higher.[68,69]
- Following and most importantly: focussing attention upon pneumonia as a separate entity may detract from good management of co-existent COPD. For example, the use of controlled oxygen or vigilance for and treatment of respiratory failure where ambiguity may lead to poor treatment decisions particularly the administration of non-invasive ventilation (NIV).

Fundamentally insisting on separation should ease diagnosis and management not complicate it. This is especially true given that these conditions are commonly managed by a generalist.[29] For these reasons not drawing an academic distinction and considering these conditions to interact is the position of this thesis. The term pneumonic exacerbation of COPD (pECOPD) will be used henceforth to describe an exacerbation of COPD with coexistent pneumonia.

1.3.5 Physiology of Respiratory Failure in COPD.

Under normal circumstances ventilation serves to facilitate gas exchange by moving oxygen from the air into the alveoli and removing carbon dioxide which is a by-product of metabolism. A potential consequence of COPD is the development of respiratory failure if the lungs can no longer provide adequate gas exchange. Respiratory failure can be acute, chronic or acute on chronic and is traditionally divided into type 1 and type 2:

Type 1 respiratory failure: Is where oxygenation can no longer be maintained. This is often due to ventilation/perfusion (V/Q) mismatch, i.e. for a given lung unit there is a discrepancy between the blood circulating through it and the air reaching the surfaces of gas exchange. For illustration, in pulmonary embolism, air will reach diffusion surfaces as normal but the blood supply distal to the blockage will be compromised; in the territory of the blocked vessel there will be a mismatch.

Type 2 respiratory failure: Is where there is failure of both oxygenation and excretion of carbon dioxide (CO_2) and is due to failure of the respiratory pump and consequently impaired alveolar ventilation. As carbon dioxide level rises homeostatic mechanisms can be overcome and acidaemia develop.

Respiratory physiology and homeostasis is a complex relationship between lung mechanics and the metabolic environment. Under normal circumstances the amount of CO_2 produced by the body is equal to the amount excreted by the lungs and there is capacity to increase alveolar minute volume and hence pulmonary excretion easily in response to greater production (for example during exercise). In COPD, ventilation may not be able to keep up with production and type 2 respiratory failure may develop; several important mechanisms are described:[38,70-74]

- Dynamic hyperinflation: rapid breathing and prolonged expiratory time (due to airflow obstruction) leads to incremental increase in lung volume as exhalation is not completed prior to the beginning of the next breath. In this state, greater effort is needed to generate a given tidal volume due to diaphragmatic flattening and reduced compliance at higher lung volumes.
- Loss of elastic recoil in the communicating airways leads to airway collapse in expiration and gas trapping.
- Respiratory muscles tire due to the above processes. Acidaemia and hypoxia have supplementary deleterious effects on muscle performance and a vicious cycle develops. As CO_2 reaches very high levels central ventilatory drive may fall.
- Low tidal volume breathing develops and has the consequence of alveolar hypoventilation. The dead space (i.e. the volume from oro-nasal cavity to the distal bronchioles that serves to transmit gas to the alveoli) is more or less fixed and does not contribute to gas exchange. For example, if dead space is 200mls and tidal volume drops from 800 to 400mls alveolar ventilation drops from 600mls to 200mls.
- If there is overlap with obesity further constraints can be placed on a failing system, abdominal adiposity limiting diaphragmatic movement and chest wall weight may prevent adequate ventilation.

COPD is not a homogenous condition with a single common pathway towards respiratory failure and in an individual these processes (and others) may be occurring to a greater or

lesser degree. For example, in some cachexia driven respiratory muscle weakness may significantly contribute to susceptibility or chronically elevated CO_2 may lead to a dulled ventilatory response to further rises.

The next important variable is time, if the above processes occur over days and weeks metabolic compensation can occur to buffer the elevated carbon dioxide level and prevent acidaemia developing. If, however it occurs more rapidly metabolic compensation cannot occur quickly enough and acidaemia eventually develops. A common occurrence is acute on chronic respiratory failure.

An oft preferred term to describe acute, or acute on chronic, respiratory failure is acute hypercapnic respiratory failure (AHRF), but this can be misleading as it does not specify the presence of acidaemia. Acidaemia due to respiratory failure is particularly important and has management implications; the term respiratory acidaemia (RA) will used in this thesis to signify type 2 respiratory failure with an arterial pH of <7.35.

1.4 Mortality and Palliative care in COPD.

1.4.1 COPD Mortality.

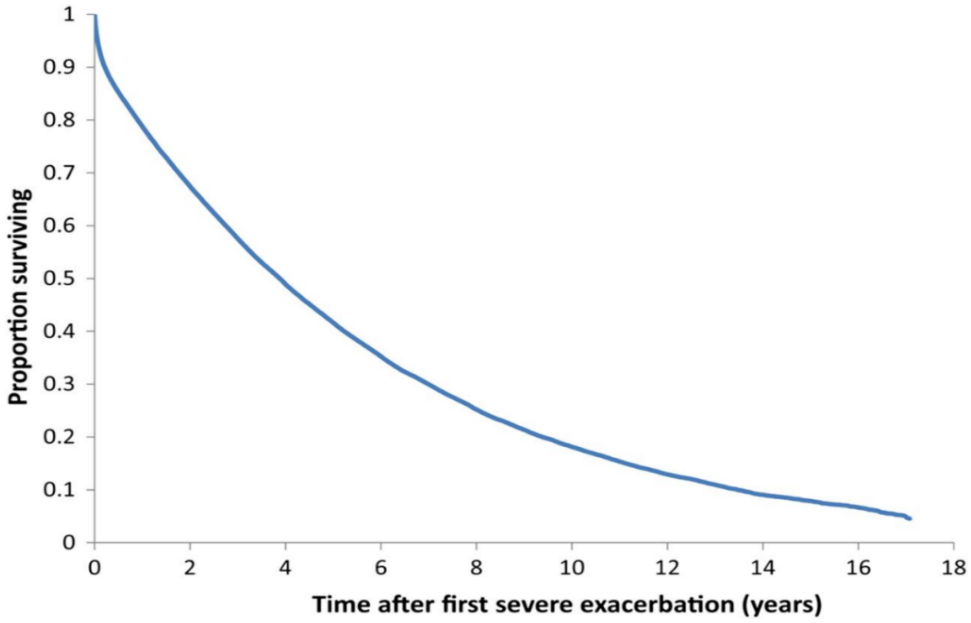
COPD is currently the fifth commonest cause of death worldwide but is expected to rise to fourth by 2030.[75] In the UK, 'chronic respiratory conditions' (of which COPD dominates) is the 4th commonest cause of death with lung cancer 5th. In the UK, between 1993 and 1999, obstructive lung disease was mentioned on 8% of all death certificates, and was the primary cause of death in 60% of those.[76] In 2012 5.3% of all deaths in the UK were attributed to COPD.[77]

It should be noted that many of those who die from lung cancer have co-existent COPD. Both are overwhelmingly diseases due to smoking, but the presence of airflow obstruction is a strong independent risk factor for lung cancer when matched for tobacco burden or age.[78] COPD and its consequent disability can limit the investigative and treatment options for lung cancer [79] and as such, absolute separation of these mortality statistics is difficult.[47] The complex relationship between COPD and comorbidity was examined in large scale in the USA, the authors conclude "*any mention of COPD in the discharge diagnosis is associated with higher hospitalization prevalence and in-hospital mortality from other comorbidities. These results highlight the fact that the burden of disease*

associated with COPD is likely underestimated." [80] In COPD stratified by FEV_1 the majority of deaths in mild and moderate disease are due to lung cancer and cardiovascular events. Only in severe disease does respiratory failure become the predominant cause.[47]

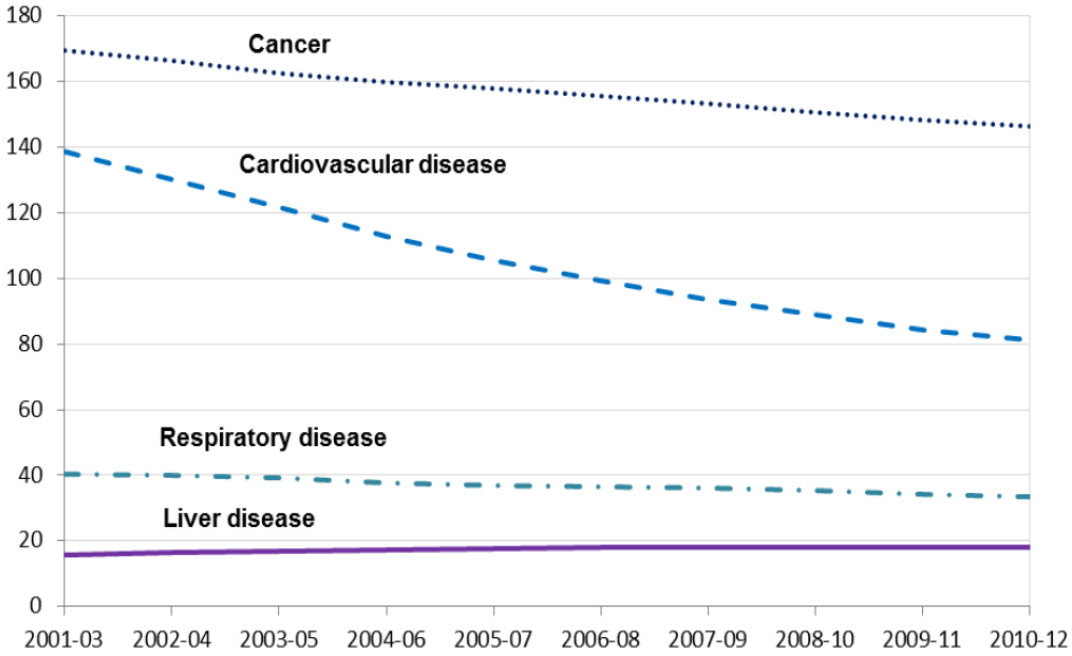
Mortality during an individual exacerbation can also be considered. The British Thoracic Society (BTS) and Royal College of Physicians (RCP) have produced large scale audits of clinical practice. In the 2015 audit in-hospital mortality for those admitted with ECOPD was 4.3%.[29] Mortality was higher in the two preceding reports (7.8% in 2008 and 7.7% in 2003) and the authors in 2015 cannot fully explain the magnitude of this change but both selection bias and updated oxygen prescribing and delivery methods may play a part.[29,81] A large time matched case series reported in-hospital mortality as 7.7%.[82] We can conclude that UK in-hospital mortality following ECOPD is in the range 4.3-7.8%. Medium to long term mortality is high in those who survive hospital admission. Canadian data shown in Figure 5 illustrates that following the first hospital admission for ECOPD, 50% of patients will not survive 4 years.

Figure 5 Survival curve following first hospitalised ECOPD



Mortality in those who develop respiratory acidaemia is likely to be substantially higher, although the mortality consequence simply of developing RA irrespective of persistence is difficult to assess. Good outcome data for those that go on to receive treatment for RA in the form of assisted ventilation is available and mortality is several times higher than those not needing assisted ventilation. Further discussion follows in subsequent chapters.

Figure 6 Age Standardised Mortality Rate (ASMR) per 100,00 population aged under 75 by cause, England. [83]



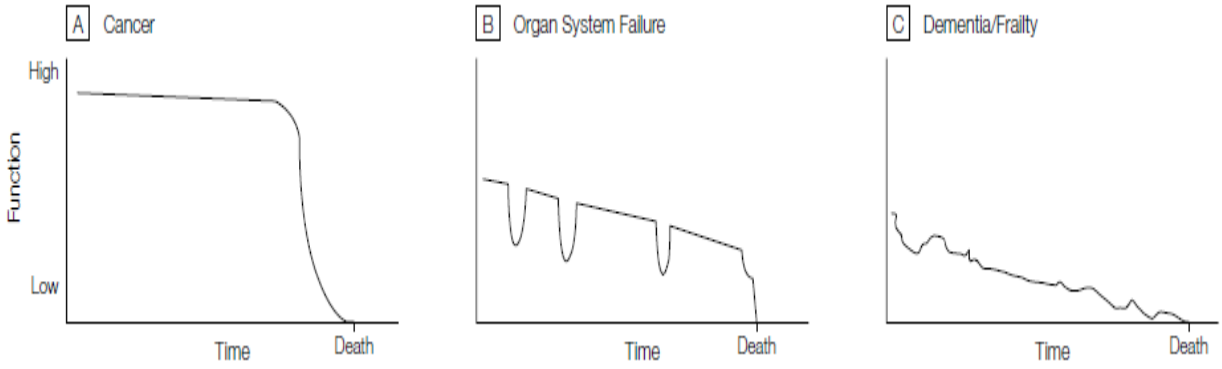
As can be seen in Figure 6, in contrast to the other two major sources of premature mortality and morbidity cardiovascular disease and cancer where much progress has been made there has been relatively less progress in respiratory disease. As diseases so strongly associated with deprivation and little chance of a healthy individual being 'struck down in their prime' there is a danger they are afforded less importance in public policy.

1.4.2 Palliative Care in COPD.

Palliative care services have traditionally focussed upon cancer care. In a UK survey of palliative care services returned by all primary trusts (NHS administrative bodies now superseded by clinical commissioning groups), the overwhelmingly majority (>75%) identified 'patients with diagnoses other than cancer' as 'group with most unmet needs in terms of end of life care.'[84] Patients with COPD often experience a high symptom burden over a prolonged period of time. A landmark study compared patients with advanced COPD as defined by $FEV_1 < 0.75L$ and one episode of hypercapnic respiratory failure to those with unresectable non-small cell lung cancer (NSCLC). The COPD cohort experienced worse symptoms across biological, psychological and social domains. Despite this no one in the COPD group received palliative care.[85]

Timely palliative care depends on accurate assessment of prognosis and an understanding of the natural history of the disease. The following graphic (Figure 7) developed originally by the RAND corporation elegantly illustrates the problem of predicting outcome in diseases of organ failure (such as COPD) and hence assigning palliative care.[86,87] Patients with COPD may have many exacerbations from which they recover prior to one from which they do not.

Figure 7 General trajectories of function and well-being over time in eventually fatal chronic illnesses.

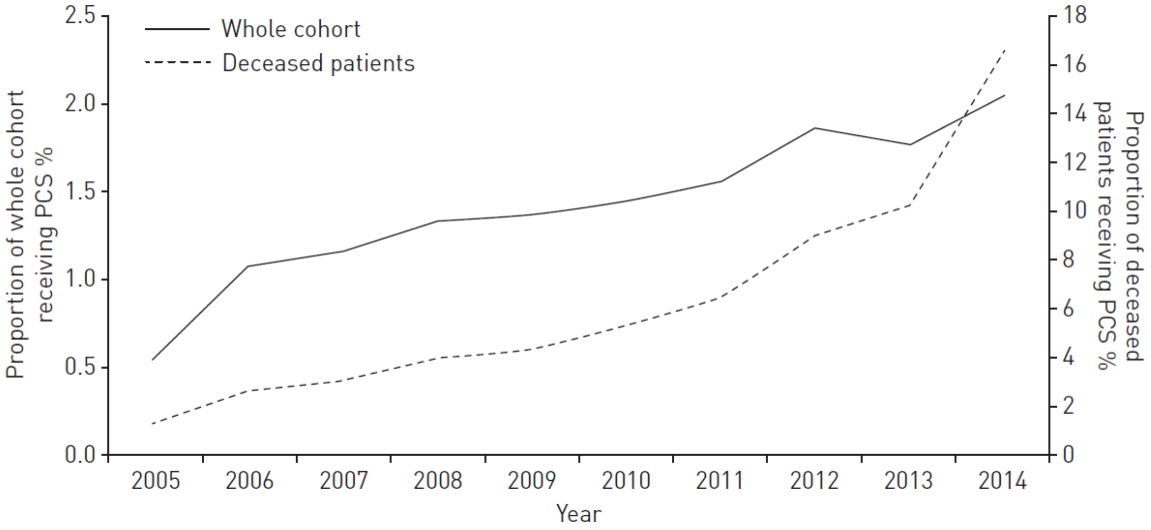


This unpredictability goes some way to explaining the under-provision of palliative care in COPD. Despite several initiatives to promote palliative care, the situation remains sub-optimal. A recent very large-scale study drawing on coding data from the UK Clinical Practice Research Datalink has directly explored receipt of palliative care in patients with COPD in the UK.[88] There are several conclusions:

- The situation is improving (study period 2004-15) but far from ideal. Amongst those who died during the study period 16.7% with COPD (without lung cancer) received some form of palliative care. Figure 8 shows total numbers accessing palliative care by each year in the study. The y axes are scaled differentially by whole population and those that died but not separated by presence of lung cancer. The almost unfeasibly large rise between 2013 and 2014 is unmentioned by the authors but does raise the question of a confounder for example changes to recording.
- The co-diagnosis of lung cancer was overwhelmingly the factor most associated with receipt of palliative care (OR 14.7). Addressing the whole cohort (rather than just those that died in the study period) 6% with COPD alone received palliative care versus 50% of those with both diagnoses.

- Those with COPD alone are more likely to receive a shorter period of palliative care with many receiving it in their final month (i.e. terminal care) than those with co-diagnosed lung cancer.

Figure 8 Proportion of COPD patients that received palliative care support (PCS) in each year during follow up.[88]



The UK national end of life care strategy was rolled out in 2008 with the specific aim of reducing non-cancer deaths in hospital.[89] Between 2001 and 2014 there was only a minor fall in those with COPD dying in hospital.[90] Patients with any respiratory disease are far more likely to die in hospital. 70% of patients with respiratory conditions will die in hospital and few in hospice whereas less than 50% of patients with cancer will die in hospital. 94% of hospice deaths in the UK occur in patients with cancer, indeed direct comparison of English only data shows 0.9% COPD deaths occur in hospice versus 15.3% of those with lung cancer [91,92] This situation is not unique to the UK, a recent population study from Belgium showed patients with COPD were far less likely to received palliative care than heart failure, dementia or cancer.[93]

1.5 COPD Chapter Summary.

COPD is a common, yet complicated and multifaceted condition often related to tobacco smoking. It represents a huge burden to healthcare and as people live longer will have an increasingly complex interaction with other comorbidities. Despite falling smoking rates prevalence is still rising and an estimated 9% of those over 70 in the UK have COPD. Acute

exacerbations confer an appreciable mortality risk and importantly also influence disease trajectory, those resulting in hospitalisation and respiratory failure are particularly pertinent to this thesis.

Little progress has been made by comparison to other major causes of death, the reasons for this are unknown but may be in part due to there being less public and political pressure to address COPD as compared to cancer of heart disease. COPD should be viewed within its societal context; social conditioning to smoke beyond individual control and other biological and environmental factors independent of tobacco burden mean this is an illness of social deprivation not just one of life choices.

Provision of palliative care is lacking with unpredictability of illness trajectory likely to be playing a role. How to strike the balance between standard versus palliative treatments is difficult. Overall, the conclusion of this section is that ‘advanced’ (i.e. complex/nuanced) decision making in COPD will become more frequent and more difficult. Good, evidenced policy will be needed to avoid inequality.

Chapter 2. Introduction: Non-Invasive Ventilation (NIV).

2.1 What is Non-Invasive ventilation?

2.1.1 Description and NIV vs Invasive Mechanical Ventilation (IMV).

NIV involves a tight-fitting mask connected to a ventilator that delivers breathing support. This definition from an early BTS guideline remains true; the *"provision of ventilatory support through the patient's upper airway using a mask or similar device. This technique is distinguished from those which bypass the upper airway with a tracheal tube, laryngeal mask, or tracheostomy and are therefore considered invasive."*[(94)].

The key difference between NIV and IMV is that the interface between patient and ventilator is outside the body not positioned within the upper airway. Unless obtunded for other reasons, IMV requires sedation to be tolerated. There are numerous practical differences between invasive and non-invasive ventilation but perhaps the most important is that patients receiving NIV are typically conscious and maintaining their own airway. This is a substantial advantage over IMV as: monitoring is less invasive; patients can eat, drink or converse with staff and visitors; airway defence mechanisms are to a large part maintained; and nosocomial infections are reduced.[(95)] Patients do not necessarily have to be managed in an intensive care setting which may reduce healthcare associated costs, [(96)] but even when managed in an intensive care unit length of stay is reduced.[(95)]

2.1.2 History of NIV.

There are historical references to the application of positive and negative pressure to provide ventilatory support dating back centuries. However, the mainstream use of mechanised positive (and negative) pressure ventilation is relatively short: Iron lung and early ventilators became widespread during the early part of the 20th century with paralysis due to poliomyelitis generating much of the early mandate. What we may recognise as modern (positive pressure) NIV is a later development stemming from the 1980s with advances in plastics allowing interfaces that create a tight enough seal to form a ventilatory circuit with sufficient comfort for viable use. Since the early trials there has been a rapid increase in NIV use driven by broadening of indications across condition, physical setting and acuity. One large survey found a doubling in the use of NIV in Intensive Care Units (ICUs)

between 1998 and 2004, with further acceleration since then discussed later.[97] This thesis is in reference to modern NIV as exemplified in Figure 9.

Figure 9 Modern non-invasive ventilation set up.

2.2 NIV basic principles.

2.2.1 Continuous Versus Bi-level Pressure.

Continuous positive airways pressure (CPAP) is sometimes erroneously described as a form of NIV. As the name implies, the delivery of gas is continuous and independent of the breathing cycle. This is used notably in the treatment of obstructive sleep apnoea (OSA) and pulmonary oedema and unless specified henceforth CPAP is not being discussed.

Unlike CPAP, NIV provides pressure support during inspiration via episodic delivery of gas along a pressure gradient. Pressure is bi-level, an inspiratory positive airway pressure (IPAP) and an expiratory positive airway pressure (EPAP). The presence of EPAP means that when receiving NIV the lung is never exposed to normal atmospheric pressure.

2.2.2 How Does NIV Work?

The mechanisms leading to the development of type 2 respiratory failure in ECOPD were described earlier. As it becomes harder to adequately ventilate the alveoli the muscles tire, tidal volumes fall and the situation spirals. Incomplete expiration leads to the intrinsic pressure in the lungs being higher than atmospheric pressure, this is known as positive end expiratory pressure (PEEP). Application of extrinsic PEEP to about 50-80% of intrinsic PEEP

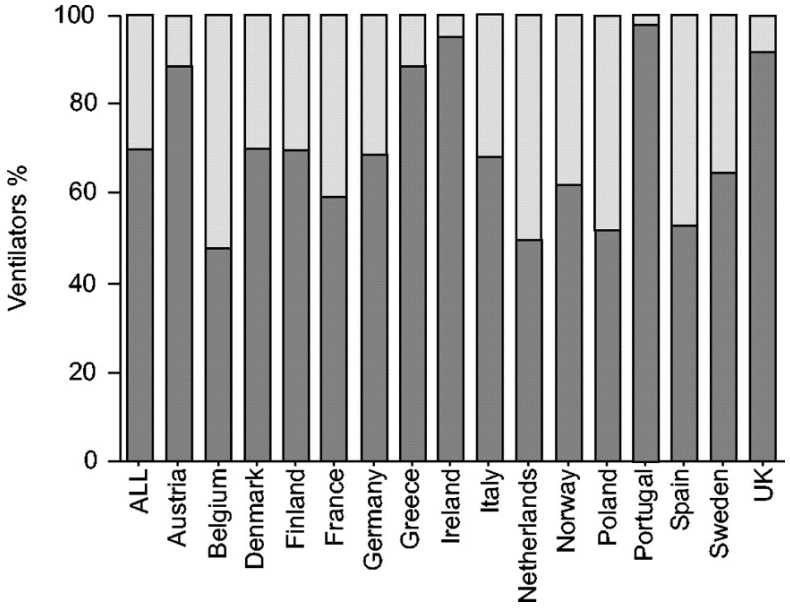
will in most cases result in a reduction in work of breathing by offsetting the amount of pressure required to initiate inspiratory flow (the inspiratory threshold load). The IPAP reduces the work of breathing further and allows respiratory muscles to rest as they no longer need to generate the force to produce flow. These changes typically result in an improved breathing pattern leading to abatement and reversal in dynamic hyperinflation, reduced respiratory rate, increased tidal volume and increased alveolar ventilation. This augmented ventilation reverses some of the immediate downward spiral effects of respiratory failure and allows time for both recovery of muscle fatigue and medical treatments such as bronchodilators, corticosteroids and antibiotics to work.[73,98-100]

2.2.3 Volume and Pressure Targeted Ventilation.

There are two basic ways of delivering positive pressure ventilation; volume targeted, or pressure targeted although modern ventilators with complex triggering and delivery algorithms are blurring such a binary distinction. In volume targeted ventilation the desired tidal volume and the time over which it will be delivered is set and the ventilator delivers this using the required pressure (which consequently varies). In pressure targeted ventilation the operator sets the maximum pressure to be delivered and the ventilator delivers this. Pressure pre-set ventilation has the advantage that it accounts for leak which is an inevitability to some degree between patient and interface.[101] There is also the advantage of negating pressure variation between breaths which may be uncomfortable for the patient. Most major trials investigating the use of NIV to treat ECOPD have used pressure pre-set ventilation modes. [102,103]

There are traditional variations in practice between countries; the Eurovent survey,[104] although now somewhat out of date and limited to home ventilation, highlights this. As can be seen from Figure 10 the UK has one of the higher rates of pressure pre-set ventilation.

Figure 10 Percentage of pressure and volume pre-set positive pressure ventilators used by all home mechanical ventilation users by country. (pressure dark grey) [104]



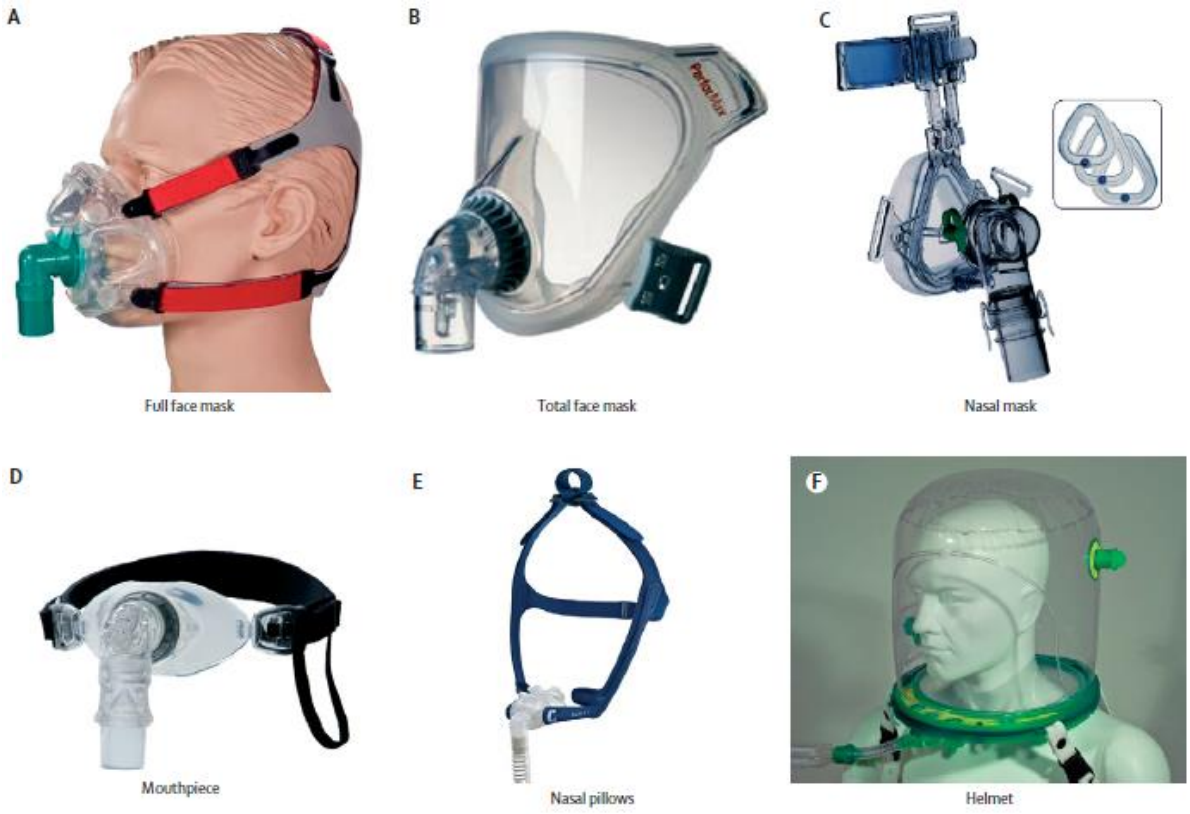
2.2.4 Spontaneous and Timed Modes.

Another consideration is when the ventilator delivers a breath. In a fully spontaneous mode the ventilator will detect the advent of the patient's inspiration and deliver its programmed cycle. In a fully timed mode the ventilator delivers a set number of breaths per minute irrespective of patient efforts. The most common way of delivering NIV is a combination of the two; breaths are initiated by patient effort but a timed back up rate (BUR) is present. Advances in breath triggering and leak compensation have made modern NIV machines more tolerable and more effective than their predecessors.

2.2.5 Patient/Ventilator Interfaces.

In addition to the ventilator settings the other major variable is the type of interface. These can be mouthpiece, nasal, oro-nasal (also termed full face mask), total face or less commonly helmet. These are depicted in Figure 11. The majority of acute NIV for ECOPD is delivered via an oro-nasal (full face) mask.

Figure 11 Non-invasive ventilation interfaces. [105]



2.3 When to Use NIV?

2.3.1 When to Use NIV: Introduction.

There are many acute situations in which NIV may be considered with variable supportive evidence. ECOPD with RA is undoubtedly the most studied with multiple randomised controlled trials. Other situations in which NIV can be used with supportive evidence include (but not limited to) neuromuscular disease (NMD), obesity hypoventilation syndrome (OHS), chest wall deformity (CWD), cardiogenic pulmonary oedema, RA in the context of immunosuppression, post-surgery, post-extubation, de-novo respiratory failure and palliative care. The evidence to support NIV use in conditions other than COPD is not reviewed.

Home mechanical ventilation (HMV) (2.3.8) is a separate issue with differing indications. A clear distinction between an acute episode of deterioration requiring supportive therapy and disease progression to the point of necessitating ventilatory support at home should be maintained (acknowledging the final insult that pushes a patient over the cusp may be an acute exacerbation of their underlying condition).

2.3.2 Trial methodology in ECOPD.

The evidence to support the use of non-invasive ventilation in ECOPD complicated by acute RA is compelling. Randomised controlled trials (RCTs) from the 1990s onwards have well established its efficacy. Of note there is the lack of blinding in most NIV RCTs due to problems creating a non-deleterious sham device although 2 trials have used a sham device they claim does not influence usual care.[106,107] Most trials compare usual care to usual care + NIV. Usual care is ill defined but fairly homogenous, it comprises for the most part: (controlled) oxygen, antibiotics, corticosteroids and bronchodilators with discretionary use of theophyllines. Whether drugs are administered intravenously or orally, the use of particular preparations or dosing varies by setting and in line with traditional regional practice. There are 3 main outcomes reported in the literature:

1) In-hospital mortality.
2) Need for endotracheal intubation.
3) Length of (hospital) stay (LOS).

Other outcomes such as relief of dyspnoea, improvement in pH or reduction in $PaCO_2$, physiological improvement, major complication rate or patient experience are variably reported. In-hospital mortality is a better outcome measure and a criticism of the literature is the absence of internationally defined 'need for intubation' criteria. It should be noted however that few of these trials are adequately powered to report mortality benefit. As so many patients have "do not intubate" orders it is important to note the difference between need for intubation by pre-defined criteria and those that were actually intubated. This is an important distinction and one that has been intermittently observed in the literature. This may be particularly pertinent to the UK where intubation rates are low and is why the Plant et al trial design acknowledged this distinction.[103]

2.3.3 Seminal Trials in ECOPD.

Early case series suggested efficacy [108-110] as did a further exploratory randomised trial of hypercapnic (but not necessarily acidotic) patients conducted in 1993 by Bott et al.[111] In 1995 Brochard et al.[102] randomised 85 patients admitted to ICU with ECOPD and RA to either usual care or usual care + NIV. Fewer patients in the intervention arm required intubation under pre-specified criteria (26% vs 74%) and mortality was lower (9% vs 29%). The next important study was published by Plant et al in 2000.[103] This large RCT has

heralded the use of NIV outside of the ICU. Participants with mild to moderate acidaemia (pH 7.25 – 7.35) and PaCO2 >6kPa were randomised to either usual care or usual care + NIV on general respiratory wards. Mortality was halved in the NIV arm (10 vs 20%) with fewer patients meeting criteria for intubation (15 vs 27%).

Table 2 summarises some of the major studies. The majority are RCTs with 2 case control series also added. Most compare usual care to usual care + NIV, a minority compare NIV to IMV. NIV investigation has been a global endeavour and several notable studies are not available in English. Several studies have included RA in the context of several underlying conditions; unless stated as mixed aetiology, studies are limited to COPD. In each study either a nasal or oro-nasal mask was used, latterly almost all trials use oro-nasal by default. Statistical test results have deliberately not been included in detail as the number of caveats required to present this data would render the table unwieldy and the useful oversight provided lost. For the primary outcome whether this is mortality or need for intubation significance has been indicated. It should be borne in mind that markedly different treatment algorithms e.g. time and intensity of intervention are used across these trials. There are few trials to have reported in the last 10-15 years; following its establishment as the mainstream treatment for RA in ECOPD it is unlikely ethical approval for a protocol without NIV in the usual care arm would be granted.

Table 2 Major studies of NIV in which some or all patients had ECOPD.

First/Last Author Year † = included in Cochrane review.	Country Setting	N	Design Centre	Outcomes (*=p<0.05) (In favour of NIV arm unless stated.) Comparative data displayed: UC vs UC+NIV	Comments Role of Pneumonia
J Bott, J Moxham [111] **1993**†	UK Ward	60	UC vs UC + NIV Multi-centre	Lower 30-day mortality (30% vs 10%)* Median LOS 9D in both arms Improved breathlessness and pH.	Mild or no acidaemia. Pneumonia unreported
L Brochard, A Harf [102] **1995**†	France ICU	85	UC vs UC + NIV Multi-centre	Lower in-hospital mortality 29% vs 9%* Lower need for intubation: 31/42 (74%) vs 11/43 (26%)* Median LOS: 35d vs 23d. Improved 1 hour encephalopathy score and pH	'severe pneumonia excluded'. Fewer pneumonic complications in NIV group
N Kramer, N Hill [112] **1995**†	USA ICU	31	UC vs UC + NIV 2 centres	Lower need for intubation: 11/15 (73%) vs 5/16 (31%)* Lower need for intubation: 8/12 (67%) vs 1/11 (9%) in those with COPD*	Mixed aetiology (74% COPD) Intubation criteria poorly defined. 2 patients each arm with pneumonia.
F Barbe, A Agusti [113] **1996**†	Spain Ward	24	UC vs UC + NIV Single-centre	No benefit in any outcome.	Mild acidaemia: pH 7.33 +/-0.01 Unusual delayed delivery and only 2 x 3hr sessions/day Pneumonia excluded.
T Celikel, S Karakurt [114] **1998**†	Turkey ICU	30	UC vs UC + NIV Single-centre	Lower need for intubation: 2/15 (13.2%) vs 1/15 (6.6%) 4 in UC had rescue NIV (predefined but subjective criteria) Median LOS: 14.6d vs 11.7d One death only in UC arm.	One death only in study in UC arm. Pneumonia present in 5/15 UC and 6/15 NIV
K Wood, M Kollef [115] **1998**	USA ED	27	UC vs UC + NIV Single-centre	Higher in-hospital mortality: 0/11 (0%) vs 4/16 (25%) Similar need for intubation: 5/11 (46%) vs 7/16 (44%)	Mixed (unbalanced) aetiology (only 22% COPD) 9/27 (33%) primary diagnosis of pneumonia. 7/9 were in NIV arm.
S Avdeev, A Chuchalin [116] **1998***†	Russia HDU	58	UC vs UC + NIV Single centre	Lower in-hospital mortality: 31% vs 8%* Lower need for intubation: 28% vs 12% Lower LOS and breathlessness score	Pneumonia not an exclusion, further details unknown

First/Last Author Year † = included in Cochrane review.	Country Setting	N	Design Centre	Outcomes (*=p<0.05) (In favour of NIV arm unless stated.) Comparative data displayed: UC vs UC+NIV	Comments Role of Pneumonia
G Bardi A Palla [117] **2000**	Italy Ward	30	UC vs UC + NIV Single-centre **Case control**	Lower in-hospital mortality: 1 (6.7%) vs 0 (0%) Lower need for intubation rate (2 (13.3) vs 1 (6.7%)	90% male, pH <7.3 excluded. Mean pH 7.36 (NIV) vs 7.39 Pneumonia unreported
P Plant, M Elliott [103] **2000**†	UK Ward	236	UC vs UC + NIV Multi-centre	Lower in-hospital mortality: 24/118 (20%) vs 12/118 (10%)* Lower need for ventilation: 32/118 (27%) vs 18/188 (15%)*	Little benefit identified if pH <7.3
G Conti, G Meduri [118] **2002**	Italy ICU	49	NIV vs IMV Single-centre	Higher in-hospital mortality: 5/26 (19%) vs 6/23 (26%) Lower 1-year mortality: 46% vs 26% (expressed as % of total not survivors)*	pH 7.2 both groups 52% of NIV group received IMV Pneumonia not excluded, reduced VAP: 13% vs 34%
O Dikensoy, N Bayram [119] **2002**†	Turkey Ward	34	UC vs UC + NIV Single-centre	Lower need for intubation: 7/17 (41%) vs 2/17 (12%)* Lower in hospital mortality: 2/17 (12%) vs 1/17(6%) Median LOS: 12.3d vs 8.0d	Not an exclusion Further details unknown.
F Thys, D Rodenstein [106] **2002**†	Belgium ED	20	UC + sham NIV vs UC + NIV Single-centre	Lower need for ventilation: 10/10 (100%) vs 0/10 (0%)* 7/10 in sham arm were then successfully treated with NIV. 2 deaths in NIV arm, 1 in placebo	Study suspended at planned interim analysis due to clear benefit of NIV. Pneumonia excluded
D del Castillo, J Castillo-Gomez [120] **2003***†	Spain 'Resp unit'	41	UC vs UC + NIV Single-centre	Lower need for intubation: 14% vs 5% Median LOS: 10d vs 7 d. Improved 2 hr RR and GCS.	Pneumonia excluded Mortality data unavailable
E Squadrone, P Navalesi [121] **2004**	Italy ICU	128	NIV vs IMV Single-centre **Case control**	Lower in-hospital mortality: 11/64 (17%) vs 16/64 (25%) Lower duration of ventilation and LOS. Fewer serious complications.	Sick population, mean pH 7.18 Prospective NIV vs retrospective controls. CAP included, 21/64 (33%) vs 19 (30%)
S Keenan, D MCormack [122] **2005**	Canada Ward	52	UC vs UC + NIV Single-centre	Need for intubation: 2/27 (7%) vs 2/25 (9%) No deaths, reduced 1 hour Borg score Median LOS: 7d vs 5d (removal of one outlier).	Large number excluded due to no bed. pH <7.30 excluded. (mean 7.4) Pneumonia excluded
T Honrubia, P Galdos [123] **2005**	Spain ICU	64	IMV vs NIV Multi-centre	In-hospital mortality: 14/33 (42%) vs 10/31 (32%) In hospital mortality COPD: 7/18 (39%) vs 3/20 (15%)	Mixed aetiology (59% COPD) Pneumonia included of whom all required IMV 4 with COPD.

First/Last Author Year † = included in Cochrane review.	Country Setting	N	Design Centre	Outcomes (*=p<0.05) (In favour of NIV arm unless stated.) Comparative data displayed: UC vs UC+NIV	Comments Role of Pneumonia
L Liu, Y Yang **2005*†**	China ICU	36	UC vs UC + NIV Single-centre	Lower in-hospital mortality: 16.7% vs 5.6% Lower need for intubation: 44.4% vs 11.1% Median LOS 8.8d vs 6.1d	Pneumonia not an exclusion, further details unknown
Collaborative research group [124] **2005*†**	China Ward	342	UC vs UC + NIV Multi-centre	Lower in-hospital mortality: 12/171(7%) vs 7/171 (4%) Lower need for intubation: 26/171 (15%) vs 8/171 (5%)* Significant improvement in 24 hour pH PaO2, RR and accessory muscle use.	pH >7.24 including many with normal pH Pneumonia not an exclusion. Low overall mortality.
P Matuska, J Skrickova [125] **2006*†**	Czech Republic ICU	60	UC vs UC + NIV Single-centre	In-hospital mortality 23% both arms Lower need for intubation: 10/30 (33%) vs 3/10 (10%)*	Pneumonia not an exclusion,
M Carrera, F Barbe [107] **2009†**	Spain Ward	75	UC + sham NIV vs UC + NIV Double blinded Multi-centre	"In-hospital mortality was similar in both groups" numbers unreported Lower need for intubation: 5/37 (13.5%) vs 13/38 (34%)* Median LOS 10.5d vs 8.5d	Significant cross over and off protocol ventilation. Pneumonia excluded
G Khilnani, S Sharma [126] **2010†**	India ICU	40	UC vs UC + NIV Single-centre	Higher in-hospital mortality: 3/20 (15%) vs 2/20 (10%) Lower need for intubation: 12/60 (60%) vs 3/20 (15%)* Mean LOS 17.8d vs 9.4d	Data collected 1999-2001 long before publication Pneumonia present at admission 45% UC, 40% NIV

2.3.4 Trials Addressing Specific, Clinically Relevant Questions.

It is not simply the case that NIV is superior to standard medical therapy at reducing IMV. Head to head trials have shown at least non-inferiority between NIV and IMV. One difficulty of such trials is that rescue therapy when meeting predefined criteria is usually IMV leading to significant cross-over. This is a necessary consequence of ethical trial protocols and does not imply that had NIV been continued death was certain. Conti et al. randomised 49 patients with RA to NIV or IMV of which 12 out of 23 initially receiving NIV were intubated. In hospital mortality was comparable, but one year outcomes favoured NIV with fewer readmitted or requiring long term oxygen therapy (LTOT).[118]

Early RCTs tended to select less unwell patients but several trials in higher risk patient groups have also been positive: 3 important patient groups have been explicitly studied:

1) Elderly Patients: Nava et al. compared NIV to standard treatment in patients with COPD aged over 75. The primary endpoint was patients meeting intubation criteria; those in standard treatment arm meeting this were then offered NIV rescue therapy. NIV was successful in 38 out of 41 patients initially randomised to receive it and in 22 of 26 patients receiving it as rescue therapy. Older patients may not be considered eligible for invasive ventilation but NIV offers an alternative, effective therapeutic option.[127] Another Italian study compared outcomes in 207 prospectively identified people aged either under or over 75 with ECOPD and RA. In-hospital mortality was 19.8% in the older cohort, which although higher than those younger, is not unacceptably high.[128]
2) Patients with a low Glasgow Coma Scale (GCS): in a prospective study, outcomes in 958 managed in an ICU setting with or without hypercapnic coma (GCS 8 or lower) were compared; the aetiology of RA was heterogeneous. NIV was considered successful when a patient avoided intubation and was discharged to a hospital ward fully conscious for at least 24 hours. Of 286 with COPD, 66 had hypercapnic coma. NIV success was high in both arms (89% no coma vs 86.3% coma) but in-hospital mortality was higher in the coma group (20.4% vs 27.2%). While this study is uncontrolled, and potentially not generalisable to those managed outside of ITU, it demonstrates that NIV is effective in those with coma with an acceptable mortality rate. It should be borne in mind that while the authors report consecutive patients

this is consecutive patients admitted to ICU which imposes considerable selection bias.[129] Similar, but perhaps more realistic conclusions were drawn from a case control study grouping patients by consciousness score. They found lower GCS to be associated with worse outcome but that treatment is not futile.[130]

3) Patients with community acquired pneumonia (CAP) and respiratory failure: In an early, mixed aetiology study patients with CAP and RA were randomised to either UC or UC + NIV. NIV reduced need for intubation but not in-hospital mortality. More importantly, of patients with COPD treated with NIV (n=12) none met intubation criteria vs 54.6% in UC arm (n=11) . In-hospital mortality was similar (8.3% vs 18.2% p=0.59) but two month mortality was markedly different in favour of NIV (11.1% vs 62.5% p=0.05).[131] This study is too small and selected to draw definitive conclusions but supports NIV in pECOPD.

2.3.5 Instances Where NIV Has Not Been Shown to be Beneficial in COPD.

Not all trials have been positive in support of NIV. NIV doesn't confer any mortality benefit if acidaemia has not developed, i.e. to prevent development of RA rather than treat it once established. Much of the evidence for this is extrapolated from trials with a mean pH close to the normal range where a substantial number are non-acidaemic rather than from specific trials in defined, non-acidotic populations..[117,122,124]

In probably the only truly negative RCT of NIV vs usual care in ECOPD, Barbe et al. recruited 24 patients to each arm. Those in the intervention arm received nasal NIV in 3 hours sessions once in the morning and once in the afternoon for 3 days. The mean pH was 7.33 in both arms and NIV wasn't commenced until 12-48 hours after admission. No benefit was identified in any outcome measure. The very small sample size and unusual manner of delivery of the intervention mean few conclusions with reference to modern NIV can be drawn.[113] Wood et al also reported no positive findings but their series included mixed aetiology and so few patients with COPD as to render any interpretation in this setting obsolete. [115]

2.3.6 Cochrane Review and Meta-Analysis.

A recent Cochrane review and meta-analysis of the use of NIV to treat RA in ECOPD (defined as pH <7.35 and PaCO2 >6kPa) included 17 studies comprising 1264 participants drew several important conclusions: [132]

- NIV provides 46% risk reduction of in-hospital death vs usual care without NIV. This translates into a number needed to treat (NNT) to save a life of 12.
- Endotracheal intubation risk is reduced by 65%. Equivalent to a NNT of 5.
- Length of stay is reduced (mean difference of 3.4 days).
- The magnitude of benefit in mortality and intubation reduction is maintained whether mild or more severe acidaemia using pre-defined pH thresholds (pH <7.3 vs those with pH of 7.34-7.30).
- Similarly, whether NIV is provided in ICU setting or on a ward does not affect magnitude of benefit. (This may be true within the clinical trials, but the authors caveat careful consideration of local factors such as staffing levels and expertise.)
- Further RCTs comparing usual care without NIV to NIV are unwarranted and unlikely to be granted ethical approval.

2.3.7 Other Observations from the Literature.

- The intervention of NIV has been heterogeneously applied both in terms of pressure support and duration: in most trials NIV is applied shortly after the identification of need and delivered semi-continuously throughout the first 24-48 hours as tolerated. NIV use in the first 24 hours varies between publications: Kramer et al report median use of 20 hours whereas Plant et. al. report a median of 8 hours. Further variation in the published literature surrounds the criteria for NIV removal. Differing weaning strategies are employed, convention in the UK is to gradually reduce the time and pressure support with guidelines recommending tapering over 2-3 days. In RCTs maximum achieved IPAP is also varied usually in the 10-18 range which lies below the modern-day UK recommendations of 20-30,[133] there is evidence to suggest higher intensity NIV is more effective.[134] An important future research topic is better quantification of NIV delivery and weaning strategies.
- Mortality in the clinical trials is lower than seen in real world practice. The reasons for this are unclear but is probably largely related to inclusion of frailer, more unwell

patients excluded from clinical trials. This raises the possibility there may be a cohort of patients receiving NIV who derive little benefit. If identification of this group were feasible it may lead to better use of palliative care.

- The role of NIV in pECOPD is poorly understood, as can be seen from the summary table the inclusion of patients with pneumonia is variable and reporting is inconsistent at best. Limited evidence supports the use of NIV in pECOPD and there are certainly no grounds for exclusion of this patient group.

Overall, there is near universal acceptance that NIV is an excellent, lifesaving treatment for patients with ECOPD complicated by RA and offers at least non-inferior alternative to IMV.

