Outcome prediction for patients with obstructive lung disease considered for admission to critical care in England Wales and Northern Ireland.

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Abstract

Objective. To develop an outcome prediction score for patients with obstructive lung disease considered for admission to critical care.

Design. Prospective cohort study using multivariate logistic regression for model building followed by score development and bootstrapping to adjust for over fitting.

Setting. Critical care and respiratory high dependency units in England Wales and Northern Ireland.

Participants. Patients aged 45 years and older with a clinical diagnosis of breathlessness, respiratory failure or change in mental status due to an exacerbation of COPD, asthma or a combination of COPD and asthma.

Main outcome measures. The primary outcome was survival at 180 days and the model was constructed to predict this. The secondary outcomes were the accuracy of clinicians' predictions at the time of critical care admission and 180-day health-related quality of life

Results. Ninety two critical care units and three respiratory high dependency units took part. Eight hundred and thirty two patients were recruited and the 651 patients without treatment limitations were used to develop the outcome score. Of the 651 patients 450 were intubated and 107 (16.4%) died in critical care, another 66 (10.1%) died in hospital and a further 47 (7.2%) had died by 180 days follow-up, giving a cumulative 180-day mortality of 33.8% (220 deaths). 420 of 518 (81.1%) survivors provided quality of life data and 400 (96.4%) would want ICU again under similar circumstances. A score using length of stay, age, sex, acute physiology , functional capacity, mid-arm circumference, atrial fibrillation, intubation status and diagnosis had an area under the receiver operating characteristic curve of 0.75 after bootstrapping and was well calibrated. Clinicians' predictions had an ROC area of 0.71 and were less well calibrated with a tendency towards pessimism.

Conclusions. This study has produced an outcome prediction score with reasonable discrimination and good calibration that has the potential to support clinicians in understanding the prognosis of patients with obstructive lung disease considered for critical care.

Acknowledgements

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Statement of Own Work

Declaration by Candidate

I have read and understood the School's definition of plagiarism and cheating given in the Research Student Handbook and I declare that this thesis is my own work, and that I have acknowledged all results and quotations from the published or unpublished work of other people.

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Chapter 1 Introduction

The aim of this study is to develop a prognostic model to predict the 180-day survival and quality of life of patients with Chronic Obstructive Pulmonary Disease (COPD) admitted to hospital with an exacerbation of sufficient severity that they may require intubation. The introduction explains why estimates of prognosis are important for these patients. It identifies the current problems that clinicians face in planning care for these patients and the potential for a prognostic model to improve things.

1.1 What is chronic obstructive pulmonary disease?

Chronic obstructive pulmonary disease (COPD) is a chronic slowly progressive disorder that results in the lungs becoming damaged and unable to support normal activity. COPD encompasses a number of related conditions including chronic bronchitis, emphysema, chronic obstructive airways disease (COAD), chronic airflow limitation and some cases of chronic asthma[1 2]. Healthy lungs allow oxygen to be transported from the air into the blood and carbon dioxide to be cleared from the blood into the air. Normal lungs at sea level will produce an oxygen partial pressure in arterial blood of around 12kPa and a carbon dioxide partial pressure less than 6kPa. In healthy lungs gas is drawn into the lungs via the connecting tubes of the airways and into alveoli which form a delicate honeycomb structure in which the air passes close to a plentiful blood supply. The interface between the air inside the alveoli and their blood supply comprises an exchange membrane which has a surface area similar to the size of a tennis court. In COPD the airways carrying air in and out of the chest become narrowed and this is often accompanied by damage to the honeycomb exchange membrane (lung parenchyma). In COPD it is usually cigarette smoking that damages the lung and typically the first objective measure of this damage will be narrowing of the airways demonstrated by a Forced Expiratory Volume (FEV_1) less than 80% predicted, and breathlessness on exertion.

There can be confusion in the terminology applied to COPD, with some patients and GPs using the term asthma to describe their breathing problems. This may be because

asthma seems to be better known and also because it does not carry the stigma of a smoking related disease. However investigations can be used to distinguish pure asthma from pure COPD, because in asthma, though airway narrowing occurs, it is reversible, whereas in COPD airway narrowing is permanent. In some asthmatics, particularly those who smoke, there may be some reversible airway narrowing superimposed on fixed obstruction, and these patients may be considered to have a mixture of asthma and COPD. Often when older patients are admitted as emergencies and old notes are not available it can be difficult to distinguish between asthma, COPD and patients with a mixture of asthma (reversible airway narrowing) and COPD (fixed airway narrowing).

1.2 The need for prognostic estimates in patients with COPD

As smokers age and lung damage progresses, airway narrowing will increase and as the FEV_1 continues to fall and the delicate honeycomb exchange membrane is damaged, sufferers will typically experience breathlessness on even trivial exertion. The oxygen in the blood may fall and the carbon dioxide rise. Patients admitted to hospital with COPD span a continuum from those with only mildly impaired lung function to those with severe lung damage. In the most badly affected patients the sufferer can be considered to have terminal respiratory failure, in that only the slightest additional deterioration will lead to death. For the milder COPD patients, though infections might impair lung function so that temporary organ support in the form of ventilation in critical care is required, the patient is able to recover sufficiently to breathe independently and enjoy an acceptable quality of life. For COPD patients with severely damaged lungs temporary lung support in the Intensive Care Unit (ICU) is likely to be attended by difficulties in weaning from support and an early death either in the ICU or shortly afterward. Non-invasive ventilation (NIV) provides respiratory support via a mask and can provide an alternative to intubation in selected patients [3]. The recent NICE guidance recommended that NIV should be used as the first line treatment for COPD patients with respiratory failure, but in recognition of the fact that some patients

will fail NIV and will require intubating in order to survive, the guidance recommends that:

"When patients are started on non-invasive ventilation there should be a clear plan covering what to do in the event of deterioration and ceilings of therapy should be agreed."[4] .

Decisions about ceilings of therapy involve identifying which patients are likely to benefit from intubation, a judgment that must weigh up the interaction between the current acute illness and the patient's position on the continuum of deterioration associated with chronic progressive disease. The General Medical Council guidance on withholding and withdrawing life sustaining therapy suggests that "prolonging life will usually be in the best interests of the patient, provided that the treatment is not considered excessively burdensome or disproportionate in relation to the expected benefits" [5].

Decision making typically involves clinicians assessing patients who have been admitted to hospital but not yet admitted to ICU, and estimating the patients' prognosis with the various potential treatment modalities available. The clinician is interested in both the possibility of survival and the quality of life that a surviving patient will enjoy. Clinicians use information about the patient's condition in the period of stability prior to the onset of the current exacerbation, and also their assessment of the severity of the current episode gleaned from clinical examination and the results of any tests such as x-rays and blood tests carried out since admission[6]. This process will be carried out at the bedside by clinicians who are usually under time pressure because of involvement in the care of other recently admitted medical patients.

1.3 How often are prognostic decisions required in clinical practice?

Large numbers of patients are admitted to hospital each year with COPD and many of them die. In England in 2000/1 there were over 100 000 hospital admissions for COPD and there are over 30 000 deaths from COPD in the UK each year[7], with COPD being the fifth most common cause of death in England and Wales (top four causes: coronary heart disease, pneumonia, stroke and lung cancer). Patients with COPD comprise

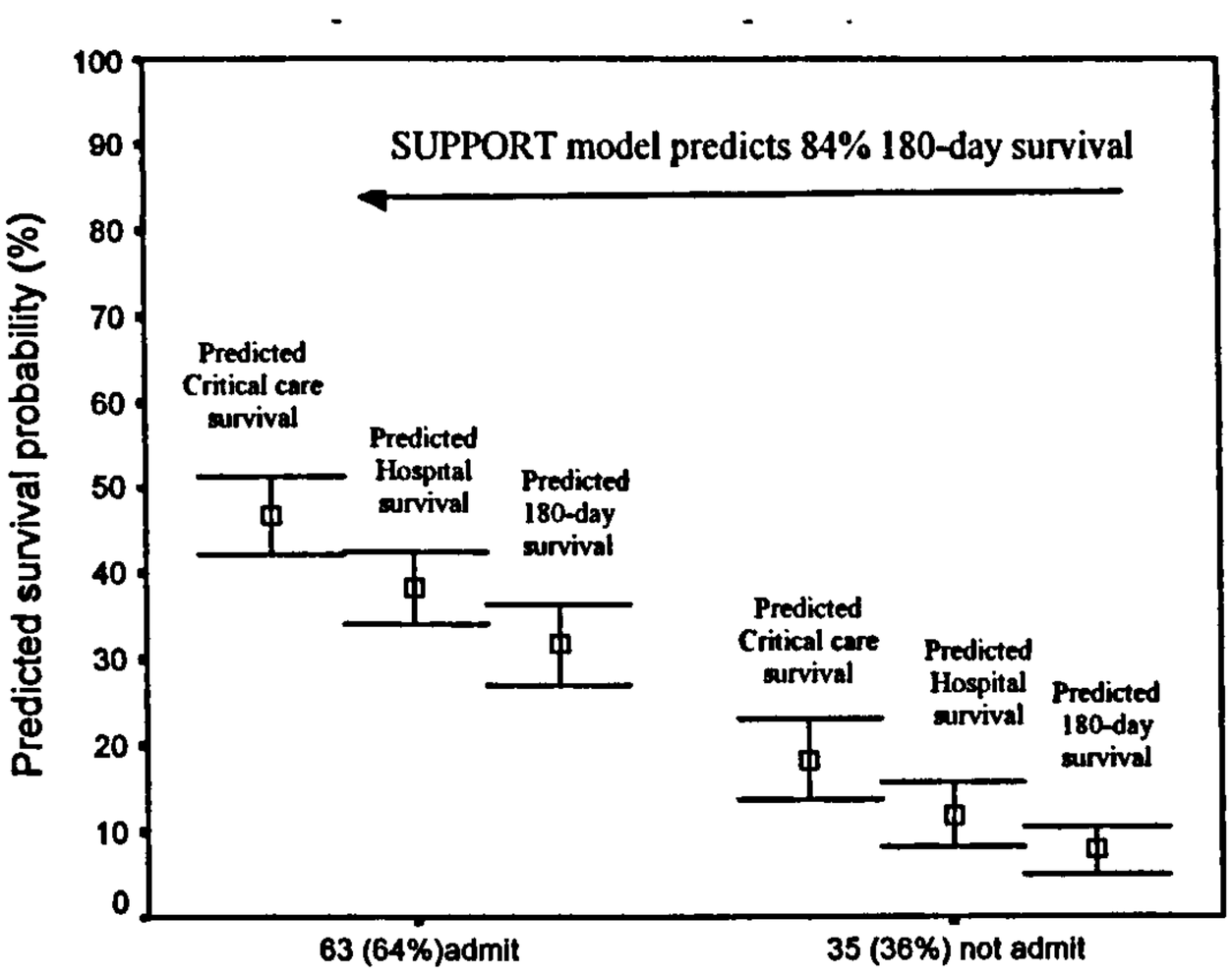
around 2.5% of ICU admissions in the UK [1]. Ninety-eight consultants, comprising 82% of all consultants providing acute care for emergency admissions in the eight hospitals of the UK Heart of England Critical Care Network, stated that they had made a median (IQR) of 10 (6.0 – 20.0) end of life/intubation decisions for COPD patients in the previous 12 months (2001-2002)[8]. The large number of hospital admissions with COPD and the large number of these patients who require treatment plans based in part upon estimates of prognosis indicate the importance of prognosis in the management of this patient group. In a recent vignette-based questionnaire study involving 381 intensive care specialists in Switzerland, more than 80% identified the prognosis of the acute and underlying disease as important or very important for making critical care gatekeeping decisions[9]. There is literature that suggests that clinicians find prognostication difficult[10] and given the importance of prognosis in this patient group it is useful to review what is known about clinicians' prognostic performance for patients with COPD.