2.3.8 Home Mechanical Ventilation in COPD.

There have been several trials investigating the use of home ventilation in COPD. Three major trials, reported in the recent past are summarised. While not the primary subject of this thesis the influence of domiciliary ventilation is likely to significantly alter the landscape of in-hospital ventilation over the coming decades.

Struik et.al: 201 patients with persistent hypercapnia (PaCO2 >6.0 kPa) 48 hours after termination of NIV used to treat acute RA were randomised to receive home NIV or usual care for 1 year. Pressures were modest, mean IPAP 19.2 (SD 3.4) and EPAP 4.8 (SD 1.0). No benefit in the primary endpoint of 1 year admission free survival was shown (65% vs 64%). Amongst those that completed the trial there was little difference in PaCO2 (6.4 vs 6.6 kPa) suggesting the intervention had little physiological impact.[135]

Koehnlein et.al: 195 patients with stable disease and a PaCO2 of >7 kPa (i.e. not related to exacerbation event) were randomised to NIV or usual care. Patients in the intervention group received high intensity NIV (both high pressure and high BUR) targeted to reduce their PaCO2 by 20%. Significant 1-year mortality benefit was seen: 12% vs 33%. The major criticism of this trial is one of generalisability, 36 centres took 7 years to recruit 195 patients suggesting that selection bias may be a lot higher than reported. Generalisability is further questioned by a low overall emergency admission rate in both groups and only 3% in the control group required acute NIV, substantially less than would be expected in such an unwell group of patients (all had persistent hypercapnia, 65% used LTOT).[136]

Murphy et. al: The trial by Struik et. al. was thought to be negative because a substantial proportion of hypercapnic patients soon after acute NIV would correct without intervention; long term, post discharge outcomes in patients with reversible hypercapnia are comparable to those with normocapnia.[137] Murphy et al. randomised 116 persistently hypercapnic (PaCO2 >7 kPa) patients 2-4 weeks following acute NIV to either HMV + oxygen or oxygen alone. Those receiving HMV had pressure support titrated to achieve CO_2 reduction of 0.5-1 kPa. They found median admission free survival of 4.3 months in the intervention group and 1.4 months in the control group although no significant difference in mortality alone. COPD exacerbation rate was median 3.8 (IQR 1.7-6.0) in the HMV arm and median 5.1 (IQR 1.0-9.2) in the oxygen alone arm.[138]

There is increasing interest in and use of home mechanical ventilation in COPD. Some patients cannot be weaned acutely from a ventilator and receive domiciliary ventilation but are not included in clinical trials as they cannot be easily randomised. This group will also grow, evidence here is derived from clinical experience rather than from RCTs. All these patients have advanced COPD and HMV will necessarily interact with any NIV service. Whilst use is increasing, results from clinical trials are less impressive than some would hope. Such a high intensity intervention comes with increased patient contact and typically direct telephone access to a clinician which may well have some treatment or admission avoidance effect. Nevertheless, it is intuitive that an intervention able to demonstrate a sustained lowering in PaCO2 will in the long run, if patient selection and NIV delivery appropriate, have positive outcomes.

2.4 Current NIV Realities, the Case for Poor Practice and NIV Underuse.

2.4.1 Information sources.

There are several excellent sources of information to give a comprehensive oversight of UK practice. Crucially these are based on case record review and not from coding databases which may give broad oversight but offer few specific insights. NHS procedure coding does not currently differentiate between CPAP and NIV providing ventilatory support, (both have the same OPCS code E85.2) [139] rendering unverified coding data of limited use.

The British Thoracic Society produced audit data of NIV practice annually from 2010 to 2013.[140-143] Several large national COPD audits (which have dedicated respiratory failure

sections) with data contributed by almost every NHS trust offer excellent generalisability.[29,81] The National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report was commissioned after concerns over rising mortality and variations in practice.[144]

2.4.2 NIV services: Speed of change.

NIV services have developed rapidly from a treatment which was the remit of intensive care units and a few centres in the early 1990s to a mainstream treatment. 100% of trusts in England and Wales responded to the 2015 national COPD audit; in only 0.2% of total cases was lack of availability of NIV recorded. For comparison, in 2003 62% of patients with pH <7.35 did not receive ventilatory support, of the 36% of cases where the reason for non-provision is known 10.9% was lack of availability. However, while NIV is available in (nearly) every acute trust service, capacity may still not yet meet demand during high requirement periods; NCEPOD reports 40% of hospitals had insufficient capacity to meet demand for acute NIV.[144]

Alongside increasing availability there has been increasing use: as a proportion of total cases of hospitalised ECOPD, NIV use rose from 8.5% in 2003 to 12% in 2014 without any obvious increased need based on ABG criteria.[29,145] This rapid development of services is not limited to the UK, in the United States of America (USA) assessing >7 million ECOPD hospitalisations between 1998 and 2008 Chandra et al. found an increase in NIV use of 462%.[146] Almost identical increases were seen in a study of the Danish national registry between 2004 and 2011 where NIV use increased 4.6 times.[147] In a large Scandinavian audit of admissions in 2005 across 3 hospitals 14% of ECOPD admissions received NIV although the authors note wide variation between centres.[148]

2.4.3 Who initiates NIV?

The NCEPOD report identified 9299 cases in February and March 2015 coded as E85.2 as described above. A random selection of up to 5 cases per hospital were selected. 432 cases had a clinician completed questionnaire including details of service provision and 353 underwent external, expert case note review. In 69.1% the indication for NIV was ECOPD and overall there is a high proportion of patients with multiple comorbidity, advanced frailty and breathlessness causing them to be housebound. The decision to initiate NIV was made by a

wide range of specialties, the commonest being general medicine. Only a third of cases (33.4%) were initiated by respiratory or critical care and the decision to initiate NIV was made by a consultant in 28.3% of cases. The specialty of the first consultant to review the patient varies and 31.7% were by respiratory or critical care. Therefore, a non-specialist junior clinician usually initiates NIV and senior review is by a non-specialist. It should be remembered that those initiating NIV are likely to be the same as those deciding not to use NIV where potentially indicated. While direct comparison to the UK is problematic, and much has changed since 2006, a survey of American practice revealed physician lack of knowledge to be the most important reason for under-utilisation of NIV.[149]

2.4.4 Where is NIV provided and the role of level of care.

The current and recently updated UK guidelines state: [133]

- *The severity of AHRF, and evidence of other organ dysfunction, should influence the choice of care environment.*

- *NIV should take place in a clinical environment with enhanced nursing and monitoring facilities that are beyond those of a general medical ward.*

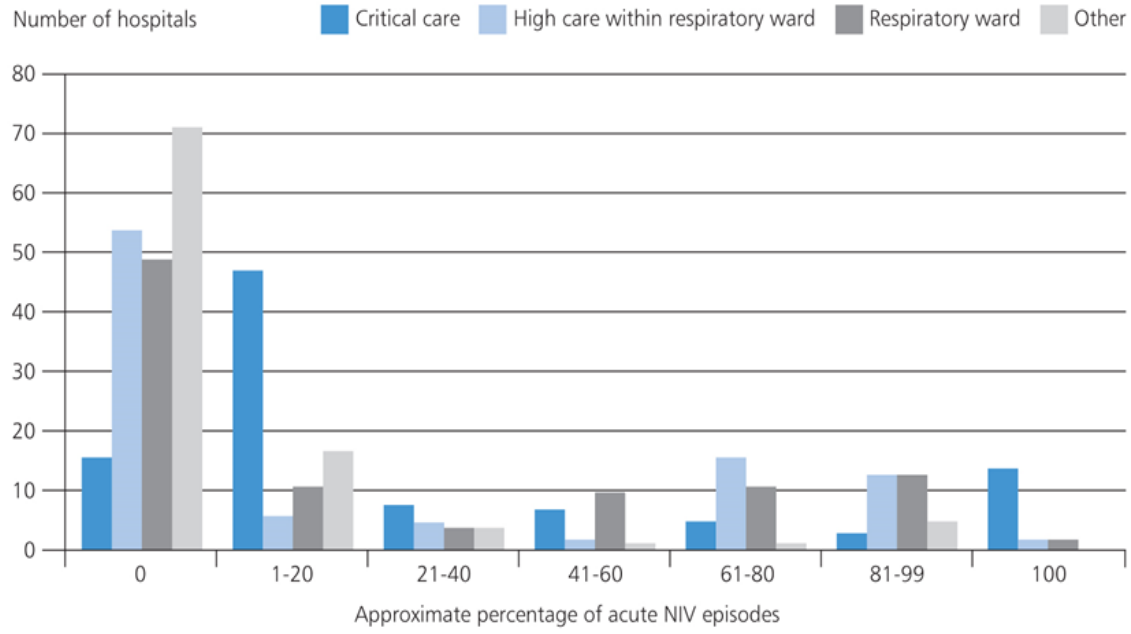
- *Initial care plans should include robust arrangements for escalation, anticipating that around 20% of AHRF cases should be managed in a level 2 or 3 environment.*

The majority of NIV is delivered on acute medical units or respiratory wards; 8-10% of cases are managed in a critical care environment.[29,143,144] It has been recommended that those with a pH of <7.26 are managed in a level 2 or 3 environment because of an increased risk of treatment failure in these patients.[133,150] What is classed as critical care may provoke debate but generally refers to a designated unit with enhanced staffing ratios and monitoring facilities. Typically, in the UK it comprises level 2 care which has 1 member of staff to 2 patients and level three has 1 to 1 care. The emerging trend toward respiratory support units (RSU) raises further nomenclature headaches. In our trust patients managed in an RSU are classed and costed as level 2 patients. The following sections seek to highlight the need to improve patient access to higher level of care beds whether in a traditional ICU

or high dependency unit (HDU) setting or in a RSU rather than assess the merits of one versus another.

In all episodes of ECOPD in the 2015 National UK COPD audit, 882/13,414 (7%) were assessed by critical care, of which 257 (1.9%) were transferred and 0.8% were intubated. From the same data set, 1612 (12%) were treated with NIV.[29] In the 2013 BTS NIV audit 91% of patients treated with NIV were managed on a ward despite 47% presenting with a pH of <7.26. Moreover, in those needing NIV due to ECOPD (61% of the total population) with a pH of <7.26, in-hospital mortality was 28% if NIV commenced in a HDU/ICU vs 40% if outside HDU/ICU.[143] Similar findings of underuse of critical care beds especially in high risk patients prompted NCEPOD report to conclude: "*This raises concerns that it has become accepted practice to provide care of NIV patients in non-critical care areas despite a high chance of treatment failure.*". The following graphic from NCEPOD (Figure 12) shows where NIV was provided. In a number of hospitals no NIV was delivered in critical care and in some all of it was, 1-20% was the commonest response.[144]

Figure 12 Percentage of NIV episodes provided in different clinical areas (NCEPOD report).



As was noted in the COPD and Asthma Outcomes Study (CAOS) there may be a herd effect within individual intensive care units leading to marked variation in practice from one hospital to another.[151] Point two of the quoted guideline is probably the most important and it seems non-adherence to this is an important conclusion of NCEPOD; it doesn't matter

whether an NIV service is based around an ICU, a (respiratory) HDU or a respiratory support unit (RSU) within a medical ward the importance is recognition that these patients require higher staffing ratios than can be offered by a normal ward. The UK has a relative shortage of critical care beds. There have been several studies comparing critical care provision between countries; it is estimated the UK has between 3.5 and 6.6 ICU beds per 100,000 population. Compared to Germany (24.6 - 29.2/100,000) France (9.3 - 11.6/100,000) or the USA (20.0/100,000) there are significantly fewer ICU beds.[152,153] Italy has developed a network of respiratory high dependency care units, a model that some trusts in the UK are attempting to mirror.[154] It is possible that as things stand, despite the sensible advice laid down in national guidance, for most hospitals in the UK provision of NIV is on a medical ward.

2.4.5 Underuse of NIV.

Despite the growth in NIV services there remains substantial underuse. In the 2008 national audit 26% of patients had respiratory acidaemia but 12% received ventilatory support (NIV and/or IPPV). Similar findings were reported in 2015. 10,315 had an admission arterial blood gas of which 22% had a pH of <7.35. 4411 went on to have a second blood gas of which 38% were acidaemic but only 12% received NIV. The outcomes are displayed in Table 3, data is lifted directly from the report where it is presented in such a way that makes drawing out the absolute number of patients meeting ABG criteria for ventilation impossible. Who developed acidaemia on later ABGs or the time gap between 1st and 2nd samples is not reported.

There is no doubt that a substantial number who could have benefitted from NIV did not receive it. It is not feasible to suggest all those in either audit with RA who did not receive ventilatory support normalised their pH without NIV. Trials of medical therapy may result in correction of respiratory acidaemia in approximately 20% of cases.[155] One may actually conclude that potential reversibility is falling as oxygen toxicity from overzealous oxygen use is falling following the publication of a definitive RCT proving its harm.[156] Evidence to support this assertion can be seen in UK audit data: median $_pO_2$ on initial blood gas has fallen from 9.2kPa in 2003 to 8.3kPa in 2015 with a similar fall in those with excess $_pO_2$ of >13kPa from 19% to 8%.

Table 3 pH results and % treated with NIV, National COPD audit 2015.

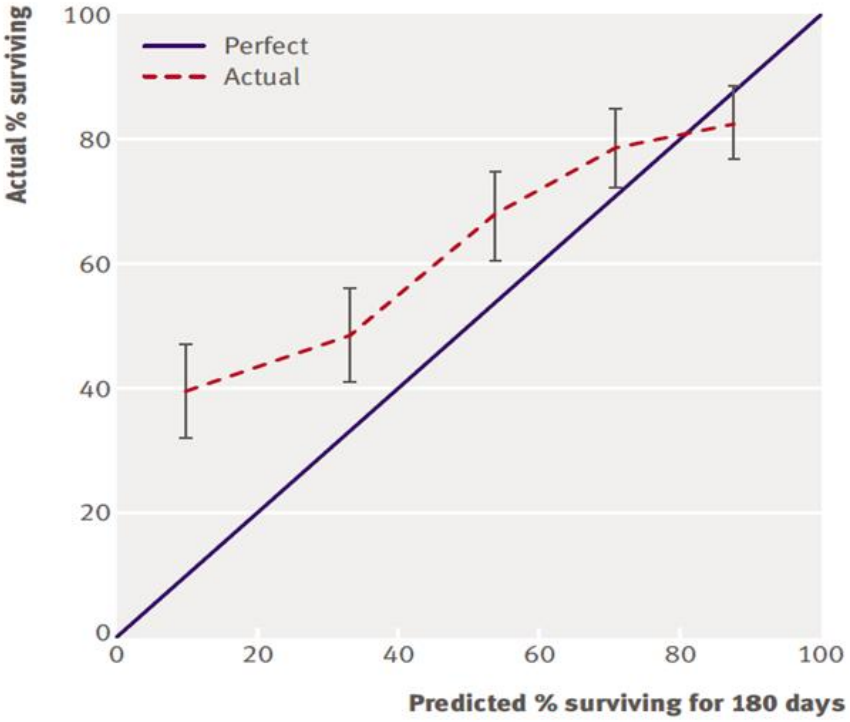
	ABG result group	Treated with NIV	
First/Only ABG	pH <7.26	507/657	77%
	pH 7.26-7.34	646/1629	40%
	pH ≥7.35	412/8029	5%
Only one ABG	pH <7.26	15/41	37%
	pH 7.26-7.34	15/323	5%
	pH ≥7.35	59/5612	1%
First and Second ABG	pH <7.26 & pH <7.26	260/307	85%
	pH <7.26 & pH 7.26-7.34	189/235	80%
	pH <7.26 & pH ≥7.35	144/526	27%
First and Second ABG	pH 7.26-7.34 & pH <7.26	81/101	80%
	pH 7.26-7.34 & pH 7.26-7.34	406/679	60%
	pH 7.26-7.34 & pH ≥7.35	144/526	27%
First and Second ABG	pH ≥7.35 & pH <7.26	53/83	64%
	pH ≥7.35 & pH 7.26-7.34	118/275	43%
	pH ≥7.35 & pH ≥7.35	182/2059	9%

In conclusion it has become customary to audit those that receive NIV and evaluate processes but there is a missing cohort of patients in whom neither the details of the decision not to offer ventilation nor the ultimate outcome is known. One potential cause of underuse other than structural inadequacy is pessimism in this patient group.

2.4.6 Prognostic Pessimism in COPD.

In COPD, clinicians' prognostic estimates have been shown to be inaccurate with widespread prognostic pessimism. The multicentre CAOS study compared clinicians' estimated six month survival with actual outcomes. 832 patients from 92 ICUs and 3 respiratory HDUs were recruited of whom 70.2% survived to discharge and 62% to 180 days. Figure 13 shows 80% of clinicians' 180-day survival predictions were pessimistic, everything above the blue line represents excessive pessimism compared to actual outcomes.

Figure 13 Actual vs predicted 180 day survival.[157]

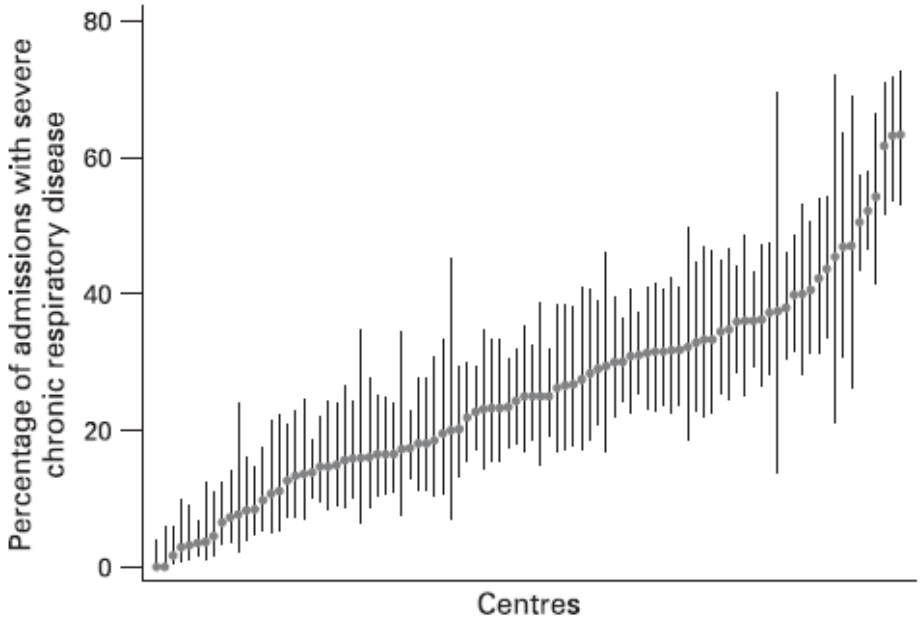


Consider all patients ranked in order of estimated clinician survival, groups can then be compared: In the lowest quintile clinicians estimated survival to be 10% compared to actual of 40%. Moreover, in the lowest decile the discrepancy is even greater; estimated survival was 3% versus actual survival of 36%.[157] It should be noted that as these patients were recruited from inside critical care environments; selection had already been imposed, we know nothing about the patients who were declined admission to critical care. However, even when asked to estimate outcome of patients who had already been selected for their treatment potential, pessimism is rife. The patients who survived to 180 days were surveyed with a high (81%) response rate. 73% said their quality was as good as, or better than, a stable period pre-index admission and 96% would choose to receive similar treatment again.[151]

Another important finding reported in a linked paper is the wide variation in practice between units. 8717 patients admitted to the participating units between 2000-6 were retrospectively assessed. Clinicians may be consistent within their institution but access to ICU for patients with COPD is not the same around the country. If everyone in a unit practices in a similar manner there is limited opportunity for feedback on judgements. Figure 14 shows that some centres have effectively closed their doors to patients with 'severe respiratory disease', i.e. those with COPD who they admit are only those with least

disability. CAOS defined severe respiratory disease as: *"Permanent shortness of breath with light activity due to pulmonary disease. Functionally, this patient is unable to work and has shortness of breath performing most normal activities of daily living, for example, walking 20 metres on level ground, walking slowly in the house, climbing one flight of stairs, dressing or standing."*

Figure 14 Percentage of patients with COPD and severe respiratory disease in a period of stability before admission to the ICUs participating in the CAOS study 2000-2006. n=8717, mean and 95% confidence intervals by centre displayed.



A similar pattern of inter-unit variability of is seen in mean age of those admitted. It should also be noted that the mean age for most units is close to 65, none is over 70 and there are only a handful of units even have an upper confidence interval over 70 years.[151] The mean age of a patient admitted to hospital in the UK with ECOPD is 72 and those receiving NIV is similar.[29,81,144] Over half of patients admitted to critical care for any reason in the UK are over 65 [158] and historical data (2008-9) closer to the study period shows the commonest age bracket was 70-74. As shown earlier in the NIV population aged >75 good outcomes can be expected and current guidance (published post CAOS) expressly recommends *"advanced age is not an important determinant of outcome with NIV treatment of AHRF."*[133] It would appear that there is considerable variation in practice and at the time of the CAOS study at least there was an age bias acting against patients with COPD admitted to critical care compared to the average ICU patient despite specific, contrary guidance.

Earlier data from the same group gives a fascinating insight into gatekeeping decisions amongst patients with COPD.[159] 98 consultants from one network (34 intensivist, 17 respiratory, 47 other) were asked to give an opinion on admission to ICU. Three hypothetical patients were presented by telephone simulating a registrar/consultant discussion. Importantly vignettes were detailed and 70% felt the simulation represented their decision very well and a further 24% quite well. Respondents reported a median of 10 gate-keeping decisions in the preceding year. Very wide estimated survival probabilities were observed in all three simulations with those choosing not to admit the patient to critical care being more pessimistic. When the same consultants were asked to identify a predicted in-hospital survival below which they would not intubate a hypothetical patient with COPD in their mid-70s the mean threshold was 22%. The in-hospital survival for a time matched UK ICU patient intubated for ECOPD of 59.4%.[160] One cannot directly compare the two, but a high threshold for intubation in ECOPD will lead to a lower overall mortality. It is likely to be that well-intentioned clinicians have selected a sensible lower limit for intubation, but their estimates of survival are inaccurate and hence too many patients are considered futile cases therefore a selection bias towards fitter patients is imposed.

2.5 NIV Policy and Guidelines.

2.5.1 British Thoracic Society Guidelines.

In the absence of clear guidance, it is perhaps more reasonable to excuse poor practice. Therefore it is important to note that there has been clear and exhaustive guidance surrounding the use of NIV in the UK dating back to 2002.[161] The most up to date guideline was released in 2016,[133] guidance is unambiguous and achievable, i.e. it does not set goals that only top performing hospitals or trusts could achieve. Some of the key recommendations are identified above (2.4.4).

2.5.2 British Thoracic Society Quality Standards.

In April 2018 six quality standards were introduced by which acute NIV delivery in the UK can be judged. Each statement is accompanied by a clear numerator and denominator to standardise audit. These standards and the document as a whole mirror some of the systematic problems highlighted. They have been included in full here for reference as they are so pertinent to the future landscape of NIV in the UK.[162]

Table 4 British Thoracic Society standards for acute non-invasive ventilation in adults.

1	Acute non-invasive ventilation (NIV) should be offered to all patients who meet evidence-based criteria. Hospitals must ensure there is adequate capacity to provide NIV to all eligible patients.
2	All staff who prescribe, initiate or make changes to acute NIV treatment should have evidence of training and maintenance of competencies appropriate for their role.
3	Acute NIV should only be carried out in specified clinical areas designated for the delivery of acute NIV.
4	Patients who meet evidence-based criteria for acute NIV should start NIV within 60 min of the blood gas result associated with the clinical decision to provide NIV and within 120 min of hospital arrival for patients who present acutely.
5	All patients should have a documented escalation plan before starting treatment with acute NIV. Clinical progress should be reviewed by a healthcare professional with appropriate training and competence within 4 hours of starting NIV and by a consultant with training and competence in acute NIV within 14 hours of starting acute NIV.
6	All patients treated with acute NIV should have blood gas analysis performed within 2 hours of starting acute NIV. Failure of these blood gas measurements to improve should trigger specialist healthcare professional review within 30 min.

Standards 1,2,3 are particularly relevant to the preceding sections and this thesis. Statement 1 is in keeping with the observation that there are an unknown cohort who do not receive NIV. The numerator/denominator recommends blood gas data is reviewed and all those meeting criteria but not receiving NIV be reviewed and discussed.

2.5.3 Strategy Bodies.

Increasing NIV usage had been recognised in NHS policy prior to the spotlight of NCEPOD, it was identified by both NHS England ("Reducing Premature Mortality") [163] and the Department of Health ("An Outcomes Strategy for COPD and Asthma") [164] as a key priority. This recognition has continued and it features prominently as one of the 'priorities for optimisation' in the 'unexpected mortality national challenge' limb of the COPD RightCare pathway. *("RightCare Pathways provide a national case for change and a set of resources to support Local Health Economies to concentrate their improvement efforts where there is greatest opportunity to address variation and improve population health.")* [165]

Not an official policy institute, but certainly influential, the most recent Cochrane review of the use of NIV in ECOPD concluded in its implications for research section that "*additional*

research would enhance our ability to more accurately select the right patients and the right levels of ventilation."[132]

2.6 NIV Chapter Summary.

NIV is one of the success stories of modern respiratory medicine. It has developed rapidly and spread from the intensive care unit onto the general medical ward. The strongest evidence base is in ECOPD with respiratory acidaemia and a pH in the 7.25-7.34 range. In this circumstance under favourable conditions in-hospital mortality is halved. However even when specified high risk groups are studied it remains efficacious.

Non-Invasive ventilation has undergone rapid change, the pace of which may have outstripped the expertise and infrastructure required to deliver it. In the UK, the vast majority of NIV is delivered on wards rather than in an intensive care or high dependency unit. Two thirds of NIV is initiated by non-specialist clinicians and, by extension, most decisions not to provide NIV must also be likewise. Only about half of patients with respiratory acidaemia during hospitalised ECOPD receive NIV. Some of these patients will respond to medical therapy but it is over-optimistic to assume that a (large) proportion of the missing would not have benefitted from NIV. The reasons why so many patients are not receiving NIV are multifaceted. There is evidence of prognostic pessimism, but other factors may include; clinicians feeling out of their depth, lack of knowledge of the treatment effectiveness, dismissal of the condition as unimportant and poor infrastructure, though these are inferred observations rather than proven facts. Specialists are prognostically inaccurate and this is likely to set an example to generalists commonly managing these patients and, in part, result in the situation described by NCEPOD where it has become normal for patients with high levels of need and high mortality to be managed on medical wards. NIV is an extremely effective treatment so in many cases a decision not to ventilate on the grounds of assumed poor outcome will be a self-fulfilling prophecy and entrench practice by confirmation bias. The need to improve and objectify NIV services has been nationally recognised.

Chapter 3. Introduction: Cognitive Biases and Predictive Modelling.

3.1.1 Introduction to Cognitive Bias.

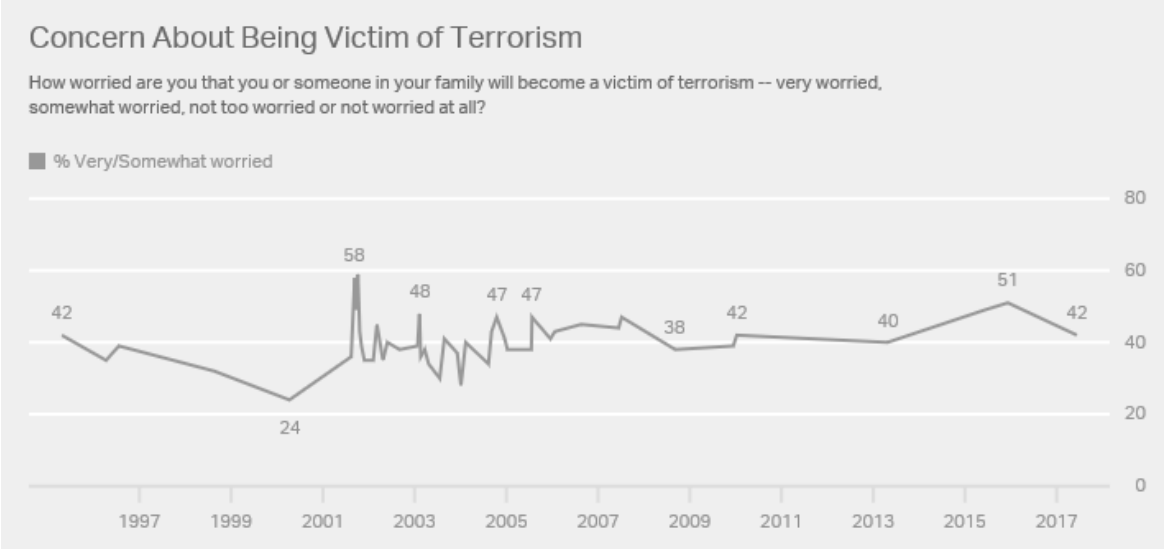
If we accept that there are a cohort of patients missing out on ventilation the next question is why? Healthcare institutions, doctors and nurses are not deliberately causing harm. How has wholesale bad practice and thinking crept in systematically? It has been alluded to that prognostic pessimism and cognitive biases may be contributing. The following sections seek to illustrate how this may be so. In a system operating under finite resource, its allocation falls to individuals on both macro (e.g. service commissioning) or micro (e.g. individual patient entrance to ICU) scales. Some variance can be attributed to differing priorities and local pressures, but it seems likely that the inherent biases of human thinking are playing a role. *"Over the past 40 years, work by cognitive psychologists and others has pointed to the human mind's vulnerability to cognitive biases, logical fallacies, false assumptions, and other reasoning failures. It seems that much of our everyday thinking is flawed."* [166] Cognitive biases unconsciously influence the analysis of information we consume and the decisions and opinions we then make and hold; knowledge and vigilance of these psychological pathways could be used by clinicians to adopt more rational diagnoses or management plans. More nefarious use is mainstream for example by marketers and advertisers to manipulate our purchasing habits.

Critical appraisal of medical literature is commonplace and is incorporated into many aspects of medical education. An appreciation of bias in clinical trials is exactly why double blinded, randomised, controlled trials are the gold standard. How bias affects the individual doctor is afforded relatively less import by the profession: there is little or no survey data on whether clinicians are aware of cognitive bias in their daily practice and there appears to be little focus in the UK upon educating doctors as to its effects on medical decision making.[167] A search of the Royal College of Physicians website [168] undertaken on 29/01/2018 returned 24 results comprising courses, workshops and online learning for critical appraisal whereas none were returned for bias or cognitive bias. Similarly, the UK specialist training curriculum for general internal medicine (GIM) returns 5 hits for critical appraisal and 1 for bias (which is subpoint 27/27 under Decision making and clinical reasoning).[169]

Gallup news has polled Americans routinely for many years on their fear of terrorism (Figure 15). The chance of an individual American being a victim of terrorism is vanishingly unlikely

and several orders of magnitude less than the more proportional fear of being a victim of non-terrorist gun crime. There are many factors at play but there is no doubt the high numbers who are either “very worried” or “somewhat worried” are not the product of rational thought but of a reflex driven by the inherent biases of the human mind. Availability bias which will be explained shortly, explains the upturn in fear that is maintained for years after the 2001 terrorist attack. This somewhat sensationalist example is included as a stark illustration of the power of cognitive bias and its ability to influence human thinking.

Figure 15 Gallup Poll: Percentage of Americans fearing terrorism.[170]



3.1.2 What is Cognitive Bias?

The understanding of decision making has evolved over time. The concept of the dual process theory (DPT) has become accepted and applied to the understanding of human decisions in many fields. Much of the modern theory and its refinements are attributed to the Nobel prize winning psychologist Daniel Kahneman and his co-worker Amos Tversky. It contends there are two types of mental process:

Type 1 or intuitive processes are dominant and account for up to 95% of our decisions. These automatic, mental processes are driven by ‘heuristics’ which are mental shortcuts derived from emotion, stereotypes and pattern recognition. Most of the time this rapid, type 1 way of thinking serves us well and prevents dealing with the thousands of decisions we make sub or barely consciously everyday. Some examples given by Kahneman include: “*solve 2+2*”, complete the phrase “*war and…*” or “*come up with a good chess move (if you are a chess master).*” However, because they are adaptive and intuitive they are

prone to failure. A systematic heuristic error is a cognitive bias. Heuristics and cognitive biases were predominately described in the 1970s by Tversky and Kahneman and have been continuously developed, now over 100 different types of cognitive bias have been described. One can imagine that there is allegory between the chess master's autopilot move and the doctor's diagnosis.

Type 2 process are slow, deliberate and analytical incorporating evidence evaluation. These processes are more reliable but are mental resource intensive hence the predisposition toward type 1 processing. Some examples include: "*dig into your memory to recognise a sound*", "*determine the validity of complex logical reasoning*" or "*determine the appropriateness of a behaviour in a social setting*." Ideally important decisions affecting patients' lives should be type 2 processes removing as much of the reflex, automatic pathway as possible.[171-174]

Table 5 shows a summary of some important cognitive biases with hypothetical examples of how it may impact upon provision of ventilation.

Table 5, Types of Cognitive Bias. Partially adapted from Croskerry, Acad. Med 2003 [175]

Type of Bias	Description	Ventilation Case example
Affect Heuristic	Risk/benefit perception is linked to strength of positive or negative effect associated with the activity being evaluated	Having an artificially high mortality estimation and consequent high threshold for admitting patient to critical care due to negative perception of COPD.
Aggregate Bias	Belief that aggregated data used to develop guidelines disproportionately does not apply to one's own patients who are special or more complicated.	Failure to offer sufficient IPAP due to fear of pressure damage and experience of historical case of pneumothorax.
Anchoring	Giving disproportion value to particular feature(s) of a case and failing to adjust perceptions with time.	Fixing upon a low FEV_1 rather than a good exercise capacity as grounds for prognostic pessimism.
Availability heuristic	Increasing the likelihood of frequently occurring or recently experienced events as they readily come to mind.	Missing opiate toxicity causing RA in patient with mild COPD and attributing unexpected respiratory failure to the more frequently experienced ECOPD.
Bandwagon effect	The tendency to do and think as others do. Leads to positive reinforcement from peers.	Individual hospitals have markedly different thresholds to use of NIV or admission to critical care as a result of the bandwagon effect.
Confirmation Bias	To cherry-pick, interpret and recall evidence favourable to one's preconceptions rather than evidence to refute it.	Patients with COPD 'never wean from the ventilator'. Citing rates of treatment failure without acknowledging other variables such as other organ failure or rate of intubation.

Diagnosis Momentum	Once someone receives a diagnostic label it sticks and gains traction through repetition in case notes.	Breathless smoker labelled by clinician as ECOPD without symptoms or airflow obstruction. Ward based NIV may be suitable for RA and ECOPD but an unsuitable treatment in the case of de novo RA.
Framing	The way in which information is presented influences outcome.	Junior may present a case with emphasis on negatives in terms of chance of death rather than the positives and chance to save life leading to treatment refusal.
Fundamental attribution error	To blame patients for their illness rather than see it within the societal context in which it occurred.	Patients with COPD or obesity may consciously or sub-consciously receive lower calibre treatment or disproportionate rationing due to perceived 'self-inflicted' illness.
Gambler's Fallacy	Belief that independent, preceding events may influence upcoming ones.	A sequence of patients failing NIV and requiring IPPV may lead to suspicion the next case will too and influence decision making.
Hindsight Bias	Knowing the outcome of events influences the experience and perception of those events.	Recall of case in which ventilation was not offered and patient died to support same action again on grounds of futility. Feedback loop with confirmation bias.
Ignorance trap	Making an error may not confer immediate detriment to the patient and unless fed back clinician may be unaware of harm.	Initial failure to act upon RA in a timely fashion may not cause immediate death but in-hospital mortality rises due to complications of prolonged acidaemia.
Illusory correlation	Perceiving causality whereas there is only correlation. Often supports a confirmation bias.	Disliking a particular type of ventilator and having consequent reluctance to use it following a death.
Overconfidence bias	The belief we know more than we do placing excessive weight upon opinion rather than objectivity.	Stating there is no chance of success in a case without reference to objective sources of information.
Playing the odds	Common outcomes are more likely than uncommon ones.	Even high-risk patients can be managed on a ward successfully but there is a greater chance of treatment failure and harm. This risk is however lower than the chance of success. Feedback loop with confirmation bias.
Super-additivity	The tendency to over or under estimate the probability of the whole as compared to its component parts.	Tying in is poor perception of summative risk, clinician may cite 2 colinear variables as grounds for treatment refusal.
Triage Cueing	Patients move through healthcare systems along established pathways. Treatment is dictated to a degree by their physical location.	Patient admitted to level 2 care as there are no remaining ward beds. Once into critical care is more likely to receive level 3 care than a similar patient not physically there.

There are many experiments that evidence individual cognitive biases in healthcare from psychiatrists over-estimating violent offense risk dependent upon probability framing [(176)] to recent experience of bacteraemia increasing clinician estimation of a blood culture positivity

[177] to a knowledge of outcome inflating ratings of care quality amongst emergency department physicians.[178]

3.1.3 Avoidance of bias: The use of Clinical Scoring Tools.

Predictive models have been used in many sectors of society to enhance forecasting. In healthcare they have been extensively used to both model diagnostic probability for example the Wells score to aid diagnosis of venous thromboembolism [179] or to calculate risk of death from surgery.[180] Since the advent of statistical modelling it has been compared to human judgement. A consistent finding in healthcare settings since the 1950s is statistical models and predictive score outperform, or are at least as good as, clinicians.[181-183] Even if type 2 pathways are consciously employed and the risk is deeply considered it is very difficult to remove the affect heuristic from the perception of factors that confer independent risk, estimate their relative weights and then add them together.[184] Added to this there are also conscious prejudices acting within both systems and individuals that detract from true objectivity.

3.1.4 Cognitive bias summary

Cognitive bias is under-recognised in healthcare as a source of systematic error. It is not a leap of imagination to conclude that some of the psychological processes described are responsible in part for some of the erroneous practices we see in the delivery of NIV in the UK. It is possible due to the reliance on timely clinical judgement to initiate treatment and the organisational implications of provision (particularly decision devolution cross specialty) that NIV is disproportionately affected. Would we be satisfied if half of patients with a myocardial infarction, stroke or upper GI bleed did not receive their evidence-based treatment? While critical appraisal and self-reflection are accepted components of the rounded 21st century medical practitioner, cognitive bias awareness is not; it is difficult to be vigilant for and eliminate practices of which one is unaware. A useful addition to complex clinical decision making is an unbiased clinical tool which have been shown to offer superior outcome prediction to clinician judgement.

3.2 Predicting Outcome in COPD

3.2.1 Why Predict Outcome?

The preceding sections have established that COPD is common, and the number and complexity of patients is increasing. NIV is an effective treatment for RA in ECOPD and has experienced a surge in use over the last 20+ years. In the UK at least, there is evidence of underuse with perhaps poor investment/infrastructure, lack of skillset and pessimism playing a role. Cognitive biases are interesting and may contribute to the establishment of (erroneous) behaviours and are a barrier to objectivity. Guidelines frequently reference high risk patients but there is a limited understanding of what a high-risk patient is and how to recognise him or her. A robust predictor of in-hospital mortality could help shared decision making, improve selection of patients to receive ventilation, guide level of care, improve early palliative care, better describe participants in future clinical trials and objectify inter-hospital variability to name a few. The following sections will give an overview of mortality modelling in general COPD patients limited to studies that have developed validated multi-variable scores and an in-depth review of literature specific to assisted ventilation.

3.2.2 Predicting Outcome in Stable COPD.

Many papers have reported both univariate associations with mortality and multiple variable models. A long follow up period is required to capture enough events (deaths) to develop a tool and then consequently validate it. As such despite much work there is relatively little of clinical utility. The BODE index reported in 2004 is the best known and adopted [185] and has been subsequently studied to translate its utility into other novel settings such as assessing response to pulmonary rehabilitation [186] lung volume reduction surgery [187] or as part of the assessment for lung transplantation.[188] BODE comprises: (B) BMI, (O) degree of airflow obstruction, (D) Dyspnoea measured on modified medical research council (MMRC) scale and (E) exercise capacity measured using six minute walk test (6MWT). Patients can score 0-10, after separation by quartile there was clear gradation in mortality over 52 months of follow-up with those in the highest risk group being 80%.[185] A potential criticism of BODE is the inclusion of the 6MWT which may be routinely available in secondary care but is not typically so in primary care where the bulk of COPD care is delivered. Other scores have been developed but without external validation or with less impact.[189-191]

3.2.3 Predicting Outcome in Exacerbations of COPD

Mortality modelling of outcomes from exacerbations of COPD, which is more pertinent to this project, has also borne fruit. Several tools have been derived and validated to predict mortality not least by our research group (DECAF programme).

BAP 65: Retrospective design from a large research database. 88,074 admissions with ECOPD were analysed. Half were used to derive and the other half to internally validate the tool.[192] Further external validation was reported in separate (existing) dataset.[193] The score comprises (B) blood urea nitrogen (BUN) >25mg/dl, (A) altered mental status, (P) Pulse >109 beats per minute, (65) Age >65. Altered mental status was defined as Glasgow Coma Scale of 14 or lower or a designation of disoriented, stupor or coma by a physician. The tool performed well with an area under the receiver operated curve (AUROC) of 0.77 in its external validation. This tool is simple to administer, uses only routinely available indices and has the advantage of development in very large cohorts. It is also validated to predict the need for mechanical ventilation. However, the potential components were limited to those captured by the database, the in-hospital mortality was both low and had unexplained significant variation (1.8% derivation/internal validation, 4.1% external validation) and no confirmation of COPD diagnosis is available. It has common ground with the CURB 65 tool [194] in confusion/altered mental status, urea/BUN, a cardiovascular assessment in blood pressure/heart rate and age of 65 but head to head comparisons are not reported in the original papers. Unsurprisingly where head to head comparison is available in the DECAF validation cohort prediction of in hospital mortality was very similar (CURB 65 AUROC 0.76 vs BAP 65 AUROC 0.77).[82]

DECAF score: Our research group derived and validated the (D) dyspnoea, (E) eosinopenia (C) consolidation, (A) acidaemia, (F) fibrillation score which is a robust predictor of in-hospital mortality in patients admitted to hospital with ECOPD.[82,195] The score was derived in 920 consecutive, unique patients and then, in a separate dataset, internally (n=880) and externally (n=845) validated. The score is simple to administer and selects a large proportion of patients considered low risk. The score employs a novel extension of the traditional medical research council dyspnoea (MRCD) scale,[196] termed extended medical research council dyspnoea (eMRCD) scale which incorporates a functional assessment of ability to wash and dress independently and has clear descriptors of progression between levels (Table 6).[197]

Table 6: Extended Medical Research Council Dyspnoea Score.

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?"**	
Only Breathless on strenuous exertion	1
Breathless hurrying on the level or walking up a slight hill	2
Walks slower than contemporaries, or stops when walking on the level for 15 min	3
Stops for breath after walking 100m, or for a few minutes, on the level	4
Too breathless to leave the house unassisted but independent in washing and/ or dressing	5a
Too breathless to leave the house unassisted and requires help with both washing and dressing	5b

Using the full 5 variable score the AUROC was 0.86 in the derivation cohort, 0.83 in the internal validation and 0.82 in the external validation indicating excellent mortality discrimination. The strongest individual predictor of outcome was the eMRCD score. A parallel between BODE and DECAF is dyspnoea assessment indicating the importance of steady state breathlessness in COPD outcome modelling. Comparison tools such as APACHE II,[198] BAP 65, CAPS [199] and CURB 65 none of which capture dyspnoea were significantly outperformed by the DECAF tool within both the internal and external cohorts. The DECAF score is shown below (Table 7).

Table 7: The DECAF Score.

Variable	**Score**
Dyspnoea: eMRCD 5a eMRCD 5b	1 2
Eosinopenia (<0.05 x 10^9/l)	1
Consolidation	1
Acidaemia (pH <7.3)	1
Atrial Fibrillation	1
Total DECAF score	/6

3.3 Predicting Outcome from Assisted Ventilation in COPD.

3.3.1 Problems Within the Current Literature.

There are several problems within the current literature which hamper interpretation. Many of the methodological decisions described in the next chapter were made to address these concerns. Balancing pragmatism and generalisability with scientific rigor is a problem for every clinical study but, in the case of predictive modelling, loss of generalisability limits the value of the work.

1) Mixed Aetiology: The indications for NIV are numerous and the disease entities that may benefit are distinct. A patient with neuromuscular disease has disease specific predictors of adverse outcome not shared by other conditions. The influence of some candidate predictors may be mitigated by a heterogenous derivation population and some may be disproportionately enhanced by differences in case mixed proportions and outcome event frequency between conditions. Fortunately, COPD is the commonest condition is most mixed aetiology series, but these effects should be remembered.
2) Misdiagnosis or unconfirmed diagnosis: Anecdotally it is common to find patients with a label of COPD with little supporting evidence. This is backed up by some evidence.[200] Airflow obstruction, as defined by a fixed FEV_1/(F)VC ratio, is 'less abnormal' in an elderly population leading to over-diagnosis of COPD [201,202] and there is frequently error differentiating asthma from COPD.[203] COPD should be objectively confirmed as misdiagnosis rates are high and, as alluded to above, outcome prediction will be affected by case mix. In one case series 75% of patients with obesity hypoventilation syndrome (OHS) admitted to the ICU had been misdiagnosed and treated for COPD in the last 2 years.[204] Data extracted from coding or unverified databases may include a substantial number of patients without COPD.
3) Selection Bias: In many of the audits and case series from which data is extrapolated selection bias has already been applied because, as established, there is a discrepancy between those with RA not correcting with medical therapy and those that receive NIV. There is a limited amount that can be done to infer the effect of this unless positively stated by authors. Very low mortality or recruitment rates among

series reported as consecutive may suggest this. ICU case series also necessarily are a product of significant selection bias.

4) Differing outcome measures: Much effort has been put into predicting failure of NIV rather than death. There are attractions to this strategy to prevent delay of intubation in high risk groups. However, there is no universal standard for diagnosis of NIV failure and subjective criteria such as accessory muscle use may be used. Moreover, if an elevated RR or low pH are used to prompt consideration of intubation and hence to diagnose failing NIV, they will inherently predict that outcome.
5) Management variation: An extrapolation of the above point; rates of intubation and the threshold to access critical care beds are very different around the world meaning the case mix of those receiving NIV varies greatly which hampers generalisability. In the UK where only 1% of ECOPD is intubated outcomes from ICU based series with high proportions receiving IMV may be less relevant. Furthermore, unlike the chemical structure of a drug, the intervention of NIV has not remained constant over time. Many of the studies reviewed are 20-25 years old, over this time there have been advances in pressures, interfaces, back up rates and ventilator algorithm. Factors identified in early studies may remain equally valid but, without a constant baseline interpretation must necessarily be caveated.
6) Modelling from non-bespoke datasets: A predictive model can only be as good as the indices collected. There are examples of modelling from existing clinical and research databases using routinely captured data to give a large n. This does not allow for inclusion of strong potential predictors of outcome for example patients' steady state breathlessness which may not ordinarily be recorded. Directly related to the point above clinical databases are routinely compiled in ICU settings, so ICU derived scores are disproportionately reported in the literature compared to the number of patients treated there.
7) Poor methodology: Reporting of univariate associations that may or may not hold up under multiple regression analysis as independent predictors of mortality. Validated findings in separate (prospective) datasets are rare. Under-powering is also common; drawing conclusions from a small number of outcome events.
8) Complexity: A clinical tool is only useful if it can be simply administered, ideally at the bedside. APACHE II has many components, it may be automatically calculated by ICU

software but is not routinely available (in the UK) at the point of NIV delivery to augment decision making. There is little chance of such a complex tool being used in day to day clinical practice.