1.4 How good are clinicians at predicting the prognosis of patients with COPD?

Pearlman used paper-based cases to understand how 205 American physicians formulated prognoses for patients with COPD and the impact of those prognoses on treatment decisions[11]. He showed that estimates of survival for identical patients were quite variable and influenced treatment recommendations. Investigations of decision-making using paper cases may be criticised because the decision making process is divorced from real life. However in real life different clinicians do not make decisions about the same patient in sufficient numbers to allow decision making to be studied. The recent Heart of England Critical Care Network study, mentioned above, exploited the fact that in the UK consultants on call will occasionally be asked to make decisions about patient management on the basis of information about the patient relayed by phone[8]. In this study of ICU gatekeeping consultants were contacted by telephone as though they were on call and the investigator, who was an experienced clinician, described the characteristics of COPD patients who required intubation, and asked the consultant to estimate the prognosis of the patient with intubation and make a decision as to whether intubation should occur.

This study showed that clinicians differed in their treatment limitation decisions for identical patients with identical preferences under conditions of identical resource availability. In addition intubaters and non-intubaters formulated markedly different prognostic estimates despite identical patient characteristics. In figure 1.4.1 the outcome predictions for admitters (who would intubate) and non-admitters (who would not intubate) are shown for the second patient that was considered in the simulation study. This was a 75 year old female COPD patient and it was explained that the patient would die if not intubated. The predicted probability of survival given the patients characteristics was calculated using the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT) model[12] and are shown on the figure. It can be seen that 64% of the consultants would intubate and 36% would not. Also the predictions of survival with intubation for intubaters versus non-intubaters differed significantly whether for ICU survival (47% vs. 19% $p<0.0001$), hospital survival (38% vs. 12% $p<0.0001$) or 180-day survival (32% vs. 8% $p<0.0001$). Indeed, estimated 180-day survival rate among intubaters was greater than critical care survival rate among non-intubaters.

Figure 1.4.1 Outcome predictions for a 75 year old female with COPD who required intubation in order to avoid death.



The Heart of England Critical Care Network study suggests that clinicians differ markedly in their prognostic estimates for identical patients, and that compared to an objective outcome prediction model their estimates may be pessimistic. The suggestion from the SUPPORT model that UK clinicians are pessimistic should be treated with caution since the model was produced in the USA and Justice points out the dangers in applying outcome prediction models in different health care systems[13]. A separate study also carried out in West Midlands critical care units and again involving consultants making prognostic estimates for patients with COPD suggested that consultants differ in the way they interpreted patient's characteristics when attempting to formulate prognoses and these differences lead to different interpretations of prognosis for identical patients[6].

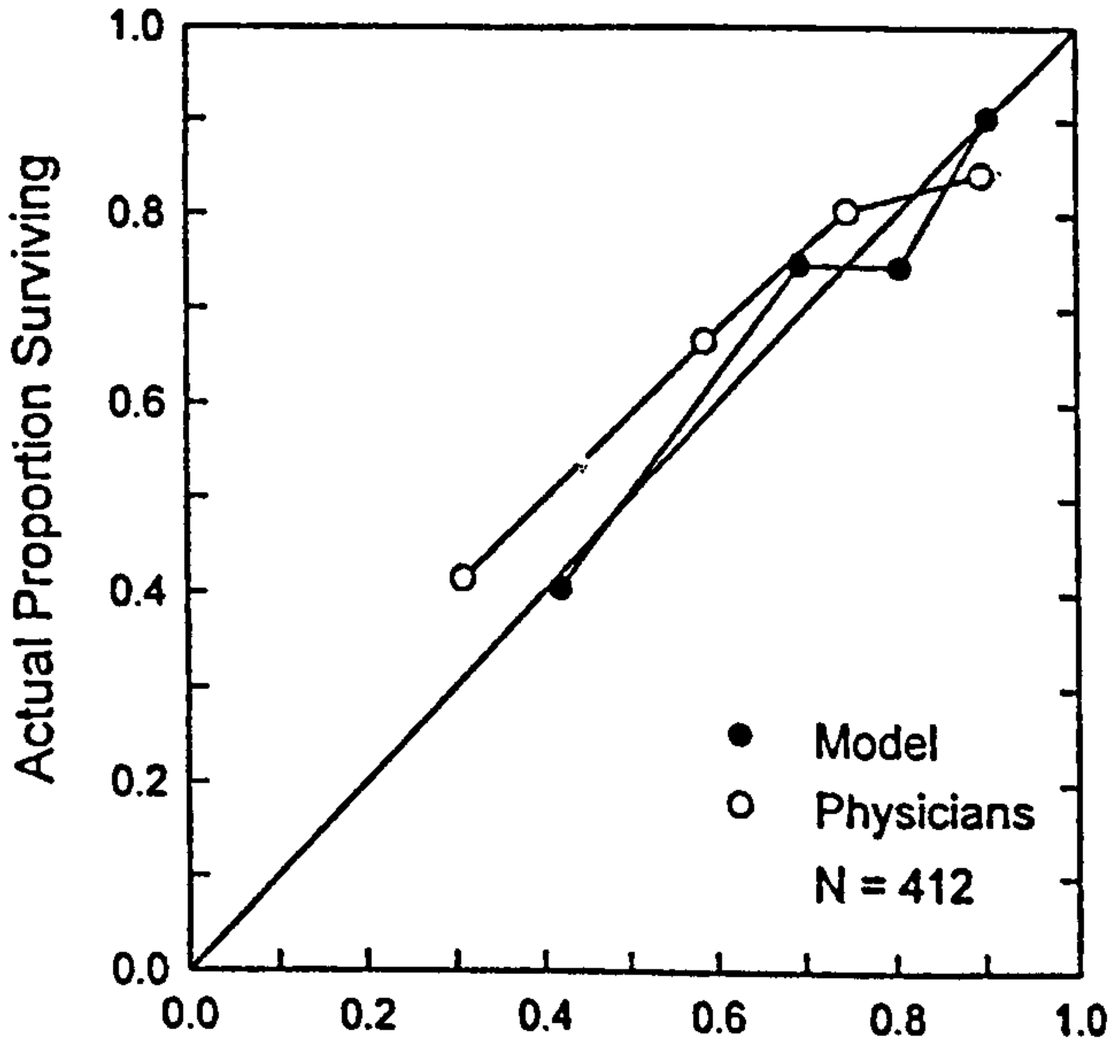
In the SUPPORT study mentioned above an outcome prediction model for COPD patients was developed in five US hospitals using a model development set of 600 COPD patients and then tested in 416 subsequent patients. This study used observations made on day three of the hospital admission and only 526 patients were admitted to critical care. The COPD model had an area under the ROC curve of 0.731 and clinicians 0.722, with the model being better calibrated and clinicians tending to be pessimistic[12]. Figure 1.4.2 (below) is taken from the SUPPORT study and shows the calibration curves for clinicians and the SUPPORT COPD model. In this study the best performance was seen when clinicians supplemented the model predictions with their own judgement with an area under the ROC curve of 0.749 and improved calibration. The SUPPORT study suggests that objective estimates of outcome can support and improve clinical decisions.

1.5 What are the likely explanations for the variability in clinicians' prognostic estimates?

Prognostication is a difficult task for clinicians, in that it demands that predictive characteristics be correctly identified, noted and weighted in the light of information about outcome. Prognostication requires clinicians to use evidence about outcomes from the literature and/or from their own experience. Chapter 3 Figure Fig 3.3.1 (All studies

reporting hospital mortality for 10 or more intubated patients) shows that individual studies report very different hospital mortality for COPD patients, so that using the literature to understand outcomes may not be easy.

Figure 1.4.2 Calibration curves for the SUPPORT COPD model and clinicians taken from the SUPPORT study [12].



Research on cognitive biases in decision making suggests that decisions tend to be unduly influenced by patients who are particularly memorable[14]. In this respect an intubated COPD patient who was difficult to wean from the ventilator and who was reviewed on many ward rounds over a number of weeks is more likely to lodge in a clinician's memory than the uncomplicated patient who was quickly weaned and discharged. Learning from experience is also hampered by the difficulty of accurately remembering all of a patient's characteristics. The clinician may not know the outcome at hospital discharge for all patients upon whom decisions are made, and it is likely that this information will be even less complete for follow-up periods in the region of 6 months. In addition the authors of the Heart of England Critical Care Network hypothesised that in a health care system where historically ICU beds have been in short supply, the confident identification of futility in patients with COPD and respiratory