3.3.2 Steady State Variables (Admission Independent).

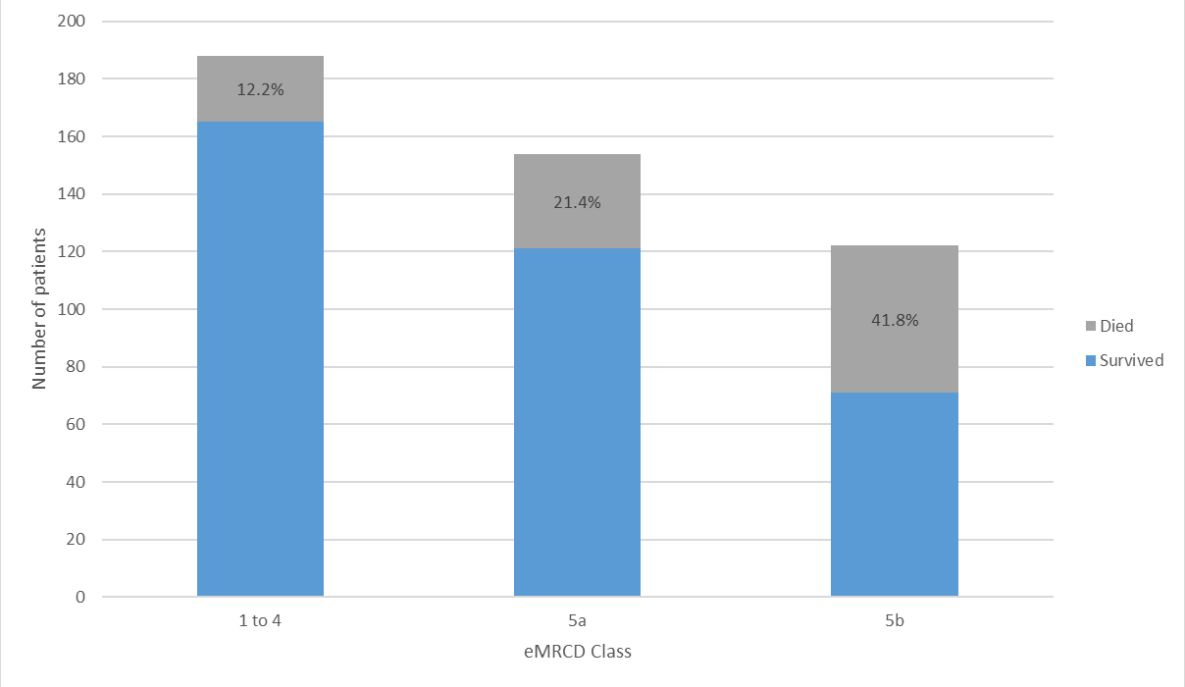
3.3.2.1 Age.

Age has an uncertain effect on outcomes described earlier an RCT of NIV vs standard medical therapy in patients aged over 75 with RA predominantly secondary to COPD, rates of endotracheal intubation and mortality were lower in the NIV group.[127] Further confirmation of good in-hospital outcomes in the over 75 group is reported by Nicolini et al but tempered by higher six month mortality.[128] In Confalonieri's work,[205] age was associated with mortality on univariate analysis but not after logistic regression, these findings were replicated in a well described, prospective consecutive case series reported by Chakrabarti et al.[206] Age has been identified as an adverse factor in other case series and national audits but it is uncertain whether this represents an independent risk or an association with other factors such as increasing disability, comorbidities or external factors such as the extent and intensity of treatment offered.[207-211] National guidance states age alone should not be used as the basis for treatment denial.[133]

3.3.2.2 Dyspnoea/Performance Status.

As described above the use of a dyspnoea score in both stable state COPD and an exacerbation of COPD is an important predictor of outcome. It has been infrequently collected specifically in the ventilated population. Examining only those with RA from the DECAF papers it can be seen there is a strong correlation between eMRCD score and inpatient mortality and we already know that eMRCD was the strongest predictor of outcome following multiple regression analysis in this population. Figure 16 shows the pooled data from the entire derivation and validation cohorts with clear gradation in mortality by eMRCD class. It also shows the value of the further division of the traditional MRCD class 5 in 5a and 5b. In an abstract addressing only the ventilated patients in the derivation cohort, eMRCD remained a strong mortality predictor.[212] Increasing dyspnoea score was also associated with higher post discharge mortality during a one year follow up period [213] and was the strongest determinant of 6 month mortality in another.[214]

Figure 16 Inpatient mortality in ventilated patients stratified by eMRCD score (Pooled data from DECAF derivation and validation).



3.3.2.3 Body Mass Index (BMI).

Low BMI is associated with both inpatient [215] and post-discharge mortality.[213,216] In a large cohort including non-ventilated patients, BMI <18.5 and unintentional weight loss were associated with in-hospital mortality, but only the former was an independent predictor.[195] In a retrospective coding cohort weight loss was associated with in hospital mortality amongst patients with COPD requiring LTOT while obesity was a protective factor.[210]

3.3.2.4 Cough effectiveness.

Cough effectiveness has shown promise [209,217] but is subjective. Nevertheless, it is intuitive that patients who are unable to clear secretions may have worse outcome, as is the case in other conditions such as amyotrophic lateral sclerosis (ALS) and bronchiectasis.

3.3.2.5 FEV_1.

There appears to be no association between FEV_1 and inpatient mortality.[206] Indeed, in one study the inverse was found.[218] Post discharge there is no association with either readmission or death to one year in one study [213] or five year mortality in another.[216]

3.3.2.6 Long Term Oxygen (LTOT) use.

No difference was found in NIV failure rates at 24 hours in those with preadmission LTOT although in-hospital mortality is unreported.[219] A large American coding series suggests 68.5% one year mortality (in-hospital + post discharge) from a poorly characterised cohort of patients with COPD requiring LTOT however in the absence of a comparison group few conclusions can be drawn from this.[210] Long term oxygen use is an independent predictor of post discharge mortality in two longitudinal studies.[213,216]

3.3.2.7 Comorbidities.

A higher generic comorbidity score such as the Charlson index [220] or one of the modifications of it is generally associated with increasing mortality.[221-223] Cardiac co-morbidities such as heart failure or atrial fibrillation (AF) may be particularly pertinent especially in the medium term.[214,224,225] In ICU populations unsurprisingly higher organ dysfunction scores are associated with increasing mortality, the observation that multiorgan failure adversely effects outcome certainly has face validity but is perhaps not readily generalisable to a real world cohort.

3.3.3 Severity and Timing of Acidaemia.

3.3.3.1 pH.

Low pH is the most commonly reported factor associated with outcome. Many studies have identified low pH as an adverse marker. Specifically, that a pH <7.25 confers worse outcome.[103,143,205,215,226,227] The National Chronic Obstructive Pulmonary Disease Resources and Outcomes Project (NCROP) report examined the acidaemic subgroup from the 2008 UK national COPD audit in detail, it shows inpatient mortality of pH 7.26-7.34 = 17%; pH ≤7.25 = 26%.[226] In-hospital mortality was even higher in the 2013 BTS audit report; pH 7.26-7.34 = 26%; pH ≤7.25 = 36%.[143]

While there is little doubt that a low pH is a univariate marker of poor outcome, there is a danger its importance has been overstated due to a paucity of good multi-variable models. Interestingly a higher CO2 level is less commonly reported as an independent associate of mortality. An explanation of this is that increased duration of low pH may be the true adverse feature and a lower nadir is merely one prolonging factor, others such as concurrent metabolic acidaemia or sepsis may be equally or more important. For example, there are

examples where pH is significantly associated with mortality or NIV failure on univariate analysis but not after multiple regression [211,228] and others where pH is non-significant.[128,129,229,230] In the case series by Chakrabati et al.[206] the pH was lower in the NIV failure group 7.22 vs 7.26, but CO2 was 10.2kPa in both groups. This does suggest that a metabolic component is contributing. It should be remembered that, by definition, pH is needed to diagnose RA and will almost always be recorded making it an easy candidate to study from clinical databases. It is also to be expected that those whose pH does not correct after initiation of a treatment designed to correct pH have worse outcomes than those that respond to treatment.

Overall, while questions may be raised pH is an extremely attractive candidate to study and probably the best described association with poor outcome. The threshold of 7.25 has been so frequently identified as clinically relevant it is very widely known outside of specialist circles.

3.3.3.2 Timing of acidaemia.

Timing of acidaemia refers to the time between hospital admission and development of RA. This may be influenced by access to healthcare and local practices but remains an important and overlooked marker of success. Notably this is not the same as late failure of NIV whereby a patient may deteriorate post treatment initiation although outcomes may also be adverse. The number of days in hospital prior to admission to ICU is negatively correlated with six-month outcomes.[214] It is intuitive to believe that RA treated with ventilation segued with acute bronchodilators, corticosteroids, antibiotics etc may have better outcomes than those that deteriorate later despite these medical treatments. The strongest evidence to support timing as important is from the NCROP report. Progressive mortality is seen when stratified thus; a) lowest pH on admission = 12%; b) acidaemia on admission but lower pH later recorded = 21%; c) normal pH on admission with subsequent acidaemia = 33%. The importance of timing as an independent predictor of in-hospital mortality was reported in a later abstract.[212]

3.3.4 Investigations.

3.3.4.1 Albumin.

Albumin has an uncertain association with mortality, in a large study in which just over one third of patients were invasively ventilated, a lower albumin was one of a small number factors associated with 6 month mortality,[225] Pacilli et al. found a 5.6 fold increase in NIV success for every 1g/dl increase in serum albumin level [223] and it was an independent predictor other small studies.[224,231] However, other authors have not identified a significant relationship.[208,215]

3.3.4.2 Glucose.

The role of hyperglycaemia has been specifically, prospectively examined in one paper.[206] Inclusion was limited to COPD and the majority (93%) had spirometry conformation. The authors found a random blood glucose of >7 mmol/l in 44/88 (50%) patients of whom only 16 had a pre-existent diagnosis of diabetes. Hyperglycaemia at this threshold was associated with mortality after multiple regression, precise mechanism was not postulated although similar findings in heterogeneous critical care admissions are noted. Other studies have not replicated this finding.

3.3.4.3 Inflammatory markers.

C-reactive protein (CRP) has been reported as a univariate determinant of mortality but not after multiple regression. [222,232] Neutrophil count emerged from one regression analysis.[212] There are equally examples of non-significance in CRP/white cell count (WCC) and neutrophil count.[208] In consecutive patients with COPD requiring intubation the role of procalcitonin (PCT) measured at time of ICU admission was investigated. Those with pneumonia were excluded but bacterial culture was actively sought via endobronchial aspirate. PCT was an independent predictor of outcome (WCC, CRP, temperature, antibiotic use were not) with ICU mortality doubled using a 0.24ng/ml dichotomy.[233] In the UK, PCT is not routinely analysed limiting use as a candidate predictor.

3.3.4.4 Troponin I.

The relationship between chronic cardiovascular comorbidity and COPD has been well documented. Balliard et al. showed in a prospective ICU cohort study that troponin I was an

independent predictor of mortality. 71 individuals with severe COPD were recruited 85% of whom were ventilated (majority NIV only), 18% had an elevated troponin I (>0.5ng/ml) in whom in-hospital mortality was 62%.[234]

3.3.4.5 Urea.

Higher urea was significantly associated with in-hospital death in an early study although much of the focus of this work was upon the use of the now rarely used respiratory stimulant Doxapram.[227] It was the only biochemical marker associated with mortality in one large, single centre case series.[208] As noted earlier urea features in both the BAP 65 and CURB 65 tools.

3.3.4.6 Pneumonia.

As discussed (1.3.4), consolidation is thought by some to invalidate a diagnosis of ECOPD. However, there is clear evidence from national audits that UK practice does not adhere to this. Pneumonia has consistently been shown to be a strong predictor of NIV failure and in-hospital mortality. [143,209,223,235] In the Pacilli paper the presence of pneumonia decreased the success probability by 62%.[223] As shown earlier the original RCTs had a mixed policy towards inclusion of patients with pneumonia, where reported outcomes are generally worse than in those without consolidation. Interestingly in the large Confalonieri cohort where 12.6% had complicating pneumonia it had no impact upon outcome.[205]

3.3.5 Clinical Observations.

3.3.5.1 Reduced Consciousness.

Whether measured using the Glasgow coma scale or otherwise reduced consciousness is, where measured, nearly always a univariate associate of mortality and is very commonly an independent predictor after regression analysis.[102,211] Several unvalidated regression models have included assessment of reduced consciousness.[234,236] In a case control study Scala et al. found fairly progressive in-hospital and 90 day mortality from normal conscious level through to greatest stupor.[130] One particular study, reviewed earlier is in contrast to these findings with no significant difference in NIV success between those with hypercapnic coma (GCS <8) and those without in the COPD subgroup.[129] Amongst the literature this Diaz paper is something of an outlier and it should be remembered that even in this paper in-

hospital mortality was significantly higher than in those with a GCS of <8, particularly if unresponsive.

The association between lower GCS and worse outcome is expected for two reasons, greater impairment of consciousness is related to a greater insult such as a higher acute rise in CO2. Secondly NIV can be quite an intrusive therapy, confusion or agitation mean chance of successful delivery of the intervention is reduced.

3.3.5.2 Respiratory rate.

Elevated respiratory rate (RR) potentially relates to greater ventilator asynchrony or a more fatigued patient and raises the possibility of greater degree of concurrent metabolic acidaemia. Several studies have found association A rate of >30 breaths per minute may be a useful cut off.[205,206]

3.3.5.3 Heart Rate and Blood Pressure.

One may suspect that those with cardiovascular instability have worse outcomes due to sepsis, heart failure or adverse response to the application of positive pressure. Many studies incorporate the observations into an acute physiology and chronic health evaluation (APACHE) or simplified acute physiology score (SAPS) score so perhaps individual reporting is less common. Some studies have found that higher heart rates (HR) or lower blood pressure (BP) (particularly unresponsive to fluid resus) are adverse features but this is not a consistent finding.[209,237] Interestingly Phua et al in a study comparing outcomes from NIV in COPD to other conditions found heart rate one hour after NIV administration to be associated with NIV failure on multivariate analysis in the non-COPD group only. A large number of the 'non-COPD' group were in fact pECOPD, it is feasible these data represent the well-established poorer outcome in RA and pECOPD in which higher heart rate may be an explainable consequence of sepsis.[235]

3.3.6 Composite tools.

3.3.6.1 Generic Scores.

SAPS II [238] and APACHE II are both frequently used in heterogeneous patients admitted to critical care and may be routinely captured. Both were derived in large, mixed case ICU series. SAPS II captures 15 variables, APACHE II 14, both with complex, graded scoring

plotted on a chart. Both are considered together as the data captured and discussion is very similar. As might be expected when so much data is incorporated into a prediction matrix they have subsequently been validated in many separate disease entities. A huge advantage of such scores in addition to individual patient assessment is their international use and routine capture by ICU software making them ideal tools for audit and performance monitoring. However, because they include such generic variables they are typically outperformed by more bespoke, organ or disease specific scores.

Individually, neither score has been shown to offer particularly strong prediction in a ventilated ECOPD population [82,199,239] and, considering the complexity and poor generalisability to the non-critical care population, their use to guide care is not recommended. Probably due to easy availability they have both been frequently shown in ECOPD to be associated with both NIV failure and in-hospital mortality.[102,228,230,231,234,236,240,241] Both are returned on lists of multivariate associates of mortality but inclusion of a complex, multi-variable score as a single index alongside other individual indices is of questionable value. Similarly, incorporation of a whole tool as a single index of a new one is fundamentally flawed.

3.3.6.2 COPD and Asthma Physiology score.

A comparable but slightly more specific score to predict in-hospital mortality was derived by Wildman et al. using data from the UK's Case Mix Programme Database (a rolling national audit). The COPD and Asthma Physiology Score (CAPS) [199] was derived in 8527 patients admitted to one of 168 ICUs, validation was then performed in a separate 7957 patients. As implied these patients were a mixture of COPD (>80%) and asthma. The vast majority of these patients were invasively ventilated. The score uses 8 variables (heart rate, mean arterial pressure, pH, sodium, urea, creatinine, albumin, white blood count) split into 41 scoring groups with differential weighting applied. As such it is complex to score unless automated. The performance was modest (prediction of in-hospital mortality, validated AUROC 0.72), but it did outperform the physiological components of comparable ICU utilised scores such as APACHE II and SAPS II within this study population. This score has little utility outside of the ICU due to its complexity and the population in which it was derived and validated. This limits its generalisability and as the authors acknowledge components are physiological and biochemical only, the absence of functional assessment is a weakness.

3.3.6.3 Confalonieri Risk of Failure Chart.

Published in the European Respiratory Journal in 2005 Confalonieri and colleagues prospectively collected data on 1033 consecutive patients in several Italian centres.[205] In keeping with the described Italian model [154] the majority were treated in respiratory intermediate intensive care units (RIICUs). The patients were admitted between 1998 and 2000 so it is possible this is a post hoc analysis of an existing, but bespoke, research database. There is no detail of how COPD was confirmed, and no spirometry data nor smoking history is reported. The study was designed to model risk of NIV failure (need for intubation) rather than death. Intubation criteria were pre-defined but include subjective criteria such as 'copious secretions' and 'agitation'. Intubation rates varied wildly between centres (0%-72.2%). Failure to correct pH, cardiovascular instability and coma development were also used to guide intubation but are candidate predictors of said outcome. Two charts were generated to predict risk of failure, firstly on admission and secondly after 2 hours treatment with NIV. Validation was performed in a separate sample of 145 patients admitted to 3 (unspecified) participating units.

Relatively few population descriptors are reported. Of those available, a high (43.1%) proportion received LTOT pre-admission and 12.6% of patients had complicating pneumonia (a lower proportion than in UK audits). 236/1033 (22.8%) had NIV failure, of which 185 were intubated. There were 142 deaths; 91 (49.2%) of the intubated patients died in hospital and an additional 51 patients with a pre-existing do-not-intubate order died without intubation. Age, GCS, APACHE II score, respiratory rate, pH, PaCO2, and PaO2/FiO2 were associated with NIV failure at admission. The same variables with the exception of respiratory rate and PaO2/FiO2 at were associated with NIV failure after 2 hours of treatment. It is unclear whether the constituent parts of the APACHE II score were individually modelled.

The two complied charts are shown in Figure 17. As can be seen they are complex to score. The user must calculate the APACHE II score, secondarily score pH, GCS and RR and finally plot onto the chart. Risk stratified into 54 different outcome boxes for 236 outcome events (deaths) is of questionable value. It should also be noted that pH, GCS and RR are all constituent components of the APACHE II score. The AUROC in the (undescribed) validation cohort was 0.71 at admission and 0.83 at 2hrs. It is little surprise there is such discord in this prediction since these variables capture many of the pre-defined intubation criteria.

Figure 17 Risk of NIV failure chart at admission and after 2 hours of NIV.

		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

Failure risk chart of noninvasive positive pressure ventilation at admission (the values in the table correspond to the percentage of patients who fail in each category). ■: 0–24%; ■: 25–49%; ■: 50–74%; ■: 75–100%. RR: respiratory rate; APACHE: acute physiology and chronic health evaluation II score; GCS: Glasgow Coma Scale.

		pH after 2 h <7.25		pH after 2 h 7.25–7.29		pH after 2 h ≥7.30	
	RR	APACHE ≥29	APACHE <29	APACHE ≥29	APACHE <29	APACHE ≥29	APACHE <29
GCS 15	<30	72	35	27	7	11	3
	30–34	88	59	49	17	25	7
	≥35	93	73	64	27	38	11
GCS 12–14	<30	84	51	41	13	19	5
	30–34	93	74	65	28	39	12
	≥35	96	84	78	42	54	20
GCS ≤11	<30	93	74	65	28	39	12
	30–34	97	88	83	51	63	26
	≥35	99	93	90	66	76	40

Failure risk chart of noninvasive positive pressure ventilation after 2 h (the values in the table correspond to the percentage of patients who fail in each category). ■: 0–24%; ■: 25–49%; ■: 50–74%; ■: 75–100%. RR: respiratory rate; APACHE: acute physiology and chronic health evaluation II score; GCS: Glasgow Coma Scale.

3.3.6.4 Scores summary

The risk of failure chart and CAPS score are the only two published, validated scores encompassing multi-variable regression analysis converted into weighted scores designed for clinical use. Both are unwieldy and suffer from limitations associated with a narrow pool of candidate indices. Neither has been incorporated into routine use in the UK and both afford only modest predictive capacity. The published evidence is lacking. No derived score has included steady state dyspnoea nor timing of acidaemia as potential indices. There is reason to suggest both would be strong predictors.

3.3.7 Post-Initiation.

3.3.7.1 Predictors of Poor Outcome.

As discussed, an assessment of outcome can be made after initiation of treatment. However, for reasons already laid out this is not our preferred option (3.3.1). Much of the evidence has been incorporated into this literature review; further in-depth review is unwarranted. NIV

failure is associated with higher APACHE II scores.[235] Failing to improve (or falling) pH is probably the strongest determinant of failure. Varying time cut offs post initiation of ventilation at which point reassessment should take place (1-4 hours) have been mooted. Similarly, failure to improve physiological indices such as GCS, RR or heart rate may indicate worse prognosis. [205,208,242]

3.3.7.2 Late Failure of NIV.

Late failure of NIV, following initial correction of respiratory acidaemia, is associated with high mortality and is more common in patients who require limited or complete assistance with ADLs (frailty). Moretti et al used the definition: "*a sudden or progressive worsening of arterial blood gas tensions (pH <7.34 with an increase in PaCO2 of >15–20% compared with previous arterial blood gas tensions), dyspnoea and/or sensory deterioration while still on mechanical ventilation for at least 6 hours/day*". In a study comparing continuing NIV to IMV in patients with COPD meeting the above definition mortality was high in both arms, but continuing NIV in lieu of invasive ventilation conferred an extremely poor prognosis, (mortality: NIV group 92%, Intubated group 53%). Of note group selection was based on patient preference, pH at the time of late failure was much lower in the NIV group and patient numbers are low.[237] In a similar ICU cohort, late failure of NIV was associated with 80% mortality.[236] Cardiac complications and nosocomial infection were important contributors to deterioration and death, however the definition of late failure included non-objective criteria, limiting wider generalisabilty. Further evidence of poor outcomes in an Indian study, despite an ill-defined population, does increase the likelihood this is a real finding.[243] In contrast in a small cohort from our institution (n=14) in whom late failure was managed with high pressure NIV, we found in-hospital mortality was substantially lower (32%).[244] Further study of late failure is warranted to draw definitive conclusion. A binary choice between intubation or palliation should late failure develop as advocated by some is questionable. Few would argue that failure after initial success places a patient in a high mortality bracket, the observed differences are likely to be largely due to differing definitions selecting patients with varying salvageability. A universal definition is needed to objectify further study.

3.3.8 Predicting Outcome in COPD Summary.

There are numerous univariate and multivariate associates of mortality that have been reported across many studies. Few have been specifically designed to address the question of risk modelling and those that have usually employed existing and limited databases. Focus upon biochemical and physiological continuous indices is a policy that has not yielded results.

Combining evidence and opinion, there are two broad characteristics that appear to increase mortality: 1) markers of more advanced (and comorbid) COPD meaning a relatively smaller insult may result in higher mortality and; 2) markers of an insult less amenable to rapid correction meaning the patient must 'stand up to' acidaemia for longer.

The strongest predictors of outcome have never been all tested together so direct comparison is limited but they probably include, steady state dyspnoea, timing of acidaemia onset, lower BMI, need for LTOT, lower pH (possibly greater metabolic component), a marker of cardiac involvement such as elevated troponin, presence of consolidation, reduced consciousness, higher respiratory rate. Others such as age, elevated urea, hyperglycaemia are strong candidates for further study.

3.4 Introduction Summary.

COPD is an extremely common disease. Due to of historical smoking rates, increased average life expectancy and improved disease specific survival prevalence continues to rise. The patients we can expect to see in UK hospitals and beyond in the coming years are likely to be more complex with greater comorbidity. While some COPD specific improvements have been seen they are starkly worse than in other conditions. Exacerbations of COPD are important systematically and individually, they lead to significant mortality and can detrimentally influence disease trajectory. Exacerbations leading to respiratory acidaemia are particularly important but can be successfully treated with non-invasive ventilation. COPD in its advanced stages confers a considerable symptom burden and palliative care is woefully lacking.

COPD is associated with deprivation and lower social class; it is incorrect to assume that smoking is; 1) the root cause of all COPD and 2) that a decision to smoke is not directly influenced by factors beyond individual control. It is however feasible that such opinions in

addition to other cognitive biases may contribute to under-resourcing. One antidote to inequality is objectivity to circumvent the inevitable biases of human nature.

In NIV we have a treatment for ECOPD complicated by RA that is extremely effective with a NNT of 12 to save a life and 5 to avoid an intubation. Further trials to prove its worth are unwarranted. The evidence suggests that NIV can be provided on a medical ward, but it is crucial that this is an appropriately staffed area overseen by appropriately trained clinicians. The UK is particularly poorly placed to deliver higher levels of care with staffing ratios appropriate to such a high intensity intervention. While the use of NIV is now routine and widespread, the pace of change, financial limitations and established barriers to higher level of care mean both the infrastructure and skilled personnel required to manage these patients safely and effectively has been outstripped. A significant proportion of patients likely to benefit from NIV are not receiving it and their details and outcomes are unknown. The NCEPOD report has belatedly drawn attention to these issues.

The reasons why an effective treatment is being erroneously omitted, and care is delivered most commonly by non-specialist staff in often inadequate surroundings, are multifactorial. The speed of change is one reason, but another contention is that cognitive bias plays a role from national and local governance down to individual patient decision making. Increasing awareness of these biases may draw more attention to poor decisions leading to such behaviours but without objective data is unlikely to effect change. Predictive modelling is more effective than clinician judgement and avoids bias and could provide this objective data. The recently published BTS quality standards lay down clear statements against which NIV services can be judged. Nevertheless, the evidence to guide prediction is poor with numerous factors individually identified but no model to determine risk in clinical use. Key indices for study are listed in the preceding section summary. There is enormous potential to positively influence practice by risk stratifying patients if a simple, accurate predictive tool can be developed. Potential benefits include increasing NIV use by objectively challenging prognostic pessimism, guiding level of care, enhancing shared decision-making including access to palliative care, improving audit and assisting less experienced clinicians. This study will seek to fill this void.

Chapter 4. Aims and Governance.

4.1 Project in Context.

Professor Bourke's group has conducted a successful programme of research focussed upon statistical modelling of clinical outcomes for patients with exacerbations of COPD. This is the fourth project in the programme, the preceding studies have derived, validated and implemented the DECAF predictive tool. This study, the NIV Outcomes study has operated under the acronym NIVO. DECAF derivation and validation studies have strong methodological similarities to NIVO.

NIVO is a large endeavour spanning 5 years. This thesis reports the derivation project in total and the in-hospital validation of the predictive model. Within validation survivors to discharge able to give consent were offered inclusion in a consenting follow up study assessing longitudinal health related quality of life, anxiety and depression and functional status. The sub-group and post discharge outcomes and in-depth longitudinal assessment will be the subject of the 5th iteration in the programme and form the basis of a separate PhD thesis. The trial manual for the validation study has been included in the appendix (12.3) as this includes an oversight of the project in total.

Aims, Outcomes and statistical methodology within NIVO are very similar for the derivation and validation aspects so are discussed here together to avoid undue repetition but results are clearly separated. The development and reporting of both derivation and validation of a predictive model is relatively unusual. Derivation alone is more common, indeed one review article reports of 86 prognostic models published in leading journals between 2006 and 2009, 61 included derivation only.[245]

4.2 Research Aims.

The overarching aim of this research project is to derive in a single centre and prospectively validate in multiple centres simple tools to predict in-hospital mortality for use in a population of patients with an exacerbation of COPD complicated by respiratory acidaemia that receive assisted ventilation. Tool development was guided by several principles; it should be simple to score, use only readily available information, be scored prior to the advent of ventilation and be generalisable to real world patients.

Two tools will be created; 1) using all variables up to the time of ventilation and 2) using only information up to the time of senior review. Their future utility is different with the second tool aimed at escalation planning, this limits the number of potential variables.

4.2.1 Principle aims.

1. Prediction of in-hospital mortality.

- The derived tool(s) will be validated prospectively, both temporally and geographically, in at least 6 diverse sites in the UK, chosen to ensure wide variation in socio-economic factors, COPD prevalence, rurality and structures of care.

2. To identify predictors of death within six months.

- Patients who survive the initial episode requiring NIV continue to have a high mortality and readmission risk following discharge. Accurate prediction of short and medium-term survival, in those patients surviving the initial admission, may further inform decisions about escalation to assisted ventilation acutely and during subsequent episodes of acute deterioration and help patients make more informed decisions regarding other aspects of care planning. This may improve access to palliative care services, currently underutilised in this condition.

3. To assess 12-month survival and readmissions both in the overall population and in patients with, and without, other key characteristics, including:

- Late failure of NIV (recurrent respiratory acidaemia, despite on-going ventilatory support).
- Long-term oxygen therapy.
- Home mechanical ventilation on discharge.
- Eosinopenia at discharge.
- Persistent hypercapnia at discharge.

4.3 The Clinical Tools.

4.3.1 Overview.

As described two tools will be generated. These will be termed the “point of deterioration tool” and the “admission tool”.

- The point of deterioration tool is for use in a patient who meets criteria for assisted ventilation and incorporates dynamic variables up to the point where the decision to ventilate is made.
- The admission tool is for use in the admission window. It is for use to model risk in those that require ventilation in the admission phase but also to plan escalation at the point of senior review for those not yet requiring ventilation admitted with ECOPD who may yet develop RA.

4.3.2 Point of Deterioration Tool.

Ventilation can occur at any point during the admission process although the majority of patients (of the order three quarters) develop it in the ‘admission phase’ i.e. within the first day when a patient will typically be transitioning through an emergency department to their first hospital ward. The aim of this tool is to use multiple variables which may or may not be dynamic to give an accurate prediction of the likely outcome. It will be used to assist a clinician treating a patient who has developed respiratory acidaemia and ventilation is being considered.

This has several potential benefits such as: giving patients and families realistic outcome estimates, refuting prognostic pessimism, preventing unnecessary treatment, guiding level of care, facilitating audit and objectifying inter-unit performance. Given the wide range of potential uses retaining discrimination across the whole spectrum of cases is important as this allows identification of both high and low risk patients. This tool will be used by clinicians of all grades. Simplicity is important to allow for routine use i.e. can be added up and interpreted mentally and quickly but recall of each individual component is not necessary. RA is a medical emergency and it is reasonable to assume that the resultant tool if adopted it will be written into local NIV guidelines or proformas for ease of reference.

It was important that the data collected and incorporated into the model was representative of the case. For example, if a patient deteriorates and receives ventilation after 5 days the

presence or absence of consolidation on their admission X-ray may be irrelevant so all modelled dynamic data is time linked to the point of the decision.

4.3.3 Admission Tool.

The potential utility of this tool is somewhat different. It is only designed to be used in the admission phase of a patient's journey. There are two aspects: 1) the tool should predict stratified mortality in those that develop their acidaemia in this admission period in the same manner as the point of deterioration tool (of the order of three quarters of patients who require assisted ventilation). 2) In those having a senior review (typically consultant 'post-take' ward round) who have been admitted with ECOPD but do not currently require ventilation it should predict their future risk of in-hospital death were they to develop RA to help guide ventilation planning. The median time to review by a consultant for a patient admitted with ECOPD was 10 hours in the latest national audit.[29]

The candidate predictive variables are consequently different to the point of deterioration tool. The use of dynamic information is more limited and must be carefully considered. The clear exception being timing of acidaemia as this necessarily interacts with admission process and can be very simply incorporated. Only information available in the admission window is a candidate for inclusion and its constituents are likely to mainly encompass variables independent of admission for example the eMRCD dyspnoea score.

This tool, if it offers comparable prediction, confers potential advantage over the point of deterioration tool due to wide utility, however there is a significant chance that due to the reduction in candidate indices accurate predictive modelling is reduced to a point whereby the advantage is lost.

4.4 Governance.

4.4.1 Funding.

Two separate, open, competitive grants totalling £130,000 were obtained. In neither case did the funder have any involvement in trial design, data collection, analysis, discussion or dissemination. Further financial support was secured for the validation aspect from the clinical research network portfolio.

4.4.2 Patient and Public Involvement.

Patient and public opinion was sought throughout development and influenced aspects, including the aims, design, and planned implementation and dissemination. The feedback on the study was overwhelmingly positive. The local research design service patient user group representing a broad spectrum of disease including COPD was consulted. Additionally, we established a local COPD focus group including patients and carers with experience of NIV who offer a disease specific viewpoint. Lay person, general medical and disease-specific opinions were obtained and informed our decisions.

The project aims were universally supported giving the proposals a strong mandate. There was concern regarding the underutilisation of NIV nationally and enthusiasm from patients for increasing NIV uptake. Carers stated that improved prognostication would reduce anxiety generated by recurrent admissions each with uncertain outcome.

The feedback cemented our pre-existent priority that the project's main focus is to optimise NIV uptake and challenge prognostic pessimism. However, in addition, the focus groups, including patients with personal experience of NIV, confirmed that NIV can be intrusive and they would only agree to treatment if it were likely to confer benefit. This supports the need for simple, robust prognostic tools to identify those patients unlikely to survive, as well as those likely to benefit.

Finally, there was endorsement of collecting data without individual patient consent and understanding of the importance of this specific point.

4.4.3 Ethical Considerations.

Of importance to the project are ethical constraints surrounding consent. To accurately model outcome and produce a generalisable tool it is vital that all potential patients are included. Patients unable to consent would not be random; those confused, most unwell or who rapidly deteriorated would be unable to give timely informed consent. These patient groups however are amongst those at highest risk and hence exclusion would have a devasting effect on both predictive capability and generalisability. For this reason, ethical approval to gather data without individual patient consent akin to an audit was sought. This does limit some of the indices available for collection and means that the intervention and clinical care is uncontrolled by the study team but is preferable to the alternate situation.

Following discussion with patient groups and presentation to local ethics committee both derivation and validation were granted ethical approval to collect data without individual patient consent.

4.4.4 Regulatory approval.

Both aspects of the trial have local Caldicott approval and Trust registration.

- Derivation project approval granted 29/4/15 by NRES Committee North West - Liverpool Central, REC reference: 15/NW/0389. IRAS project ID 174869.
- Validation project ethics approval granted 11/7/16 by HRA North East - Tyne & Wear South Research Ethics Committee REC reference: 16/NE/0213 IRAS project ID 206694.
- Validation project Health Research Authority (HRA) approval granted 27/7/16.

4.4.5 Protocol registration.

Both aspects were separately registered with the ISRCTN registry.

- Derivation: ISRCTN16977236
- Validation: ISRCTN22921168

4.4.6 Participating sites.

4.4.6.1 Derivation.

The derivation of the clinical tool was exclusively from a single trust, Northumbria Healthcare NHS Foundation Trust. Two sites contributed patients, North Tyneside General Hospital and Wansbeck general hospital. The former drains a largely urban population with areas of high deprivation and the latter a mixed urban/rural population encompassing most of the sparsely populated English county of Northumberland.

4.4.6.2 Validation.

Northumbria undertook internal validation, nine external sites contributed patients to the external validation (Table 8). Of note internal validation has been reported in many studies from a random selection of the derivation cohort. The internal validation in NIVO is a separate, prospective cohort from a different timeframe. During validation recruitment

Northumbria trust underwent reorganisation that resulted in all NIV being delivered in a third, newly opened hospital. We self-imposed a limit of 200 patients to prevent the validation total being dominated by the sponsor organisation.

Table 8 Participating Sites.

	Town/City	Hospital(s)
1	Gateshead	Queen Elizabeth Hospital
2	Leeds	St James' Hospital
3	Llanelli	Prince Philip Hospital
4	London	St Thomas' Hospital
5	Northumbria	North Tyneside General Hospital Wansbeck General Hospital Northumbria Specialist Emergency Care Hospital
6	Nottingham	Queens Medical Centre City Hospital
7	Oxford	John Radcliffe Hospital Churchill Hospital
8	Plymouth	Derriford Hospital
9	South Shields	South Tyneside General Hospital
10	Taunton	Musgrove Park Hospital

An element of site selection was employed in an attempt to minimise the effect of excessive patient selection on clinical grounds. Prior to accepting a site details of their ventilation practice including number, patients' functional status and mortality were studied. Other factors such as number of ventilators and service design were considered. This process was designed to avoid inclusion of sites selecting out the most unwell patients as this potentially prevents identification of the most adverse factors. No absolute criteria were imposed and there is inherent subjectivity in this approach, but it was felt to be a better method than no selectivity at all. Essentially if we were convinced NIV was used liberally to appropriate patients the site was accepted. Sites were further selected to widely encompass a cross section of rurality, ethnicity and deprivation. We also deliberately included small district general hospitals, larger general hospitals and large tertiary hospitals. In the results section external sites are anonymised.

During data collection external sites were not informed of the final predictive model as there was fear this may influence usual care. For example, knowledge of a particularly poor predicted outcome based on unvalidated model may lead to a clinician not offering

ventilation and hence reducing the chance of that validating that very finding by non-inclusion. Similarly, the details of the strongest predictors of outcome were withheld from public presentation until the very end of the recruitment window.

Each site had a physical site initiation visit by the study team with ongoing support available 7 days a week by dedicated telephone or email.

4.4.7 Data Management.

For the validation aspect of the study a bespoke, online data submission and management system was commissioned. Real time data monitoring by the study team was performed throughout. This system conformed to all encryption standards and is password protected. Sites could only access their own data and patient identifying details are held by the local site only.

4.4.8 Trial Steering Committee.

Regular meeting with teleconferencing were held 3 monthly during the recruitment period. These teleconferences were opportunities to discuss any issues arising ‘day to day’ and proactively identify problems. Independent chair and lay representative were present and meeting minutes recorded.

Chapter 5. Methods.

5.1 Patient Identification.

5.1.1 Derivation.

The DECAF derivation and validation projects aided patient identification. These cohorts were robustly identified by prospective daily screening to ensure consecutive patients admitted with ECOPD running 12/2008-06/2010 and 01/2012-05/2013. These two cohorts were the starting point from which to identify every ventilated patient. Patients could only be included in these studies once, so anyone ventilated during subsequent admissions would not be captured and there is a lengthy interim period. A number of steps were taken to ensure complete capture of consecutive ventilated patients:

1. Any patient recorded in derivation project as ventilated was included.
2. Any patient in derivation not initially ventilated had subsequent admissions checked and if ventilated included.
3. Any patient ventilated in the validation project were included unless after checking preceding admissions an earlier episode of ventilation from the interim period between the cohorts was identified. If an earlier episode were identified it was selected.
4. Non-ventilated patients in the validation cohort had preceding admission from the interim period checked and subsequent admissions in the validation window checked.
5. Coding searches were performed over the entire period particularly to pick up patients ventilated during the interim period.
6. NIV service database and ICU database was interrogated to identify ventilated patients.
7. Following steps 1-6 any potential ventilation event was further filtered as feasible by electronic record review (particularly to remove CPAP) and any duplicates removed. The remaining records had case note review to ascertain whether they met selection criteria.

In order to achieve the best possible coding search different coding searches were tested against the known cohorts to ensure they picked up the patients we definitively knew were ventilated at that time.

Final search criteria of: Age >34 + Any ICD10 J96 (Respiratory failure) or E85 procedure code filtered by: a primary diagnosis of influenza or pneumonia (ICD-10: J10 - J18) and a secondary diagnosis of COPD (J41 - J44) or a primary diagnosis of COPD (J41 - J44). As already noted, CPAP shares the E85 procedure code with NIV so many were ineligible (2.4.1).

5.1.2 Validation.

Validation recruitment was prospective: At all sites screening of physical locations delivering ventilation was undertaken in real time. Local arrangements were implemented dependent on service design to ensure consecutive patients were captured. Cross reference with service records and coding was recommended. The ideal situation is that the (key predictive) data is collected prior to outcome i.e. whether survived to discharge or not is known. This is impractical to achieve in all cases (for example if a patient is admitted, ventilated and dies within one night the researcher is likely to know the outcome prior to data collection). However, as described the external sites were unaware of which indices were the key predictors and internally the model of care and resources available made collection without knowledge of outcome easily achievable.

5.2 Selection Criteria.

5.2.1 General Observations.

It is important that a predictive model is readily generalisable to the target population. Models are often applied more broadly than the populations in which they were derived; this can lead to clinicians acting upon false information. An example can be seen in the case of CURB 65, patients from nursing care were excluded but the score is frequently applied to such populations.[194] With this is mind, the selection criteria were kept as unrestrictive as feasible. For example, no upper limit was placed upon BMI, patients with high BMIs could still be included provided the site lead felt the predominant process leading to respiratory failure was ECOPD. Similarly, patients with pECOPD were included in keeping with our position that it is arbitrary to differentiate between a predominate airways versus parenchymal process. For full inclusion we mandated objective confirmation of COPD by

spirometry demonstrating airflow obstruction prior to the index admission in addition to a history of smoking. This was to minimise the effect of misattributed diagnosis.

5.2.2 Inclusion criteria.

- **Age 35 years or older.**
    - No upper age limit was imposed, it is likely that someone under the age of 35 has a primary process other than COPD, for example asthma.
- **Smoking history greater than or equal to 10 pack years.**
    - In keeping with the above point there may be instances where COPD is exclusively due to non-smoking exposures, however these patients are comparatively rare in the UK and imposing a relatively modest minimum tobacco burden is likely increase overall diagnostic accuracy.
- **Obstructive spirometry (FEV1/FVC < 0.7).**
    - Spirometry must precede admission. Allowing spirometry during the index admission would impose a significant survival bias as only those reaching a stable state would typically be able to perform the test. Any spirometry irrespective of how old was counted with the most recent obstructive spirometry recorded. Where available primary care records were sought.
- **ECOPD primary diagnosis.**
    - Specifically, those admitted for a reason clearly unrelated to ECOPD were ineligible even if they subsequently met all other criteria. For example, a trip and fracture with post-operative RA would be excluded whereas someone who fell as a consequence of drowsiness and hypercapnia due to evolving RA in ECOPD would be eligible.
- **Respiratory acidaemia treated with NIV or IPPV (arterial blood gas pH <7.35, pCO2 > 6.5).**
    - Of note between completion of the derivation aspect and commencing the validation the BTS guidelines changed the $PaCO_2$ threshold from 6.0 to 6.5.[133,150] Criteria mirrored this change to reflect current practice therefore the derivation study has a lower threshold of 6.0 in keeping with the guidance at the time of protocol development.

5.2.3 Exclusion Criteria.

- **Previous inclusion in the study.**
    - There are pros and cons to allowing an individual patient to be included multiple times or only count a single episode. Using only single episodes increases the proportion of outcome events and mitigates the effect of a single patient with multiple admissions.
    - In one specific instance a patient could be 'included' twice: If a patient had the reduced ('clinical diagnosis') dataset collected but was then readmitted having had spirometry in the intervening period and met all criteria then this second case would now be eligible for full inclusion. This patient would therefore only be analysed once for the primary outcome.
- **Other illness likely to limit survival to less than 1 year.**
    - This principally refers to metastatic cancer and sites were instructed to consider someone as eligible as their default position. Treatment in someone expected to die may be substantially different to treatment in others. Expected mortality due to COPD did not count towards this exclusion.

N.B. In the validation aspect patients in whom no pre-admission spirometry was available but in whom the lead clinician made a clinical diagnosis of ECOPD had a reduced dataset collected. If adopted into clinical practice the resultant tool is likely to be applied to such patients. This approach allows us to ensure it works in such a population and further enhances generalisability. These patients however did not count towards the minimum number of patients to achieve power.

5.3 Data Collection.

5.3.1 Collection Methods and Notes.

For both aspects of the study all volumes of notes and electronic data such as laboratory results, radiology or digital records were viewed. Data was entered onto a case report form (CRF) and then transcribed onto an electronic database.

One of the problems with predictive modelling from existing databases is a narrow pool of candidate indices. Data collected was extensive, indices were selected following discussion and literature review. It is important that candidate indices be readily available to maximise

utility, some potentially interesting variables could not be collected within the observational design, so we could not for example, mandate that PCT be recorded for study purposes. Not all information is intended for entry into a regression model, much is to accurately describe the population under study. For practical reasons the information in the validation aspect was reduced to areas of particular interest, population descriptors and indices associated with mortality.

The following sections will expand on several, key areas and indices, discussion of all indices collected would be exhaustive, some further details of data collection are recorded in the trial manual listed in the appendix (12.3). Many of the indices were recorded at admission and if different the point of ventilation. This is to allow differential modelling. This does add some complexity to data recording.

5.3.2 Timing of Data Collection.

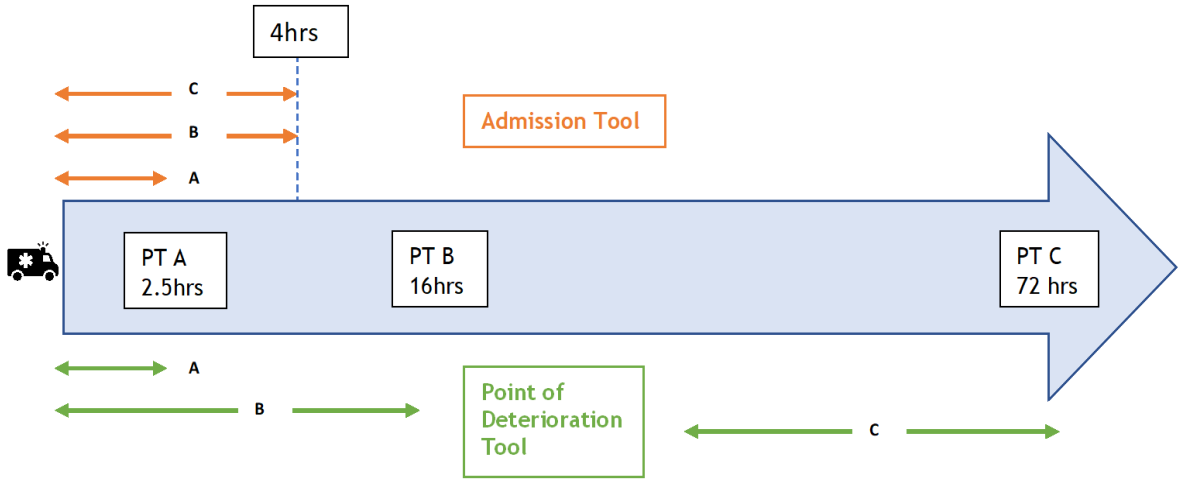
Conceptualising the timings of these tools can be challenging and were a primary focus of site initiation visits and ongoing external site support. Figure 18 shows the time frames data would be collected for 3 hypothetical patients who develop their acidaemia at different points into admission.

In the admission tool we collected data from the admission window (4 hours), curtailed by the point the index acidaemia developed if this occurred within the admission window. This is designed to replicate data that could be expected to be available to a consultant or senior initially reviewing the patient or on a post take ward round. Practically this consists of data from the initial radiology and blood sciences. The worst (i.e. most abnormal) bedside observations and the presence of AF were recorded from a period up to a maximum or four hours prior to development of RA. Considering the hypothetical patients in Figure 18, Patient A develops acidaemia early so the data collection window closes prior to the 4-hour window i.e. from admission to 2.5 hours. Patients B and C both develop their acidaemia after 4 hours, so the maximum ‘admission’ window is open for data collection.

The point of deterioration tool is very different, this is all available data in the 24 hours prior to deterioration, data prior to admission or post deterioration is not however collected irrespective of timings. Therefore, patient A has data collected from admission to 2.5 hours. The rules around admission window do not apply here so patient B has data collected from

admission to deterioration covering 16 hours. Patient C deteriorates later into admission after 72 hours. Data here is collected from 24 hours prior to point of deterioration ie from 48-72 hours; (If this patient deteriorated after 26 hours data would be collected from hours 2-26).

Figure 18 Time windows for data collection for three hypothetical patients.



n.b. boxes represent development of acidaemia, arrows represent data collection windows.

5.3.3 Demographics and Descriptors.

Full patient identifying information was not submitted centrally. Date of birth could, following ethics committee approval, be submitted to calculate age on admission. Date of birth, gender and ethnicity are important not only as population descriptors but also for calculation of predicted spirometry values. Time of admission was taken from patient administration system (PAS) unless an earlier time could be objectively verified e.g. From an ABG result or notes entry. This situation is common amongst critically unwell patients in whom clinical actions may slightly precede entry onto electronic systems. The timing of other key points in a patient admission were recorded such as admission to inpatient ward or senior review. Post ED senior review was defined any consultant other than A+E consultant.