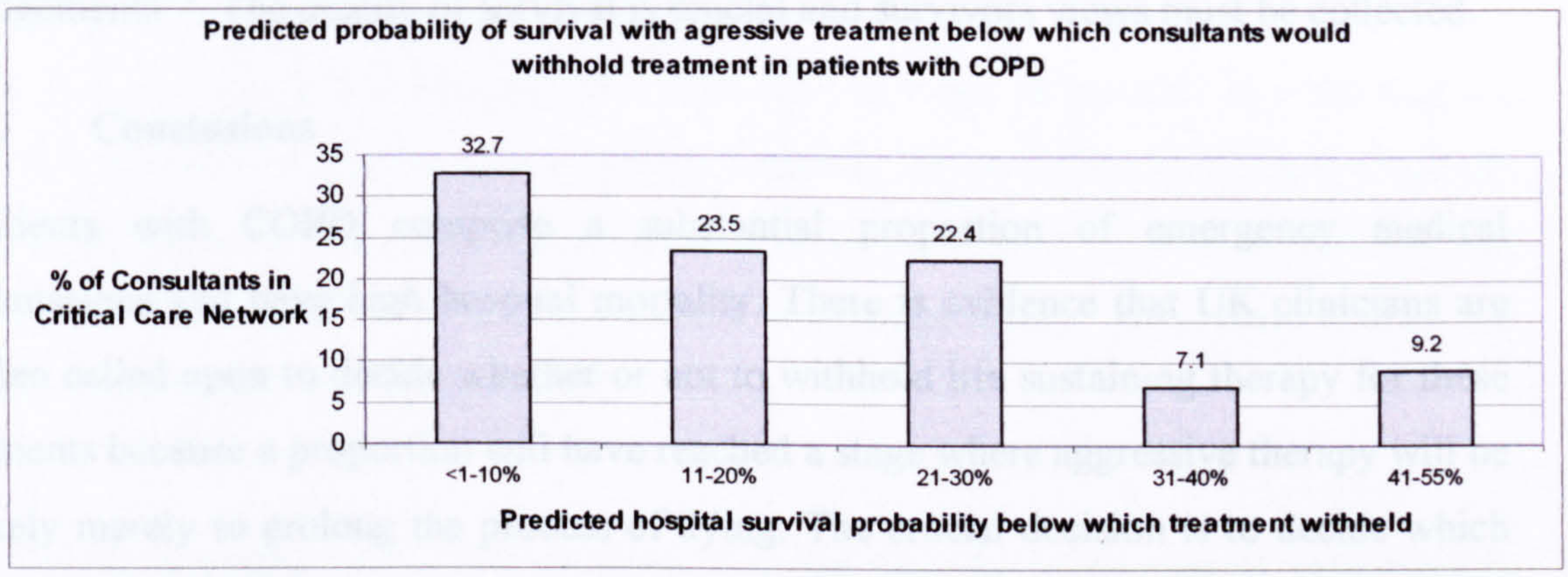
failure may have eased the cognitive dissonance otherwise experienced when ICU beds were unavailable[8]. The habitual identification of futility resulting in certain groups of patients being rarely admitted to ICU might result in a self-fulfilling prophecy leading to the development of a tacit folklore of pessimism about outcomes for that patient group.

1.6 What characteristics would a prognostic model require to improve COPD decision making?

The foregoing suggests that given the evidence of difficulties in decision-making for COPD patients and the cognitive challenges faced by an individual clinician who wishes to make better decisions, there may be a role for prognostic models in supporting decision making. This assertion is consistent with the improved discrimination and calibration seen when American clinicians supplemented their clinical judgement with the SUPPORT model[12]. An understanding of the information required to make a decision is very important when considering the potential for a decision aid to support decisions making. Producing a decision aid that distinguishes a patient with a 5% risk from a patient with 7% risk of death or an aid that is required to identify patients certain to have no (0%) chance of survival is much more difficult than producing a model that identifies patients above a given risk threshold, such as above 30%. Clinicians in the Heart of England Critical Care Network were asked at what predicted probability of hospital survival they would move from intubating to not intubating a COPD patient in their mid seventies, given that the patient would die if not intubated [8]. The distribution of the clinician's responses is shown in figure 1.6.1. Out of 120 clinicians making intubation decisions in the network, 82% responded and 94% of these (93 clinicians) were able to suggest a survival probability below which they would withhold intubation. The mean (SD) predicted hospital survival threshold with intubation below which the consultants would move from intubating to not intubating a patient was 22% (13.2%), so that a prognostic model that could reliably identify patients with a greater than 22% chance of hospital survival would have the potential to support decision making. In other words UK decision making did not require the identification of

patients with a 0% chance of survival with treatment and nor did decision making turn on making fine distinctions between patients for example differentiating between a 5% or a 7% chance of survival. However clinicians clearly vary in their thresholds, and if this is seen as a justifiable element of their clinical discretion, the model would have to be reasonably accurate over a range of risk thresholds, say from 10% to 40%.

Figure 1.6.1 Predicted probability of survival with aggressive treatment below which consultants would withhold treatment in patients with COPD



Note Five (5.4%) of study participants felt unable to provide a threshold survival probability below which they would withhold aggressive treatment.

As highlighted in section 1.2 above, decision making typically involves clinicians under time pressure, and occurs at the bedside using the information obtained from history, clinical examination and the results of readily available emergency investigations. Any prognostic model that supports this process would need to be quick and easy to use and the sort of model that might be summarised on a single page of the Oxford Handbook of Medicine that most junior doctors carry in their pockets.

It is important to bear in mind that models make predictions for groups of patients with certain characteristics. They can indicate for example what proportion of 100 patients with these characteristics will be dead at a defined time point. Ninety-five percent confidence intervals can be calculated for that prediction, but these intervals will be for the group, not the individual. Any given individual can only live or die. On occasions it has been suggested that since the prediction of the model only applies to groups of

patients rather than to the individual patient and since the uncertainty for the individual must be greater than for the group[15] it is wrong to use the model to support decision making. Though the limitations of group predictions for individual patients cannot be disputed the response to the recognition of limitations is often to reject the model and fall back upon clinical judgement. However as outlined above there is evidence in the case of COPD patients that when compared head to head, clinicians judgements have poorer discrimination than models and are less well calibrated[12]. Studies of decision making by UK clinicians has reinforced the variability of clinicians unaided judgements[6 8]. The quality of survival is crucial and survivors views must be collected.