Northumbria healthcare operates a system of cottage hospitals to accommodate such a large geographical region. Many patients are discharged to these hospitals to convalesce prior to returning home or are admitted to 'step-up beds' from the community. They are more akin to a nursing home; little acute care is available with typically one doctor ward

round a week. As such length of stay is often quite prolonged and patients only go to these hospitals when 'medically fit'. For the purposes of the study a discharge to a cottage hospital it counted as the end of their period of acute care and the day of transfer recorded as the discharge date. In line with this position if they were admitted from one it was counted as an admission from the community and the date and time of admission to the general hospital used.

5.3.4 COPD Details.

Date and details of prior spirometry were recorded. In rare cases, inclusion was allowed without the precise spirometry values available. This was in cases where there was definitive evidence of spirometry having been performed and airflow obstruction being proven. For example, if a specialist makes a specific reference to airflow obstruction in their letter but the values are not included and missing this patient could be included. It is important to note a simple mention of COPD did not count in this regard. Requirement of supplementary oxygen was LTOT only as defined by conventional criteria, not short burst or palliative oxygen.

5.3.5 The Extended Medical Research Council Dyspnoea Scale (eMRCD).

The traditional MRCD [196] grades patients from 1 to 5 and has been used in research and clinical practice for many years. While the original scale is excellent a novel extension [197] developed by this research group (3.2.3) is a potential improvement in two principle areas:

Firstly, it clearly lays out the rules on how to score between levels which have been somewhat ambiguously applied historically and the measurement window is defined "*in the last 3 months when feeling at your best.*" Grade 4 in either score reads "*stops after walking 100 m, or for a few minutes, on the level.*" If the patient can walk 20 yards only how would the dyspnoea be graded? eMRCD specifies that the dyspnoea must achieve all specified aspects of the higher (worse) dyspnoea grade before being scored as such. Another area of grading contention lies in the role of assistance: Exemplifying this, consider a patient who is helped out of their house to the supermarket by a family member, perhaps pushed in a wheelchair. Is this patient housebound or not? eMRCD specifes that the patient must be able to do the activity unassisted (and under their own steam i.e. an electric scooter counts as assistance) to avoid the confounding role of assistance. Other scoring

specifications include that even if other disability (not dyspnoea) is the predominant reason why a higher grade is scored the higher score stands.

Secondly, the traditional highest dyspnoea level 5 ("*too breathless to leave the house*") is split into 5a ("*Too breathless to leave the house unassisted but independent in washing and/ or dressing*") and 5b ("*Too breathless to leave the house unassisted and requires help with both washing and dressing*"). This distinction recognises the difference between those that can complete activities of daily living autonomously and those that cannot.

Collection of eMRCD can be simple or comparatively difficult depending on the quality of note-keeping. Fortunately, a good assessment of functional status is usually included in cases where ventilation is required. Using a combination of inpatient and outpatient medical notes, occupational therapist, nursing, and physiotherapy notes a good assessment can usually be made. Prospectively if there was uncertainty the patient could be approached to verify.

5.3.6 Comorbidities and Medications.

All components of the Charlson index and APACHE II score were collected according to their specified definitions for the derivation study, to ease data collection the Charlson index was dropped from the validation study. Atrial fibrillation (AF) was of particular interest following the DECAF projects. AF was defined as present whether chronic, paroxysmal or de novo. A single transient episode of AF in the context of historical acute illness did not count as paroxysmal atrial fibrillation (PAF) but 2 or more did. Certain medications associated with COPD outcomes were recorded at admission and discharge for accurate population description.

5.3.7 Observations, Physical Measurements, Blood Tests.

Readily available observations and constituents of comparison tools were recorded as continuous variables. The worst value (greatest deviation from accepted normal) was recorded within the given timeframe, readings did not need to come from the same set of observations. Most recent height and weight was recorded preferentially. Weight was ideally from the same admission but prior readings accepted provided no history of weight loss. Blood tests were recorded according to APACHE II rules and pre-discharge if applicable.

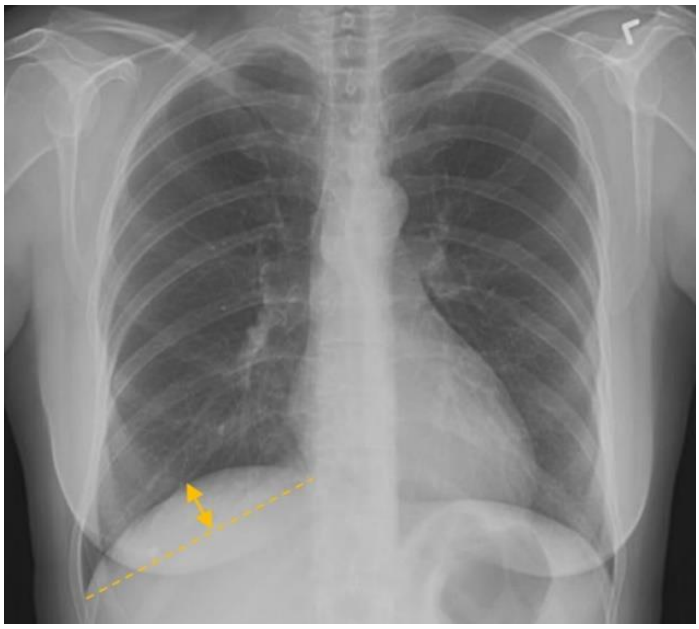
5.3.8 ABGs.

ABGs including date, time, FiO2 and sampling method were recorded at admission, first recorded RA, NIV initiation, 24 hours post and after cessation prior to discharge if application. The time pH corrected was separately recorded. If CO_2 was reported as 'high' this was imputed as the maximum integer that analyser could return. In the case of the derivation project this was 20.

5.3.9 Radiology.

Presence or absence of consolidation at admission and at ventilation recorded in following hierarchy: attending physician interpretation (to mimic reality), radiologist report, researcher interpretation. Diaphragm height was recorded in attempt to model hyper-expansion. The maximum elevation from a straight line drawn between lateral and medial hemi-diaphragm insertion points was taken (Figure 19). This data is being captured in an exploratory capacity and there will be inter-user variability around marking diaphragm insertion points particularly the medial insertion point but this has not been evaluated and no kappa value is available. The right hemithorax was used preferentially.

Figure 19 Diaphragm height measurement.



5.3.10 Timing of acidaemia.

The time of acidaemia onset was expected to be an important predictor of outcome. Ventilation typically occurs after several decision-making steps and therefore, a sequence of

time points in the decision-making process to instigate ventilation that could be used. Hospital arrival is always the starting point. From here time to a) index episode of acidaemia (i.e. ignoring episodes of acidaemia that occur earlier but correct with treatments other than ventilation); b) the ABG that prompted NIV or c) the point that ventilation is initiated are all valid indices. There are advantages and disadvantages to each method and moreover, after binary categorisation there will always be little difference in the populations, but it is important to understand what is being referred to.

No single time-point is perfect however, the problem with a) is differences in medical treatments between units may make this a less standardisable unit and c) is that a short-term issue with bed or ventilator availability may be being measured. The preference in the NIVO population is to take the time of the ABG that prompted NIV as this is highly reproducible and less exposed to variation not captured in the recorded data.

5.3.11 Ventilation.

Previous acute ventilation and HMV details were recorded for context. Date and time of initiation, ventilator settings after 1 hour and maximally and discontinuation time and reason describe the onset, duration and intensity of the intervention. Far greater detail would have added little, NIVO did not control the intervention and the focus is upon modelling prior to initiation.

5.3.12 Late failure.

Varying definitions of late failure have been used (3.3.7.2), while simple conceptually i.e. those that deteriorate after a period of correction the definition becomes quite complex. Our definition was designed to avoid capturing those who have early oscillations and may dip transiently back into the acidaemic range. Those that have a clear, late deterioration were the desired target. Our definition reads: *"Late failure is recurrence of respiratory acidaemia prior to discontinuation of ventilation. pH should drop to below 7.35 with a rise in CO2 of at least 1kPa and to >6.5kPa from the lowest recorded post pH correction at least 24 hours after pH correction."*

5.3.13 Relapse

A subsequent episode of ventilation within the same admission was termed relapse provided 24 hours were elapsed after cessation of index event. If less than 24 hours had elapsed this was considered failure of weaning and therefore a continuation of the index event.

5.3.14 Outcomes.

In-hospital mortality was extended out to one week if a patient was discharged with expressed palliative intent on a care of the dying pathway. Advanced care planning such as not for readmission to hospital or addition to a primary care palliative care register would not fulfil these criteria. Outcomes such as readmission, HMV usage, death to one year were recorded. Post discharge outcomes in the validation arm are not reported in this thesis.

5.4 Statistical Plan.

5.4.1 General plan and approach.

5.4.1.1 Power.

In order to estimate the sensitivity of the tool (and assuming a standard error of 5%) 85 deaths should be studied in each cohort (assuming an expected sensitivity of 70%). With an estimated in-hospital mortality rate of 20% at least 425 patients are required in both the derivation and validation cohorts.

5.4.1.2 Missing Data.

For both derivation and validation cohorts, missing variables were imputed by expectation maximisation algorithm, to minimise bias. All subsequent analysis were performed on complete dataset. Comparison to original dataset will be made to ensure no statistically significant discrepancy.

5.4.1.3 Population Description.

Parametric variables were identified by visual inspection of the histogram. To characterise the patient sample, proportions will be used for categorical variables, means with standard deviations (SD) for parametric variables, or medians with inter-quartile ranges (IQR) for non-parametric variables.

5.4.1.4 Univariate Analysis.

To compare characteristics and outcomes between population groups, Chi-Squared test was used to compare categorical variables, Student's T-test to compare parametric data, and Mann-Whitney U to compare non-parametric variables. To examine for trends across multiple sites, ANOVA were used for parametric data and Kruskal-Wallis for non-parametric variables.

Two-sided p values are reported unless specified. When the independent samples T test was used. Variance was assessed using Levene's test. This test would be statistically significant if there was unexpected variance between the samples. Assuming Levene's is non-significant the significance level the 'assumption of equal variance two sided significance level' will be reported.

5.4.2 Multivariate analysis.

5.4.2.1 Multivariable Analysis Background.

A number of methodological steps are required to advance from a pool of candidate indices to a model that has utility. The following sections will explain the steps taken. There remains within the statistical literature significant debate as the best way to achieve this end. There is a balance to be struck between 'pure' statistical methodology which usually entails a parsimonious approach of minimal assumption and the alternative approach of greater simplification for example by categorising a continuous variable which may lead to less exact prediction but potentially creation of a model that is wieldy enough to translate to clinical practice. It is important to remember that handling one or more variables as continuous within a model requires computation.

The greatest criticism of prognostic modelling is the reporting of outcomes from (small), selective, retrospective datasets without validation in separate cohorts. In an excellent summary paper on the topic Steyerberg et al [(245)] suggest: reliable models for clinical practice are more likely to be obtained when they are:

- Developed using a large, high quality dataset.
- Based on a study protocol with a sound statistical analysis plan.
- Validated in independent datasets obtained from different locations.

The presence of a defined, published protocol is particularly important to avoid the otherwise subversive effect of publication bias as coherently argued by Hemingway and colleagues.[246]

5.4.2.2 Principles of Regression Analysis.

All forms of regression analysis attempt to draw unknown (predictive) information from available data. The outcome or dependent variable is predicted by the predictor or independent variable(s). In linear regression using continuous variables a model is an equation to represent the line of best fit through the data. Knowledge of this equation allows prediction of outcome from new data. Simple regression refers to a single predictor variable and multiple regression to more than one predictor variable.

Consider a scatter plot where the y axis outcomes are either 0 or 1, it appears as two parallel lines. There is no possibility of drawing a line of best fit through this data as there is no linear relationship (which is a basic assumption of linear regression). To predict outcome from independent variables in this instance, where the outcome variable belongs to one of two mutually independent states, logistic regression is employed. The logit conversion overcomes this violation of linearity and the outcome value will be between 0 and 1. So if an outcome value is closer to 1 is probable from the model the outcome will belong to the group assigned to 1.

In the case of NIVO it was necessary to model a binary outcome (alive or deceased) from several variables therefore multiple logistic regression is employed. Other considerations that will be further discussed include variable selection, collinearity, method of entry into a model, assessment of how well the model fits the data.[247,248]

5.4.2.3 Variable Selection.

Many variables collected are to explore and report interesting associations or accurately describe the population under review and were never considered as candidate predictors. It is important to both include feasible variables and remove extraneous ones. One cannot simply enter every variable into a multiple regression analysis as this would result in over-fitting. Overfitting occurs when the model is too tightly tied to the source data and will not predict new outcomes in different datasets well. As a rule of thumb there should be about

15 cases or 10 outcome events for each predictor candidate predictor.[247-249] Therefore, which variables are to be entered into a regression analysis must be carefully selected.

Following extensive literature review as described a pool of potential candidates was generated which was initially narrowed by limiting to univariate associations with outcome. Again, using Chi-squared test to compare categorical variables, Student's T-test to compare parametric data, and Mann-Whitney U to compare non-parametric data. Those with significance of <0.1 were eligible for further screening prior to entry into multiple regression.

Only variables with potential for utility could be taken forward: for example, the gradation by ejection fraction on echocardiogram may be an accurate predictor but this data is not readily available in an emergency department outside of normal working hours when the tool must be able to be applied. Similarly, the presence or absence of a medication may be strongly associated with outcome but there is such strong bias attached to this it is a poor candidate predictor.

5.4.2.4 Screening of Variables with Univariate Significance (<0.1).

To progress further to inclusion in the regression analysis predictors underwent several further screening steps:

- Assessment of face validity, there must be a plausible association between the outcome and the predictor otherwise excluded.
- Asymmetrical split, categorical variables with only a small proportion of the population in one category (<10%) were excluded.
- Collinear variables, if two (or more variables) have substantial overlap only one was carried forward to the final model (see next section)

5.4.2.5 Assessment of Collinearity.

Collinearity exists where variables are measuring (in part) the same thing. For example, white cell count and neutrophil count are highly likely (and in our case were found to be) collinear. Not all associations will be as conceptually obvious as this and statistical assessment will reveal more occult associations. If variables were found to be highly collinear only one was taken forward to regression analysis. The most clinically relevant variable was selected or the most statistically significant if no conceptual advantage.

Three assessments were used: [247,250]

1. Pairwise correlation co-efficient >0.7 using Pearson's correlation for parametric or Spearman's for non-parametric.
2. Variance inflation factor of >3.
3. High conceptual correlation, for example WCC and neutrophil count. These variables would very likely be identified by the above assessments but if not only one would be considered for entry into final regression equation as they clearly measure a similar concept.

5.4.2.6 Entry into Regression Model.

After selecting candidate variables there are several methods of entry. Stepwise methods are commonly employed in predictive model building. Forward stepwise entry method sequentially adds the variable most strongly associated with outcome until all variables that achieve a prespecified significance level are entered. Backward stepwise methods sequentially remove the least significant associate until only those achieving a prespecified level of significance remain.

A backward stepwise method was chosen for NIVO with a significance level of $p < 0.05$.[251]

5.4.3 Assessment of Model.

5.4.3.1 Model Fit.

Considered selection of candidate variables and the significance level within the regression equation are the most important determinants of a well-fitted model. The predictive model will produce an outcome probability for each case. A residual is the difference between observed outcome and predicted outcome. To render these values interpretable and apply standard cut-offs they are converted into standardised or studentised residuals, studentised being considered most accurate. Greater than 5% of cases having a studentised residual of +/-1.96 is indicative of a poorly fitting model. Cook's distance is a further method of examining outliers with values >1 a cause for concern.[247] Further examination of outliers was warranted if these assumptions were violated.

5.4.3.2 Calibration.

Calibration refers to how well the predicted outcomes relate to the observed outcomes. To assess this, cases are grouped (usually 10 groups in large sample sizes) and the number of predicted outcomes to the number of observed outcomes in each group compared. The line of best fit of this plotted graphically is informative. Perfect calibration has a gradient of 1.[247] A further method of comparison is using the Hosmer-Lemeshow goodness of fit test (HLGFT), non-significance is indicative of good calibration.[252]

R^2 is a further assessment of a model. It describes how much of the variability in outcome can be explained by the model itself. A value of 1 indicates all variation in outcome is accounted for by the model. Ultimately the optimum assessment of calibration is successful validation in a separate dataset.

5.4.3.3 Discrimination.

Discrimination is how well the model can distinguish between a high risk and a low risk patient. In logistic regression this is commonly assessed by the area under the receiver operated curve (AUROC). This is a measurement of sensitivity and specificity. A straight, 45-degree line would give an AUROC of 0.5 akin to pure chance. Perfect discrimination would be 1.[247]

5.4.4 Tool Building.

5.4.4.1 Background and Guiding Principles.

The final tool must adhere to several principles:

- Offer good prediction.
- Be simple to administer.
- Have face validity.

Selection of which variables to include, the number of variables, and assignation of weighting should strike a balance between these principles.

5.4.4.2 Handling of Continuous Variables.

For maximum utility all variables in the tool(s) will be split into two or three categories. Ideally a dichotomy unless significant reward in terms of model accuracy is offered. To select the appropriate cut off the following hierarchy was used: 1) ROC curve analysis, 2) results from previous research, 3) a clinically meaningful value, 4) a median split.

To ascertain a split point from ROC curve analysis an individual continuous variable is plotted against outcome and the curve inspected. The presence of a clear 'shoulder' closest to the top left hand corner (assuming a positive relationship) corresponds to be optimum cut off in terms of sensitivity and specificity.

5.4.4.3 Selection and Weighting.

Following the steps outlined a small list of categorised variables was developed. This was then converted into a clinical tool by ascribing numerical weighting to presence of adverse features to allow each case to be given a score.

No absolute rules can be imposed upon variable selection, the appearance of the resultant tool and the weighting applied to the composite indices. The ideal situation is that a small number of predictors offer excellent performance, can be added together in a simple manner and weighting requires only one or two integers.

To assess variable weighting a proportional beta coefficient was created by dividing each beta coefficient by the smallest beta coefficient of all included variables. By definition this will result in the least influential variable being divided by itself and returning a value of 1. The Wald test is another commonly reported assessment of the relationship between variables in a model and will be used as a secondary guide and handle in a similar manner. Clinical judgement must also be used in tool building, the reasons why particular decisions are made is outlined.[253]

Mortality at each step of any developed score was inspected to ensure progressive mortality is seen. Final assessment of the resultant clinical tool will be by AUROC.

Addendum following Viva examination suggesting extra clarity: *"Add a description of the work undertaken in this thesis within the methods sections. It was clear at oral exam that Dr Hartley undertook a huge amount of work to complete this impressive work"*

The entire derivation database was generated 'bespoke' by myself with reference to source data. All analysis is my own and exclusive to this work. This was not interrogation of an existing database. For both studies; all CRFs, manuals, IRAS forms and ethics was myself. Development of online data management system was myself working directly with a IT company. Shortly after recruitment began to the validation study day to day workload was then split 50:50 with Dr Lane. All analysis of data in this thesis is my own.

Chapter 6. Results: Derivation study Part 1, Population Characterisation.

6.1 Data Handing.

6.1.1 General.

The derivation project is reported in this thesis in full, but validation study results are limited to a description of the population and the validation of the predictive tool. A more fulsome exploration of the validation results will be presented in the next thesis from Professor Bourke's group.

Data was exported from database into Microsoft Excel and then into IBM SPSS v22. Some variables were computed immediately for example the time timing of acidaemia was calculated from the between first attendance and the relevant ABG time.

6.1.2 Data screening.

Where able, data was ranked by value and outliers examined. Data entry errors were identified and rectified. Spot checking of random CRFs did not reveal additional significant data entry error.

6.1.3 Missing Data.

Rates of missing data were low in indices collected for the primary aims of clinical tool creation. Most indices with higher rates were blood tests that are not requested routinely. Indices with >1% missing values up to the point of deterioration are reported. Phosphate 87.9% and troponin 87.0% were by far the most commonly missing and were not considered further. Glucose (serum or BM) 25.8%, bilirubin 23.1%, total protein 20.2%, albumin 19.0%, potassium 6.7%, CRP 4.7%, previous pulmonary rehabilitation 4.7%, oxygen saturation 4.5%, haemoglobin 4.5%, Eosinophils 4.1%, WCC 3.9%, platelets 3.9%, haematocrit 3.9%, neutrophils 3.9%, sodium 3.3%, urea 3.3%, base excess 3.1%, diastolic blood pressure 1.6%, systolic blood pressure 1.4%, heart rate 1.4%.

Missing values were imputed where appropriate by expectation-maximisation algorithm. Univariate analyses were repeated using the original dataset to ensure no difference in

significance. Indices with >10% missing data were not considered for further analysis irrespective of imputation results.

Due to the uncontrolled study design, the rates of missing data post NIV initiation and at hospital discharge are variable and are reported in the relevant sections. These aspects are clearly separate from the primary aims and should not be confused. An illustration of this is arterial blood gases; we could rely on this data being available for collection in the initiation phase of NIV, but collection of blood gases at 24, 48 and 72 hours is variable and often missing.

6.2 Population Description.

6.2.1 Headline summary.

489 unique cases were identified admitted to hospital between 30/11/2008 and 19/5/2013 of whom, 365 survived to discharge and 124 (25.4%) died in-hospital.

6.2.2 Demographics.

The population of North Tyneside and Northumberland is homogenous, with over 95% of the population in both areas reported as white British and born in the UK in the 2011 census.[254,255] Every patient in this cohort was coded as white British.

Table 9 Whole population demographics.

Variable	Value
Female	62.6%
Age*	72.8 (10.0)
Admitted to North Tyneside General Hospital,	52.2%
Cigarette Pack Years*	49.5 (26.0)
Current smoker	48.7%
1(+) respiratory admission in last 12 months	38.7%
1(+) non-respiratory admission in the last 12 months	17.8%
Charlson Index	2 (1-3)

*Mean (SD) †Median (IQR)

The high proportion of females is notable as compared to the national COPD audits where there is a rising proportion of females but still significantly lower than our sample. Proportions of females in national audits are: 2003 (47%), 2008 (49%) and 2015

(51%).[29,81,145] Unfortunately, the gender of those receiving ventilation is not reported in these audits. It is noteworthy that the NCEPOD report has a higher proportion of females at 56.9% [144] than the best estimate of time matched background prevalence (51% 2015 report). The local background (admitted) COPD population is well characterised by the DECAF derivation and validation which span the same time period in which 56.4% were female.[82,195] In this context 62.6% female represents the same proportional increase from our background population as that seen in the national figures.

The reason(s) why females appear to be over-represented in UK NIV populations is unclear. Survival long enough to develop severe disease without succumbing to other conditions commoner in males particularly cardiovascular disease may be one explanation.

6.2.3 Home Circumstances.

Most patients are admitted from their own home with 10% admitted from institutional care (a combination of residential care, nursing care or a community hospital).

Table 10 Pre-admission home care circumstances.

Admitted From	Percentage of Total
Home	70.1
Home + formal carers	12.1
Sheltered accommodation	5.1
Sheltered accommodation + formal carers	2.7
Residential care	4.3
Nursing care	3.7
Community hospital	2.0

Anecdotally, a large number of patients received informal care from family or friends. This is not definitively captured by the data. There is, however some supportive objective data: as shown in Table 12 over half of the population are housebound due to breathlessness (eMRCD 5a and 5b) but only 25% have formal support at home.

6.2.4 COPD details.

Selecting patients with ECOPD resulting in RA has resulted in a population with severe COPD based on spirometry gradation (1.1.3). Between a quarter and a third require LTOT and the

median eMRCD grade of 5a indicates marked functional limitation. This is a cohort of with a high level of morbidity.

Table 11 Key descriptors of COPD.

Variable	Value
FEV_1 (L)*	0.81 (0.36)
FEV_1 (%)*	38.0 (16.4)
FEV_1/FVC*	0.44 (0.12)
Exacerbations reported in the last year*	2 (1-4)
Previous pulmonary rehabilitation	14.6%
eMRCD†	5a (4-5a)
LTOT on admission	29.2%

* Mean (SD) †Median (IQR)

Exacerbation history is difficult to ascertain from retrospective records and this was only recorded if positively identified. These exacerbations are not verified against standardised criteria but are as accurate a possible estimation from inpatient notes, clinic letters, GP correspondence and GP prescription records where available. No data either positive or negative could be reported in 113 (23.1%).

6.2.5 eMRCD.

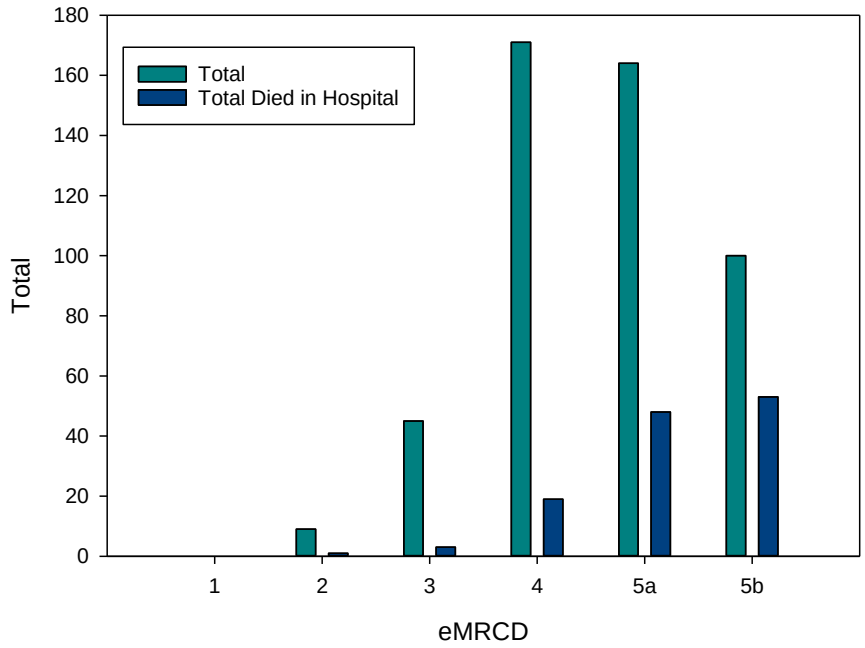
The eMRCD score was expected to be an important predictor of in-hospital mortality and we are fortunate to have robust comparison data from previous research. Table 12 shows most NIVO patients fall into the three highest dyspnoea categories with over 50% housebound due to dyspnoea. In both cohorts there is a clear and progressive increase in in-hospital mortality the higher the dyspnoea category. There is an upshift in eMRCD score by comparison to the DECAF derivation cohort (patients admitted with ECOPD but not necessarily requiring ventilation) collected in the same trust. This upshift, and that mortality is higher in each dyspnoea category, is unsurprising given our cohort is selected from those requiring ventilation. Some patients will be included in both cohorts.

Table 12 eMRCD comparision between NIVO and DECAF derivation cohorts.

	NIVO		DECAF	
eMRCD	N (% of total population)	Mortality (% within dyspnoea grade)	N (% of total population)	Mortality (% within dyspnoea grade)
1	0 (0%)	0 (0%)	6 (0.7%)	0 (0%)
2	9 (1.8%)	1 (11.1%)	46 (5.0%)	0 (0%)
3	45 (9.2%)	3 (6.7%)	171 (18.6%)	4 (2.3%)
4	171 (35.0%)	19 (11.1%)	382 (41.2%)	15 (3.9%)
5a	164 (33.5%)	48 (29.3%)	173 (18.8%)	30 (17.3%)
5b	100 (20.4%)	53 (53%)	142 (15.4%)	47 (33.1%)
Total	489	124 (25.4%)	920	96 (10.4%)

Figure 20 is a graphical representation of the distribution of patients from the NIVO cohort by eMRCD score and the associated number of in hospital deaths in each division.

Figure 20 Number of Patients admitted in each eMRCD category and corresponding in-hospital mortality count (NIVO data).



6.2.6 Admission Medications

Selected medications are displayed. These are presented to accurately characterise the population but are not candidates for inclusion in a predictive model. While there are prescription guidelines and therefore theoretically some degree of standardisation, in practice the reasons why a particular patient is or is not taking a medication may be

numerous and have no valid association with mortality risk. The exception to this is the use of long term oxygen which is a drug, but its prescription is based upon objective physiological criteria and hence it has been handled separately. Exemplifying that medications are unsuitable candidate predictors of in-hospital mortality, the only medication here significantly associated with mortality is Carbocisteine where there is a weakly significant result (2 tailed p=0.046) favouring increased mortality when taking the drug.

Table 13 Selected pre-admission medications.

Medication	Percentage taking on admission
Long term steroid	11.0
Diuretic	44.4
ACE inhibitor	29.7
Beta Blocker	10.8
Statin	41.3
Benzodiazepine	12.7
Opiate	7.4
Long Acting Beta Agonist (LABA)	82.0
Long Acting Muscarinic Agonist (LAMA)	76.6
Inhaled Corticosteroid (ICS)	83.4
Carbocisteine	22.5
Theophylline	7.0
Azithromycin	6.5

The prescription of diuretic is high as many patients were prescribed diuretics particularly Bendroflumethiazide for hypertension. With changes to hypertension guidelines this is likely to fall in the validation cohort.

The number of patients receiving LAMA may seem lower than expected, however a number of patients were prescribed regular nebulised ipratropium bromide (a short acting muscarinic agonist) and hence were not concurrently prescribed a long acting muscarinic agonist. The precise numbers are unavailable.

6.2.7 Chest X-ray Findings and Pneumonia.

Each chest x-ray was examined by the same researcher to determine presence or absence of pleural effusion, number of posterior ribs and diaphragm height. Presence or absence of

consolidation was collected differently, this was determined from the clinical notes irrespective of the researcher's interpretation of the x-ray.

Table 14 Chest X-ray findings.

Variable	Value
Chest X-Ray consolidation (admission)	43.6%
Chest X-Ray consolidation (at ventilation)	47.2%
Any pleural effusion (admission)	18.8%
Number of posterior Ribs†	9 (8-9)
Diaphragm Height (cm)*	2.1 (0.93)

* Mean (SD) †Median (IQR)

The rate of consolidation is high, this may reflect the severity of exacerbation or may be artificially so due to poor x-ray interpretation by attending clinicians, this point is however moot if the results are generalisable within the validation cohort, and it is important that the data is reflective of real life so as not to include data in a clinical tool which is not readily generalisable.

6.3 Timing of Acidaemia.

6.3.1 Timing data handling.

In most cases the date and time of the first development of acidaemia is recorded. If the initial episode of acidaemia resolved this was recorded and the time of acidaemia associated with the first episode of ventilation was taken. In 7 cases the initial episode of acidaemia was either not recognised or did correct but the objective verification of such is missing. In these 7 cases there is mild acidaemia (mean pH 7.32) and a prolonged time gap between the initial acidaemic blood gas and the blood gas that prompted ventilation (median 1914 minutes IQR 1836m-2613m). As such in these 7 cases the initial acidaemia is considered to have resolved and the time of blood gas prompting ventilation is used. The derivation data was collected prior to electronic storage of ABG results so loose print outs were frequently missing.

6.3.2 Notes on timing of acidaemia.

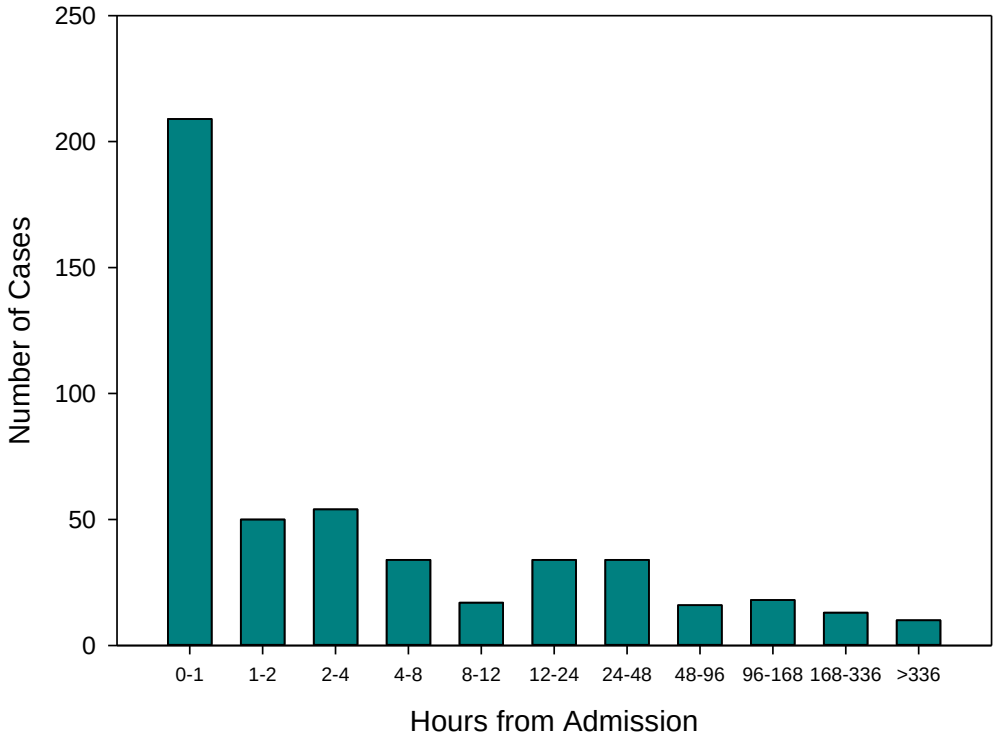
The interaction between timing of acidaemia and outcome must be carefully considered in the context of the clinical situation and the realities of provision of care. The majority of patients develop their acidaemia early in their admission phase, in 361 (73.8%) cases the

index episode of acidaemia occurs in the first 12 hours. The hypothesis is that those that deteriorate later into admission have done so despite the provision of active medical treatment for their ECOPD and that this represents an independent mortality risk. Pre-hospital variables and fluctuations in staffing ratio, time of day, day of week or how busy an emergency department is may well interact in the short term with identification of acidaemia and/or instigation of medical treatment. Therefore, ascribing a cut-off too close to the admission time may well capture confounders devoid of reproducible meaning. 12 hours was selected for its clinical significance in the admission sequence and ease of recall. The NHS standard is for patients to be seen by a consultant within 14 hours of admission to hospital [256] and as already stated the mean time to consultant review of a patient with ECOPD is 10 hours. Having a cut off within this key decision-making window is sensible to maximise the real-world applicability of the results.

As stated in 5.3.10 the time of greatest interest in the NIVO cohort is the time from first admission to hospital to the time of the ABG that prompted ventilation.

6.3.3 When does acidaemia develop?

Figure 21 Time from admission to episode of acidaemia prompting ventilation.



It should be noted that in Figure 21 the X axis scale is non-linear.

6.3.4 Relationship between time and in-hospital mortality.

Twelve hours is a compelling cut-off due to the described associations with existing models of UK care. Other potentially useful thresholds are 24 hours and 48 hours which are shown in Table 15.

Table 15 In-Hospital mortality graded by acidaemia development after 12, 24 and 48 hours.

	Under threshold		Over threshold	
Threshold	Number	Mortality	Number	Mortality
12 hours	361 (73.8%)	65 (18%)	128 (26.2%)	59 (46.1%)
24 hours	395 (80.8%)	74 (18.7%)	94 (19.2%)	50 (53.2%)
48 Hours	430 (87.9%)	87 (20.2%)	59 (12.1%)	37 (62.7%)

As expected, there is a progressive mortality the later into admission the index acidaemia occurs but with fewer patients captured the later the threshold is placed. The particularly high in-hospital mortality after 48 hours may be a useful threshold where identification of patients at high risk of death has greater priority over stratification across the risk spectrum.

6.3.5 Clinical differences between early and late deterioration.

The data presented in Table 15 illustrates the starkly increased mortality between those that present with RA and those that develop it further into admission, in whom, depending on the time threshold used mortality is 2.5 to 3 x higher. It appears that the later into admission this occurs the worse the outcomes are. It may be that time is merely a surrogate marker of other adverse markers or it may be as hypothesised that those patients that deteriorate despite medical treatment are inherently less salvageable.

Table 16 explores whether there are significant differences between the groups. Groups have comparable FEV_1, requirement of LTOT and need for institutional care, there is no evidence of increased renal failure, metabolic component of acidaemia, inflammatory response or physiological derangement at the time of ventilation as measured by the CAPS score. Those deteriorating later have significantly higher pH which does not account for excess mortality. These patients are however, older, more frequently have chest X-ray consolidation and have a higher eMRCD score with a greater proportion of those with greatest disability, eMRCD 5b.

Table 16 Clinical differences between patients developing their acidaemia <12 hours versus>12 hours.

Variable	<12 Hours	>12 Hours	P value
eMRCD†	5 (4-5a)	5 (4-5b)	0.034
eMRCD 5b	64 (17.7%)	36 (28.1%)	0.015
LTOT	110 (30.5%)	33 (25.8%)	0.366
Institutional Care	36 (10.0%)	13 (10.2%)	1.000
FEV_1%*	37.6 (16.2)	39.3 (17.0)	0.310
Age*	71.8 (9.93)	75.5 (9.83)	<0.001
Urea†	7.0 (5.2-11.1)	7.65 (5.33-10.4)	0.925
CRP†	50 (15-123)	56 (15-113)	0.811
WCC*	13.4 (5.5)	13.0 (8.9)	0.124
pH†	7.26 (7.19-7.30)	7.28 (7.23-7.31)	<0.001
Base Excess*	3.9 (6.5)	3.5 (6.5)	0.589
Confusion at ventilation	69 (19.3%)	33 (25.8%)	0.130
Consolidation	43.5%	57.8%	0.006

* Mean (SD) †Median (IQR) (dynamic clinical data e.g. ABG data is worst in 24 hours pre NIV)

6.4 Ventilation.

6.4.1 Ventilation Description.

The focus of the study is NIV but those receiving IMV are also included to make the population as generalisable as possible. A large majority of this population received exclusively NIV. This is in keeping with UK practice.

Table 17 Descriptors of ventilation.

Variable	Value
Formal Oxygen trial	38.4%
Exclusively NIV	94.5%
Duration ventilated whole days completed†	3 (1-5)
Duration ventilated hours†	84 (37-128)
Previous NIV ever	21.9%
NIV in last 12 months	10.0%
HMV admission	2%
Worst pH pre-ventilation†	7.26 (7.20-7.30)
Worst PaO_2 pre-ventilation†	8.3 (6.9-9.9)
Worst $PaCO_2$ pre-ventilation†	9.9 (8.5-11.7)

* Mean (SD) †Median (IQR)

Duration ventilated in hours is taken from the initiation to discontinuation time. It does not imply continuous use.

Formal oxygen trials are recorded if the acting clinician(s) identified RA and prior to the delivery of ventilation administered a trial of treatment for one hour that included active control of the delivered FiO_2. From retrospective notes, no assessment of how well this trial was delivered is feasible.

There was no statistically significant association between ever receiving NIV or receiving NIV in the last 12 months and in-hospital mortality.

6.4.2 Intubated Patients.

27/489 patients were intubated of whom 13 had received NIV prior to intubation. Intubated patients were significantly younger, had both lower pH and base excess at outset and were less likely to be in receipt of long term oxygen. Percent predicted FEV_1, consolidation on X-ray and CO_2 level were not significantly different.

There was no significant association between intubation and in-hospital mortality (one tailed p= 0.372) nor whether NIV was initiated prior to intubation or not so the population will be handled as a whole. This is representative of the real world and avoids unnecessary subgrouping of the population.

6.4.3 Ventilator Settings.

Table 18 Ventilator settings for those receiving NIV at initiation, 1 hour and maximum achieved.

Variable	Initiation	1 hour	Maximum
IPAP†	16 (16-18)	18 (16-20)	20 (18-20)
EPAP†	4 (4-5)	4 (4-5)	4 (4-5)
Back up rate†	12 (12-12)	12 (12-12)	12 (12-12)

* Mean (SD) †Median (IQR)

During the period of study, the default back up rate of the ventilator applied as per the local guideline was 12 breaths per minute. Latterly there has been a tendency towards higher back up rates (and higher target pressures) which may well be shown in the data from the validation study. As might be expected there is a progression in IPAP from initiation to 1

hour to maximum and is perhaps an indication of good care with active titration over the acute period.

6.4.4 Ventilation summary.

Previous work by the study group has focussed upon the outcomes of patients admitted with ECOPD modelling based upon their admission indices alone. Across all the group's modelling studies the intervention is uncontrolled. Treatment for uncomplicated ECOPD however is comparatively simple and standardised and so there is less chance that poorly delivered treatment influences outcome significantly.

This population are in receipt of a potentially heterogeneously applied intervention which confers a large mortality benefit therefore there is greater potential for intervention variation to cause outcome variation. Comparing mean pressures or duration of treatment between those who died or survived would reveal little of value in an uncontrolled setting. That, as a population these patients had well established RA, received several days of NIV with adequate pressure support is important. It establishes that the population being treated are readily generalisable and the ventilation being provided was of a high average standard. Some comparative national data would support this. In 2011 the mean IPAP at one hour was 15 and in 2012 the mean maximum in the first 24 hours was 16.5 [141,142] both of which are exceeded here.

6.5 Arterial Blood Gases.

6.5.1 Arterial Blood Gases Pre, During and Post Ventilation

A wealth of ABG data was collected. It is all presented but it transpires that the regularity of ABGs drops off markedly after ventilation is established. The rate of missing data is variable due to frequent non-sampling at the designated timepoints on clinical grounds. As the rates of missing data are variable and high, the data is simply presented in its rawest form without imputation.

Rates of missing data are not always the same within a time category. For example, occasionally only the pH and CO_2 may be written into the medical notes and others omitted. It may seem erroneous that there be missing data at the point of NIV but this is not so. All patients had confirmed RA by blood gas criteria, occasionally the last blood gas prior to NIV

is missing and only prose remains such as 'still acidaemic, for NIV' or equivalent. For the regression analysis the worst pH in the 24 hour period prior to ventilation was used rather than the NIV ABG as displayed here to reduce the effect of confounders.

Table 19 Arterial blood gas data at various time points.

Time	Missing	pH†	pCO_2*	pO_2*	BE*	Bicarbonate*
Admission	9	7.30 (7.23-7.36)	9.34 (2.94)	7.29 (8.19)	4.8 (6.0)	32.9 (6.9)
At NIV	13	7.27 (7.21-7.31)	9.34 (2.94)	7.29 (8.12)	4.8 (6.0)	33.24 (6.9)
1 Hour	26	7.31 (7.26-7.35)	9.09 (2.49)	9.64 (4.13)	4.5 (6.2)	32.9 (7.1)
4 hours	61	7.34 (7.28-7.38)	8.42 (2.27)	9.82 (3.75)	5.2 (6.5)	32.8 (7.3)
24 hours	264	7.36 (7.32-7.41)	7.95 (2.01)	9.59 (3.47)	6.2 (5.7)	33.2 (7.9)
48 hours	364	7.37 (7.32-7.43)	7.94 (1.77)	9.87 (4.19)	7.3 (6.9)	34.4 (7.4)
72 Hours	394	7.39 (7.34-7.44)	8.05 (1.86)	9.04 (2.54)	8.9 (8.2)	35.8 (8.7)
Steady	360	7.42 (7.39-7.45)	7.56 (1.40)	8.48 (1.85)	10.0 (5.6)	34.7 (6.4)

* Mean (SD) †Median (IQR)

Despite the very high rates of missing data which is unlikely to be missing at random the results here are broadly in line with expectations. Acidaemia is steadily eroded as CO_2 falls but few other conclusions should be drawn.

6.5.2 pH correction

Blood gases are conventionally sampled at 1-2 hours, 4-6 hours and then thereafter daily until clinically unnecessary or as prompted by clinical status. There are many influences upon when and why these blood gases are actually sampled, if at all. Therefore, in an uncontrolled study such as this there is 'noise' in the data surrounding pH correction. The time of first blood gas showing a corrected pH (≥7.35) after ventilation was instigated was recorded. Patient refusal to have further blood gases may result in that patient being recorded as 'did not correct'. Assumption of correction on clinical grounds by the attending team may also result in several blood gases being 'skipped' and therefore an artificially prolonged time to correction being recorded. However, even with these caveats in place the trends in the following data are interesting.

In order to capture the above clinically relevant time points while acknowledging the real-world sampling variation the data was split into those that correct 0-2 hours, 2-8 hours, 8-36 hours, >36 hours and those that did not correct. The median time to pH correction (amongst

those that did correct) was 499 minutes (8 hours, 19 minutes) with an interquartile range of 121-1498 minutes.

Table 20 Time to pH correction after instigation of ventilation.

Time to Correction	Total	In-hospital Mortality
0-2 hours	103 (21.1%)	17 (16.5%)
2-8 hours	97 (19.8%)	19 (19.6%)
8-36 hours	143 (29.2%)	21 (14.7%)
>36 hours	70 (14.3%)	11 (15.7%)
Did not correct	76 (15.5%)	56 (73.7%)

As expected from a population in whom a large majority survive most patients (84.5%) correct their pH at some point after instigation of ventilation, moreover, and most of these patients survive to discharge (83.5%). It is also unsurprising that failure to correct pH confers a very poor outcome. 20 patients in this group did survive to discharge so presumably did correct their pH at some point but it was not shown on a blood gas. These patients could be assumed to belong to the >36 hour group in which case an alternative way of presenting this is to combine the '>36 hours' and the' did not correct' data. 146 patients had not objectively corrected by 36 hours and the in-hospital mortality was 66 (45.2%).

6.5.3 Time to pH correction in those with late deterioration.

Another possible reason why mortality differs between those who deteriorate early and late may be delayed correction of pH, i.e. failure to correct quickly and hence the more prolonged exposure to the physiological stress of low pH. Table 21 shows there aren't marked differences in time to pH correction whether deterioration occurs early or late, proportions in each time category are similar. Indeed, a greater proportion of late deteriorators correct rapidly. Given that mortality is much higher in the later deteriorating group a greater shift toward later or no correction may have been expected. The mortality data reveals that by far the greatest proportion of deaths come from those that do not correct pH in early deteriorators, amongst late deteriorators this is the largest group, but deaths are more spread across the time categories with a majority of deaths coming in patients that did correct their respiratory acidaemia at some point after ventilation was instigated.

Table 21 Comparison of time to correction and in-hospital mortality stratified by early or late deterioration.

	Early deterioration <12 hours		Late deterioration >12 hours	
Time to Correction	Number *	In-hospital mortality †	Number *	In-hospital mortality #
0-2 hours	67 (18.6%)	4 (6.2%)	36 (28.1%)	13 (22.0%)
2-8 hours	73 (20.2%)	8 (12.3%)	24 (18.8%)	11 (18.6%)
8-36 hours	115 (31.9%)	11 (16.9%)	28 (21.9%)	10 (16.9%)
>36 hours	56 (15.5%)	7 (10.8%)	14 (10.9%)	4 (6.8%)
Did not correct	50 (13.9%)	35 (53.8%)	26 (20.3%)	21 (35.6%)

* Percentage of column total.
† Percentage of total <12 hour in-hospital deaths.
# percentage of total >12 hour in hospital deaths.

6.6 Time to discharge or death

As stated in (6.2.1) 124/489 (25.4%) patients died in hospital. Comparison to national data is tricky as it assumes similar levels of patient selectivity. Despite these misgivings this mortality rate is in the region expected. The decision to collect unique patients is also likely to have an effect: previous NIV is a recognised factor associated with better outcome. Therefore, one could expect the earlier component of the cohort to have lower mortality as it captures the 'frequent flyers'. Later the proportion requiring NIV for the first time will be greater. This effect is indeed seen: 1st 100 patients have in-hospital mortality of 17.5% and the remainder have in-hospital mortality of 27.1%.

Table 22 Time to discharge or death

Variable	Duration (days)
Length of stay (survivors to discharge n=365) †	10 (7-17)
Days to inpatient death (n=124) †	7 (2-14)

* Mean (SD) †Median (IQR)

Further details of the outcomes following discharge are reported in Chapter 8. Length of stay is quite prolonged as one may expect following a life-threatening event and in the context of high levels of pre-admission morbidity. The days from admission to inpatient death show a wide interquartile range in keeping with the capture of a broad spectrum of patients.