1.7 Conclusions

Patients with COPD comprise a substantial proportion of emergency medical admissions and have high hospital mortality. There is evidence that UK clinicians are often called upon to decide whether or not to withhold life sustaining therapy for these patients because a proportion will have reached a stage where aggressive therapy will be likely merely to prolong the process of dying. The crucial decision is to decide which patients will benefit from intubation. The identification of patients who will benefit requires clinicians to make prognostic estimates, and there is evidence that UK clinicians show important variability even when considering an individual patient with identical characteristics and identical preferences under conditions of identical resource availability. Simulation studies suggest that UK clinicians are pessimistic, and one explanation for this is it that pessimism has grown up as a defence against the cognitive dissonance faced by clinicians who have historically been unable to offer intubation to some COPD patients because of a shortage of beds[8].

The SUPPORT study in the USA also found that clinicians tended to be pessimistic. However it also showed that outcome prediction models for COPD patients can be produced and that the models show better discrimination and calibration than unaided clinicians[12]. The best outcome predictions occurred when clinician's judgement was used along with a carefully produced outcome prediction model.

One option in producing a model to improve UK decision making would have been to simply carry out an external validation study of the SUPPORT model in the UK. However the SUPPORT study had a grant of $25 million dollars and concentrated data collection in five hospitals with full time study staff dedicated to data collection. This allowed them to collect relatively complicated variables such as body mass index and ensure that difficult to collect variables such as PaO_2/FIO_2 were collected well. Experience in the UK during pilot studies suggested that collecting all the data required for a replication of SUPPORT would be too difficult using data collectors whose primary responsibility was not CAOS in around 100 units rather than five. For this reason it was decided to simplify data collection as much as possible in order that the burden placed on collaborators would be reduced, for example the 19 item Charlson comorbidity scale was used instead of the 42 comorbidities used in SUPPORT and alternative strategies were used to estimate body mass index. This meant that all the data in SUPPORT was not collected.

Given the frequency of COPD admissions in the UK, the suggestion of variability in decision making for identical patients, and the potential for this decision making to be improved by objective outcome models, this study set out to develop an outcome prediction model to help clinicians predict 180-day mortality for COPD patients with respiratory failure considered for intubation.

Chapter 2 Developing prognostic models

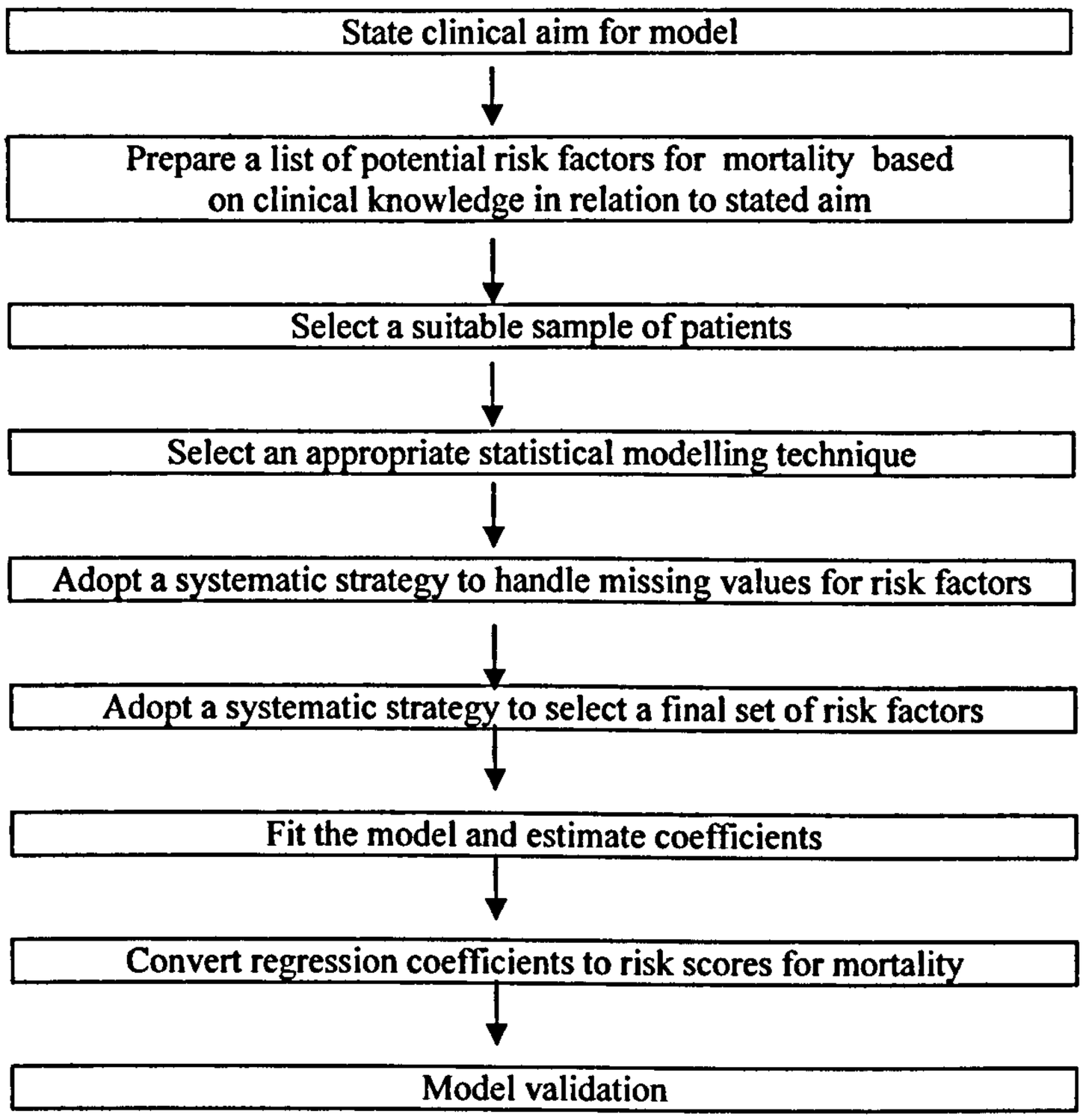
2.1 Introduction

In chapter 1 it was argued that accurate information about a patient's prognosis plays a central role in equitable decision making for patients with COPD considered for intubation, and that the most accurate prognostic estimates are likely to result when clinicians are supported by well developed prognostic models. In this chapter the methodological approach required to produce robust prediction models is reviewed.

2.2 Methodological aspects of outcome prediction

There is now a good understanding of the important methodological issues that underlie a rigorous randomised controlled trial (RCT) and most journals require that RCTs are reported systematically using the CONSORT guidelines[16]. A similar consensus statement has not yet emerged about the development of prognostic models[17]. However a number of authors have highlighted the methodological pitfalls that may occur in prognostic studies[18] and summarised the crucial aspects of prognostic model development[19-21]. Omar has recently suggested a systematic approach to the reporting of the model development process[22]. The development of the COPD and Asthma Outcome Study (CAOS) model will be reported using a modification of this framework as outlined in Figure 2.1 below. Harrell has pointed out that prognostic models can be inaccurate because of "violation of assumptions, omission of important predictors, high frequency of missing data and/or improper imputation and especially with small data sets, overfitting"[21]. Systematic reporting of the processes of prognostic model development should allow readers to understand clearly how the various threats to model validity have been dealt with, so that models that are likely to be accurate can be distinguished from those that are not. The robustness of model development should then be explored by well designed and adequately powered studies in further data sets to allow external validation.

Figure 2.1 Prognostic model development frameworks. [22]



2.3 The clinical aim of the model

There are many decisions to be made in the design of a study to produce an outcome prediction model, and it is crucial that the clinical aim of the model is clearly understood since this understanding will inform the design of the study. For example to understand the performance of individual surgeons, highly detailed information about individual patients will be needed and in general this requires prospective data collection [23]. If the mortality rate is low (for example 2%) investigators will require thousands of cases. If decision making requires the identification of patients with a zero probability of survival with treatment in order to limit that treatment, the model will require rigorous external validation before it can be used. Attempts to produce models that predict death with certainty have been disappointing and confidence in their use is often undermined when their specificity in external validation has been shown to be less

than 100%[24]. The ability of outcome models to identify patients certain to die has intuitive appeal but in many clinical situations patients at a very high risk of death are rare and are usually so ill that any benefits that might come from the early move from aggressive to comfort care may be minimal since even with the most aggressive care the patients will die quickly[25]. In the SUPPORT Study, 4301 patients with a series of medical conditions (including 1016 patients with COPD) thought to have a high risk of hospital mortality were studied, and prognostic models produced with the aim of allowing patients with dire prognoses to choose comfort over aggressive care[26]. Only 115 patients (2.7%) out of the 4301 patients had a predicted probability of 2-month survival of <1%, indicating that among even the sickest of hospitalised medical patients the identification of patients with virtually no chance of survival is difficult[25].

The clinical aim of a model to support decision-making for COPD patients has been highlighted in sections 1.2 and 1.6. It will involve estimates of individual patient's risks of mortality and so will require prospective collection of data describing individual risk factors, but since the mortality rate after critical care admission with COPD is in the region of 38% the sample size needed to achieve this will be relatively moderate[27]. In addition the aim is to produce a bedside model, so there will be an emphasis on identifying variables for which it is easy to collect data reliably and which can be quickly used to generate a survival probability.