Chapter 7. Derivation Results Part 2: Creating Clinical Tools

7.1 Univariate Associations with Mortality

7.1.1 General

In order to develop two tools, data must be analysed differentially. Largely speaking only indices that are independent of the admission can be considered for the admission tool otherwise too many caveats would be introduced into an escalation plan.

Some data, for example the presence of a particular comorbidity, is independent of the timeframe but others WCC, for example, fluctuates. It does not stand up to face validity to include the admission WCC to predict the outcome of an event that may occur 2 weeks later. In specific circumstances where we hypothesised a dynamic variable may be associated with outcome using the admission data the relationship with outcome in those deteriorating after 12 hours was examined to test the hypothesis. In this manner we ascertained that the presence of admission consolidation still predicted outcome later but admission eosinophil count was rejected as it did not.

For the point of deterioration tool if the decision occurred 2 hours into an admission, then only data from the first two hours would be available for analysis. If the decision occurred 4 days into an admission, then the information analysed in this case would be that in the 24 hours prior to the decision. Secondly, as previously outlined (5.4.2.3) many of the population descriptors are not suitable for inclusion as candidate predictors.

7.1.2 Factors Independent of Admission

Table 23 Association with in-hospital mortality - demographics

	Total Population	Survived to discharge	Died in hospital	P value
Gender (Female %)	62.6%	61.9%	64.5%	0.605
Age*	72.8 (10.0)	71.0 (10.0)	77.9 (8.1)	<0.001
Admitted from institutional care	10%	7.9%	16.1%	0.09
BMI*	24.6 (7.3)	24.3 (7.3)	22.4 (6.8)	<0.001

* Mean (SD) †Median (IQR). Institutional care here is residential, nursing or community hospital.

7.1.2.1 Comorbidities

Defining comorbidities can be problematic, the definitions used in the project are included in NIVO manual (12.3). Few show a clinical or statistical relationship with mortality but are important to describe the population under study.

Table 24 Association with in-hospital mortality - Comorbidity

Comorbidity	Total Population (%)	Survived to Discharge (%)	Died in Hospital (%)	P Value
Asthma	9.8	9.0	12.1	0.323
Bronchiectasis	7.6	7.4	8.1	0.808
Obesity Hypoventilation Syndrome	1.0	1.1	0.8	0.782
Obstructive Sleep Apnoea	4.3	4.9	2.4	0.233
Cor Pulmonale	18.6	18.4	19.4	0.815
Chronic Atrial Fibrillation	10.9	8.8	16.9	0.012
Paroxysmal Atrial Fibrillation	6.8	5.2	11.3	0.020
Atrial Fibrillation at time of Acidaemia	15.5	11.9	26.0	<0.001
Congestive Cardiac Failure	13.5	11.0	21.0	0.005
Ischaemic Heart Disease	28.6	26.8	33.9	0.135
Left Ventricular Systolic Dysfunction (LVSD)	14.1	12.1	20.2	0.025
Myocardial Infarction	14.9	13.7	18.5	0.190
Peripheral Vascular Disease	6.1	6.0	6.5	0.865
Anxiety	20.4	21.9	16.1	0.167
Cerebrovascular Disease	11.5	10.1	15.3	0.117
Cognitive Impairment	8.6	7.7	11.3	0.214
Depression	29.2	31.2	23.4	0.097
Dementia	3.9	3.3	5.6	0.241
Hemiplegia	1.2	1.4	0.8	0.622
Connective Tissue Disease	2.5	2.2	3.2	0.520
Diabetes	13.3	13.7	12.1	0.650

Cardiac comorbidities are of particular interest and both AF and LVSD are significantly associated with mortality. Of note AF here is split 3 ways. Of interest is AF at time of

acidaemia which includes chronic AF, PAF and acute (i.e. between admission and acidaemia). Another observation is that both depression and anxiety are protective. Interpretation should be with caution as they were not formally assessed using a validated tool but recorded from clinical notes. Therefore diagnostic inaccuracy and recording bias are likely to be contributary.

7.1.2.2 COPD Factors

Table 25 Association with in-hospital mortality - COPD factors

Variable	Total Population	Survived to discharge	Died in hospital	P value
Cigarette pack years*	49.5 (26)	50.3 (1.3)	47.3 (2.6)	0.278
Current smoker %	48.7%	55.6%	28.2%	<0.001
FEV_1 (L)*	0.81 (0.36)	0.82 (0.36)	0.77 (0.35)	0.109
FEV_1%*	38 (16.4)	37.6	39.2	0.372
FVC*	0.44 (0.12)	1.88 (0.69)	1.81 (0.76)	0.356
FEV_1/FVC Ratio†	0.44 (0.35-0.53)	0.44 (0.36-0.53)	0.44 (0.33-0.52)	0.334
eMRCD†	5 (4-5a)	4 (4-5a)	5 (5a-5b)	<0.001
LTOT	29.2%	26.3%	37.9%	0.014
Previous NIV	21.9%	22.5%	20.2%	0.592

* Mean (SD) †Median (IQR)

The apparent survival benefit of being a current smoker is due to confounders. There are numerous significant differences between the populations. Ex-smokers are older; mean (76.2 vs 69.2 years), with higher eMRCD dyspnoea score median 5a vs 4. FEV_1 was not significantly different but slightly lower in ex-smokers despite a significantly lower average tobacco burden. LTOT was far commoner amongst ex-smokers (40.2% vs 17.6%) but this is likely to be due in part to safety concern leading to reduced prescription of oxygen to active smokers even if they have physiological need.

Other important observations are: The hypothesised strong association between steady state dyspnoea and mortality is observed and a similar but less significant association is seen with LTOT prescription. In keeping with previous studies FEV_1 is not associated with mortality in this cohort as either an absolute value or as a percentage of predicted. Interestingly previous NIV is also not associated with mortality. One may have expected it to be protective; i.e. to have survived treatment with NIV once or more makes one more likely to have a positive outcome if ventilated again. Collecting only unique patients rather than

unique episodes will have undoubtedly diluted this effect. Nevertheless, one may have expected a stronger protective signal.

7.1.3 Dynamic factors.

7.1.3.1 Clinical Findings Including Radiology.

Chest X-rays were reviewed by the same researcher to verify presence of effusion, number of ribs and presence to measure diaphragm height. Consolidation was recorded in the hierarchy of clinical team interpretation (to mirror reality), radiologist report or researcher interpretation.

Table 26 Association with in-hospital mortality - Clinical and X-ray factors.

Variable	Total Population	Survived to discharge	Died in hospital	P value
Consolidation at Ventilation	47.2%	40.5%	66.9%	<0.001
Consolidation at admission	43.6%	38.4%	58.9%	<0.001
Confusion at ventilation	20.9%	16.4%	33.9%	<0.001
Pleural Effusion admission	18.8%	13.8%	33.6%	<0.001
Diaphragm Height (cm)*	2.1 (0.93)	2.13 (0.95)	1.95 (0.85)	0.063
Number of posterior Ribs†	9 (8-9)	9 (8-9)	9 (8-9)	0.937
Accessory Muscle Use	37.7%	38.8%	34.4%	0.384
Ineffective Cough	86.0%	90.0%	74.2%	<0.001
Purulent sputum	43.6%	43.6%	43.5%	0.998
Pedal Oedema on admission	36.5%	35.5%	39.7%	0.405

* Mean (SD) †Median (IQR)

Several indices here are subjective and potentially unsuitable for inclusion in subsequent predictive models. For example, we were interested in whether presence of effusion or surrogate markers of hyper-inflation were associated with mortality. These are exploratory, in this cohort we see effusion is associated with mortality, but markers of hyper-expansion are not (although diaphragm height could be retained for consideration by our criteria). As such both of these are interesting for future verification but not for inclusion in final model. As expected, consolidation is significantly associated with in-hospital mortality. Similarly, ineffective cough is strongly associated with mortality, there is an inherent bias in collecting this from retrospective records without a default assessment on all patients. It is however

intuitive that those with most impaired cough have higher mortality. This another variable that requires further exploration in the future.

7.1.3.2 Physiological Observations (in the period prior to ventilation).

Table 27 Association with in-hospital mortality – Observations.

Variable	Total Population	Survived to discharge	Died in hospital	P value
Systolic Blood pressure*	123.0 (32.4)	124.9 (32.5)	117.4 (31.8)	0.026
Diastolic Blood Pressure*	69.7 (19.2)	70.3 (19.4)	67.8 (18.5)	0.223
Mean Arterial Pressure*	87.4 (21.9)	88.5 (22.1)	84.4 (21.0)	0.071
Heart Rate*	112.4 (22.1)	111.3 (22.6)	115.7 (20.4)	0.057
Respiratory Rate*	28.6 (8.1)	28.1 (8.3)	29.8 (7.3)	0.041
Temperature*	35.8 (5.8)	35.8 (6.1)	35.9 (4.8)	0.832
Lowest oxygen Saturations*	83.4 (10.7)	84.3 (10.5)	82.5 (11.3)	0.115
GCS†	15 (14-15)	15 (14-15)	14 (12-15)	<0.001

* Mean (SD) †Median (IQR)

Several routinely observations, many of which are constituents of the APACHE II and CAPS tools are associated with in-hospital mortality. The worst (greatest deviation from normal) was recorded. Very few patients oscillate either side of normal ranges within a given window so collection of this data is straightforward and determining which was 'worst' is largely unambiguous.

7.1.3.3 Blood Tests (in the period prior to ventilation).

A number of other blood tests were also recorded but the rate of missing data was unacceptably high and hence they are not reported. These include phosphate (88%) troponin (87%), total protein (23%) and bilirubin (20%).

19% of Albumin and 25.7% of Glucose values were also missing, these are reported due to the strong association with mortality in previous work, but they are not included in model development (3.3.4).

Table 28 overleaf shows this data.

Table 28 Association with in-hospital mortality - Blood Tests.

Variable	Total Population	Survived to discharge	Died in hospital	P value
Haemoglobin (g/dL)*	13.6 (2.1)	13.9 (2.1)	12.8 (2.1)	<0.001
Haematocrit (L/L)*	0.420 (0.063)	0.428 (0.062)	0.396 (0.063)	<0.001
Platelets (x10^9/L)*	291 (123)	286 (117)	306 (141)	0.127
WCC (x10^9/L)*	13.6 (6.6)	13.2 (6.7)	14.9 (6.0)	0.016
Neutrophil Count (x10^9/L)*	10.9 (5.3)	10.5 (5.2)	12.4 (5.4)	0.001
Eosinophil Count (x10^9/L)*	<0.01 (<0.01-0.1)	<0.01 (<0.01-0.1)	<0.01 <0.01-<0.01)	<0.001
Sodium (mmol/L)*	136.6 (5.2)	136.5 (5.2)	136.9 (5.3)	0.409
Potassium (x10^9/L)*	4.6 (0.7)	4.6 (0.63)	4.7 (0.86)	0.141
Urea (x10^9/L) †	7.2 (5.3-10.9)	6.7 (5.0-10.1)	9.35 (6.5-14.5)	<0.001
Creatinine (x10^9/L) †	89 (71-119)	88 (72-115)	90 (67-137)	0.658
Albumin (g/L)*	37.8 (5.4)	38.5 (5.1)	35.5 (3.4)	<0.001
Glucose (mmol/L)*	8.6 (3.8)	8.6 (4.0)	8.5 (3.4)	0.856
CRP (mg/L) †	52 (15-120)	48 (13-108)	69 (25-155)	0.005

* Mean (SD) †Median (IQR)

7.1.3.4ABGs (in the period prior to ventilation).

Table 29 shows that lower pH, base excess, bicarbonate and time to acidaemia are all associated with in hospital mortality when analysed as continuous variables. BE and bicarbonate are likely to be highly correlated. The much wider interquartile range in time to acidaemia adds credence to the hypothesis that those that deteriorate later into admission are a select group in whom outcomes are worse.

Table 29 Association with in-hospital mortality - blood gases.

Variable	Total Population	Survived to discharge	Died in hospital	P value
pH†	7.26 (7.2-7.3)	7.27 (7.21-7.31)	7.25 (7.17-7.29)	0.003
$PaCO_2$	9.9 (8.5-11.7)	10.0 (8.7-11.7)	9.5 (8.3-11.7)	0.139
PaO_2	8.3 (6.9-10.7)	8.4 (6.9-10.7)	8.3 (6.8-10.8)	0.737
Base Excess	3.8 (6.4)	4.4 (6.1)	2.0 (7.2)	0.001
Bicarbonate	33.4 (6.9)	33.9 (6.6)	31.7 (7.6)	0.005
Time to acidaemia (minutes)	146 (56-852)	133 (60-494)	585 (62-5224)	<0.001

* Mean (SD) †Median (IQR)

7.1.4 Pruning of Candidate Indices.

From the above univariate analyses, all indices p<0.1 are potential candidates for further analysis. Some of the reported associations are interesting and candidates for further study but the retrospective design did not allow robust enough collection to reliably include for further analysis. This is particularly true of subjective indices, not measured on a standardised scale. For example, the effectiveness of cough is strongly correlated with outcome but not reliably recorded, associated with reduced conscious level and highly subjective unless formally assessed in a standardised way. Therefore, it is not a candidate for inclusion in a clinical tool.

Table 30 Variables associated with in-hospital mortality p<0.1 but not candidates for regression model.

Variable Removed	Reason
Admitted from institutional care	Ethically dubious method of stratification, availability of family support may well alter threshold.
Congestive Cardiac Failure	No universal definition.
Current smoker	Lacks face validity to reduce risk category, confounded.
Ineffective Cough	No standard definition, high risk recording bias.
Mean Arterial Pressure	No routinely available at bedside.
Albumin	19% Missing data.
BMI	13.9% missing data and not routinely available at admission.
Chronic Atrial Fibrillation	Replaced by composite variable.
Paroxysmal Atrial Fibrillation	Replaced by composite variable.
Atrial Fibrillation at time of Acidaemia	Replaced by composite variable.
Diaphragm Height	Exploratory only. Inter-user variability not characterised.

To remove ambiguity for both tools the presence of AF at any point whether that be chronic, paroxysmal or de novo up to the point of decision will be used. (In the NIVO study historical paroxysmal AF specifically excluded a single previous episode in the context of acute illness).

7.1.4.1 Correlation Assessment.

With reference to methods section 5.4.2.5, several variables amongst those with significance <0.1 are conceptually measuring the same thing and so were evaluated immediately. These initial suppositions include WCC and neutrophil count, haemoglobin and haematocrit, and bicarbonate and base excess.

Table 31 Variables associated with in-hospital mortality p<0.1 removed following correlation analysis

Variable Removed	Reason
Neutrophil Count	Highly correlated with WCC: Pearson's 0.848
Haematocrit	Highly correlated with haemoglobin: Pearson's 0.95
Bicarbonate	Highly correlated with base excess: Pearson's 0.93

Aside from the three expected above there were no other significant correlates identified using a correlation matrix. Mean VIF was 1.324 with no individual value >2.

7.1.4.2 Final List of Candidate Indices Point of Deterioration Tool.

Table 32 and Table 33 show the indices to be taken forward for multivariate analysis.

Table 32 Candidate predictors: point of deterioration tool.

Variable for further evaluation	P Value
Age	<0.001
Any atrial Fibrillation up to deterioration	0.012
Left Ventricular Systolic Dysfunction	0.025
Depression	0.097
eMRCD	<0.001
LTOT	0.014
Consolidation at Ventilation	<0.001
Pleural Effusion admission	<0.001
Confusion at ventilation	<0.001
GCS	<0.001
Systolic Blood pressure	0.026
Heart Rate	0.057
Respiratory Rate	0.041
Haemoglobin	<0.001
WCC	0.016
Eosinophil Count	<0.001
Urea	<0.001
CRP	0.005
pH	0.003
Base Excess	0.001
Time to acidaemia	<0.001

All eligible variables can be considered for the point of deterioration tool whereas 'dynamic' variables are unsuitable for the admission tool. The exception drawn here is the presence or absence of consolidation as this is 'less dynamic' and there is face validity that presence or absence of pneumonia will influence events further into admission in those not already acidaemic at the time of senior assessment. Compilation of observations into a clinical trigger score for example NEWS score is a potential way forward however there have been several iterations used in UK hospitals and future changes to national practice may render any tool redundant or difficult to calculate at the bedside, furthermore international adoption would be problematic.

7.1.4.3 Final List of Candidate Indices for Admission tool.

Table 33 Candidate predictors: Escalation tool.

Variable for further evaluation	P Value
Age	<0.001
Any atrial fibrillation (up to senior review)	0.012
Left Ventricular Systolic Dysfunction	0.025
Depression	0.097
eMRCD	<0.001
LTOT	0.014
Consolidation (up to senior review)	<0.001
Time to acidaemia	<0.001

7.2 Multivariate Modelling: Point of Deterioration Tool

7.2.1 Full model

Entering all variables as continuous variables and reporting all that do not 'drop out' using a significance level of p>0.05 during the backward elimination process gives an estimation of the best achievable model. Using this process and entering the list of variables in Table 32 produces the results shown in Table 34.

Table 34 Results of regression analysis - full model.

Variable Included in final model	B	S.E	Wald	Sig	Odds Ratio (95% CI)
Age	0.062	0.17	13.0	<0.001	1.06 (1.03-1.10)
Atrial fibrillation	0.773	0.316	6.0	0.014	2.17 (1.17-4.02)
Base Excess	-0.066	0.022	8.9	0.003	0.94 (0.90-0.98)
Consolidation	0.629	0.285	4.9	0.027	1.88 (1.07-3.28)
Eosinophil count	-3.680	1.087	11.5	0.001	0.03 (0.003-0.21)
eMRCD	0.710	0.171	17.3	<0.001	2.033 (1.46-2.84)
GCS	-0.215	0.047	20.9	<0.001	0.81 (0.74-0.88)
Heart rate	0.013	0.007	3.9	0.048	1.01 (1.00-1.03)
LTOT	0.864	0.321	7.3	0.007	2.37 (1.27-4.45)
Respiratory rate	0.040	0.019	4.7	0.030	1.04 (1.004-1.08)
Time to acidaemia	<0.001	<0.001	18.9	<0.001	1.00 (1.00-1.00)

Intercept: -9.607, R^2 0.498, Percentage correct after final iteration, 84.7%. Hosmer and Lemeshow 0.177. AUROC 0.885.

Studentised residuals: 3.3% of cases were >+/-1.96 including 0.8% +/-2.58. These proportions are within the predefined acceptable levels (5.4.3). Only one case had a Cooks distance of >1 this case (206) also had the studentised residual furthest from 0.

Case 206 is exerting considerable influence, this is evidenced by a Cook's distance of 1.857 and a studentised residual of 3.134. This patient fully recovered from their episode of ventilation but deteriorated some time later from ischaemic bowel while awaiting discharge. The default position is to include all cases to avoid overfitting but, in this instance, due to excessive influence and after careful consideration case 206 was removed from future modelling of in-hospital mortality.

Re-running the analysis with 206 removed does not affect the number of indices remaining in the full model but does obviously alter the results subtly. The full table is not reported as the indices are to be categorised but the key descriptives are:

Intercept: -10.05, R^2 0.517, Percentage correct after final iteration, 84.8%. Hosmer and Lemeshow 0.358. Unless specified case 206 has been removed from the remaining multivariate modelling.

Figure 22 ROC curve, full point of deterioration model, Case 206 removed.

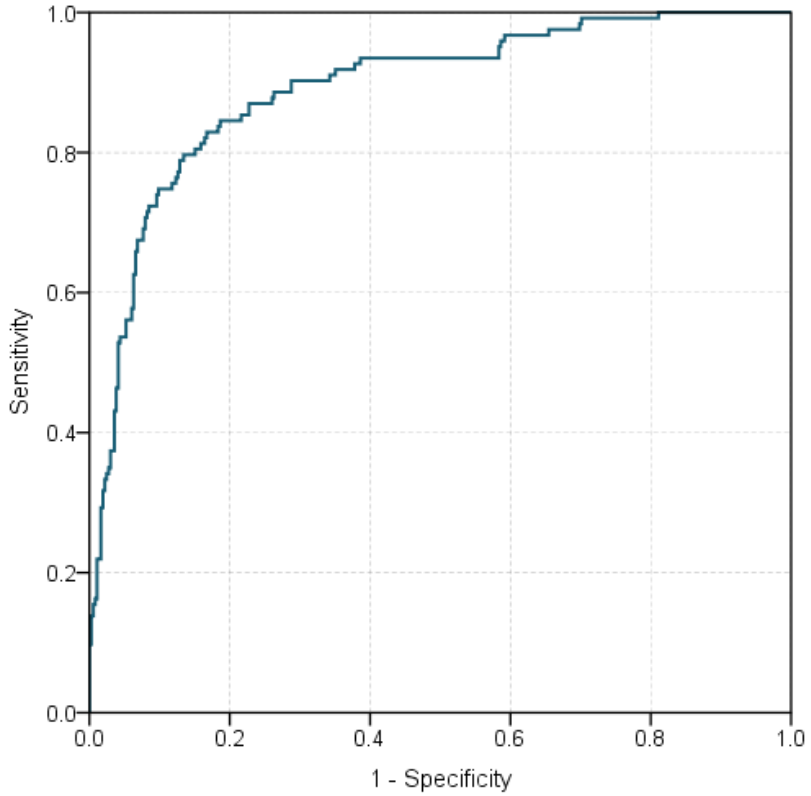
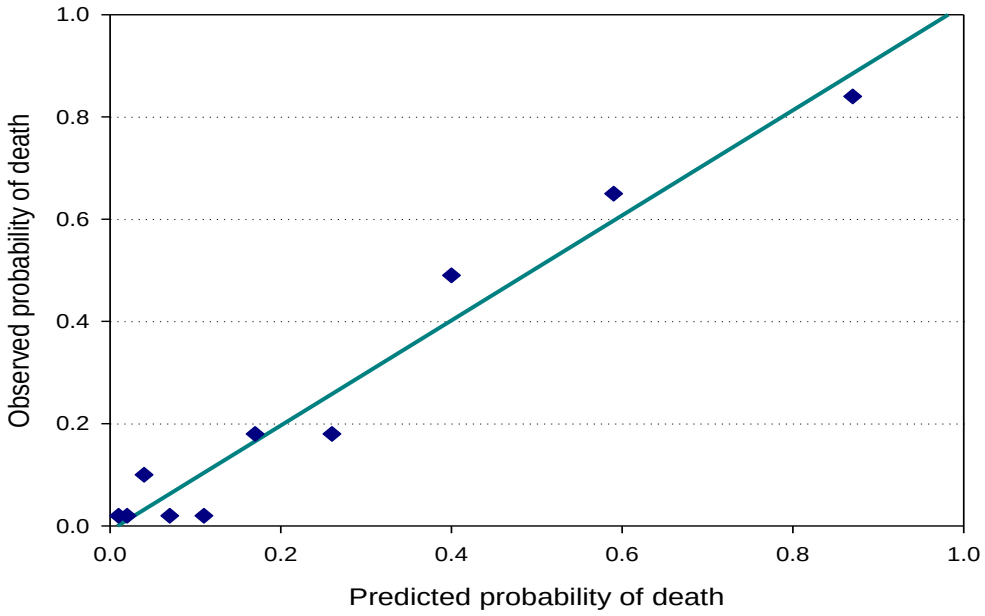


Figure 22 shows the ROC curve of predicted probabilities versus actual outcome using the full model (which maintains continuous variables as continuous). The AUROC for this curve is 0.892 (slightly higher than with outlying case included) indicating excellent discrimination.

Figure 23 Calibration plot of observed versus predicted probability of in-hospital death by decile of predicted risk. Case 206 removed.



This calibration plot takes the predicted probability for each case from the regression model and ranks them in ascending order remembering from section 5.4.3 that all will lie between 0 (lowest predicted probability of outcome) to 1 (highest probability). Cases are then grouped by decile of predicted risk, n = 488 so there are 48 or 49 cases in each decile. The mean of the predicted risk in each decile is then plotted against the observed number of cases (expressed as n died/total in that decile). Given that most patients survive most points are clustered close to zero i.e. low predicted and low observed risk. Perfect calibration would see each point lying on a line of best fit with a gradient of 1. Good calibration is shown here, as the predicted risk from the model increases the number of actual (observed cases) within that decile also increases across the risk spectrum with no unexpected outlying deciles on visual inspection.

7.2.2 Point of Deterioration Model Discussion.

It is notable that pH drops out of this model whereas base excess remains. It was hypothesised in section 3.3.3 that the importance of pH as an absolute value may have been overstated and this finding is certainly worthy of exploration. There is some collinearity as may be expected between pH and base excess. The very fact that both do not simultaneously remain in a model together shows this. While pH is widely considered to be an important predictor of outcome it is pertinent to note that CO_2 is not a significant predictor of outcome in this dataset. It may, however, be the case that in this dataset there is an unexpectedly high rate of concurrent metabolic acidaemia exerting an undue influence (I.E. overfitting to source data).

Guidance suggests that variables should be selected using results of previous research and that clinical intuition is important to avoid such overfitting to source data. Therefore, a separate model was generated replacing base excess with pH.

7.2.3 Conversion to Categorical Variables.

Using the criteria described in 5.4.4.2 continuous variables are converted into categorical (ideally binary divisions) variables to facilitate development of a clinical tool that can be applied simply at the bedside. Table 35 shows the final categorical variable states. eMRCD is such a strong predictor of mortality in previous research that it has been stratified into 3 groups rather than a simple binary division.

Table 35 Categorical variable assignation.

	Categorical value applied in regression equation.		
Variable	0	1	2
Age	<75	≥75	
Atrial fibrillation	No	Yes	
Base Excess	≥0	<0	
Consolidation	No	Yes	
Eosinophil count <0.05 x10^9/L	≥0.05	<0.05	
eMRCD	1-4	5a	5b
GCS	15	≤14	
Heart rate	<110	≥110	
LTOT	No	Yes	
pH	≥7.25	<7.25	
Respiratory rate	<30	≥30	
Time to acidaemia	<12 hours	≥12 hours	

7.2.4 Regression Using Categorical Variables.

7.2.4.1 Base Excess Model.

Following conversion to categorical variables the regression analysis is re-run. It is possible the when a continuous variable is reduced to a simple binary division it no longer imparts independent risk and drops out of the final model.

Table 36 Regression results: Categorised variables using base excess.

Variable	B	S.E	Wald	Sig	Odds Ratio (95% CI)
Respiratory rate	0.747	0.272	7.5	0.006	2.11 (1.24-3.60)
LTOT	0.895	0.310	8.3	0.004	2.45 (1.33-4.50)
GCS	0.922	0.282	11.8	0.001	2.51 (1.45-4.37)
Consolidation	0.980	0.280	12.3	0.001	2.66 (1.54-4.61)
Base Excess	1.079	0.296	13.3	<0.001	2.94 (1.65-5.25)
Atrial fibrillation	1.242	0.329	14.3	<0.001	3.46 (1.82-6.59)
eMRCD 5a	1.247	0.337	13.7	<0.001	3.48 (1.80-6.74)
Time to acidaemia	1.397	0.290	23.1	<0.001	4.04 (2.29-7.14)
Eosinophil count <0.05 x10^9/L	1.606	0.319	25.3	<0.001	4.98 (2.66-9.32)
eMRCD 5b	2.033	0.377	29.0	<0.001	7.64 (3.65-16.00)

Intercept -4.852, R^2 0.486, Percentage correct after final iteration, 84.8%. Hosmer and Lemeshow 0.06.

Table 36 shows that after categorisation that both age and heart rate drop out of the final model. They will therefore not form any part of the final score. This is an interesting example of the outcome from multi-variable modelling: Age is starkly associated with mortality on univariate analysis but when using multiple variables it imparts little additional independent information to the model. This is likely to be because the much of its association with mortality is absorbed into other variables. For example, the additional mortality effect of increasing age may be due to frailty as captured by eMRCD, higher likelihood of confusion as captured by GCS and more cardiac comorbidity as captured by AF.

7.2.4.2 pH model.

Table 37 shows that if pH <7.25 is substituted for a BE <0 then the same two variables age and heart rate drop out of the final model. It is also interesting (and unsurprising from a clinical perspective) that if BE is removed from the matrix then pH becomes and remains an independent predictor of in-hospital mortality albeit less significant. Furthermore, the final model performance is comparable.

Table 37 Regression results: Categorised variables using pH.

Variable	B	S.E	Wald	Sig	(Odds Ratio 95% CI)
pH	0.571	0.280	4.2	0.042	1.77 (1.02-3.07)
Respiratory rate	0.675	0.270	6.3	0.012	1.97 (1.16-3.33)
LTOT	0.764	0.302	6.4	0.012	2.15 (1.19-3.88)
GCS	0.803	0.280	8.2	0.004	2.23 (1.29-3.87)
Consolidation	1.019	0.276	13.6	<0.001	2.77 (1.61-4.76)
eMRCD 5a	1.159	0.329	12.4	0.001	3.19 (1.67-6.07)
Atrial fibrillation	1.298	0.328	15.7	<0.001	3.66 (1.93-6.96)
Time to acidaemia	1.484	0.291	26.0	<0.001	4.41 (2.49-7.80)
Eosinophil count <0.05 x10^9/L	1.538	0.315	23.8	<0.001	4.66 (2.51-8.64)
eMRCD 5b	1.981	0.372	28.4	<0.001	7.25 (3.50-15.03)

Intercept -4.619, R^2 0.465, Percentage correct after final iteration, 82.8%. Hosmer and Lemeshow 0.262.

7.2.5 Variable Weighting.

A maximum of 8 variables were desired therefore respiratory rate was dropped as a candidate for inclusion in the final tool as this is both the weakest predictor and conceptually the least reliable as it is highly dynamic and inherently linked to the frequency of observation. For the pH model, pH was included in lieu of base excess irrespective of its odds ratio as this is the desired exploration of the data.

To ascribe weighting the Wald score and odds ratio for each independent variable following regression analysis in categorical states (Table 36) was divided by that of the lowest included variable (LTOT) the result of which is displayed in Table 38. Two methods of weighting are proposed, a simple one and a more complex one. Unless significantly better prediction or discrimination is offered by the complex weighting the simple weighting will be the final proposed model to maximise utility.

The weighting of eosinophil count requires some consideration. This variable may be underweighted in the simple score however, clinically it is likely that severe steady state dyspnoea requiring assistance with ADLs (eMRCD 5b) is a stronger predictor of outcome than eosinopenia and hence ascribing the lower weighting of one is the preferred initial option. Another consideration in the weighting of the eosinophil count is the role of oral corticosteroids. Many patients receive steroids acutely in line with national and international guidance. In the DECAF studies all information was applied in the admission phase; whether eosinopenia was driven by failed primary (pre-admission) steroid therapy or sepsis it is plausible that this would be associated with worse outcome. In modelling the point of deterioration tool 25% of the population are deteriorating later into the admission and almost all will have been treated acutely with oral corticosteroids. The longer the duration of treatment the greater the chance corticosteroids will have induced eosinopenia but we can also see that later development of acidaemia is associated with increased mortality. Because this effect is only occurring in a minority of the patients it may not be identified by a correlation matrix but have a disproportionate effect on outcome due to the increased number of outcome events in the late deteriorating group. This is not easily testable with the available data but is a strong hypothesis and an additional reason not to overweight the eosinophil count in the initial phase of analysis.

It is reasonable and accepted practice to re-evaluate weightings (known as re-calibrating) in a validation cohort and adjust if a marked discrepancy is seen.[245]

Table 38 Variable weighting.

Proposed model variable	Wald/8.327	Odds Ratio/2.45	Simple Weighting	Complex Weighting
LTOT	1.0	1.0	1	1
GCS	1.4	1.0	1	1
Consolidation	1.5	1.1	1	1
Base Excess	1.6	1.2	1	1
eMRCD 5a	1.6	1.4	1	1
Atrial fibrillation	1.7	1.4	1	1
Time to acidaemia	2.8	1.6	1	2
Eosinophil count <0.05 $x10^9/L$	3.0	2.0	1	2
eMRCD 5b	3.5	3.1	2	3

7.2.6 Predictive Score Development.

Eight potential models are reported here; firstly using 8 variables and then using 6. A model is then created substituting pH for base excess. Each of these 4 potentials is then reported with the simple and complex weighting imposed. The following tables overeaf show in-hospital mortality at each point of each tool from 0 to its maximum.

7.2.6.1 Eight Variable models.

Table 39 Eight variable models with stepwise N and in-hospital mortality.

	Simple scoring, (N, % Mortality)		Complex Scoring, (N, % Mortality)	
Tool Score	**Model 1 (BE)**	**Model 2 (pH)**	**Model 3 (BE)**	**Model 4 (pH)**
0	24 (0%)	22 (0%)	24 (0%)	22 (0%)
1	50 (0%)	46 (0%)	29 (0%)	28 (0%)
2	101 (5.0%)	91(4.4%)	62 (0%)	55 (0%)
3	104 (13.5%)	106 (12.3%)	78 (7.7%)	74 (6.8%)
4	89 (25.8%)	87 (25.3%)	79 (13.9%)	82 (12.2%)
5	66 (59.1%)	76 (53.9%)	74 (25.7%)	72 (23.6%)
6	33 (72.7%)	35 (62.9%)	47 (44.7%)	56 (42.9%)
7	18 (83.3%)	21 (81.0%)	42 (57.1%)	40 (57.5%)
8	3 (100%)	4 (100%)	25 (76.0%)	30 (70%)
9	0	0	17 (88.2%)	17 (82.4%)
10			8 (62.5%)	9 (66.7%)
11			3 (100%)	3 (100%)
12			0	0

7.2.6.2 Six variable models.

The two least influential predictors of in-hospital mortality from Table 36; LTOT and GCS are removed in the following models (therefore the maximum achievable score is reduced).

Table 40 Six variable models with stepwise N and in-hospital mortality.

	Simple scoring, (N, % Mortality)		Complex Scoring, (N, % Mortality)	
Tool Score	**Model 5 (BE)**	**Model 6 (pH)**	**Model 7 (BE)**	**Model 8 (pH)**
0	35 (0%)	30 (0%)	35 (0%)	30 (0%)
1	88 (3.4%)	77 (3.9%)	47 (0%)	44 (0%)
2	136 (8.8%)	126 ((5.6%)	76 (5.3%)	70 (4.3%)
3	105 (26.7%)	121 (24.8)	103 (10.7%)	96 (8.3%)
4	76 (53.9%)	79 (51.9%)	71 (28.2%)	84 (25.0%)
5	33 (84.8%)	39 (79.5%)	23 (39.7%)	66 (39.4%)
6	13 (69.2%)	14 (64.3%)	53 (52.8%)	43 (53.5%)
7	2 (100%)	2 (100%)	21 (85.7%)	31 (77.4%)
8			12 (91.7%)	13 (84.6%)
9			10 (60%)	9 (55.6%)

7.2.6.3 AUROC, Models 1-8.

Figure 24 and Table 41 show the areas under the receiver operated curves for the models described in Table 39 and Table 40. All show excellent discrimination.

Figure 24 Area under the receiver operated curves for point of deterioration models 1-8.

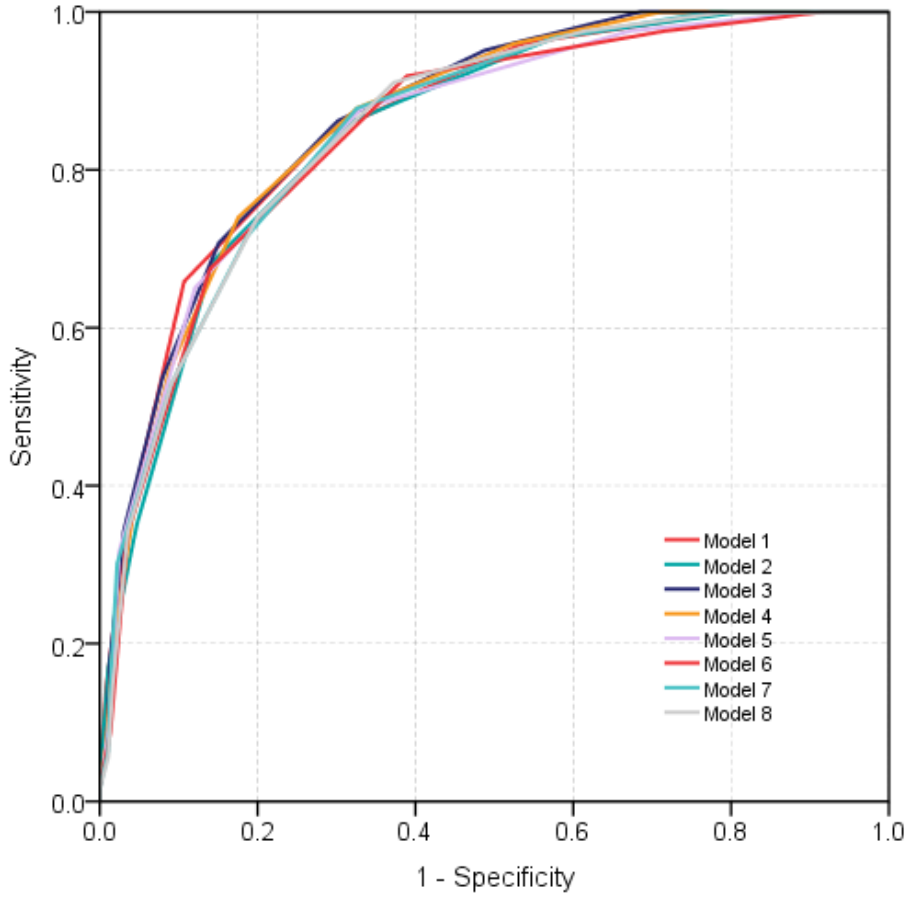


Table 41 Area under the receiver operated curves for point of deterioration models 1-8.

Model	Description	AUROC (95% CI)
Model 1	8, BE, Simple	0.86 (0.83-0.90)
Model 2	8, pH, Simple	0.85 (0.82-0.89)
Model 3	8, BE, Complex	0.87 (0.83-0.90)
Model 4	8, pH, Complex	0.86 (0.83-0.90)
Model 5	6, BE, simple	0.85 (0.81-0.89)
Model 6	6, pH, Simple	0.85 (0.81-0.89)
Model 7	6, BE, Complex	0.85 (0.82-0.90)
Model 8	6, pH, Complex	0.85 (0.82-0.90)

7.2.7 Model Evaluation

As can be seen from Figure 24 and Table 41 all of the models offer good prediction of in-hospital mortality. From the 8 different models there here are 3 decisions to be made:

1. To retain base excess or substitute in pH.
2. To use an 8-variable or a 6-variable model.
3. To use the simple or complex scoring system.

In this population base excess is the better predictor and pH is being forced into the model. However, both models offer good predictions and the validation population will inevitably differ from the derivation population due to both inclusion of multiple centres and changes to national practice. The lower limit for CO_2 has also risen in national guidance from 6.0 to 6.5 kPa meaning potentially fewer patients with primarily metabolic acidaemia are selected. Furthermore Table 36 shows that the Hosmer and Lemeshow assessment of calibration is very nearly significant which would be indicative of a poorly calibrated model when using BE. This is not the case for the same model using pH although this observation is no longer present after categorisation. For these reasons the final proposed model will include both pH and BE as an either/or category.

8 variables do produce slightly better prediction than 6 and particularly in those at higher risk of death which is important for score utility in clinical practice. If, however in the validation cohort good prediction is offered by 6 variables it would be reasonable to further prune GCS and LTOT to create the simplest model achievable.

Finally, the simple scoring system is clearly superior for two reasons. Firstly, the greater stratification of the complex score leads to non-progressive mortality. Secondly, the simple score maintains in all its iterations a clear shoulder where risk jumps from the order of 25% to >50%. This jump has potential clinical utility.

The position from these data is to use 8 variables and the simple scoring system with BE<0/pH<7.25 as described above. The main question to be answered by the validation cohort is to ensure the weightings remain accurate and see whether a six variable model can offer good results.

7.2.8 The Final Proposed Model.

The final proposed model is the culmination of the steps taken above to create a simple bedside score to model in-hospital mortality in this cohort. The maximum achievable score is 9 (remembering that one cannot score for both eMRCD 5a and 5b).

Final Proposed Model	Points
Atrial fibrillation	1
Consolidation	1
Eosinophil count <0.05 x10^9/L	1
eMRCD 5a	1
eMRCD 5b	2
GCS ≤14	1
LTOT	1
Time to acidaemia >12 hours	1
Base Excess <0 or pH<7.25	1

This model clearly outperforms the more complex clinical scores in its derivation population. The full model is included as a 'best achievable' comparator however use of the full model is not easily achievable in current clinical practice as it requires complex computation of continuous variables. With greater digitalisation of healthcare records a model using continuous variables may have future utility.

Table 42 Final proposed model: mortality by each point.

Tool Score	Number	Mortality
0	20	0 (0%)
1	41	0 (0%)
2	93	4 (4.3%)
3	101	11 (10.9%)
4	93	21 (22.6%)
5	73	38 (52.1%)
6	39	25 (64.1%)
7	24	20 (83.3%)
8	4	4 (100%)
9	0	N/A

Figure 25 ROC curves for point of deterioration tool: Full model, final proposed model and comparison scores from previous research.

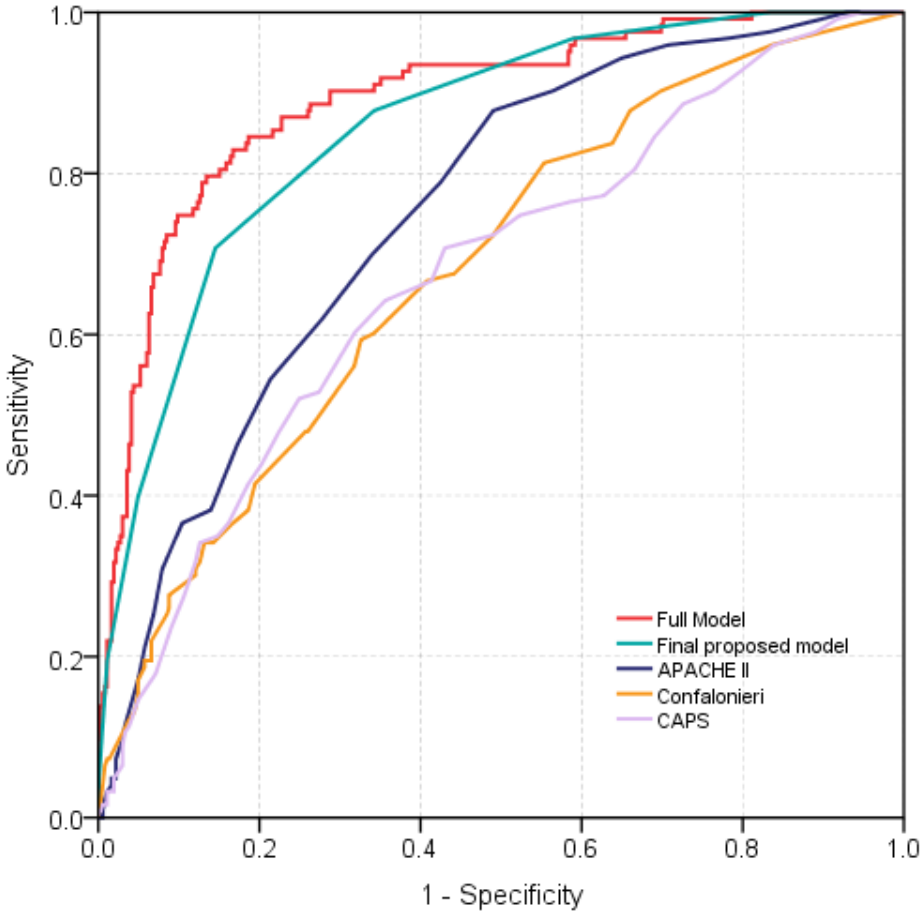


Table 43 Area under the receiver operated curve for full model, model 1 and comparison scores.

Model	AUROC (95%CI)
Full Model	0.89 (0.86-0.93)
Final proposed model	0.86 (0.82-0.89)
APACHE 2	0.75 (0.70-0.80)
CAPS	0.67 (0.62-0.73)
Confalonieri Risk of Failure Chart	0.68 (0.63-0.73)

The Confalonieri risk of failure chart 3.3.6.3 plots each patient into a risk group based upon three indices. This does not result in a variable easily interpretable for comparison so the odds ratios from the regression equation used to build the risk chart as reported in the original paper were taken and applied to relevant index. In this manner an individual score was built for each patient and used for comparison. Performance in this population is comparable to the AUROC (0.71) in their own internal validation.

7.3 Multivariable Modelling: Admission Tool

Two tools were always intended to be created: The variables identified in Table 33 were entered into a backward, stepwise regression model as continuous variables as per the point of deterioration tool. Case 206 removed. Methodology will follow the same stepwise method as earlier but reporting is somewhat reduced for simplicity.

7.3.1 Full Regression results

Table 44 shows the results following entry of all eligible admission tool variables.

Table 44 Admission tool: Regression results: All variables entered as continuous variables.

Variable Included in final model	B	S.E	Wald	Sig	Odds Ratio
Age	0.48	0.15	11.1	0.001	1.05 (1.02-1.08)
Atrial fibrillation (Chronic +PAF)	0.626	0.316	3.9	0.480	1.87 (1.01-3.47)
Consolidation at senior review	0.898	0.249	13.0	<0.001	2.45 (1.51-4.00)
eMRCD	0.883	0.148	35.4	<0.001	2.42 (1.81-3.23)
Time to acidaemia	1.249	0.257	23.6	<0.001	3.49 (2.11-5.77)

Intercept -9.94, R^2 0.348, Hosmer and Lemeshow 0.432 Percentage correct after final iteration 79.5%, AUROC 0.822

7.3.2 Categorisation and Weighting.

eMRCD was handled as previously 7.2.3. There is no obvious split from ROC curve analysis of age. 75 was chosen as a round number close to the median split. However, following categorisation, age drops out of the final model. In order to maximise the chance of identifying a high-risk patient cohort in whom ventilation may be futile a time threshold of 48 hours was selected.

Table 45 Admission tool: Regression results: Independent predictors entered as categorical variables.

Variable Included in final model	B	S.E	Wald	Sig	Odds Ratio
Atrial fibrillation (Up to Senior)	0.792	0.293	7.3	0.007	2.21 (1.24-3.92)
Consolidation at senior review	1.108	0.251	19.4	<0.001	3.03 (1.85-4.95)
eMRCD 5a	1.383	0.303	20.9	<0.001	3.99 (2.20-7.22)
Time to Acidaemia >48hours	1.973	0.344	32.9	<0.001	7.19 (3.66-14.12)
eMRCD 5b	2.210	0.327	45.8	<0.001	9.11 (4.81-17.28)

Table 45: Intercept -2.017, R^2 0.346, Hosmer and Lemeshow 0.222 Percentage correct after final iteration 79.5%, AUROC 0.820

Using the methods described independent categorical predictors were assigned weights to develop a prognostic tool.

Table 46 Admission Tool: Variable weighting assignation.

Proposed model variable	Wald/7.7	Odds Ratio/2.21	Simple Weighting	Complex weighting
Atrial fibrillation (Up to Senior)	1.0	1.0	1	1
Consolidation at senior review	2.7	1.4	1	1
eMRCD 5a	2.9	1.8	1	2
Time to Acidaemia >48hours	4.5	3.3	3	3
eMRCD 5b	6.3	4.1	3	4

7.3.3 Score development and evaluation.

Unlike with the point of deterioration tool the score is comparatively simple to develop as the only decision to make is which weighting system to adopt. Clearly, with only four independent variables remaining all four will be included in the model and as no blood gas data is included there is no BE vs pH differential.

Table 47 In-hospital mortality by both simple and complex admission tool score.

	Simple Score		Complex Score	
Tool Score	**Number**	**Mortality**	**Number**	**Mortality**
0	102	2 (2.0%)	102	2 (2.0%)
1	162	18 (11.1%)	94	9 (9.6%)
2	77	22 (28.6%)	77	10 (13.0%)
3	50	24 (48.0%)	78	27 (34.6%)
4	52	26 (50.0%)	48	21 (43.8%)
5	21	13 (61.9%)	45	24 (53.3%)
6	10	5 (50.0%)	20	12 (60%)
7	N/A	N/A	10	5 (50%)
8	N/A	N/A	11	10 (90.9%)
9	N/A	N/A	3	3 (100%)

Figure 26 ROC curves for admission tool: Full model, simple score, complex score and comparisons from previous research.

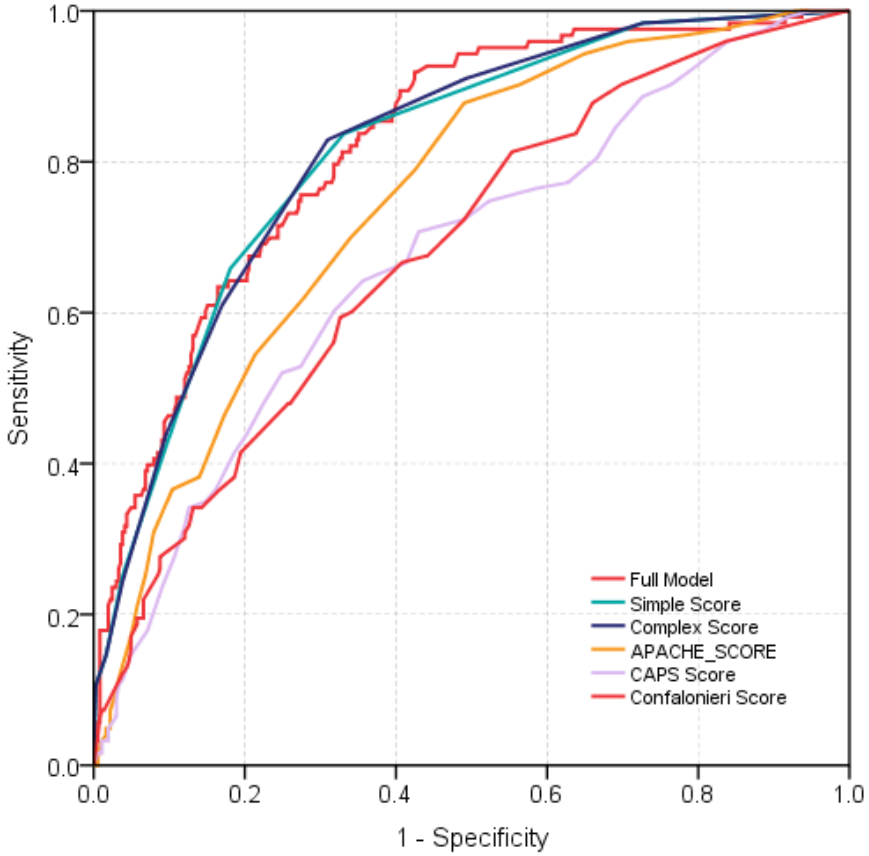


Table 48 Area under the receiver operated curves for various models of Admission Tool.

Model	AUROC (95%CI)
Full Model	0.82 (0.78-0.86)
Simple score	0.82 (0.77-0.86)
Complex Score	0.82 (0.78-0.86)

Curves for other tools is included on Figure 26 for visual comparison. AUROC data for these comparison tools is the same as in Table 43.

7.3.4 Admission Tool Comments.

There is an important conceptual difference for the admission tool. The potential indication is for use in the admission window to give stratified risk. The median time for consultant review is 10 hours by which time in about three quarters of patients the indication for ventilation has already arisen and the tool is therefore used in real time. The other use is to assist the senior clinician to make treatment escalation plans; i.e. to proactively involve the

patient not currently needing assisted ventilation in a discussion regarding what to do if they were to subsequently deteriorate to the point where they might need it. These two subpopulations are distinct; those acidaemic at admission are more numerous with lower mortality risk. The performance of this tool should be examined in both of these subpopulations to ensure consistent performance.

When only those patients that deteriorate after 12 hours are selected the simple tool has an AUROC of 0.768 (0.687-0.848) and the complex weighting tool has an AUROC of 0.775 (0.696-0.854). This means that the scoring in this group is somewhat poorer with wider confidence intervals.

7.4 Multivariable modelling: Rule of Thumb.

7.4.1 Aim and Approach to Creating a Rule of Thumb?

Sometimes a tool no matter how simple and refined, is more complex than clinicians require, and therefore not used. In some instances, a very simple piece of information to guide a decision is useful. The rule of thumb does not need to be differentially weighted by odds ratios and the aim is not to identify stratified risk merely to give a very simple guide to be incorporated into a larger decision framework. Detailed and more bespoke risk can be obtained by using a more elegant and specific model as already described.

The rule of thumb attempts to identify a group of patients with a high short-term mortality risk that could influence clinical decisions (death in-hospital or within 90 days of discharge).

7.4.2 Rule of thumb Development

The strongest three predictors were used to develop the rule of thumb; eMRCD count, the eosinophil count and the time to development of acidaemia. Eosinophil count was excluded immediately because does not identify progressively higher mortality risk in the same way and is unlikely to work as well in the desired rule of thumb so was dropped.

The following tables display in-hospital and 90-day mortality (including hospital deaths) using the three identified time cut offs and the eMRCD score, first using just 5b and secondly combining 5a and 5b (i.e. the traditional MRCD grade 5). Each table is presented in four groups: neither adverse risk present (i.e. (e)MRCD 1-4 and early deterioration), only the

adverse (e)MRCD score without late deterioration, only late deterioration but without adverse (e)MRCD risk and both adverse indicators present.

Table 49 Rule of thumb chart using eMRCD 5b and acidaemia after 12 hours

Adverse feature(s)	Total	I/P mortality	90 Day Mortality
Neither	296	37 (12.5%)	62 (20.9%)
eMRCD 5b only	64	27 (42.2%)	41 (64.1%)
Acidaemia >12 hours only	92	33 (35.9%)	37 (40.2%)
Both eMRCD 5b AND acidaemia >12 hours	36	26 (72%)	28 (77.8%)

Table 50 Rule of thumb chart using eMRCD 5b and acidaemia after 48 hours.

Adverse feature(s)	Total	I/P mortality	90 Day Mortality
Neither	352	51 (14.5%)	80 (22.7%)
eMRCD 5b only	77	35 (45.5%)	49 (63.6%)
Acidaemia >48 hours only	36	19 (52.8%)	19 (52.8%)
Both eMRCD 5b AND acidaemia >48 hours	23	18 (78.3%)	20 (87.0%)

Table 51 Rule of thumb chart using MRCD 5 and acidaemia after 12 hours.

Adverse feature(s)	Total	I/P mortality	90 Day Mortality
Neither	173	9 (5.2%)	17 (9.8%)
MRCD 5 only	187	55 (29.4%)	86 (46%)
Acidaemia >12 hours only	51	13 (25.5%)	14 (27.5%)
Both MRCD 5 AND acidaemia >12 hours	77	46 (59.7%)	51 (66.2%)

Table 52 Rule of thumb chart using MRCD 5 and acidaemia after 48 hours.

Adverse feature(s)	Total	I/P mortality	90 Day Mortality
Neither	205	12 (5.9%)	22 (10.7%)
MRCD 5 only	224	74 (33%)	107 (47.8%)
Acidaemia >48 hours only	19	10 (52.6%)	10 (52.6%)
Both MRCD 5 AND acidaemia >48 hours	40	27 (67.5%)	30 75%)

7.4.3 Rule of Thumb Discussion.

The addition of dyspnoea severity scoring to late acidaemia development identifies a much higher mortality risk than either factor individually. Exploring the data in late deteriorators only shows 128 patients deteriorate after 12 hours of whom 59 (46%) die in hospital (Table 15). Table 51 shows that 77 of these 128 patients (60%) had a traditional MRCD score of 5

(or eMRCD 5a and 5b combined). Of these 77 patients 46 die in hospital. Therefore, using this single index 12 hours after admission over three quarters (78%) of the future inpatient deaths in those receiving assisted ventilation are captured. This is a potentially powerful way of selecting those to instigate active escalation planning. By extension the 51 patients deteriorating after 12 hours with an MRCD score of 4 or less have an in-hospital mortality of 25.5% more or less identical to the overall population mortality.

There is potential to identify those with high mortality using both the traditional and extended MRCD. This information may be informative to a clinician faced with a patient deteriorating after the admission period. The highest mortality is seen in those deteriorating after 48 hours with an eMRCD of 5b.

Chapter 8. Derivation Results Part 3: Mortality, Readmissions, Predictors of Key Post Discharge Events and Sub-group Analysis.

8.1 Mortality

124 patients died in hospital. Figure 27 is a Kaplan Meier plot is of the entire population up to 2 years after admission date, including those that die in hospital.

Figure 27 Kaplan Meier survival curve, whole study population from admission to Two years.

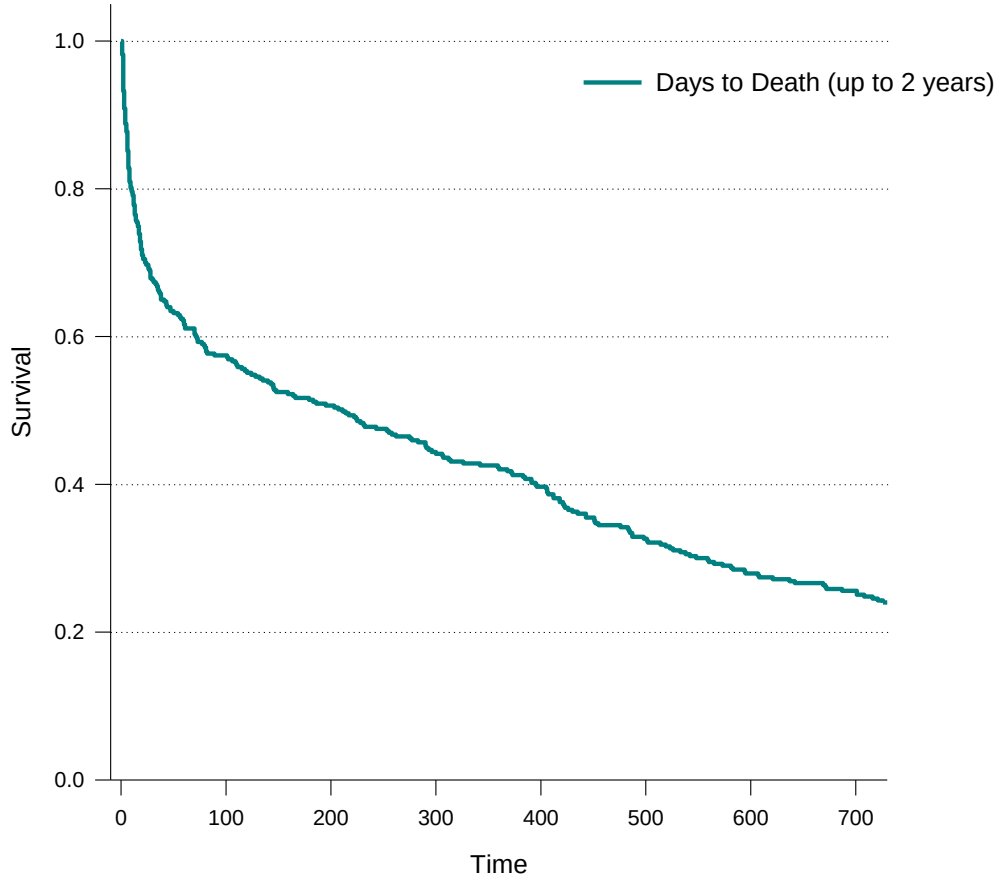


Table 53 is limited to survivors to discharge. In this population over half of patients ventilated for their ECOPD who survive to discharge will be alive after two years. As can be seen from Figure 27 and Table 53 there is a steady attrition of survivors to discharge without any particular shoulder or threshold where mortality rate changes markedly. Nearly half of those surviving to discharge are still alive after 2 years.

Table 53 Post discharge mortality amongst survivors to discharge up to 2 years.

Amongst Survivors to Discharge (n=365) Time point (from admission)	Deceased (Percentage of survivors)
30 day mortality	16 (4.4%)
90 day mortality	47 (12.9%)
180 day mortality	70 (19.2%)
1 year mortality	106 (29.0%)
2 year mortality	174 (47.7%)

8.2 Prediction of Six-month mortality.

This section aims to identify predictors of death in the 70 patients who survive to discharge but then die within 6 months. Methodology is the same as that used for creation of previous tool(s) 5.4. Only those indices that conceptually have association with readmission are included. Due to the low numbers here are lower this data analysis should be considered with caution and has not been subject to separate power calculations.

8.2.1 Univariate Associations with Six-month Mortality.

Table 54 reports the univariate associations with six-month mortality amongst the 365 patients who survived to hospital discharge. There is no missing data amongst these variables. Ischaemic heart disease (IHD) is patients with a history of one or both of angina or myocardial infarction (MI). Cardiovascular disease is consistently associated with mortality in COPD. Due to small numbers in this cohort a composite cardiovascular risk score was also created including: LVSD, cor-pulmonale, IHD or cerebrovascular disease (CVD). This was modelled as conceptually it is a potentially useful way of including medium term risk of death from co-morbidity into a single simple entity. There were variable rates of missing data amongst the 'pre-discharge' blood tests. The only blood tests recorded reliably in the pre-discharge window are the constituents of a full blood count (FBC) and urea and electrolytes (U+E). Missing data rates here were typically 10-13%. Albumin was rarely collected pre-discharge but admission albumin has some face validity to predict medium term prognosis so is used in lieu. Only admission albumin imparted independent risk upon multivariable modelling but was subsequently dropped. Pre-discharge blood gas data is also frequently missing; the majority did not have sampling after cessation of ventilation (Table 19) and this therefore, has not been analysed (127/365 survivors had an ABG).

Table 54 Associations with 6-month mortality amongst survivors to discharge.

Variable	Total Population N=365	Alive after 6 months N=295	Died within 6 months N=70	P value
Age*	71.0 (10.0)	70.2 (9.8)	74.5 (10.4)	0.001
Gender (% female)	226 (61.9%)	178 (60.3%)	48 (68.6%)	0.220
FEV_1%*	37.6 (16.1)	37.9 (16.0)	6.6 (16.8)	0.553
eMRCD†	4 (4-5a)	4 (4-5a)	5 (5a-5b)	<0.001
LTOT	96 (26.3%)	70 (23.7%)	26 (37.1%)	0.034
Previous NIV	82 (22.5%)	64 (21.7%)	18 (25.7%)	0.524
Consolidation	148 (40.5%)	118 (40.0%)	30 (42.9%)	0.686
Late Deterioration	69 (18.9%)	58 (19.7%)	11 (15.7%)	0.501
Late Failure	23 (6.3%)	19 (6.4%)	4 (5.7%)	1.000
Asthma	33 (9.0%)	26 (8.8%)	7 (10.0%)	0.816
Bronchiectasis	27 (7.4%)	19 (6.4%)	8 (11.4%)	0.200
IHD	98 (26.8%)	68 (23.1%)	30 (42.9%)	0.001
MI	50 (13.7%)	34 (11.5%)	16 (22.9%)	0.019
LVSD	44 (12.1%)	32 (10.8%)	12 (17.1%)	0.155
Cor-Pulmonale	67 (18.4%)	49 (16.7%)	18 (25.7%)	0.087
AF (Acute, Chronic or PAF)	42 (11.5%)	32 (10.8%)	10 (14.3%)	0.409
Anxiety	80 (21.9%)	62 (21.0%)	18 (25.7%)	0.422
Depression	114 (31.2%)	92 (31.2%)	22 (31.4%)	1.000
Cognitive impairment	28 (7.7%)	18 (6.1%)	10 (14.3%)	0.041
CVD	37 (10.1%)	27 (9.2%)	10 (14.3%)	0.194
Composite Cardiovascular (R/LVF, IHD, CVD)	170 (46.6%)	128 (43.4%)	42 (60.0%)	0.016
Benzodiazepine	53 (14.9%)	41 (14.2%)	12 (17.9%)	0.449
Regular strong Opiate	24 (6.8%)	15 (5.2%)	9 (13.4%)	0.027
Diuretic	167 (47.0%)	138 (47.9%)	29 (43.3%)	0.501
Beta Blocker	42 (11.8%)	31 (10.8%)	11 (16.4%)	0.209
ACE inhibitor	85 (23.9%)	72 (25.0%)	13 (19.4%)	0.427
Statin	143 (40.3%)	120 (41.7%)	23 (34.3%)	0.333
LABA	338 (95.2%)	276 (95.8%)	62 (92.5%)	0.335
LAMA	320 (90.1%)	264 (91.7%)	56 (83.6%)	0.066
ICS	341 (96.1%)	277 (96.2%)	64 (95.5%)	0.733
Carbocisteine	87 (24.5%)	72 (25.0%)	15 (22.5%)	0.753
Theophylline(s)	22 (6.2%)	18 (6.3%)	4 (6.0%)	1.000
Azithromycin	28 (7.9%)	22 (7.6%)	6 (9.0%)	0.801
Long term steroid (adm)	38 (10.4%)	31 (10.5%)	7 (10.0%)	1.000

Table 55: Reporting of relationship between 6-month mortality amongst survivors to discharge: Variables with Missing data.

Pre-Discharge Blood Test.	Missing %	Total Population N=365	Alive after 6 months N=295	Died within 6 months N=70	P value
BMI*	8.5%	25.3 (7.3)	26.1 (7.2)	22.2 (6.6)	<0.001
Haemoglobin*	11.0%	13.0 (2.0)	13.2 (2.0)	12.3 (1.7)	0.001
WCC*	11.0%	10.4 (5.2)	10.2 (3.7)	11.6 (9.0)	0.039
Platelet count*	10.7%	307 (121)	310 (125)	296.0 (101)	0.374
Eosinophil count†	9.6%	0.1 (<0.05-0.2)	0.1 (<0.05-0.2)	0.1 (<0.05-0.2)	0.043
Sodium*	10.1%	139.0 (3.9)	139.1 (2.4)	138.4 (3.2)	0.110
Potassium*	11.0%	4.2 (0.5)	4.2 (0.5)	4.2 (0.5)	0.910
Urea†	10.1%	5.6 (4.5-8.1)	5.6 (4.5-7.7)	5.8 (4.5-9.1)	0.460
Creatinine†	10.4%	79 (65-96)	79 (66-97)	77 (61-100)	0.425
CRP†	19.5%	14 (5-34)	13 (5-32)	19 (5-44)	0.146
Albumin*	13.2%	38.9 (4.7)	39.4 (4.5)	37.1 (4.9)	<0.001
Admission Bicarbonate*	4.1%	33.9 (6.7)	33.8 (5.9)	33.7 (5.9)	0.936

* Mean (SD) †Median (IQR). (n.b. Eosinophil count, lower value confers increased mortality)

There are several noteworthy observations from the univariate analysis:

- Having received NIV prior to the index event is not associated with medium term mortality in either direction.
- In this cohort few medications impact upon 6-month mortality. Strong opiates (in small numbers) does.
- In keeping with previous observations as described in 3.3.2.7 cardiovascular disease appears to exert a stronger influence upon medium term outcomes with IHD strongly significant.
- Albumin and BMI both of which were also associated with in-hospital mortality but not carried forward for multivariable analysis (missing data in case of albumin and unsuitability for a point of emergency care tool in case of BMI) are of significant prognostic value. While 13% missing data in the case of albumin is not extremely high it is greater than our stated 10% cut-off. Additionally, this requires using the admission albumin rather than discharge. These combined uncertainties render further modelling using this variable troublesome and so has not been carried forward.

8.2.2 Multivariate Modelling of Six-Month Mortality.

15 variables: Age, eMRCD, long term oxygen prescription, history of ischaemic heart disease, MI, cor-pulmonale, cognitive impairment, composite cardiovascular, prescription of strong opiate on discharge, long acting muscarinic agonist, BMI, haemoglobin, white cell count, eosinophil count and serum albumin were associated with 6-month mortality after univariate analysis with a p value of <0.1. Variables were categorised using the previously described hierarchy. Opiate use and cognitive impairment capture less than 10% of the population so were not carried forward. MI is captured within the IHD variable but captures a smaller percentage of the population and is less significant so was also not entered into regression analysis.

Following categorisation the variables in Table 56 remain independent predictors of outcome. The same variables remain in the equation whether run categorised or as continuous variables. Assessed as categorical variables no case had a Cook's distance of >1 and 10 (3.7%) had a studentised residual of +/- 1.96 indicating good model fit. (Continuous variables no case had a Cooks distance of >1 and 15/365 (4.1%) had a studentised residual of +/- 1.96).

Table 56 Independent predictors of six-month mortality.

Variable	B	S.E	Wald	Sig	Odds Ratio
Cor Pulmonale	0.638	0.372	2.947	0.086	1.89 (0.91-3.92)
Albumin <38 g/dL	0.695	0.305	5.184	0.023	2.00 (3.16-16.80)
IHD	1.170	0.331	12.48	<0.001	3.22 (1.68-6.16)
eMRCD 5a	1.379	0.351	15.47	<0.001	3.97 (1.98-7.89)
BMI <20	1.556	0.333	21.758	<0.001	4.74 (2.64-9.11)
eMRCD 5b	1.986	0.426	21.70	<0.001	7.29 (3.16-16.80)

R^2 0.315, Percentage correct after final iteration, 83.3%. Hosmer and Lemeshow 0.374. AUROC 0.821.

If only the three strongest predictors are used: eMRCD categorised, IHD and BMI <20 there results an AUROC of 0.801, R^2 of 0.285 and Hosmer and Lemeshow of 0.779.

As may be expected when using so few variables and modelling from a smaller number of outcome events there is greater instability in the model. The R^2 value of 0.285 indicates less

of the variation is explained by the model than for example when using the NIVO score. Nevertheless, an AUROC of >0.8 is encouraging.

8.2.3 Simple Score to Predict Six-month Mortality.

A very simple score can be generated using 1 point for IHD, BMI and eMRCD 5a and 2 points for eMRCD 5b. The resultant maximum 4 point score outcomes are shown in Table 57.

Table 57 Six and twelve-month mortality by simple score.

Mortality Score	Number	6 Month-Mortality	12 Month-Mortality
0	125	5 (4.0%)	14 (13.2%)
1	121	16 (13.2%)	28 (26.4%)
2	86	29 (33.7%)	38 (35.8%)
3	29	16 (55.2%)	22 (75.9%)
4	4	4 (100%)	4 (100%)

The comparator 5 variable model and 3 variable model AUROC values shown in Table 58 are generated from probabilities using full regression equation for the categorised variables and handles beta coefficients in absolute terms.

Table 58 Area under the receiver operated curves for models of six month mortality amongst survivors to discharge.

Model	AUROC (95%CI)
5 Variable model (categorised)	0.82 (0.77-0.88)
3 variable model (categorised)	0.80 (0.74-0.86)
Simple score	0.79 (0.73-0.84)

8.2.4 Six-month Mortality Model Discussion

Importantly these variables are conceptually sound and discrimination is maintained beyond six months adding credence to this model of risk of medium term death. Having a score of 0 or 1 identifies two thirds of the population (67.4%) who are at relatively lower risk of post discharge death, 8.5% by 6-months and 17.1% by twelve months.

Albumin was omitted from this model due to high rate of missing data, the fact that we were forced to use admission data rather than pre-discharge values and the attraction of using less dynamic values to model the medium to long term.

8.3 Readmissions

Of the 365 patients who survived to discharge there were 381 readmissions in the year following. 142 (38.9%) had no readmission although this figure will include those that die at home without being readmitted (n=35). 23% of patients were re-admitted within 30 days and 35.3% by 90 days. The median number of readmissions was one (IQR 0-2) and 14.5% of the population had 3 or more admissions in the subsequent year following discharge.

8.4 Sub-Groups

5 sub-groups were identified 'a priori' to examine mortality and readmission rates in greater detail.

- Late failure of NIV
- Long-term oxygen therapy.
- Home mechanical ventilation on discharge.
- Eosinopenia at discharge.
- Persistent hypercapnia at discharge.

Due to the uncontrolled study design we were unsure whether data would have been collected by the managing clinical team to accurately characterise these sub-populations. Persistent hypercapnia at discharge and eosinopenia are both reliant on blood sampling in the period prior to discharge once a patient is stable. I.e. There was no way of knowing whether data would be complete enough to accurately define the subgroup until the analysis phase.

The in-hospital outcomes for late failure and those in receipt of LTOT are interesting and data is pertinent to the population receiving the primary intervention so the comparisons are for the entire population not just the survivors unless specified. Post discharge outcomes are expressed as a proportion of those that survive.

8.4.1 Subgroup 1: Late Failure

8.4.1.1 Definition

As has been discussed in detail in 3.3.7.2 there is no universally agreed definition of late failure (LF) but it refers to a cohort who deteriorate after initial improvement with an associated high mortality. We used the following definition: *"Late failure is recurrence of respiratory acidaemia prior to discontinuation of ventilation. pH should drop to below 7.35 with a rise in CO_2 of at least 1kPa and to >6.5kPa from the lowest recorded post pH correction at least 24 hours after pH correction."* Of note a lower CO_2 threshold of 6.0kPa was used in the derivation study in keeping with the guidelines of the time.

8.4.1.2 Late Failure Population

35 (7.2%) patients met the precise definition above. There were many others that met part of the definition but not all facets. The imposition of a time between correcting pH and subsequent fall of at least 24 hours excluded many that may have been captured using other group's definition. This was to ensure that those that transiently correct pH to ≥7.35 are not included.

Of these 35 patients experiencing late failure none were intubated, 3 were immediately palliated and a further 5 had NIV withdrawn within 24 hours. Excluding 3 immediately palliated, NIV was provided for mean 12.4/24h pre LF and 17.1/24h post. Median pressures were modestly increased from median 18/4 to 20/5. Patients experiencing late failure had higher eMRCD score and a trend toward increased LTOT prescription. Compared to those not experiencing late failure in hospital mortality is significantly higher if late failure occurs (12/35, 34.3%) however, is far lower than the 92% quoted in a paper by Moretti et. al. (see section 3.3.7.2) when they continued NIV in the setting of late failure.[237] There is no significant difference in post discharge mortality to 1 year or readmissions to 90 days in patients with late failure.

Table 59 Description and outcome of patients with and without late failure of NIV.

	Late Failure Present (n=35)	Without LF (n=454)
Age*	74.5 (8.1)	72.6 (10.2)
FEV1 % *	36.0 (16.0)	38.2% (16.4)
LTOT	15 (42.9%)	128 (28.2%)
Consolidation at Ventilation*	11 (31.4%)	220 (48.5%)
Acidaemia development >12 hours after admission	13 (37.1%)	115 (25.3%)
eMRCD #	5a (5a-5b)	5a (4-5a)
Proportion eMRCD 5b	10 (28.6%)	90 (19.8%)
APACHE 2 score at ventilation outset†	19 (15-22)	20 (16-24)
Deceased in hospital #	12 (34.3%)	112 (24.7%)
Deceased by 90 Days	16 (45.7)%	153 (33.7%)
Deceased by 365 Days	20 (57.1)%	208 (45.8%)
1+ Readmission 90 Days (survivors)	5/23 (21.7%)	124/342 (36.3%)

* Mean (SD) †Median (IQR) # p<0.05

8.4.2 Subgroup 2: Patients receiving LTOT at admission.

In a population of patients with advanced COPD requiring assisted ventilation a large proportion (29.2%) were prescribed LTOT.

Table 60 Description and outcome data in patients prescribed LTOT or not on admission.

Variable	LTOT n=143	No LTOT n=346
Age*	74.1 (9.1)	72.2 (10.3)
%FEV_1 * #	34.4 (15.0)	39.6 (16.6)
Consolidation at Ventilation	63 (44.1%)	168 (48.6%)
Acidaemia development >12 hours after admission	33 (23.1%)	95 (27.5%)
eMRCD #	5a (4-5b)	4 (4-5)
Proportion eMRCD 5b† #	51 (35.7%)	49 (14.2%)
APACHE 2 score at ventilation outset	20 (17-24)	20 (15-23)
Deceased by 90 Days (survivors)#	21/96 (21.9%)	26/269 (9.7%)
Deceased by 365 Days (survivors)#	42/96 (43.8%)	64/269 (23.8%)
1+ Readmission 90 Days (survivors)#	42/96 (43.8%)	87/269 (32.3%)
1+ Readmission 365 Days (survivors)#	72/96 (75.0%)	139/269 (51.7%)

* Mean (SD) †Median (IQR) # p<0.05

Those in receipt of LTOT have more severe COPD; specifically, percent predicted FEV_1 is lower and eMRCD score is higher. In hospital mortality is higher in those requiring LTOT at admission (7.1.2.2) and furthermore among those surviving the index admission, there is a significant increase in both short and medium term death and readmission.

8.4.3 Subgroup 3: Home Mechanical Ventilation (HMV) on Discharge

The time period under review in the derivation project predates several of the major trials in HMV and home ventilation for COPD was used infrequently, but accurate national data is not available. Only 10 patients were admitted who were in receipt of HMV and 6 of these died during their admission. A further 7 were commenced on HMV during their index admission giving a total of 11/365 (3.0%) discharged patients receiving HMV.

Table 61 Description and outcome data in patient receiving home mechanical ventilation at discharge.

Variable	HMV at Discharge	No HMV
Age*	69.7 (9.5)	71.1 (10.1)
%FEV_1*	30.6 (7.9)	37.9 (16.3)
LTOT	5/13 (38.5%)	91/352 (25.9%)
eMRCD†	4 (4-5b)	4 (4-5a)
Deceased by 90 Days	1/13 (7.7%)	46/352 (13.1%)
Deceased by 365 Days	4/13 (30.8%)	102/352 (29%)
1+ Readmission 90 Days (survivors)	7/13 (53.8%)	122/352 (34.7%)
1+ Readmission 365 Days (survivors)	10/13 (76.9%)	201/352 (57.1%)

* Mean (SD) †Median (IQR)

Statistical comparison to the total population has not been included for those with HMV at discharge due to small numbers. Given that this intervention was quite restricted there is likely to be a significant level of patient selection on clinical grounds in addition to the enhanced level of support these patients receive rendering statistical analysis obsolete.

8.4.4 Subgroup 4: Eosinopenia at discharge.

Eosinopenia was defined as <0.05 $x10^9$/L and the last blood test prior to discharge was used with none more than 7 days prior to discharge included. Dates were not recorded but anecdotally a large proportion had blood tests within 48 hours of discharge. 35/365 patients did not have an eosinophil count so imputed values were used.

Table 62 Description and outcome data in patient with and without eosinopenia (eosinophil count <0.05 x10^9/L) in survivors to discharge.

Variable	With Eosinopenia (n=118)	Without Eosinopenia (n=247)	P value
Age*	72.2 (11.0)	70.5 (9.5)	0.131
%FEV_1*	38.0 (16.1)	37.4 (16.1)	0.731
LTOT	28/118 (23.7%)	68/247 (27.5%)	0.525
eMRCD†	4 (4-5a)	4 (4-5a)	0.764
Deceased by 90 Days	21/118 (17.8%)	26 /247 (10.5%)	0.066
Deceased by 365 Days	34/118 (28.8%)	72/247 (29.1%)	0.947
1+ Readmission 90 Days	43/118 (36.4%)	86/247 (34.8%)	0.815
1+ Readmission 365 Days	66/118 (55.9%)	145/247 (58.7%)	0.651

* Mean (SD) †Median (IQR) # p<0.05

This data suggests that eosinopenia on the last pre-discharge sample is not a useful predictor of post discharge outcome with no significant differences between groups identified although short term post discharge mortality may warrant further study. It may be the case that re-sampling of the eosinophil count in the weeks post discharge so the influence of the acute period is mitigated on such a dynamic value may afford greater insights.

8.4.5 Subgroup 5: Persistent Hypercapnia at Discharge

Of the 365 patients who survived to discharge, only 127 had a steady state ABG defined as the last available pre-discharge after complete weaning from ventilation. Therefore, this sub-group cannot be accurately defined and will not be explored in any greater detail.

8.5 Derivation Results Summary

This historical cohort of 489 patients admitted to hospital with ECOPD complicated by RA and requiring assisted ventilation has yielded many insights. The patients were collected consecutively and with a high degree of confidence that all eligible are captured.

Our desire was to maximise generalisability leading to inclusive selection criteria; our typical patient was or is a heavy tobacco smoker, is housebound, has an FEV_1 of 38% predicted, and is soon to turn 73. Polypharmacy and comorbidity are the norm. They receive good quality ventilation but despite this a quarter will die in hospital and amongst survivors over a third

will be re-admitted by 90 days and a fifth will not survive to 6 months. In short this is convincingly a real-world population.

We have shown that accurate prediction of in-hospital mortality is feasible, and the final proposed model is workable if successfully validated. The key predictors of outcome have face validity and all have previously been shown to be associated with mortality risk though not in the same tool. A rule of thumb to help guide escalation planning and post discharge outcome scores offer further potential utility to the attending clinical teams.

Prioritising generalisability and by extension not controlling usual care means that the data at the time of discharge is less complete than in the acute phase (when blood tests and other clinical data are more complete) and thus drawing out common threads is perhaps less reliable.

Amongst subgroups late failure was found to be associated with higher in-hospital mortality but continued optimised NIV in this cohort yielded much better outcomes than previous studies suggest with very close to two thirds surviving to discharge. Those in receipt of LTOT have poorer long term outcomes whereas pre-discharge eosinophil count did not influence post discharge outcomes in this population.

Chapter 9. Validation Results.

9.1 Introduction.

The results from the validation study are not reported in the same detail as the derivation study. The report is limited to population descriptors to give insights into generalisability, some methodical steps and the validation of the predictive model. Repetition of univariate associations with mortality has not been done unless pertinent to the population description, or to emphasise similarities or differences between the derivation and validation cohorts. Further exploration of the data and post discharge outcomes are the subject of another thesis as previously indicated. Fewer indices were collected per patient in the non-consenting aspect of the validation study so not all reported outcomes from derivation, for example number of exacerbations in the year preceding index admission, are unavailable from the validation dataset.

9.2 Data Handling.

9.2.1 Data Verification.

Throughout the project, real time data verification took place and potentially anomalous results and missing data were queried with local sites via email. All physiological parameters had upper and lower limits imposed by the database to prevent anomalous values being entered. As an additional screen once data entry complete, data were sorted by value and outliers examined and any potentially anomalous results were verified with source data. When examining dates and times all calculated values for example the time from X to Y were similarly ranked by value post calculation to ensure potentially anomalous results were identified. This identified several suspicious instances which were verified with source data. This process was not to exclude any data but to maximise data quality.

9.2.2 Data Verification Visits.

Upon recruitment closure each external site had an on-site data verification visit at which key indices were verified with source documentation. The PI at each site made the final decision whether to action or not any queries raised.

9.2.3 Data Import.

In keeping with the derivation results the final dataset was exported into excel and then into IBM SPSS v22.

9.2.4 Missing Data.

Missing data rate was low amongst the variables with a univariate association with mortality from the derivation project. Most missing data relevant to the validation of the predictive models was found in patients who deteriorated late and did not have a repeat set of bloods in the 24 hours prior to commencing NIV. Amongst univariate associates with mortality missing data was:

AF 0%, consolidation 0%, eMRCD 0%, LTOT 0%, LVSD 0%, pH 0%, Time to NIV 0%, base excess 1.1%, haemoglobin 1.4%, WCC 1.4%, confusion 1.5%, systolic blood pressure 2.2%, respiratory rate 2.2%, Glasgow coma scale 2.3%, eosinophil count 2.9%. Missing data amongst components of the NIVO tool was low. In the validated model, the only missing data was in the recording of GCS.

Missing data is greatest in the point of deterioration blood tests. In this table the rate of missing data is included for information.

Missing data was imputed using the expectation-maximisation algorithm. Unless specified, EM data is presented.

9.3 Population Description.

9.3.1 Headline Summary.

733 unique cases were captured across 1 internal and 9 external NHS trusts. Recruitment opened on 14/10/16 and closed on 28/2/18. Overall inpatient mortality was 20.1%. Internal recruitment closed when the 200 patient limit was met. External sites closed when a pre-agreed target was met or on 28/02/2018. Recruitment targets have been withheld to maintain site anonymity.

9.3.2 Demographics – All Sites.

The typical patient in NIVO is most likely to be white and female, in their seventh decade, a current and historically heavy smoker with a two thirds chance of a hospital admission in the last year.

Table 63 Selected population descriptors.

Variable	Value	Derivation data (for comparison)
Female	58.3%	62.6%
Age*	70.5 (9.3)	72.8 (10.0)
Cigarette Pack Years*	44.8 (23.7)	49.5 (26)
Current smoker	63.1%	48.7%
1(+) admission in last 12 months	68.9%	48.0%
Caucasian	98.0%	100%

* Mean (SD) †Median (IQR)

The fact that the population is so strongly Caucasian is at first appearance a concern for generalisability. 86% of the population of England and Wales is Caucasian, however, 95.5% of over 65s are Caucasian.[257] Therefore, while there is some discrepancy perhaps due to regional demographics the population is close to representative. Current smoking rates are higher than in the derivation study, the reasons for this are unclear. Admissions in the preceding year are also higher, variance in local practice may be contributing. Our own trust has well established and longstanding community and hospital outreach services in COPD which may have contributed to an artificially low number of admissions in the derivation study. It should also be noted that mortality is lower, this means a larger cohort of survivors in whom hospital admission is common.

9.3.3 Site Recruitment and Mortality.

733 patients were included, 147 (20.1%) died in hospital. Table 64 shows hospital mortality varies by site with highest mortality seen in site E (28.4%) and the lowest at site I (12.2%). Site mortality data is provided for interest, variation in mortality is expected as individual sites are underpowered. Median length of stay amongst survivors was 8 (6-14) days, post discharge outcomes are not reported for the validation cohort in this thesis.

Table 64 Recruitment by site and associated in hospital mortality.

Site	N	In-hospital mortality (%)
A	200	18.0
B	116	19.8
C	77	19.5
D	69	26.1
E	67	28.4
F	60	18.3
G	49	12.2
H	44	25.0
I	37	13.5
J	14	21.4
Total	733	20.1

Figure 28 shows the distribution of recruiting centres all of which are in England or Wales. Sites were deliberately dispersed around the country encompassing metropolitan and more rural areas.

Figure 28 Geographical distribution of recruiting centres to NIVO validation in England and Wales.

9.3.4 Effect of Unique Patients on Mortality.

Both derivation and validation collect unique patients. This is likely to increase the reported mortality as previous successful treatment with NIV is a protective factor. Therefore, patients with frequent admissions but favourable outcome are equally represented initially, but subsequently excluded. This was seen in the DECAF validation study (employing unique patient methodology) where mortality was higher than in national audit data (7.7 vs 4.3%).[29,82]

A similar effect was seen in the NIVO study: In the derivation study mortality in the first 100 patients is 17.5% vs 27.1% in the remainder. In the validation study the same analysis would be unhelpful as not all sites started recruitment at the same time. Therefore; the first 20% at each site were compared to the remainder and mortality rises from 14.4% to 21.6%. This observation is important to be aware when considering the results in a wider context.

9.3.5 Home Circumstances.

Three quarters of the patients were admitted from their own home without any formal care package (Table 65). It is highly likely that a large number receive informal care from family or friends, given the median eMRCD score was 5a (i.e. housebound but not requiring assistance with washing and dressing), but this is not captured in the data. The rate of formal care has risen from the derivation study (derivation 12.1%) which may reflect regional variation

Table 65 Pre-admission home care circumstances.

Admitted From	Percentage of Total
Home	74.8
Home + formal carers	17.5
Sheltered accommodation	1.4
Sheltered accommodation + formal carers	1.0
Residential care	3.1
Nursing care	1.6
Community hospital	0.4
Homeless	0.3

9.3.6 COPD Details.

Spirometry values and proportion of LTOT prescription are consistent with the derivation study adding credence to their validity. In keeping with previous studies (section 3.3.2.5) neither FEV_1 as an absolute value (p=0.185) or as percent predicted (0.953) was significantly associated with in-hospital mortality using a two tailed T test.

Table 66 Key Descriptors of COPD.

Variable	Value	Derivation data for comparison
FEV_1 (L)*	0.84 (0.36)	0.81 (0.36)
FEV_1 (%)*	37.2 (15.4%)	38.0 (16.4)
FEV_1/FVC*	0.44 (0.12)	0.44 (0.12)
1+ value missing but airflow confirmed	35 (4.8%)	N/A
eMRCD†	5a (4-5a)	5a (4-5a)
BMI*	25.5 (7.96)	24.6 (7.3)
LTOT on admission	28.6%	29.2%
Previous NIV	35.9%	21.9%
Home ventilation on admission	8.7%	2.0%

* Mean (SD) †Median (IQR)

In cases where either the FEV_1, the FVC or both were missing but there is objective evidence that airflow obstruction has been confirmed by another specialist clinician, patients could be included. If no objective evidence of airflow obstruction then, irrespective of duration of COPD diagnosis or clinical likelihood, patients would be eligible for the clinical diagnosis dataset only (section 5.2).

The objective criteria for LTOT prescription have been established for many years and hence the only minor observed variation between derivation and validation is to be expected. However, as described in the introduction there is an ongoing evolution in both acute and long-term ventilation practice with greater availability so it is unsurprising that rates of previous NIV and HMV increased in the modern cohort.

9.3.7 Comorbidity.

Limited data on comorbidity was collected in the validation dataset, only components of the APACHE II score and univariate associations with mortality from the derivation study were collected. There is no missing data.

Table 67 Selected comorbidity.

Comorbidity	Percentage present
Cor Pulmonale	22.5
LVSD	14.1
Depression	23.6
AF admission	18.7
IHD	22.5
Cerebrovascular disease	9.7
Cognitive impairment	7.8

9.3.8 eMRCD.

The strongest predictor of mortality from the derivation study remains significantly associated with mortality (Mann-Whitney U, $p<0.0001$). Table 68 shows a strong positive association between eMRCD score and mortality. 118/147 (80.2%) deaths occurred in patients with eMRCD score of 5a or 5b which between them make up 56.0% of the total number of patients.

Table 68 eMRCD: Frequency and in hospital mortality.

eMRCD	Total	% of Total	In Hospital Mortality
1	9	1.2	0%
2	18	2.5	0%
3	53	7.2	3.8%
4	242	33.0	11.2%
5a	251	34.2	24.7%
5b	160	21.8	35.0%

9.3.9 Admission Medications.

Amongst the recorded medications, patients were prescribed a median of 4 (3-6) with 97.4% taking 2 or more. No data was collected for any additional medications not specifically reported in the table here; there is no missing data.

In comparison to the derivation data there are several noteworthy observations, accepting the problem of comparing a single centre to multiple centres. Table 69 shows the proportion prescribed diuretics has fallen; potentially because, since 2011, diuretics are no longer

considered first line treatment for hypertension.[258] Prescription of beta blockers has risen; there is more widespread acceptance that cardio-selective beta blockers are not harmful in COPD.[259] Prescription rates for Carbocisteine and Azithromycin are higher which may represent their acceptance as mainstream treatments in selected patients with COPD. Certainly since 2011 the evidence to support the use of Azithromycin in some circumstances has expanded.[260] The dramatic expansion in Carbocisteine prescription is less explainable but probably relates to variations in local prescribing habits. Those not recorded as taking LABA/LAMA may have regular nebulised bronchodilators not captured.

Table 69 Admission medications.

Medication	Percentage taking on admission (Validation)	Percentage taking on admission (Derivation)
Long term steroid	10.2	11.0
Diuretic	36.7	44.4
ACE inhibitor/ARB	26.9	29.7
Beta Blocker	23.2	10.8
Statin	44.2	41.3
Long Acting Beta Agonist (LABA)	89.5	82.0
Long Acting Muscarinic Agonist (LAMA)	78.9	76.6
Inhaled Corticosteroid (ICS)	79.0	83.4
Carbocisteine	47.3	22.5
Theophylline	10.0	7.0
Azithromycin	12.3	6.5

Finally, the unsuitability of medications as predictors of mortality was also discussed in section 6.2.6 and that taking Carbocisteine was significantly associated with increased in-hospital mortality, albeit weakly (Chi squared p=0.046). This was thought to be a quirk of data collection and a statistical anomaly and, as expected, this finding is not replicated in the validation cohort (Chi squared p=0.415).

9.3.10 Observations.

These observations represent the worst recorded post admission in the 24 hours prior to the ABG that prompted the decision to ventilate. Time frames for data collection are explained in section 5.3.2 .

Table 70 Clinical observations post admission and up to 24 hours pre-decision to ventilate.

Observations 24 hours prior to ventilation	Value
Systolic Blood pressure*	133.3 (34.2)
Diastolic Blood Pressure*	75.4 (20.7)
Mean Arterial Pressure*	94.7 (23.3)
Heart Rate*	109.9 (21.4)
Respiratory Rate*	28.4 (7.4)
Temperature*	36.7 (0.98)
Lowest oxygen Saturations*	84.2 (9.8)
GCS†	15 (14-15)

* Mean (SD) †Median (IQR)

9.3.11 Blood Tests and Chest X-ray.

Blood tests are included for accurate characterisation of the study population. There are no results that stand out as anomalous in Table 71.

Table 71 Blood test results post admission and up to 24 hours pre-decision to ventilate.

Blood Test	% Missing	Value
Haemoglobin (g/dL)*	1.4	13.7 (2.1)
Haematocrit (L/L)*	1.6	0.433 (0.064)
Platelets (x10^9/L)*	1.5	272 (107)
WCC (x10^9/L)*	1.4	13.1 (6.8)
Eosinophil Count (x10^9/L)*	2.9	<0.05 (<0.05-0.1)
Eosinophil count <0.05	2.9	53.5%
Sodium (mmol/L)*	1.5	136.9 (5.5)
Potassium (x10^9/L)*	6.5	4.62 (0.64)
Urea (x10^9/L) *	3.1	8.49 (5.26)
Creatinine (x10^9/L) *	1.8	87.2 (49.1)
Albumin (g/L)*	19.6	37.7 (5.2)
Glucose (mmol/L)*	14.1	8.18 (3.36)
CRP (mg/L) †	4.6	40 (13-110)

* Mean (SD) †Median (IQR)

Many patients will have their liver function tests and serum glucose checked on admission to hospital but not routinely thereafter unless indicated. Therefore, it is unsurprising that in the 24 hours prior to the point of deterioration, which in 17.9% of patients is >24 hours into admission, the most common missing data are albumin and glucose. Albumin is perhaps of

less clinical value in the assessment of a deteriorating patient and it is possible glucose was more frequently measured but less well recorded as it may be a bedside test. Potassium is more likely to be missing than other results from the same panel due to haemolysis occurring during venesection or analysis.

9.3.12 Arterial Blood Gases.

Table 72 shows acidaemia at outset of ventilation is very similar to the derivation study where it was median pH 7.27, IQR 7.21-7.31. Mean CO_2 is slightly higher (derivation pCO_2 9.34 (2.94); this is likely explained (at least in part) by the lower limit for inclusion rising from 6.0 KPa to 6.5 KPa to reflect national guidelines changing.

The blood gases in Table 72 do not include EM data as there is a complete dataset for the main point of interest (NIV decision) and the other data is for description only.

Table 72 Arterial blood gas results at various time points.

Time	Missing	pH†	pCO_2*	pO_2*	BE*	Bicarbonate*
Admission	2.7%	7.30 (7.24-7.34)	9.35 (2.86)	8.78 (5.4)	4.9 (6.5)	30.3 (6.7)
At NIV	0%	7.27 (7.22-7.30)	10.22 (2.71)	9.02 (5.04)	4.6 (6.6)	30.5 (6.8)
24 hours	14.5%	7.37 (7.33-7.41)	7.50 (1.93)	8.42 (2.45)	5.7 (6.2)	30.3 (6.3)
Steady	43.7%	7.41 (7.38-7.45)	7.14 (1.65)	8.08 (2.14)	8.3 (5.7)	32.8 (5.7)

* Mean (SD) †Median (IQR)

9.3.13 Non-invasive Ventilation Description.

One of the greatest challenges in NIVO is that the intervention being assessed is not controlled; to do so would have rendered the data poorly generalisable. Limited data was collected about the intervention provided (Table 73). The sites were selected for their well-developed and streamlined services to mitigate this. All sites deliver high quality NIV, adhere to national guidance and provide NIV liberally.

Door to mask time (DTMT) measures the time from patient's presentation to initiation of ventilation. Of those with a blood gas indication for NIV within 12 hours of admission, who did not correct with medical therapy there was a median of 123 minutes (IQR 61-236 minutes) from door to mask. In the entire population i.e. including those in whom deterioration occurs later into admission, the median time and is prolonged with a pronounced rightward tail to the population distribution; median 198 minutes (IQR 85-828

minutes). DTMT has limitations as a metric in an individual case, but it remains a useful broad measure of the NIV service provided and is included in the recent quality standards. The target is less than 120 minutes for those who meet "*evidence based criteria for acute NIV*" on presentation to hospital. [162] In the NIVO study, 74.1% of those with an initial pH of <7.35 achieved the 2-hour door to mask target.

In all patients, time from the ABG prompting ventilation to ventilation initiation was 42 minutes (19-76 minutes) within the 60 minute target from the quality standards.[162] These metrics paint a picture of well-functioning services.

Table 73 NIV Settings.

Variable	1 hour	Maximum
IPAP†	18 (14-21)	20 (18-24)
EPAP†	5 (4-5)	5 (4-6)
Back up rate†	14 (12-16)	14 (12-16)

* Mean (SD) †Median (IQR)

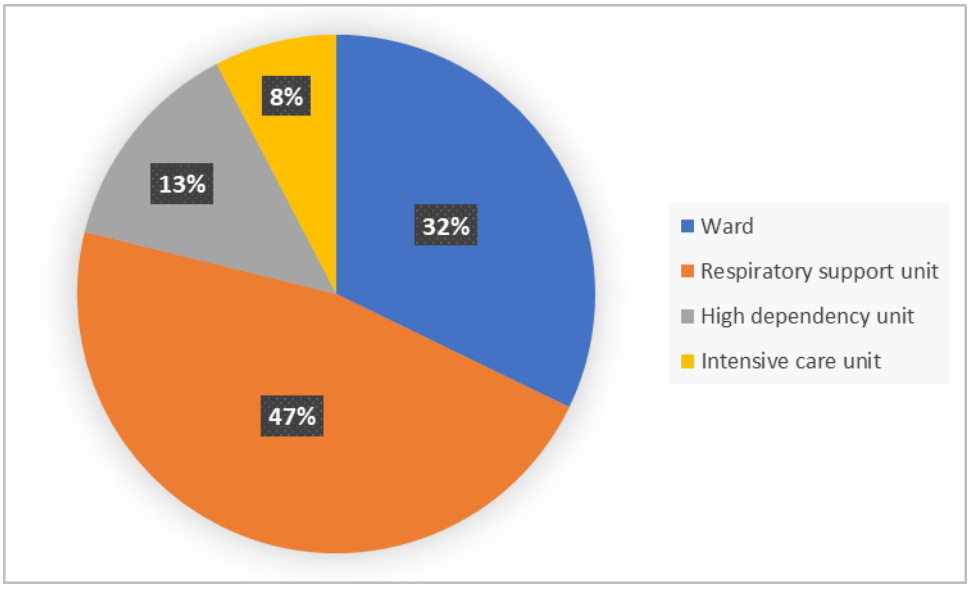
Ventilation was delivered for a median of 62 hours (25-109 hours). It should be remembered the period of ventilation includes those that may deteriorate and die quickly and those ventilated for a very long time so is perhaps of limited use beyond giving a flavour of the intervention delivered.

9.3.14 Ventilation location, Modality and Escalation Decision.

9.3.14.1 Location of NIV Delivery.

There are a number of physical places within a hospital where NIV can be provided (2.4.4). Invasive ventilation is delivered in an intensive care unit. Figure 29 shows the largest proportion of NIV is delivered in a respiratory support unit, however, if Site A (the largest recruiter where all patients are managed on an RSU) is excluded, the distribution is slightly altered as follows: ward 38.1%, RSU 35.8%, HDU 16.5%, ICU 9.6%. If a patient is ventilated in more than one place the highest level of care is recorded along the hierarchy; ward, RSU, HDU, ICU.

Figure 29 Location where NIV delivered.



9.3.14.2 Modality of Ventilation.

In keeping with the derivation study, the majority of patients received non-invasive ventilation alone. 21 patients (2.86%) received invasive ventilation of whom 15 had received prior NIV. In hospital mortality amongst those receiving NIV alone was 19.9% and was 23.8% in those invasively ventilated.

9.3.14.3 Do Not Attempt Resuscitation and 'Level of Care' Decisions.

All patients at the outset of ventilation should have an active decision made about resuscitation and 'level of care' i.e. whether this patient would be suitable for intensive care treatment.[133] 294 (40.1%) were considered eligible for escalation to invasive ventilation and 328 (44.7%) remained for resuscitation in the event of cardiac arrest.

The NIVO manual states: "*unless actively stated to the contrary, patients should be assumed to be considered for full escalation. If a senior clinician changes this status at the first senior review (provided within 24 hours of initiation of ventilation) then record this as the status. Changes made after 24 hours irrespective of clinician grade do not affect this status.*"

Amongst those that died in hospital, at outset of ventilation, 21.1% were for consideration of invasive ventilation and 23.1% remained for resuscitation.

9.3.15 Timing of Acidaemia.

The median time from admission to the blood gas informing the decision for ventilation was 137 (41-767) minutes. The wide IQR is because this encompasses those that deteriorate late into their admission. Arterial pH corrected to ≥7.35 post ventilation initiation in 643 patients; median time to correction was 522 (176-1490) minutes. In 190 (29.5%) patients' first pH correction was within 4 hours of ventilation commencement.

The time from admission to development of acidaemia was a strong univariate predictor of outcome; Mann Whitney U p<0.0001 median 137 (41-767) minutes and is similar to that observed in the derivation study 146 (56-852) minutes. When split by the previously explored time thresholds incrementally increased mortality is seen.

Table 74 Mortality and time to acidaemia development.

Time to acidaemia development	% of total	Mortality if deteriorate earlier than threshold	Mortality if deteriorate later than threshold
>12 hours	25.2	81/548 (14.8%)	66/185 (35.7%)
>24 hours	17.9	93/602 (15.4%)	54/131(41.2%)
>48 hours	10.1	110/659 (16.7%)	37/74 (50.0%)

9.3.16 Comparison Scores.

A number of comparison scores were recorded and calculated. The scores presented here were calculated using data from the 24-hour period prior to ventilation being initiated.

Score	Potential Range	Median (IQR)
DECAF	0-6	3 (2-3)
CURB 65	0-5	2 (1-3)
CAPS	0-100	22 (16-28)
APACHE II	0-71	19 (16-22)
Confalonieri*	0-12.33	5.37 (4.08-6.63)

*See Table 43 for data handling .

9.4 Selected Descriptors by Recruiting Site.

The breakdown of the components of the final predictive model is shown in Table 84. Further population descriptors are shown in Table 76.

Table 75 Selected descriptors of population by recruiting site 1.

Site	Female (%)[Ω]	Age*	Current smoker (%)[Ω]	Admitted home W/O care (%)	1+ Admission last 12 months (%)	BMI*	eMRCD[†]	FEV_1% Predicted*	LTOT (%)[Ω]	Prev NIV (%)[Ω]	HMV (%)[Ω]
A	56.5	71.9 (9.2)	39.0	75.0	61.5	25.9 (8.3)	5 (4-5)	40.5 (16.6)	25.0	40.0	5.5
B	62.9	68.9 (8.5)	89.4	80.2	73.3	23.2 (6.7)	5 (4-5)	34.5 (14.6)	30.2	37.1	10.3
C	62.3	70.2 (10.1)	87.0	74.0	64.9	26.9 (8.4)	5 (4-5)	38.6 (13.3)	26.0	28.6	9.1
D	63.8	72.8 (10.1)	52.2	71.0	76.8	24.8 (3.5)	4 (4-5)	38.1 (16.2)	33.3	29.0	4.3
E	53.7	70.5 (9.6)	65.7	73.1	86.6	28.1 (9.6)	5 (4-6)	38.1 (15.5)	35.8	34.4	4.5
F	50.0	67.7 (9.1)	66.1	55.0	73.3	25.5 (7.8)	4 (4-5)	30.6 (13.8)	38.3	58.3	30.0
G	46.9	71.8 (8.6)	59.2	81.6	69.4	25.7 (7.1)	4 (4-5)	35.8 (13.4)	24.5	28.6	6.1
H	63.6	70.1 (9.6)	77.3	84.1	56.8	26.7 (7.7)	4 (4-5)	36.5 (13.4)	15.9	20.5	2.3
I	56.8	68.9 (8.3)	70.3	73.0	62.2	24.5 (7.3)	5 (4-6)	36.9 (16.7)	35.1	37.8	13.5
J	78.6	68.3 (10.5)	42.9	92.9	71.4	21.1 (6.2)	3 (2-4)	34.0 (13.8)	21.4	21.4	7.1
Total	58.3	70.5 (9.3)	63.1	74.8	68.9	25.5 (8.0)	5 (4-5)	37.2 (15.4)	28.6	35.9	8.7
P Value	0.316	0.015	<0.0001	0.015	0.007	0.002	0.002	0.002	0.281	0.003	<0.0001

Table 76 Selected descriptors of population by recruiting site 2.

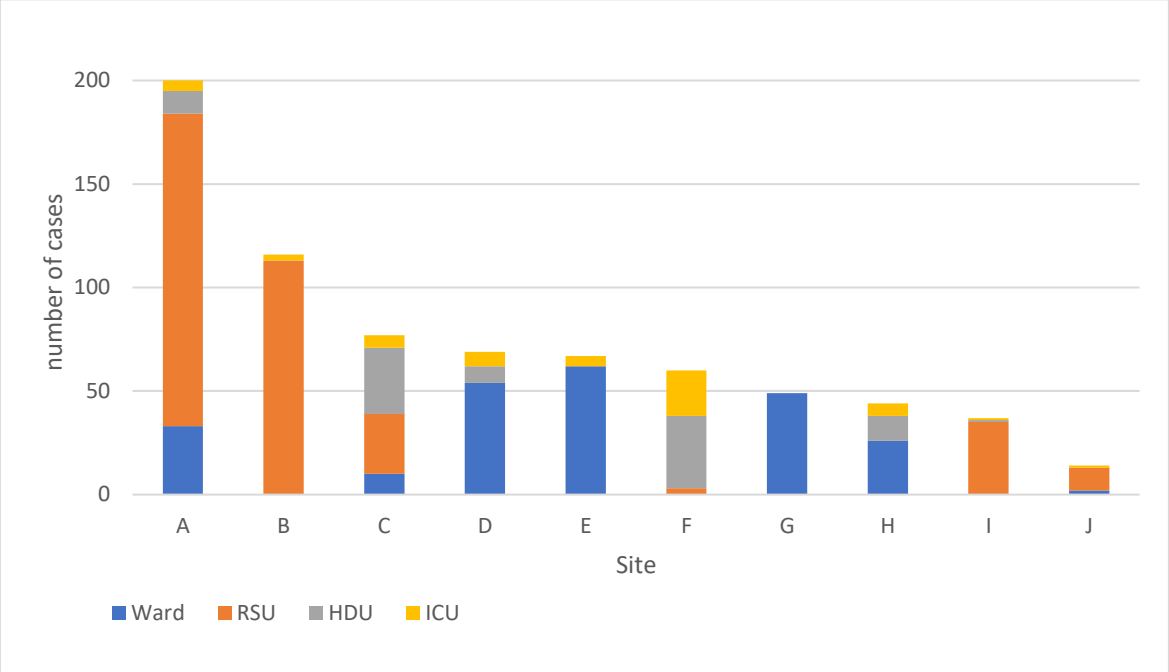
Site	Hb*	WCC*	Creatinine*	CRP†	CO2 at ventilation	Duration Vent (hours)	Worst pH†	APACHE II score†	IMV (%)Ω	DNAR (%)Ω	Max IPAP†
A	13.6 (2.0)	14.4 (8.7)	103.4 (49.4)	34 (12-99)	10.1 (2.7)	95 (59-135)	7.27 (7.22-7.30)	19.5 (15-23)	2.0	66.0	24 (22-26)
B	14.3 (2.0)	11.5 (5.5)	68.1 (37.7)	39 (15-128)	9.9 (2.6)	61 (35-81)	7.26 (7.21-7.29)	18 (16-22)	1.7	44.0	20 (15-22)
C	13.6 (2.2)	14.1 (7.3)	84.1 (46.0)	49 (24-120)	10.3 (2.2)	39 (17-89)	7.26 (7.19-7.29)	20 (18-23)	1.3	59.7	17 (14-20)
D	13.8 (2.2)	12.8 (6.4)	95.5 (75.9)	40 (13-103)	10.1 (3.5)	31 (18-67)	7.27 (7.21-7.29)	19 (16-22)	5.8	53.6	20 (16-22)
E	12.9 (2.3)	11.0 (4.1)	77.9 (33.1)	60 (17-144)	10.1 (2.6)	91 (51-123)	7.30 (7.23-7.32)	18 (14-20)	4.5	31.3	20 (16-22)
F	13.7 (2.1)	12.0 (4.9)	81.8 (45.8)	24 (9-91)	10.0 (2.4)	33 (12-72)	7.26 (7.22-7.29)	18.5 (14-22)	8.3	48.3	21 (17-27)
G	13.5 (2.0)	12.6 (4.9)	89.4 (50.1)	67 (12-116)	10.6 (2.2)	36 (15-99)	7.23 (7.17-7.27)	18 (16-23)	0.0	83.7	20 (16-20)
H	13.6 (2.0)	13.1 (5.2)	90.4 (43.1)	25 (9-67)	10.1 (2.5)	52 (24-132)	7.27 (7.20-7.30)	18 (14-21)	2.3	50.0	22 (17-27)
I	14.5 (2.2)	14.1 (7.3)	79.2 (31.0)	63 (17-136)	11.7 (3.3)	24 (12-123)	7.25 (7.17-7.27)	21 (18-24)	2.7	64.9	20 (20-25)
J	13.5 (2.2)	15.1 (5.6)	66.1 (30.1)	51 (17-154)	11.5 (3.2)	32 (9-94)	7.21 (7.16-7.29)	16 (14-23)	0.0	14.3	20 (14-20)
Total	13.7 (2.1)	13.1 (6.8)	87.2 (49.1)	40 (13-110)	10.2 (2.7)	65 (25-111)	7.26 (7.21-7.30)	19 (16-22)	2.9	55.3	20 (18-24)
P value	0.006	0.002	<0.0001	0.091	0.042	<0.0001	<0.0001	0.001	0.215	<0.0001	<0.0001

* Mean (SD), ANOVA † Median (IQR), Kruskal-Wallis Ω %, Fishers Exact test

9.4.1 Location of Ventilation by Site.

There was marked variation in the location within a hospital where ventilation was provided between sites. Most sites have a clear 'default' location where ventilation is provided representing the majority of cases in that particular site.

Figure 30 Highest level of care by site.



In all the description sections above further, more in-depth, analysis is interesting, warranted and will follow in a forthcoming thesis.

9.5 Examination of the Proposed Derivation Model.

9.5.1 Validation Multivariate Analysis Introduction.

The derivation study has selected the important, independent predictors of in hospital mortality and the appropriate categorisation thresholds. The validation study's principle role is to ensure this model was not overfitted to the population in which it was derived and is hence generalisable to a wider population.

The validation process included two important steps: whether to use pH or base excess in the final model; and whether the final model can be simplified or recalibrated in improve performance and utility. Regarding base excess, in the derivation population, it is a stronger

predictor than pH, but the change in ventilation guidelines that occurred after the derivation study completed recruitment may alter this (7.2.7).

Only variables included in the final NIVO model using the thresholds selected for that model were eligible for evaluation. It is important that the results are not a rederivation of a model in a second population.

9.5.2 Validation Step 1: pH vs BE.

As has been stated (7.2.7) there was suspicion that the inclusion of base excess was a result of overfitting (predominately temporally rather than geographically). The first simple step is to assess pH vs BE, naturally the 9 variables are categorised as determined by the derivation results.

Table 77 Components of predictive model from derivation results.

1	Base Excess <0
2	Atrial Fibrillation up to NIV
3	Consolidation on CXR up to NIV
4	Eosinophil count <0.05 $x10^9$/L in 24 hours prior to NIV
5	eMRCD (categorised 1-4,5a,5b)
6	GCS ≤14 24 hours prior to NIV
7	LTOT
8	pH <7.25 24 hours prior to NIV
9	Time to acidaemia >12 hours from admission

If all variables are forced into the model together, the relative strength of BE vs pH can be determined. In this instance: BE is a non-significant predictor p=0.620 in contrast to pH p=<0.001. Therefore, base excess will be replaced by pH in all subsequent models.

9.5.3 Validation step 2: Model Simplicity.

Predictive models are a balance of accuracy versus utility. In a non-automated setting, utility becomes akin to simplicity. If the number of variables in the model can be reduced while maintaining accuracy, then this is attractive to the end user. Again, it is important to stress that only those variables and categorisation thresholds determined by the derivation study should be assessed.

Therefore the 8 variables were re-examined using backward regression Table 78. Variables not imparting independent prediction to the model are removed using a significance level of 0.1.

Table 78 Results of backward, logistic regression using predictors from derivation less base excess.

Variable	B	S.E	Wald	Sig	Odds Ratio (95% CI)
Consolidation	0.358	0.210	2.9	0.089	1.43 (0.95-2.16)
GCS <15	0.658	0.217	9.2	0.002	1.93 (1.26-2.95)
AF	0.842	0.239	12.4	<0.001	2.32 (1.45-3.71)
pH <7.25	0.961	0.222	18.7	<0.001	2.61 (1.69-4.04)
Time to Acidaemia >12 hours	1.289	0.225	32.8	<0.001	3.63 (2.33-5.64)
eMRCD 5a	1.425	0.267	28.5	<0.001	4.16 (2.46-7.02)
eMRCD 5b	1.960	0.287	46.7	<0.001	7.10 (4.05-12.46)

Intercept -2.832, R^2 0.285, Percentage correct after final iteration, 81.9%. Hosmer and Lemeshow 0.130.

As can be seen two variables drop out of the model namely the eosinophil count and LTOT prescription. This model comprises 6 variables with the eMRCD categorised into 1-4, 5a and 5b. CXR consolidation is the weakest predictor with a significance level of 0.089. However, in order to make as few changes to the derived model as possible it is retained.

LTOT was one of the weakest predictors from the derivation. There are question marks about the suitability of the eosinophil count in this setting (7.2.5). The role of acute prescription of oral corticosteroid treatment influencing the eosinophil count renders this variable conceptually unreliable at the very least. Those deteriorating late into admission are likely to have greater exposure to steroid and also have worse outcome raising the prospect of a confounding element. There is no value in carrying forward non-significant variables, that they were originally significant is probably representative of overfitting to the derivation study. Therefore, the eosinophil count and LTOT will be dropped.

9.5.4 Validation Step 3: Weightings

It is accepted practice to re-examine weightings in a final model. Having decided to reduce the number of variables one must re-examine weightings as the relative weights necessarily alter.[261,262]

The same process as in the derivation model is followed whereby the beta co-efficient is divided by the lowest value to give easier to follow proportionality. In this case it is chest X-ray consolidation. The relative strength of the variables gives rise to a simple weighting system.

Table 79 Relative weightings.

Variable	B/1.43 (CXR B)	Wald	Weighting
Consolidation	1.0	2.9	1
GCS <15	1.4	9.2	1
AF	1.6	12.4	1
pH <7.25	1.8	18.7	1
Time to Acidaemia >12 hours	2.5	32.8	2
eMRCD 5a	2.9	28.5	2
eMRCD 5b	5.0	46.7	3

9.5.5 The NIVO Score.

The final model is shown here, it has been named the NIVO score for simplicity.

Table 80 The NIVO score

NIVO score	Points
Consolidation	1
GCS <15	1
AF	1
pH <7.25	1
Time to Acidaemia >12 hours	2
eMRCD 5a	2
eMRCD5b	3
	/9

Following validation steps 1-3 the validated model (NIVO score) is shown in Table 80. Six variables and a simple weighting system yield a maximum score of 9 (one can only score 5a or 5b not both).

9.6 Assessment of NIVO Score.

9.6.1 Mortality by NIVO Score.

The following table shows the mortality for each point of the NIVO score. There is a progressive increase in mortality as the score increases, except between 1 and 2 when the small absolute number of deaths results in a minor fall in mortality percentage. When converted to risk categories this is inconsequential.

Table 81 Mortality at each point of NIVO tool.

Tool Score	Survived	Died	Total	Mortality
0	67	0	67	0%
1	72	7	79	8.9%
2	126	7	133	5.3%
3	129	23	152	15.1%
4	94	22	116	19.0%
5	63	34	97	35.1%
6	25	29	54	53.7%
7	9	17	26	65.4%
8	1	7	8	87.5%
9	0	1	1	100%
Total	586	147	733	20.1%

Using data in Table 81 three risk categories (Table 82) have been assigned and identify clinically distinct groups, with nearly 40% falling into the low risk group. Mortality here is low (5.0%) and has potential clinical applications to including guiding level of care. As one may expect only very few patients fall into the very high-risk group and further verification of mortality in these small numbers is warranted.

Table 82 NIVO score risk categories.

Risk category (score)	Survived	Died	Total	Mortality
Low (0-2)	264	14	279	5.0%
Medium (3-4)	223	45	268	16.8%
High (5-6)	88	63	151	41.2%
Very High (7-9)	10	25	35	71.4%

Table 81 and Table 82 are important and encouraging assessments of the NIVO score. They show that the model provides robust risk stratification; a simple 6 variable tool identifies 4 groups of patients with clearly distinct mortality risks. If the results showed non-progressive mortality the validity would be called into question, however, across different sites, models of care and demographics the findings are encouraging.

The predicted mortality is the averaged mortality for all patients at a site calculated from their NIVO scores and associated mortality. The total predicted, and actual mortality shown in Table 83 must be identical as the mortality for each increment generated from the same data and therefore the totals must necessarily equate.

Table 83 Mortality by recruiting site: Predicted vs actual.

Site	n	Score	Predicted mortality (%)	Actual Mortality (%)
A	200	3 (2-5)	21.4	18.0
B	116	3 (2-5)	19.1	19.8
C	77	3 (2-4)	20.4	19.5
D	69	3 (2-5)	21.9	26.1
E	67	3 (2-5)	21.9	28.4
F	60	3 (1-3)	15.6	18.3
G	49	3 (2-5)	20.0	12.2
H	44	3 (2-4)	19.1	25.0
I	37	3 (2.5-4.5)	19.5	13.5
J	14	2 (1-4)	13.6	21.4
Total	733	3 (2-5)	20.1	20.1

The breakdown across the sites is interesting: One would not expect to see a perfect spread as numbers in each site are not large enough for this but there is clearly a correlation between actual and predicted mortality, the correlation is better in the centres with greater numbers. The 'unique patient effect' described earlier (9.3.4) may also be having differential contribution due to varying n at each site.

Table 84 Components of NIVO score by recruiting site.

	Percentage in which adverse indicator present.						
Site	**CXR**	**GCS**	**AF**	**pH**	**Time**	**5a**	**5b**
A	41.5	38.0	21.0	34.0	25.0	38.0	22.0
B	31.9	32.8	13.8	43.1	24.1	40.5	19.0
C	24.7	39.0	22.1	40.3	26.0	37.7	24.7
D	39.1	27.3	18.8	37.7	39.1	26.1	21.7
E	41.8	28.4	22.4	28.4	26.9	35.8	29.9
F	31.7	28.3	11.7	38.3	18.3	30.0	18.3
G	40.8	46.9	30.6	59.2	24.5	24.5	18.4
H	56.8	27.3	20.9	38.6	27.3	27.3	18.2
I	45.9	32.4	18.9	45.9	13.5	32.4	32.4
J	28.6	50.0	14.3	71.4	14.3	21.4	0.0
Total	38.1	36.2	19.5	38.6	25.2	24.5	18.8

For each of the components of the NIVO score there is variation within sites. This will partly be due to numbers at each site however variation is good and will enhance generalisability. The fact that patients are accruing their total score via varying components and the score performs well is in itself encouraging.

9.6.2 Model fit.

The results for the final model are shown under Table 78. The model is well calibrated (Hosmer and Lemeshow test = 0.130) and Nagelkerke R squared shows the model accounts for 28.5% of outcome variable variance.

9.6.3 Area under the receiver operated curve.

Figure 31 shows the plots of the receiver operated curves for the NIVO score and its comparators. Table 85 shows the absolute values and the confidence intervals.

Figure 31 Areas under the receiver operated curve for various models of in-hospital mortality prediction.

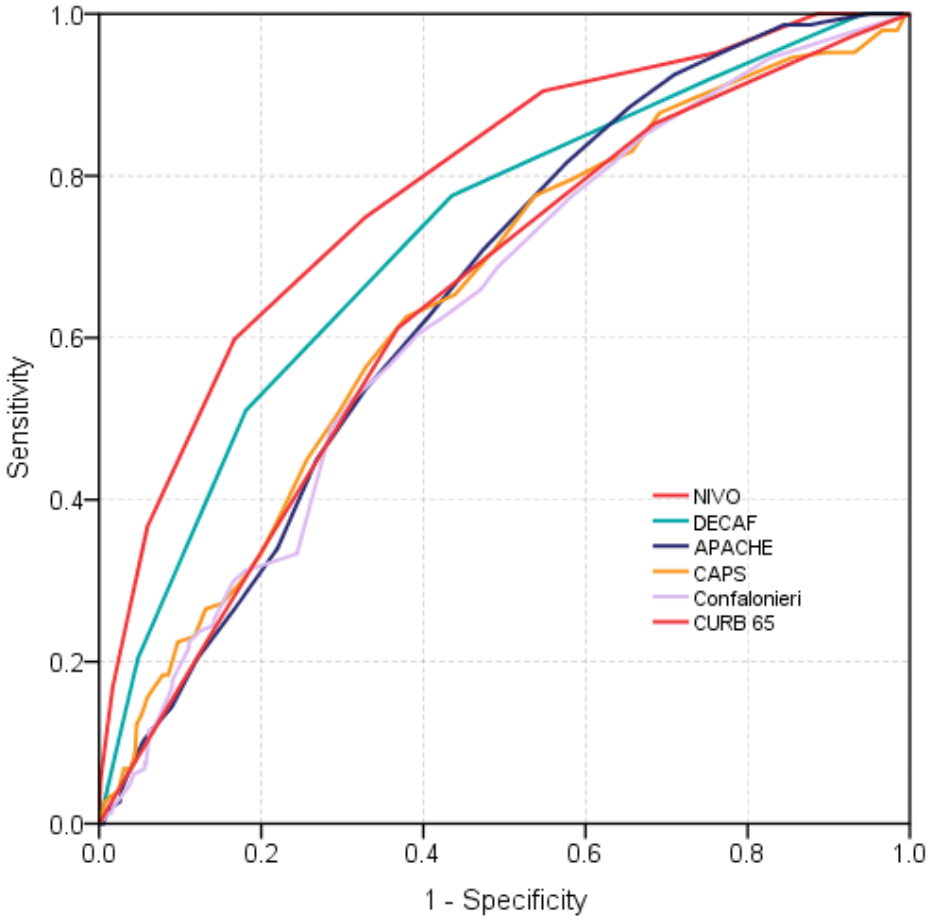


Table 85 AUROC and confidence intervals for predictive models.

Model	AUROC (95%CI)
NIVO score	0.79 (0.75-0.83)
DECAF score (in 24 hours pre vent)	0.73 (0.68-0.77)
APACHE II score	0.66 (0.61-0.70)
CAPS score	0.65 (0.60-0.70)
Confalonieri score	0.64 (0.59-0.68)
CURB 65 (in 24 hours pre vent)	0.64 (0.59-0.69)

Using only 6 variables, 5 of which are binary, and one has 3 categories the NIVO score outperforms comparators in this independent population. Three of the scores (APACHE II, CAPS and Confalonieri) are complicated to administer. The closest performing score is the DECAF which score was designed for use on admission in patients with an exacerbation of COPD, here it has been scored in the 24 hours prior to deterioration. It is the only

comparator to include an assessment of steady state dyspnoea which is likely to account for its superior performance. The other 'simple' score here is CURB 65 which was never designed for use in this population but is included as a useful comparison and is inferior to the NIVO score.

Of note if, instead of using the simple categories the 6 variables are entered as continuous variables the AUROC is minimally increased to 0.80 (7.6-8.4). The NIVO score also works well in the derivation population using the ascribed weighting, AUROC 0.83 (0.79-87).

9.7 Rule of Thumb.

The combination of deterioration after a 12-48 hour threshold and a high eMRCD score conferred a high in-hospital and 90 day mortality in the derivation study. Using these very simple indices shows promise again. In-hospital mortality data only is available for the validation study. Table 23 shows mortality for differing combinations of (e)MRCD and time from admission to acidaemia.

MRCD 5 is the combination of eMRCD 5a and 5b. The added mortality risk conferred by eMRCD 5b is less dramatic than in the derivation data (1337.4.2). While there is a rise in the mortality at each threshold by selecting only those with eMRCD 5b as opposed to the combined 5a and 5b it leads to fewer deaths being captured. This table again illustrates that selecting those with high mortality is possible using only limited and simple indices. Half, rising to two thirds, of patients will not survive to discharge depending on how steady state dyspnoea and time to deterioration are combined.

Table 86 Rules of thumb: Mortality by steady state dyspnoea and timing of acidaemia.

Rule of thumb	VALIDATION In-hospital mortality	DERIVATION In-hospital mortality
MRCD 5 + 12 hours	50/101 (54.6%)	46/77 (59.7%)
eMRCD 5b + 12 hours	21/38 (55.3%)	26/36 (72%)
MRCD 5 + 48 hours	30/45 (60.8%)	27/40 (67.5%)
eMRCD 5b + 48 hours	14/21 (66.7%)	18/23 (78.3%)

9.8 Validation Results Summary.

The research team collected a large volume of data in 733 patients across 10 hospital trusts. These trusts are disparately spread and draining differing populations and using differing models of care. However, distribution by ethnicity was low with the population being overwhelmingly Caucasian. Predictors of outcome identified by the derivation project have been proven to be robust predictors of outcome in a separate population of prospectively collected patients. The hypothesis that base excess may have been overfitted to the derivation population at the expense of pH was proven correct and there is sound logic and clinical intuition to support this. Thereafter, we were able to remove two variables from the score that were probably overfitted to the derivation population. Models can be 're-calibrated' by addition of new variables but this would probably warrant re-validation. Removal of variables is uncontentious but there are no clear guidelines as to what to do following this and whether further validation is needed is context specific. In this instance it is reasonable to assume re-validation is unnecessary.[261,262]

The final model is simple, effective and produces clinically meaningful risk categories. Rules of thumb employing time of deterioration and steady state dyspnoea alone again select patients with high in-hospital mortality.

Chapter 10. Discussion

10.1 Summary of main findings

10.1.1 Derivation study summary.

489 retrospective patient records were included following robust identification of consecutive patients. All patients came from the same centre in the North East of England. Modelling using structured and established methodology (5.4) and guided by reported evidence and clinical intuition allowed identification of a number of variables independently associated with mortality. The final variables selected for further study were atrial fibrillation, chest X-ray consolidation, Eosinophil count, eMRCD score, Glasgow coma scale, long term oxygen prescription, timing of acidaemia relative to admission time, base excess and pH. A simple model using these variables outperformed any previously reported model (in this dataset) substantially. Using data from the time of deterioration clearly outperformed using only information available at admission. Several 'rules of thumb' also help to identify risk of in-hospital death using only two variables.

10.1.2 Validation study summary.

Patients were recruited prospectively in ten UK centres. Inclusion criteria were subtly altered to reflect change in national guidance. Data collected was more focussed than during the derivation study. Further analysis of this data will form a further thesis, so analysis has been limited to validation of a model and key descriptors to allow assessment of generalisability.

Of the candidate variables not all remained significant indicating overfitting to source data in the derivation cohort so two were dropped from the model. The presence of eosinopenia and prescription of long-term oxygen were the removed variables. A simplified model outperformed all pre-specified comparison models in both derivation and validation cohorts and is shown below. Stratification using this score allows creation of 4 clinically meaningful risk categories showing progressive mortality from low (5.0% in hospital mortality) up to very high (71.4% in hospital mortality).

Table 87 The NIVO score.

NIVO score	Points
Consolidation	1
GCS <15	1
AF	1
pH <7.25	1
Time to Acidaemia >12 hours	2
eMRCD 5a	2
eMRCD5b	3
	/9

10.2 Potential uses of NIVO tool.

Most of the ideas here have been previously mooted but in this section they have been expanded and linked directly to the results of the study.

1) Shared decision making. During a period of critical illness close communication between clinical team and a patient and their family is essential. Being able to offer factual expectations rather than unverified estimation is desirable and in keeping with the empirical basis on which modern medicine is built. For example, if a patient falls into the high risk group (49% in hospital mortality) they may be more motivated to persevere with NIV knowing the threat to life or a family member may feel better able to judge whether to travel to visit.
2) Enhanced decision making, particularly reducing inappropriate pessimism. For example, it could be argued if a patient is admitted and falls into a medium risk (mortality 18.2%) category there is almost no reason not to offer ventilation unless a highly individual counter reason exists. This objectification could prevent delay and denial of treatment. Given clinicians inherent cognitive biases and fallacies (3.1.3), objectification of decision making can lead to a a more equitable distribution of finite healthcare. In the small number of very high-risk patients (in-hospital mortality 88.9%), knowledge of the chances of a favourable outcome may open discussions about alternative palliative care.
3) Guiding level of care. As has been shown (2.4.4) limited access to higher level of care beds exists and anecdotally even where provision is good demand can exceed supply

in busy periods. Targeting enhanced staffing and monitoring to those in high or very high-risk groups (41.2% or 71.4% in hospital mortality) may help to bring overall mortality down. This also has benefit which is very hard to measure such as relieving pressure on out of hours staff by placing high acuity patients appropriately. Whilst it can be argued that all patients requiring NIV should be cared for in areas with enhanced staffing (RSU, for example), this may not be practicable in many hospitals. The NIVO tool could be used to identify low risk patients who can be more safely cared for in a ward based setting. Furthermore, considerable emphasis is quite correctly placed upon proactive escalation planning ideally in consultation with patient and family. Empirical data can only enhance this process.

4) Identification of outlying trusts. It is likely that with increasing digitisation of patient records occurs scrutiny of outcomes will become easier and more frequent. Objectification of expected vs actual outcome allows for targeted improvements.

10.3 Further Questions the NIVO Study Will Address.

This thesis is not the complete evaluation of a vast amount of data. The further analysis of the validation study results is ongoing and will form a separate thesis. Remaining questions we hope to address include but are not limited to:

- More in-depth assessment of in hospital data beyond validation of the predictive model.
- Validation of post discharge survival findings with reference to identification of high-risk patients to consider enhanced palliative care.
- Multi-centre evaluation of patients experiencing late failure of NIV.
- Evaluation of longitudinal quality of life and patient attitudes to assisted ventilation.
- One-year outcomes in specified subgroups including HMV.

10.4 Strengths and weaknesses of the study.

10.4.1 Strengths

We were able to learn from previous similar studies. We deliberately narrowed our focus of attention to COPD rather than all situations where NIV may be used. This is because the conditions are heterogenous, mortality (and therefore frequency of outcome events) varies

and most crucially while some factors associated with mortality may be shared others are likely to be disease specific. Making this methodological decision and determining a dataset prior to data collection based upon previous literature and expert opinion maximised the chance of successfully answering a well-defined research question.

This study is the largest that we know of to attempt to derive and prospectively validate a predictive model in this population. Other large studies have used existing datasets or coding data to derive predictive models, but this approach severely limits the potential indices available for analysis and there are concerns regarding the diagnostic accuracy of coding records.[263] The derivation study was a single site and included 489 patients; the validation project included 10 sites and recruited 733 patients. Overall 1222 patients were included across both arms. The wide geographical spread of a large number of recruiting centres representing urban and rural areas and both large and small hospitals is a strength.

This study's methodology is also relatively rare within the reported literature addressing similar questions. We observed good research practice: Public and patient opinion was sought in trial design, our protocols including defined outcomes and analysis plan were publicly available ahead of recruitment opening, research governance best practice as mandated by regulatory bodies was observed. Regular trial steering committee meetings took place with an independent chair and data verification has been extensive.

As illustrated in the introduction many studies have been published identifying univariate associations with mortality or derived models that have no or weak validation. Recommendations are clear that there is no substitute for validation of findings in a second dataset. This study achieves the gold standard of validation; our validation dataset is both temporally and geographically separate to the derivation dataset. The findings are upheld in the validation study which adds plausibility that the predictors of mortality are true and not the product of chance. The fact that we are presenting a fully derived and validated model based on a pre-determined analysis plan is clearly a strength of this work.

The data we have collected is generalisable to real world practice. This population was ventilated predominately on a ward or in an RSU within a ward. This is a strength as ICU populations are inherently not the same as the population seen outside of the ICU. As discussed previously (3.3.1), much of the previous data has stemmed from ICU populations. There is, however, no acid test of generalisability, one must to a degree rely on anecdote. A

criticism oft levelled at randomised controlled trials is that the population studied is not the same as the one seen in day to day clinical practice. For the results of our study to have any utility it was essential that the population was generalisable. The methodology was designed in such a way to maximise this and few selection criteria were imposed. Similarly, both cohorts represent consecutive patients. Patients are not missed at random, those that are admitted to particular parts of a hospital, at particular times of day or those who die very soon after admission may be more likely to be missed. Unless all patients are captured generalisability will be compromised.

We acknowledge that certain methodological decisions are open to debate, for example the decision to use a conventional 70% cut off in FEV_1/(F)VC rather than the perhaps more nuanced lower limit of normal model. Given the accepted heterogeneity in COPD we did not want to over define our population and hence limit modelling to a limited cohort of those that receive ventilation under the umbrella of COPD.

In late failure of NIV we have defined a clear cohort of patients who have been recognised in the past as having very high mortality. Our pilot data challenged this which has been substantiated by the derivation study, the validation study will further explore this subgroup. With further verification one would hope guidance may shift more definitively in this group toward continuing NIV.

Prior to outset the two variables we were most interested in were the steady state dyspnoea as measured by the eMRCD and the timing of acidaemia. While both have an intuitive basis, the supporting evidence is of variable quality. If nothing else, from this work, the evidence that these two variables are strongly linked to in-hospital mortality has been furthered.

The predictive model we have generated is a robust predictor of outcome. It would be expected to outperform comparison scores in its derivation population. However, in the validation population the only comparison score approaching similar performance is the DECAF score which shares a number of components and was created by the same research group. Not only is the score a good predictor of outcome but the score stratifies patients into clinically meaningful risk groups which have implications for clinical practice. It is also far simpler to administer than particularly the Confalonieri, APACHE II or the CAPS score which was a desire from the outset.

10.4.2 Weaknesses

One of the main reasons why we thought this study necessary is the underuse of ventilation nationally amongst patients experiencing an exacerbation of COPD who meet ventilation criteria. This in itself presents a challenge for study design. To accurately identify the predictors of outcome it is essential that systematic biases are not included. For example, older patients may be disproportionately less likely to receive ventilation. Those over a given age threshold that are ventilated inherently then become a selected group which may impact upon whether or not that variable is significant or not. We were confident in our own ventilation practices for the derivation study with a well-resourced and established service. We could however only mitigate this potential bias rather than eliminate it. We selected sites with well set up, streamlined ventilation services and assessed their audit data for signs of selection bias. As previously described no absolute criteria were imposed. Overall, the risk that the validation study collected a biased cohort is real but cannot be quantified and efforts were made to mitigate this risk.

The second and linked weakness is another direct consequence of study design, albeit a conscious decision. As described, we view the attempt to capture a readily generalisable population as a strength of the study. In order to achieve this, it was essential that the validation data did not require individual patient consent which would have meant that the most unwell patients or those unable to consent would not be included. The absence of consent does mean that the intervention under study is not controlled (although all sites follow the same national guidelines). To consider this absence of a controlled intervention three influences are important: 1) that the condition (RA in ECOPD) confers a high mortality, 2) that the intervention is highly effective at reducing mortality but delivery of the intervention requires coordination of complex human and system factors and 3) that the results really pertain to outcome event i.e. deaths. The ideal scenario is one where all sites delivered an identical intervention and no consent is required however this is not achievable. Therefore, it must be borne in mind that the outcome events may in part be related to variation in practice both within and between sites.

Having decided to study COPD alone the next question was how to define it. It is, as described in the introduction, a heterogeneous condition. There are varying opinions as to how best to impose spirometry criteria to diagnosis of COPD. In using a FEV_1/(F)VC ratio of <0.7 we acknowledge that there are patients some would consider as having COPD that we

excluded. This may be particularly pertinent to the group with emphysema but without significant airflow obstruction. All these patients whom the primary investigator thought to have IECOPD as their primary reason for RA are captured as 'clinical diagnoses' and will be analysed in the next thesis from the group. These patients were also allowed in if they had confirmation of airflow obstruction prior to any subsequent admissions meeting other selection criteria.

This population, while readily generalisable to the UK is the product of UK systems of care and ventilation practices. Individual overseas hospitals or countries may compare favourably but others particularly a US model of care may be very different and hence results may be less generalisable. One variable that may hinder international comparison is probably the frequency of IMV both as an index and rescue treatment which in this study was low in keeping with UK practice.

The recommendations for data-handing from an influential group in prognostic modelling are explicit and contrary to our approach, they favour retaining continuous variables rather than dichotomisation or categorisation.[251] It is intuitive that the greater the number of divisions in a particular continuous variable the closer it remains to the original variable. Deciles have been proposed as acceptable. The purest form is to use the formula for the line of best fit. However, whilst this will offer better prognostication when the change in risk is linear across the range encountered, this is often not the case. If the distribution of risk is highly skewed (e.g. eosinopenia in DECAF), dichotomisation may offer similar performance. Furthermore, methods that require computation will dramatically reduce potential utility outside of automated systems. We decided to adopt an approach of dichotomising continuous variables to achieve maximum simplicity. One can contend that the recommendations are fit for only certain types of prognostic model. The final NIVO model only includes one variable that could be considered continuous, the GCS however both it and the eMRCD could also be argued to be categorical. Truly continuous variables such as serum creatinine or age are not included. Nevertheless, the handling of continuous variables in our study is at odds to some recommendations although, is in line with previous prognostic research, is an acceptable method of creating simple tools and again, this was a conscious decision. We assessed the impact of this approach; it was minimal (NIVO AUROC = 0.79, NIVO continuous AUROC = 0.80).

The fact that the originally derived model was not the best final model in the validation dataset could be a weakness. There are no rules as to how this situation should be handled. We could have carried an unmodified model to final validation however this seemed counter-intuitive as it meant carrying additional variables and hence complexity for no additional prognostic value. We do not feel that this significantly detracts from the final validation as only those variables in their final format were considered for inclusion and hence this is clearly not a re-derivation.

Some analyses in the derivation section of the results have not yet been repeated in the validation section and are allocated to the next wave of analysis. Drawing firm conclusions from the derivation dataset alone is premature with a larger, more up to date, multicentre sample available to verify or refute findings. Therefore, final judgement should be reserved for the time being an example is the post discharge model to predict 6 month mortality. Similarly, with the exception of late failure, our prespecified subgroups yielded disappointingly incomplete data. The uncontrolled nature of the study means that while we specified these groups a priori we could not mandate the data would be present to analyse. It transpired that rates of HMV were very low and pre discharge blood tests and arterial blood gases are rather sporadically collected rendering study difficult. These problems may be replicated in the validation study.

10.5 Response to NCEPOD and national quality standard recommendations

The previous results in this field have been extensively reviewed previously and found to be somewhat lacking. The results clearly outline the performance of the NIVO tool in comparison to other tools; it markedly outperforms them. The NIVO study was grounded upon observations of poor care that have been soundly echoed by influential bodies recently and hence this section is included as a response to these calls rather than the published work.

During the time this study has been conceived and executed a major report into NIV provision in the UK has been published. This study has been referenced numerous times from the introduction onwards. Many of the concerns that led to this study were raised by the report and not to specifically reference its findings would be an oversight. The

importance of NCEPOD reports in driving change in NHS practice is considerable with the scope widening from their initial inception in the 1980s as reviews of surgical deaths. 21 specific recommendations were made including that national quality standards (now published) be developed.

Broadly the NCEPOD report and the quality standards recognise that NIV care has been poor and provide a road map to national improvement. The recommendations and quality standards attempt to ensure that respiratory acidaemia is seen as the medical emergency it is and that hospitals and trusts are adequately placed to respond. Attention is specifically paid to not missing those who could benefit, and that care is delivered and overseen by appropriately trained staff.

We feel that the aims and results of this study are aligned with national priorities in the field of ventilation and have a role in addressing the recommendations. Of the 21 NCEPOD recommendations all are relevant to this study in some way, several have been specifically selected.

Recommendation 7: *"All hospitals where acute NIV is provided must have an operational policy that includes, but us not limited to: a) appropriate clinical areas where acute NIV can be provided, and in those areas the minimum safe level of staff competencies; b) staff to acute NIV patient ratios, c) escalation of treatment and step down care procedures; d) standardised documentation; e) minimum frequency of clinical review and seniority of reviewing clinician."*

Recommendation 9: *"All patients treated with acute NIV must have a treatment escalation plan in place prior to starting treatment. This should be considered part of the prescription for acute NIV and include plans in relation to: a) escalation to critical care; appropriateness of invasive ventilation; c) ceilings of treatment. This should take into account d) the underlying diagnosis; the risk of acute NIV failure and the overall management plan"*

Recommendation 19: *"All acute NIV services should be audited annually. These results should be reported to the hospital board."*

Recommendation 20: *"All hospitals should monitor their acute NIV mortality rate and quality of care. This should be reported at board level."*

The final concluding paragraph reads: *NCEPOD strongly encourages the establishment of quality improvement work both locally and nationally to target the issues identified by this study… Effective quality improvement initiative and their results should be shared locally and nationally wherever possible. NCEPOD would support dissemination of this work at future report launches and NCEPOD newsletters.*

In response to these recommendations this body of work and the NIVO tool may directly have a role to play. The NIVO tool could specifically be used to aid compliance with recommendations 7,9,19 and 20.

10.6 Suggestions for future research.

While we hope this work provides a solid evidence base to support the use of the NIVO model to guide clinical decision making in this precise population several questions arise from the project. Further validation in other countries which may have differing structures of care or populations would be desirable if the NIVO score were being considered outside of the NHS.

The UK COPD audit provides an excellent basis by which a larger population could be assessed to further verify this model. The caveat being that within a research project we have the additional capacity to gather data robustly on consecutive admissions as described and were able to mitigate the effect of selection bias.

Several questions raised in the derivation study will be answered at least in part by the validation study as the large volume of data is analysed. Subgroups were explored and indeed the next thesis from the research group will address some of these questions. Of particular interest are the validated findings within the late failure of ventilation. The derivation data suggests as we hypothesised supported by pilot data that mortality with continued, optimised NIV is far lower as prior evidence had suggested.

With the increasing role of HMV in the population of patients with COPD there is cause to believe that there may be ‘a shifting of the goalposts.’ Hypothetically this could occur by altering those surviving to discharge by preventing aggressive weaning amongst those with persistent hypercapnia. The demographic of admitted patients may also shift if those most

'brittle' who historically required ventilation following minor triggers less frequently require a discrete episode of ventilation as they are adequately treated at home. Conceptually it may be the case that markers of severity of acute insult become more important at the expense of markers of disease severity in this case. Re-validation of the findings in a population adequately powered to investigate HMV may be necessary if national rates of HMV do alter significantly.

Chapter 11. Conclusions.

There is an underuse of assisted ventilation in exacerbations of COPD. The reasons for this are varied but are likely to include both systematic/infrastructure factors and human factors related to decision making. No previous work in this field has produced any prognostic model that has to our knowledge passed into routine clinical use in the UK.

This study has derived and validated a predictive model to determine the risk of in-hospital death in exacerbations of COPD complicated by respiratory acidaemia requiring assisted ventilation. The model outperforms other tools which may be used in this setting.

The study design was robust and the extensive validation in a highly generalisable population allows this, if desired, to pass directly into clinical usage.

Chapter 12. Appendices

12.1 A, Glossary of Abbreviations.

6MWT	6 Minute Walk Test
ACE (inhibitor)	Angiotensin Converting Enzyme (inhibitor)
AF	Atrial Fibrillation
AHRF	Acute Hypercapnic Respiratory Failure
ALS	Amyotrophic Lateral Sclerosis
APACHE	Acute Physiology and Chronic Health Evaluation
ASMR	Age Standardised Mortality Rate
AUROC	Area Under the Receiver Operated Curve
BMI	Body Mass Index
BP	Blood Pressure
BPH	Benign Prostatic Hypertrophy
BTS	British Thoracic Society
BUR	Back Up Rate
CAD	Coronary Artery Disease
CAOS	COPD and Asthma Outcomes Study
CAP	Community Acquired Pneumonia
CAPS	COPD and Asthma Physiology Score
CHF	Congestive Heart Failure
Cm	Centimetre
CO_2	Carbon Dioxide
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airways Pressure
CRF	Chronic Renal Failure
CRP	C-Reactive Protein
CT	Computerised Tomography
CVA	Cerebrovascular Accident
CWD	Chest Wall Deformity
CXR	Chest X-Ray
DECAF	Dyspnoea, Eosinopenia, Consolidation, Acidaemia, Fibrillation (score)
DJD	Degenerative Joint Disease
DPT	Dual Process Theory
ECOPD	Exacerbation of Chronic Obstructive Pulmonary Disease
eMRCD	Extended Medical Research Council Dyspnoea (scale)
EPAP	Expiratory Positive Airway Pressure
FBC	Full Blood Count
FEV_1	Forced Expiratory Volume in one second

FVC	Forced Vital Capacity
GERD	Gastroeosphageal Reflux Disease
GCS	Glasgow Coma Scale
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HDU	High dependency Unit
HMV	Home Mechanical Ventilation
HR	Heart Rate
ICU	Intensive Care Unit
ICS	Inhaled Corticosteroid
IHD	Ischaemic Heart Disease
IMV	Invasive Mechanical Ventilation
IPAP	Inspiratory Positive Airway Pressure
LABA	Long Acting Beta Agonist
LAMA	Long Acting Muscarinic Agonist
LF	Late Failure
LOS	Length Of Stay
LTOT	Long Term Oxygen Therapy
MI	Myocardial Infarction
MRCD	Medical Research Council Dyspnoea (scale)
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
NCSLC	Non-small Cell Lung Cancer
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIV	Non-invasive Ventilation
NIVO	Non-invasive Ventilation Outcomes (study)
NMD	Neuromuscular Disease
NNT	Number Needed to Treat
OHS	Obesity Hypoventilation Syndrome
OSA	Obstructive Sleep Apnoea
PAD	Peripheral Artery Disease
PAF	Paroxysmal Atrial Fibrillation
PCS	Palliative Care Support
pECOPD	Pneumonic Exacerbation of Chronic Obstructive Pulmonary Disease
PEEP	Positive End Expiratory Pressure
$_pO_2$	Partial Pressure of Oxygen
RA	Respiratory Acidaemia
RCP	Royal College of Physicians
RCT	Randomised Controlled Trial
RR	Respiratory Rate
RSU	Respiratory Support Unit
SAPS	Simplified Acute Physiology Score

TNFα	Tissue Necrosis Factor alpha
U+E	Urea and Electrolytes(s)
UK	United Kingdom
USA	United States of America
VC	Vital Capacity
VIF	Variance Inflation Factor
V/Q	Ventilation/Perfusion
WCC	White Cell Count

12.2 B, Validation Study CRF

NIVO Study. Validation CRF v1.5 Northumbria Healthcare NHS NHS Foundation Trust

Name: NHS number: Hospital number:

✂----------

Admitting Hospital: M F

Ethnicity: DOB: PATIENT ID:_____

Inclusion Criteria: Primary diagnosis AECOPD: ☐ Respiratory Acidaemia (pH <7.35, CO2 ≥6.5) treated NIV or IMV: ☐

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: Admission to Ward Date: Senior RV date:

Arrival A&E Time: Admission to Ward Time: Senior RV 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 ____ IHD ☐ CVD ☐

Cognitive impairment ☐ Cor Pulmonale ☐ Depression ☐

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 ☐

Height: (m) Weight (kg) (BMI:)

CXR Consolidation on admission ☐ CXR Consolidation at ventilation ☐

Diaphragm height: (cm) LTOT on admission ☐

Medication	Admission	Discharge
Long term Steroid		xxx
Diuretic		
Beta Blocker		
ACE/ARB		
Statin		
LABA		
LAMA		
ICS		
Carbocisteine		
Azithromycin		
Theophylline		

Previous episode of NIV prior to this admission? Yes No

Date first episode of NIV _____ Total episodes in last year

Home NIV (HMV) admission ☐ Home NIV (HMV) discharge ☐

Resolved acidaemia pre NIV? ☐ Date resolved acidaemia _____

Ventilation initiated: Date Time

Ventilation discontinued: Date Time

pH Correction: Date Time

	IPAP	EPAP	BUR
1 hour			
Max			

Reason for cessation: Weaned ☐ Poor tolerance ☐ Palliative care initiated ☐

Died receiving ventilation ☐ Other ☐ (specify)

At time ventilation initiated was patient:

For intubation ☐ For Resuscitation ☐

Highest Level of care received:

Ward ☐ RSU ☐ HDU ☐ ICU ☐

Patient invasively ventilated? ☐

If yes: NIV pre ☐ NIV post ☐

Duration invasively ventilated: (days)

✂----------

4hr/Ventilation: BP: HR: RR: Temp: GCS: Sats/FIO2*:

24hr pre Vent: BP: HR: RR: Temp: GCS: Sats/FIO2*:

If ventilation is initiated within the first 4 hours leave second row blank and tick this box ☐

Record Flo2 as RA (room air), V (Venturi) + the % or Un (uncontrolled) and the flow rate in litres.

Confusion 4 hr/NIV ☐

Confusion 24hr pre NIV ☐

ABGs	Admission	1st acidaemia	NIV decision	24Hr Post	Steady
Date/Time					
FiO2*					
pH					
PCO2					
PO2					
BE					
Bicarb					
Art/Venous					
tcCO2 (if applic)					

Record pH correction!

BLOODS	Admission	NIV Decision	Discharge
Na			
K			
Urea			
Creatinine			
Creat Base		xxx	xxx
Albumin			
Bilirubin			
CRP			
Glucose/BM			
Hb			
Platelets			
Hct			
WCC			
Eosinophils			
	xxx	same as adm ☐	xxx

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

Has HMV been commenced at or within one year of discharge? Yes ☐ No ☐

If Yes, Date_____

Reason *(tick all that apply)*
Recurrent admission requiring NIV ☐
Symptomatic Hypercapnia ☐
To facilitate LTOT in CO2 retainer ☐
HOT-HMV criteria ☐
Other (Specify in comments) ☐

Readmissions up to 1 year

Adm Date	Dsc Date	R/O	NIV?	Diagnosis

LF/R: Does this patient experience Late failure or Relapse? If so please check box and complete CRF. ☐

Longitudinal study status:

Eligible and participating ☐ Eligible but declined ☐

Ineligible ☐ Reason Ineligible*

Comments

12.3 C, Validation Trial Manual.

In order to embed this guidance here the formatting from originally distributed document has been changed but content identical. Original document available upon request. It should also be noted that a number of aspects within this manual are not relevant to this thesis but are included so as faithfully replicate the information presented to external sites. Of note this was presented with a PowerPoint presentation and discussion during a face to face site initiation visit.

Introduction:

Welcome to the NIVO Study. We are excited to work with a group of progressive hospitals and research departments to deliver what we hope will be practice changing results.

This manual will explain the principle aims of the study, itemise documents, guide information flow, give data collection guidance and provide useful information. Any oversights you identify or additional information you think would be useful for inclusion please let us know.

Study Overview

We have developed a clinical tool to predict in-hospital mortality in patients with an exacerbation of COPD who experience respiratory academia requiring ventilation. Following on from this, the current study has two distinct but closely related components, the understanding of which is essential (see flow diagram overleaf).

The first component of the study will 'validate' this prognostic tool in a separate, geographically and demographically diverse group of patients to check whether the prediction model remains sound. This component of the study is termed the validation study and is NON-CONSENTING. It is akin to a national audit where routinely available data is collected from the patients' records and notes by the usual care team (this includes a wide range of personnel). Within this data are all the indices we require to validate our tool, and to compare performance to alternative tools. This is principally a study of patients receiving NIV and a much smaller number of patients who receive invasive mechanical ventilation (IMV) (either initially, or following a trial of NIV). Separately, in patients with a clinical

diagnosis of COPD but without spirometric confirmation we will capture a minimum dataset, provided all other selection criteria are met. This is because our prognostic tool is likely to be used in this population, if shown to be a robust predictor of outcome.

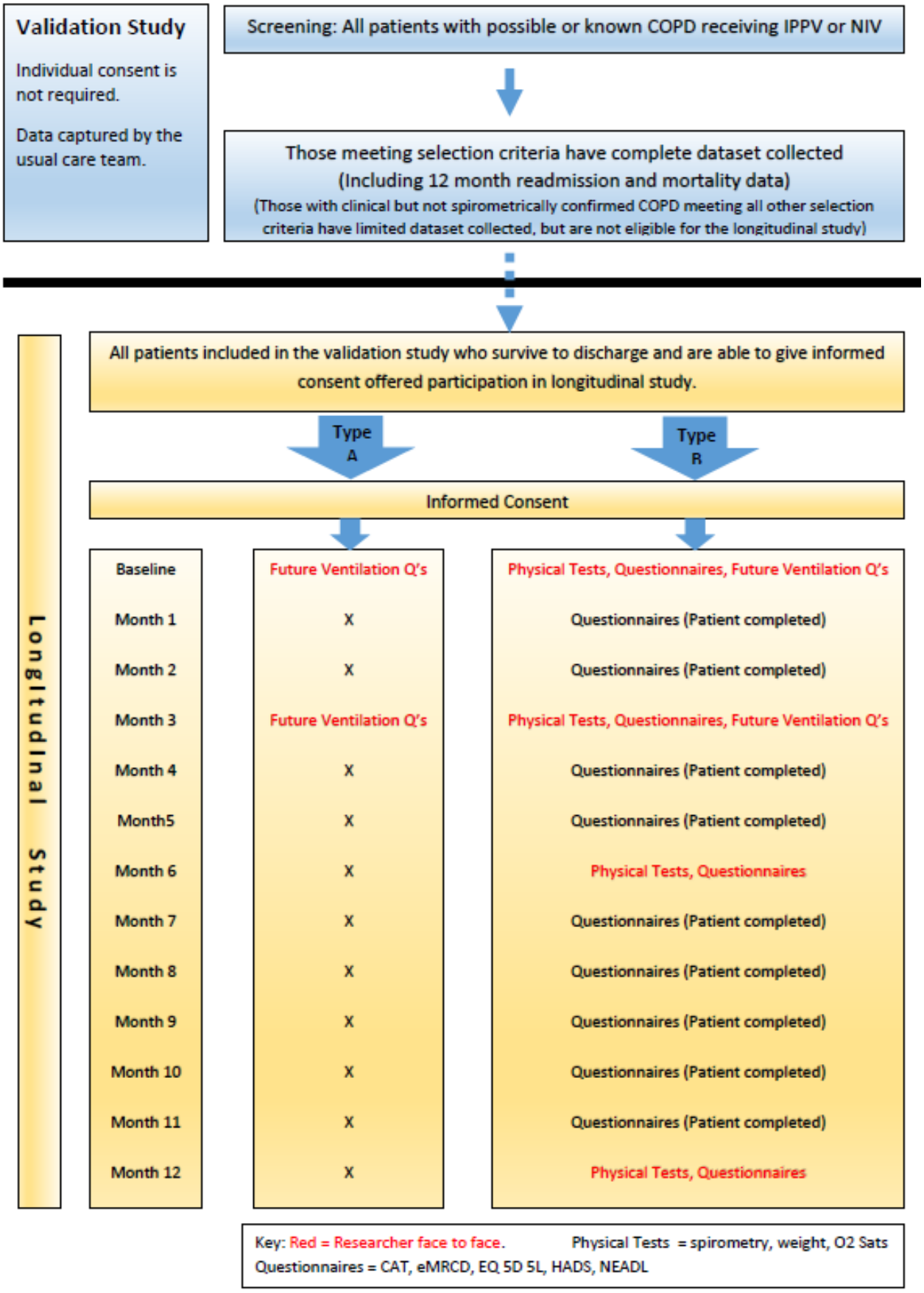
The second component of the study involves the longitudinal follow up of patients from the validation study who survive to discharge over one year and will assess their quality of life, functional status, levels of anxiety and depression, their attitude to future ventilation and some basic physical measurements. This component of the study is termed the Longitudinal study and will require INDIVIDUAL PATIENT CONSENT. Patients without spirometric confirmation of COPD (see above) will not be eligible.

Lastly, it is important to note that there are two 2 site types within the longitudinal study (a and b) and the distinction will outline the scope of data collection required in the longitudinal study. Your site will be fixed from the start and the majority will be type b sites.

Ethical and HRA Approval

The Study has been reviewed by: North East - Tyne & Wear South Research Ethics Committee with a favourable opinion granted, Ref: 16/NE/0213, IRAS ID 206694. HRA approval is in place.

NIV OUTCOMES STUDY, Participant Schedule by Site Overview. V1.0 10/5/16



Documents

Document	Version	Notes
NIV Outcomes study	2.4	Full study protocol.
Validation CRF	1.4	CRF for use in all patients meeting inclusion criteria.
NIVO study manual	1.4	This document
Clinical Diagnosis CRF	1.1	Limited data capture CRF for use in patients with a clinical diagnosis of COPD, but without previous confirmation of obstructive spirometry. NOTE DEFINITIONS.
Late Failure/Relapse CRF	1.1	A subgroup of validation patients will experience 'late failure' or 'relapse' this group require this record to be completed in addition to the Validation CRF. NOTE DEFINITIONS.
Longitudinal CRF Type A	1.1	CRF for use in type A sites only, this is the single CRF for type A sites. For use in consenting patients.
Longitudinal Baseline Type B CRF	1.1	For use in patients who have consented to inclusion in the longitudinal study at type B sites. This should be completed pre discharge.
HMV CRF	1.0	For use in anyone commencing home ventilation during the index admission or over the 12 month longitudinal study at type B sites.
Longitudinal CRF Type B	1.2	Large document to be given to the patient to take home. Includes all information and assessments for each month of the longitudinal study.
Consent form	1.2	Universal consent form for use in the longitudinal study
GP letter type A site	1.0	Information letter for a Patient's GP informing them of involvement in the longitudinal study
GP letter type B site	1.0	Information letter for a Patient's GP informing them of involvement in the longitudinal study
Patient Information sheet, type A site	1.3	Information sheet about the longitudinal study at type a sites for patient reference prior and post consent.
Patient information sheet, type B site	1.3	Information sheet about the longitudinal study at type B sites for patient reference prior and post consent.

Useful Contacts

NAME	Role	Email	Phone
Stephen Bourke	Chief Investigator	Stephen.bourke@nhct.nhs.uk	Secretary: 0191 2934026
Tom Hartley	Research fellow	tomhartley@doctors.org.uk tom.hartley@nhct.nhs.uk	07793107550
Vicky Ferguson	Trial Administrator	Victoria.ferguson@nhct.nhs.uk	0191 293 4160

Glossary/Definitions

ABG	Arterial blood gas
ACE inhibitor	Angiotensin converting enzyme inhibitor, eg Lisinopril
ARB	Angiotensin II receptor blocker, eg Irbesartan
AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
BUR	Back up rate
CXR	Chest X-Ray
EPAP	Expiratory positive airways pressure (typically 2-10 cmH20)
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
HDU	High dependency unit
HMV	Home Mechanical ventilation (Home NIV)
ICU	Intensive care unit
IPAP	Inspiratory positive airways pressure (typically 10-30cmH20)
LTOT	Long term oxygen therapy
IMV	Invasive Mechanical Ventilation

NIV	Non-invasive ventilation
RSU	Respiratory support unit
VC	Vital Capacity

Site Administration/Communication/Data Flow

Each site will receive at least one initiation visit with a member of the team from the lead trust. Further queries should be directed to either site PI, Victoria Ferguson for administration queries or Tom Hartley. Data entry is via an online database hosted by Northumbria Healthcare, this is within the NHS N3 secure communications network. www.nivo.org.uk

Paper documents should be stored in a locked filing cabinet in a locked office. Once patient information has been collected on paper a new patient should be created on the online database. This will generate a unique study number (note these numbers may not be consecutive within your institution) which should be immediately added to the paper CRF. At each site you should create a password protected database "Site Demographic Database" of unique study numbers and corresponding patient demographics. This database should only be accessible by an individual site and should be automatically backed up. Date of birth, ethnicity and gender may be uploaded to the online database. A scanned copy of the CRFs minus patient identifying information should be sent to the lead site for data verification purposes.

Validation Component Notes

We recommend daily screening of all areas where ventilation is provided to identify participants. It is vital that all consecutive, eligible patients are included. The vast majority of participants will receive Non-Invasive ventilation (NIV) however those that receive Invasive Mechanical Ventilation (IMV) may also be eligible. Patients who die shortly after admission are more likely to be missed during screening of relevant units, but it is particularly important that we capture them. We therefore recommend additional screening of coding records. If a patient is retrospectively identified (i.e. post death or discharge) they should be

included in the validation component and the 'validation CRF' completed, but will not be eligible for the longitudinal component.

In potentially eligible patients, all possible sources of previous spirometry should be checked, including lung function department, clinical letters, notes, and primary care records. Patients who are being treated as an exacerbation of COPD based on a clinical, but not spirometrically confirmed, diagnosis of COPD will be identified (predominantly new diagnosis).* In this instance a reduced dataset should be collected and entered onto the database. The clinical diagnosis should be confirmed by the site PI in the first instance, if the PI is not available then another respiratory consultant should be approached (typically the patient's consultant). Such patients will not count towards recruitment targets (they will not be included in the primary outcome analysis) and are not eligible for the longitudinal study. This CRF is termed 'Clinical Diagnosis CRF'. It is important to note that spirometry performed during their inpatient stay or post discharge is not sufficient and obstructive spirometry must have been performed pre-admission for an individual to be eligible for full data collection and the longitudinal study. Please record the number of patients you exclude based on unlikely to survive a year grounds and remember this is intended to be inclusive and that expected death from COPD does not count.

We are interested in a subgroup of patients who experience late failure or relapse after treatment with ventilation. Please familiarise yourself with the definitions of both. If late failure or relapse occurs an additional CRF: 'Late Failure/Relapse CRF' should be completed.

* Note this is different to confirmed airflow obstruction with missing values, see later.

Validation Component Data Collection Guidance

General:

Complete 'validation CRF' in entirety in all eligible patients. All indices should be recorded and no indices should be identified as unavailable until all potential sources of information have been exhausted. Any unavailable information will need to be positively identified on the database so please actively record unavailable information. A tick or cross should be used in marked boxes to identify a positive or negative result. For certain key indices yes or no should be ringed to indicate a positive or negative result. Not all individual indices have

been explained as some are self-explanatory. They are grouped as they appear on the CRF and database.

Demographics

Largely self-explanatory. Hospital number refers to your institution's specific identifier and is for your own ease of identification.

Ethnicity is either Caucasian, Afro-Caribbean, Asian.

Patient ID is a unique identifier for the NIVO study and is generated by the online database (instructions above). This must be added to the CRF (and all other CRFs) at the earliest opportunity (you require only date of birth, ethnicity and gender to create a new patient record). Please also record the NIVO Patient ID with full identifying information in the locally held "Site Demographic Database".

Selection Criteria (Inclusion Criteria)

Primary diagnosis of AECOPD (Acute exacerbation of COPD)

In likelihood, this will be the diagnosis given by the consultant on the post take ward round. If it is apparent from the notes that the initial working diagnosis was incorrect and the patient does have an AECOPD then they should be considered for inclusion in the study; similarly patients who were incorrectly diagnosed with AECOPD should be excluded. Please note initial consultant ward round diagnoses may be incomplete.

Please note the following diagnoses refer to an acute exacerbation of COPD (AECOPD), this list is not exclusive. If you are unsure please check with the Principle Investigator.

- Infective exacerbations of COPD
- Non-infective exacerbations of COPD
- Lower respiratory tract infections in patients with COPD
- Chest infections in patients with COPD (both viral and bacterial)
- Pneumonia in patients with COPD.

The term “primary” refers to the main reason they have been admitted. For example, if the main reason a patient is admitted is appendicitis and they happen to incidentally have an AECOPD then this does not fulfil the “primary diagnosis of AECOPD” criterion. Please be aware, though, that if a patient is admitted with confusion because they have an AECOPD then it would be acceptable to include this patient.

If a patient has severe bronchiectasis and mild COPD, and they have a diagnosis of a lower respiratory tract infection this should be regarded as an exacerbation of bronchiectasis. It is not uncommon for patients with severe COPD to have secondary bronchiectasis. These patients may have an AECOPD (rather than exacerbation of bronchiectasis) and can be included in the trial. Clinical judgement may be required and these patients can be discussed with the Primary Investigator.

Respiratory Acidaemia (pH <7.35, CO2 ≥6.5) treated NIV or IV

An arterial blood gas corresponding to the initiation of ventilation must show respiratory acidaemia. The pH must be less than 7.35 and the CO2 must be greater than or equal to 6.5.

Smoking ≥10 pack years

20 cigarettes/day for one year = one pack year. 60 cigarettes/day for 1 year = 3 pack years. Note that 50 grams of tobacco a week for 20 years is approximately 14 pack years. 5 cigars a day for 20 years is 20 pack years. (Two ounces of tobacco is approximately 50 grammes). http://smokingpackyears.com/calculate

Spirometry FEV1/FVC <0.7

Any obstructive spirometry prior to ventilation is valid, if more than one result is available record the most recent obstructive result. FEV1/FVC ratio is the forced expiratory volume in one second divided by the forced vital capacity. Ideally, the patient will also have performed a slow/ relaxed VC. If the FEV1/VC (slow/ relaxed vital capacity) has also been recorded the lowest ratio (i.e. the most obstructive) should be recorded. Some patients terminate forced spirometry before expiration is complete (“early finish”), and the presence of airflow obstruction may only be evident on the ratio of FEV1 to slow/ relaxed VC.

NOTE: if obstructive spirometry is confirmed but precise values are unavailable they may still be eligible for full inclusion, see guidance on page 10 under 'Obstructive spirometry confirmed but values unavailable'

Age >35 (self-explanatory)

Selection Criteria (Exclusion Criteria)

Previous inclusion in the study

Note that as this component of the study does not require individual patient consent the patient will not know if they have previously been included. It will not be uncommon for a patient to have more than one admission requiring ventilation during the recruitment period, so please check your site demographic database if you are unsure whether a patient has previously been included.

Other Illness limiting life to less than one year

This does not refer to expected mortality related to their COPD; co-morbidity is common in this group of patients and we are keen not to inappropriately exclude anyone. This criterion principally refers to metastatic cancer with an expected poor outcome, and a small number of other serious diagnoses. If in doubt ask your principle investigator.

Date/Time of key events

A&E: This is the time of arrival in A&E or equivalent acute receiving environment. It most circumstances this is the time recorded on PAS (not the time seen in triage etc). Occasionally (usually in the case of emergency treatment) entry onto PAS occurs after other key times as ABG or initiation of ventilation. If there is a discrepancy where the PAS time is obviously delayed, record the earliest time you can objectively identify.

Senior review: This is the Consultant physician or intensivist (but excludes the A/E consultant).

Ward: This is the time the patient passes from A+E to their next destination including: admissions unit, respiratory ward, respiratory support unit (RSU), HDU, ICU,

Background

Home Circumstance: select the one, most appropriate option.

Smoking status: Either current (incudes up to 6 weeks prior to admission) or Ex.

Pack Years: Record total number rounded to whole number following guidance above.

Number of Admissions in last year: Admissions for any reason.

eMRCD: This is probably the most important piece of information recorded. It is vital this is accurately scored. It is different from the traditional MRCD score, notably 1) the term "housebound" is replaced by "unable to leave the house unassisted"; 2) transition between levels is clearly defined; and 3) level 5 is separated into 5a and 5b. Please take time to familiarise yourself with this score as it is prominent throughout the study.

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)	
Only Breathless on strenuous exertion	1
Breathless hurrying on the level or walking up a slight hill	2
Walks slower than contemporaries, or stops when walking on the level for 15 min	3
Stops for breath after walking 100m, or for a few minutes, on the level	4
Too breathless to leave the house unassisted but independent in washing and/ or dressing	5a
Too breathless to leave the house unassisted and requires help with both washing and dressing	5b

Guidance notes:

Remember that you are asking the patient about their level of breathlessness on a good day over the preceding 3 months, not breathlessness during an exacerbation / on admission.

A patient only achieves a higher grade if they are as breathless as defined in that higher grade.

- for example, if worse than defined in eMRCD 3, but not as bad as eMRCD 4, they remain eMRCD 3.

A key distinction is between eMRCD 4 and eMRCD 5a/5b:

- only score 5a or 5b if the patient cannot leave the house without assistance.

- if a patient can only walk 30 to 40 metres, but can leave the house unassisted, they are eMRCD 4.

- if a patient can walk 5 or 10 metres, perhaps from their front door to a car, but need a wheelchair otherwise, they require assistance: eMRCD 5a or 5b. Simple walking aids do not constitute assistance.

If a patient requires assistance in personal washing and dressing they are eMRCD 5b. If they only require assistance in washing or dressing they are eMRCD 5a. Remember to ask about putting on socks and shoes.

If patients are limited for a reason other than breathlessness, score based on their functional limitation.

Most recent obstructive spirometry: See guidance above in inclusion criteria.

Obstructive spirometry confirmed but values unavailable: This is NOT THE SAME as a clinical diagnosis. In this instance you can objectively identify that spirometry has taken place prior to admission and it was obstructive but the values are incomplete or unavailable. For example an outpatient letter may say 'there is evidence of airflow obstruction' or 'obstructive spirometry' but then precise values are unavailable. Only tick this if all sources of actual values have been exhausted, these sources include, Lung function department, inpatient notes, outpatient letters, GP (this is often recorded in a COPD annual review.) If in doubt ask your PI.

Comorbidities

LVSD (left ventricular systolic dysfunction): May be referred to as left heart failure. This diagnosis should be confirmed on an echocardiogram or cardiac MRI or on clinical grounds (such as a previous documented episode of pulmonary oedema with cardiomegaly or BNP>2,000, or confirmed by a cardiologist). Have a higher index of suspicion if patient takes beta blockers/ACE or ARB. Record NYHA class in those with LVSD using the following guidance notes:

New York Heart Association (NYHA) Classification of Heart Failure

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, rapid/irregular heartbeat (palpitation) or shortness of breath (dyspnea).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, rapid/irregular heartbeat (palpitation) or shortness of breath (dyspnea).
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, rapid/irregular heartbeat (palpitation) or shortness of breath (dyspnea).
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of fatigue, rapid/irregular heartbeat (palpitation) or shortness of breath (dyspnea) are present at rest. If any physical activity is undertaken, discomfort increases.

IHD: Ischaemic heart disease, any diagnosis of angina or previous MI.

CVD: Cerebrovascular disease, any diagnosis of stroke (ischaemic or haemorrhagic) or TIA.

Cognitive impairment: any diagnosis of chronic confusion, cognitive impairment or dementia.

Cor Pulmonale: Right heart failure due to respiratory disease may be a clinical or echo diagnosis. Old letters must be reviewed as well treated right heart failure may not be readily apparent on admission. Have a higher index of suspicion if patient takes diuretics.

APACHE II Liver Failure: The score will be compared to existing scores one of which is the APACHE II score so accurate scoring is necessary. A positive result is defined as: “Biopsy proven cirrhosis and documented portal hypertension; episodes of past upper GI bleeding attributed to portal hypertension; or prior hepatic failure/encephalopathy/coma.”

APACHE II Renal Failure: Receiving chronic dialysis (haemodialysis or peritoneal)

APACHE II Immunocompromise: The patient has received therapy that has suppressed resistance to infection within 4 weeks of admission, eg immunosuppression, chemotherapy, radiotherapy, high dose steroids (>1.5mg/kg). Has immunosuppressive disease such as leukaemia, AIDS, lymphoma. Please ensure should not be excluded on basis of estimated 1 year survival.

AF: This is recorded at 2 time points, up to 4 hours (the admission period) and up to ventilation. This is to be able to differentiate those that develop AF after the admission

period prior to ventilation (these time points will more often than not be the same). AF is recorded as being present if chronic AF, paroxysmal AF or acute AF are noted.

Medications

Record whether patient was prescribed at admission and discharge. Long term steroid is for at least 1 month continuously prior to admission. Admission medication listed on records but with verified non-adherence should not be included.

LABA=long acting beta agonist, LAMA= long acting muscarinic antagonist, ICS=inhaled corticosteroid. Please note you should tick all that apply. There are a number of combination inhalers on the market containing either LABA/ICS or LABA/LAMA. Please check in the BNF or with a pharmacist. Of note, many doctors are unfamiliar with these newer medications so they may be inaccurately recorded initially.

Clinical Information

Effective cough: This is the ability or inability to effectively clear secretions. It is often recorded by respiratory physiotherapists. Only record ineffective cough if patient clinically appears to have excess secretions in their airways that they cannot clear independently. If a patient has a reduced GCS they are more likely to have an ineffective cough.

Height: Record in meters. Historical spirometry records are often a good source of this information. (A reading taken in the future may be retrospectively added for this variable).

Weight: This should be most recent available. Previous values are acceptable if the patient does not report weight change in the intervening period.

BMI: Please only record BMI if height and weight separately are unavailable and always record height if at all feasible.

CXR consolidation on admission: Presence or absence of consolidation on the first technically adequate chest X-ray taken. Interpretation should be that of the most senior clinician available (often a consultant will comment on an X-Ray on a post take ward round taken the previous day.) Consolidation may also be termed pneumonia, infiltrate, opacity etc. It may

be misinterpreted as pulmonary oedema, if you have suspicion of this, or are uncertain for any other reason please ask the principle investigator or supervising clinician.

CXR consolidation at ventilation: Particularly relevant if ventilation occurs later in the admission.

Diaphragm height: This is the height in centimetres from a line drawn between the lateral and medial insertion points on a CXR and the maximum height of the dome. Use the right hemidiaphragm preferentially.

LTOT on admission: Long term oxygen, (not short burst or palliative).

NIV

Previous Episode: Record number of distinct (max one per admission) previous episodes of NIV (not invasive mechanical ventilation or CPAP) for any reason.

Domiciliary NIV admission/discharge. Be aware this is NIV at home and NOT CPAP. Patients themselves and frequently non-specialist doctors and nurses are imprecise about home ventilation. Of note if a patient has home NIV the initiation time will correspond to the deviation from their normal ventilation routine (including change onto a different ventilator). Discontinuation will correspond to the re-establishment of their normal ventilation pattern or the establishment of a new chronic ventilation pattern.

Ventilation initiated date/time: This is the time that NIV or IMV was initiated (time mask applied, time of intubation). If the precise time of initiation of ventilation is unavailable, please use the best estimate available from the notes (e.g. time of ABG prior to initiation, time of decision to initiate ventilation if recorded).

Ventilation discontinuation date/time: This is when a continuous period of ventilation has ended. If a patient goes from NIV to IMV and back to NIV this is one period of ventilation. If there is more than 24 hours gap between 2 periods of ventilation, the first episode of ventilation would be considered complete and second episode a relapse. Gaps of less than 24 hours are considered part of one continuous period of ventilation. Note for the purposes of this study we consider ventilation to have ended when the mask is removed from a patient NOT when the machine is removed from the bedspace (which may be some timelater). Frequently during weaning this will be first thing in the morning. If no time is

documented for morning removal following a final night on NIV then use 08.00 as a default in this specific situation.

pH correction: The first time that pH is greater than or equal to 7.35 after ventilation has been initiated irrespective of whether it subsequently drops again. If pH never corrects then record in comments.

IPAP/EPAP/BUR 1-2hr and max: IPAP is the inspiratory pressure and EPAP is the expiratory pressure. Often recorded as, for example, 24/5 (where 24 is the IPAP and 5 is the EPAP). BUR is the back up rate provided by the ventilator. Record these pressures for NIV only. Patients will typically have a review after 1hr on NIV with a review of the setting in conjunction with an ABG. It is the pressures achieved after this review we are seeking to capture and clinicians other duties can contribute to delays; please be flexible in interpretation of the 1 hour guide and allow up to 2 hours. Max is the maximum achieved at any point during their NIV. Note that especially those experiencing late failure may achieve their maximum values late into their admission.

Reason for cessation: The reason ventilation was discontinued.

At the time of ventilation was the patient for intubation/resuscitation: unless actively stated to the contrary, patients should be assumed to be considered for full escalation. If a senior clinician changes this status at the first senior review (provided within 24 hours of initiation of ventilation) then record this as the status. Changes made after 24 hours irrespective of clinician grade do not affect this status.

Highest level of care received. This is the actual level received NOT the hypothetical ceiling of care.

Was patient invasively ventilated? If yes: NIV pre and/or NIV post: Note: this refers to whether the patient received NIV before and/or after IMV. See guidance on recording ventilation initiation and discontinuation time.

Duration invasively ventilated: Note this is the time invasively ventilated, not total ventilation time which may include NIV also. If a patient receives a tracheostomy this is considered invasive ventilation.

Observations

4Hr/Ventilation: Record the worst available observations either up to the point NIV is initiated or up to 4 hours whichever comes first.

24hr pre Vent: If ventilation is initiated within the first four hours of admission these readings are not relevant (i.e. will be by definition the same) so tick box and leave blank as directed on the CRF. If ventilation occurs after 4 hours record the worst available readings (even if they are the same as the 4 hours) up to a maximum of 24 hours prior to ventilation

BP record the lowest.

HR record the greatest deviation from 70.

Temp record the greatest deviation from 37.0

GCS record the lowest, (if not accurately documented record the best guess from available information, table below)

O2 sats/FiO2 record the lowest O2 sats, document Fi02 as follows: RA (room air), V (Venturi) + the % or Un (uncontrolled) and the flow rate in litres.

Confusion: Any confusion objectively recorded. Note if confused GCS must be 14 or lower.

Glasgow Coma Scale		
Eye Response	Open Spontaneously	4
	Open to Verbal command	3
	Open in response to pain	2
	No response	1
Verbal Response	Talking / Orientated	5
	Confused speech / Disorientated	4
	Inappropriate Words	3
	Incomprehensible sounds	2
	No response	1
Motor Response	Obeys commands	6
	Localizes pain	5
	Withdraws from pain	4
	Abnormal flexion	3
	Extension	2
	No response	1

ABGs

Admission is the first ABG recorded.

1st acidaemia is the first blood gas showing respiratory acidaemia and may be the same as admission.

NIV decision is the ABG that prompted ventilation. This must, by definition, show respiratory acidaemia.

24 hours post is 24 hours (+/- 12 hours) after ventilation initiated.

Steady is steady state, it must be after acute ventilation has ceased, use the closest to discharge available. (note guidance about discontinuation in domiciliary ventilation).

Date and Time is vital to allow interpretation of key indices. A best guess is better than nothing if not objectively available.

pH/PaCO2/PaO2 self-explanatory. BE may be positive or negative please ensure accurate recording of such. Bicarb (bicarbonate) is sometimes routinely reported in U+Es. Use venous bicarbonate if no ABG is available for the specified time.

Art/venous. By default, assume ABGs are arterial. If an ABG is objectively recorded as being venous (as opposed to an attempted ABG being recorded as ?venous) then specify as venous. tcCO2 is transcutaneous CO2 (TOSCA) some centres may use this in to supplement venous gas. More commonly, PtcCO2 will be unavailable / not recorded.

Bloods

Admission: use the first recorded bloods within 24 hours of admission (ie. by default, the first recorded bloods.) Creat base is the pre admission creatinine: document the lowest value recorded in the last 3 months preceding admission. If no results within this timeframe, record stable state creatinine during the last 12 months.

NIV decision: In approximately 75% of cases this will be the same as admission. If so, tick box and leave blank.

If ventilation occurs later than 4 hours, a new set of bloods may be needed (particularly in those with acidaemia developing more than 24 hours after admission). Record bloods taken within 24 hours prior to ventilation initiation. For example if NIV is instigated on day 7 of admission at 14.30 then additional bloods should be recorded in the NIV decision column using bloods taken between Day 6, 14.30 and day 7, 14.30.

Discharge is the last available bloods (they do not need to come from the same time).

n.b Na=Sodium, K=potassium, Hb=haemoglobin, Hct=Haematocrit, WCC=white cell count. Do not neglect eosinophils - this is another of our key indices.

Outcomes

Did the patient survive to discharge: Largely self-explanatory.

If the patient is dying and requests transfer out of a hospital setting to die for example in a hospice or home on a care of the dying pathway and dies within 7 days of leaving the acute hospital we consider this an INPATIENT death. In this setting select NO (did not survive to discharge) and record details in comments. This situation is NOT the same as going home with an Emergency Healthcare Plan (EHCP) stating they should not be readmitted .

Date of discharge: Leave blank if does not survive to discharge.

Home NIV (HMV) commenced within 1 year post discharge? Yes/No include HMV commenced upon discharge from index admission and record date commenced.

Reason commenced: Answer yes to all that apply.

Date of death: Includes deaths up to 12 months post discharge.

Cause of death: Details from death certificate.

Readmissions

Readmission for any cause up to 12 months post discharge date.

Adm date= Admission date, Dsc date= discharge date, R/O = respiratory/other, NIV? = whether patient received NIV during this readmission, diagnosis if available.

Late failure/Relapse

Late Failure (LF) is recurrence of respiratory acidaemia prior to discontinuation of ventilation. pH should drop to below 7.35 with a rise in CO2 of at least 1kPa and to >6.5kPa from the lowest recorded post pH correction at least 24 hours after pH correction.

(It is not simply delayed correction of initial respiratory acidaemia).

This definition may seem complex, however, if you consider the group under study it becomes easier to understand: We wish to capture those who deteriorate on treatment (still receiving ventilation) after initial improvement (ie after pH correction). We don't want those that have an early 'wobble' (hence >24 hours after pH correction"). We want to capture respiratory deterioration rather than a new metabolic acidaemia (so a rise in paCO2 of >1KPa to greater than PaCO2 6.5) but we require a reference point to measure this rise (so lowest recorded after correction).

Relapse is recurrence of respiratory acidaemia 24 hours after NIV cessation. (if less than 24 hours after discontinuation consider as late failure.)

Only capture LF occurring during primary episode of ventilation not during any subsequent episodes (ie relapses)

The CRF is otherwise self-explanatory.

Clinical Diagnosis

In potentially eligible patients, all possible sources of previous spirometry should be checked, including lung function department, clinical letters, notes, and primary care records. Patients who are being treated as an exacerbation of COPD based on a clinical, but not spirometrically confirmed, diagnosis of COPD will be identified (predominantly new

diagnosis). In this instance a reduced dataset should be collected and entered onto the database. The clinical diagnosis should be confirmed by the site PI in the first instance, if the PI is not available then another respiratory consultant should be approached (typically the patient's consultant). Such patients will not count towards recruitment targets (they will not be included in the primary outcome analysis) and are not eligible for the longitudinal study. This CRF is termed 'Clinical Diagnosis CRF'. It is important to note that spirometry performed during their inpatient stay or post discharge is not sufficient and obstructive spirometry must have been performed pre-admission for an individual to be eligible for full data collection and the longitudinal study.

Longitudinal Component Notes

This component of the study will require individual patient consent. All patients surviving to discharge should be considered for inclusion with inability to provide informed consent being the only exclusion criteria. Participants should be approached when they have achieved clinical stability in the 2-3 days prior to their expected discharge date. They should be given the site specific patient information sheet (PIS) and have time to consider it and ask any questions regarding it. If a patient wishes to partake, consent should be taken using the provided consent form. A letter to send to the patient's GP is also provided informing them of the study.

Type A site: There is only one CRF for type A sites termed: 'Longitudinal CRF Type A'. The pre discharge component of the CRF should be completed. Patients should be given a copy of their consent form and the 'Patient Information sheet, type A site'. No additional CRF needs to be given to the patient for type A sites. The remainder of CRF should be completed at 3 months.

Type B site: This is most (or all) sites and represents a much more thorough follow up schedule. Before discharge from hospital complete 'Longitudinal baseline type b CRF'. Patients should be given a copy of the longitudinal CRF, a copy of 'Patient Information sheet, type B site' (if not already) and a copy of 'Longitudinal CRF Type B' in a single file. A large, addressed, postage paid envelope should also be provided. Patients must be educated how to complete their assessments and advised on the dates they should be completed. If the

discharge date is definitively known it can be entered onto the database and an interview schedule generated to include in the patient pack. Please only use this function if you KNOW the patient is going home on the specified day. Otherwise this can be printed at a later date and posted to the patient. Each month's post discharge assessment should be taken from the discharge date NOT the consent date. Following discharge the patient should complete assessments themselves 1 and 2 months after discharge (they will also do this at month 4/5 and 7-11). Some sites have opted to phone participants each month to complete the assessments with them over the phone to enhance data completion. This method is encouraged but not mandated from the sponsor. The 3rd, 6th and 12th month assessment is face to face with a researcher either in the patient's own home or in hospital, which we will leave to the discretion of individual sites. At each face to face visit please clarify with the patients that any readmissions you have identified did occur and any others to other trusts or missed admissions. The number of COPD exacerbations either treated or requiring admission since last assessment should be recorded. Note this is not cumulative and is from 0-3 months then 3-6 months and finally 6-12 months. Please ensure you take a copy of all study documents with you. At these visits completed assessments should be collected. Please also verify the patient has the required documents to complete any outstanding assessments, including the schedule filed at the front (bring a copy of the schedule to the first visit) and that they understand the schedule between your current face to face contact and the next. Readmissions you have identified electronically should be verified with the patient, when possible.

This group of patients have a high one year mortality and so there is a significant chance the participant may not survive to the end of the follow up period. Please ensure there is a local system for checking survival prior to any patient contact. Ensuring that the patient pack always has a prepaid envelope and collecting assessments regularly should maximise data capture. In the event of a patient's death between visits, please sensitively arrange for the study file to either be posted back in the provided envelope, or collected.

The assessments to be completed each month are CAT, EQ 5D 5L, eMRCD, HADS, NEADL. Please familiarise yourself with these assessments.

Please assume your site is a type B site unless expressly told otherwise. Type A sites have a single CRF. Type B sites have a baseline CRF (to be completed pre discharge) and a longitudinal CRF.

Longitudinal Component Data Completion Guidance.

Patient ID must be added to all sheets.

Height need only be entered once, weight should be entered at each face to face assessment.

Record FiO2 as per Validation guidance.

Spirometry should be measured for the baseline (pre-discharge) assessment and at each face to face visit, do not input old values.

Future ventilation questions are sensitive and should be handled so. Please remind the patient of the dates of their index admission as they may have subsequent admissions and become confused.

Each tool has completion guidance attached, please read each tool prior to use with a patient, if there is any uncertainty around completion please ask.

Of Note in the HADS score the top right question reads 'I feel as if I am slowed down' this refers to slowed down mentally not physically which should be specifically pointed out to the patient.

HMV CRF

Anyone who commences HMV during the index admission or subsequently during the longitudinal follow and has consented to involvement in the longitudinal study should complete the HMV CRF. If they start on HMV from discharge the whole CRF should be

completed. If they commence after 5 months complete the 6 and 12 month boxes and mark the 3 month box as not applicable.

If in doubt about the indication for initiation (particularly the HOT-HMV criteria please ask your PI)

Please note that to activate the additional information to be recorded in the database HMV must be selected in the OUTCOMES section which will reveal additional tabs in the longitudinal study.

Database

A database hosted by the Northumbria NHS foundation trust has been commissioned. It is accessible at: http://n3.nivo.org.uk All data entry should be via here and unique study numbers will be generated by the database. A work list will be generated for you and details of missing data flagged for completion. All study documents are also available for download. Missing data must be actively identified. All fields have a small check box which if ticked positively identifies the field as missing. Please check all available sources of information and if information is still missing check the missing data box. Training will be provided at site initiation visit. If you are struggling with the database please contact Tom (mobile above).

Data Monitoring

When Validation CRF is completed (one year post index admission) after readmission data has been collected. This form should be scanned and emailed (minus identifying information) to Vicky Ferguson (email address at the beginning of this document). There is no requirement to send on Longitudinal study CRFs. There is no planned formal monitoring visit.

Adverse Event Monitoring

As the study has no active intervention no adverse events related to study activity are anticipated.

12.4 D, Missing data analysis (Derivation Study)

Variable	%missing	Mean original	SD original	Mean EM	SD EM
Phosphate	87.9	N/A, immediately discarded.			
Troponin	87.0	N/A, immediately discarded.			
Glucose	25.8	8.41	3.58	8.57	3.84
Bilirubin	23.1	9.93	6.81	9.77	6.44
Total protein	20.2	69.5	6.82	69.1	6.82
Albumin	19.0	37.9	5.40	3.78	5.38
Potassium	6.7	4.65	0.70	4.63	0.70
Oxygen saturations	4.5	83.8	10.7	83.9	10.7
Haemoglobin	4.5	13.64	2.15	13.62	2.14
Eosinophil count	4.1	0.094	0.18	0.095	0.18
White cell count	3.9	13.73	6.61	13.63	6.58
Platelet count	3.9	291.1	123.5	294.6	126.0
Haematocrit	3.9	0.420	0.063	0.420	0.063
Neutrophil count	3.9	10.95	5.34	10.87	5.33
Sodium	3.3	136.6	5.26	136.6	5.23
Urea	3.3	9.15	5.65	8.96	5.69
Base excess	3.1	3.78	6.35	3.78	6.46
Diastolic blood pressure	1.6	70.1	18.8	69.7	19.2
Systolic blood pressure	1.4	123.9	31.5	123.0	32.4
Heart rate	1.4	112.8	21.9	112.4	22.1

Univariate Associations with mortality	Original Dataset	P Value EM
Age*	<0.001	<0.001
Any atrial Fibrillation up to deterioration	<0.001	<0.001
Left Ventricular Systolic Dysfunction*	0.025	0.025
Depression*	0.097	0.097
eMRCD	<0.001	<0.001
LTOT*	0.014	0.014
Consolidation at Ventilation*	<0.001	<0.001
Pleural Effusion admission	<0.001	<0.001
Diaphragm Height	0.063	0.063
Confusion at ventilation	<0.001	<0.001
GCS*	<0.001	<0.001
Systolic Blood pressure	0.008	0.026
Heart Rate	0.085	0.057
Respiratory Rate	0.041	0.041
Haemoglobin	<0.001	<0.001
WCC	0.025	0.016
Eosinophil Count	<0.001	<0.001
Urea	<0.001	<0.001
CRP	0.002	0.005
pH*	0.003	0.003
Base Excess	<0.001	0.001
Time to acidaemia*	<0.001	<0.001

12.5 E, Presented Abstracts.

Only abstracts directly pertaining to the NIVO study are listed:

1. *Predicting Outcome from Exacerbations of COPD requiring Assisted Ventilation: Results from the NIV Outcome (NIVO) study*. Oral presentation, British thoracic Society (BTS) winter meeting, 2019.

2. *Late Failure of NIV in Exacerbations of COPD: All is not lost*. Poster presentation and discussion, BTS winter meeting, 2018.

3. *NIV in exacerbations of COPD: Prognostication is not all baseless.* Oral presentation at BTS winter meeting, 2018.

4. *The NIVO Study: attitudes to ventilation following acute NIV.* Poster presentation and discussion, ERS International Congress, Paris 2018 (Presented by Dr Nick Lane)

5. *Timing of Acidaemia onset in exacerbations of COPD requiring assisted ventilation and in-hospital mortality.* Oral presentation, BTS winter meeting 2017.

6. *The Role of Ventilation in Pneumonic Exacerbations of COPD (pECOPD)*. Poster presentation and discussion, BTS winter meeting 2017.

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