2.4 Relevant potential risk factors for mortality based on clinical knowledge.

Simon and Altman [20] suggest the classification of prognostic factor studies into phase I, phase II and phase III studies. In phase I studies tentative relationships between risk factors and outcomes are explored and positive associations are considered to generate hypotheses. They include assay refinement in this stage. In phase II studies exploratory analyses are carried out, for example to generate the hypothesis that an age change of 10 years is associated with an increased risk of death. In phase III studies pre-stated hypotheses are tested and the magnitude of effects confirmed. Though Simon and Altman's emphasis is on prognostic factors rather than prognostic models, their classification is helpful in stressing the importance of avoiding multiple data driven

comparisons and exploratory analyses other than in phase I studies. In the development of the CAOS model a systematic review of COPD outcome studies was carried out in such a way as to fulfil as far as possible the role of Simon and Altman's phase I and phase II studies. Critical appraisal of the COPD outcome studies provided greater insight into the likely robustness of risk factors/outcome associations, with relationships that had been identified in numerous well conducted studies given more weight than associations only identified in one study of poor quality. This allowed much of the variable selection used to produce the final model to be carried out prior to explorations of the relationship between predictors and mortality. In addition knowledge about the likely robustness of predictors could be linked with information from the study about ease of data collection to make choices about variables without resorting to data driven choices. Furthermore a clear understanding of which variables are robust becomes important if stepwise selection methods are used in the ultimate stages of model development. For example, it might be decided to force a well-established variable into a model, whilst accepting that a variable shown to have an association in only one poorly conducted previous study should be dropped. The systematic review of the literature is outlined in Chapter 3 below.

2.5 Selecting a suitable sample of patients

Altman points out that ideally the development of prognostic models should use an inception cohort of patients[28], that is to say patients who are all at the same point in the illness. The identification of such patients may be easiest at the onset of a disease process. However identifying an inception cohort is not always possible and then it becomes important that care is taken to differentiate and classify patients according to the characteristics which classify their severity. In addition care must be taken to avoid selection bias so as to ensure that the patients used to develop the prediction model are representative of those in which the model will be used in the future. These issues are discussed in more detail in the sections below.

2.5.1 Defining the diagnosis of patients included

As explained in section 1.1, airways obstruction can be caused by pure asthma, pure COPD or by a mixture of asthma and COPD. A clear distinction can be impossible clinically and may even be controversial after extensive laboratory tests. For this reason the patients to be included were all those patients over the age of 45 with airways obstruction, with clinicians classifying the patients on clinical grounds as pure asthma, pure COPD or a mixture of COPD and asthma. The age 45 was used as a cut-off as the aim of the study was to support decision-making for patients in whom clinicians might consider that treatment should be limited because the probability of survival was so low. COPD is a chronic progressive disorder that is unlikely to reach a state associated with severe respiratory failure below the age of 45 and young patients with terminal disease are likely to be atypical. Thus most patients with airways obstruction requiring intubation below the age of 45 would be likely to have asthma and there is consensus that all these patients should be intubated if they require it. Rather than use the finite resources of the study to collect data about patients for whom decision support is not required an age cut-off of 45 years was used.

2.5.2 Selecting a subset of hospitalized patients with airways obstruction

The clinical aim of the model dictates which of the hospitalised patients with airways should be selected for the model. The clinical aim is to help clinicians to decide whether aggressive care is likely to enable a patient with COPD to realise their goals for treatment or whether aggressive care is likely merely to prolong the process of dying. In order to realise this aim it is necessary to understand how patient characteristics available prior to the institution of aggressive care predict outcome with that aggressive care. It is for this reason that the patient characteristics in the 24 hours prior to ICU entry will be the basis of this study. It is also crucial that associations between patients' characteristics and outcome are understood in the context of all appropriate care being available, and it is for this reason that model development should include only those patients who would be considered eligible for intubation if conservative treatment including non-invasive ventilation failed. The importance of assessing the significance

of prognostic factors in patients treated the same way has been stressed by Altman [17] and is particularly relevant in COPD patients given that there is evidence of variation in treatment limitation decisions[6 8 29] and the majority of patients who require intubation will die if it is withheld.

2.5.3 Estimating sample size

Sample size calculations were informed by the recommendation that for each prognostic variable, the dataset should include at least 10 events in order to develop a robust model[30]. It should be noted that a risk factor with k categories contributes k-1 levels to the model, e.g. with age categorised into three levels, 20 deaths are required to allow reliable estimates of the contribution of each age category to the risk of death. An estimate of the likely number of levels in the CAOS model was based on the SUPPORT COPD model that was developed and tested in a sample of 1016 patients[12] and had an ROC area of 0.73 and good calibration. The SUPPORT model was a Cox proportional hazards model which contained 10 variables; age, PaO_2/FiO_2 , Body Mass Index, no Body Mass Index, activities of daily living, albumin, an acute physiology score, congestive cardiac failure as a cause, cor pulmonale and number of comorbid illnesses. It was considered likely that the CAOS model would contain similar predictors, but because it was intended to categorise variables for ease of bedside scoring, it, was likely that 10 predictors might result in 20 levels in the model. On this basis it was likely that 200 deaths would be required. The SUPPORT model was developed on the first 600 patients recruited and then tested on the subsequent 416 patients. The CAOS model development strategy involved bootstrapping (section 2.11 below) so that the whole sample could be used in model development and validation without any loss of external validity in comparison to SUPPORT. If the 180-day mortality in CAOS was similar to the 33% observed in SUPPORT this would require a minimum sample size of around 600 patients. However it was unclear at the start of the study what proportion of patients would have treatment limitations and also the larger the sample size the lower the risk of over-fitting during model development. For this reason it was decided to stop the study either when 1500 patients had been recruited or at the latest date that allowed

adequate time for follow-up and analysis, as long as there was a minimum of 200 deaths in patients without treatment limitation.

2.5.4 Patient selection: implications for external validity

A clear understanding of patient selection is crucial in understanding which patients the model might be applied to in the future. If there is any selection bias, attempts should be made to define this and an appropriate warning attached to the model when it is used in clinical practice. The observation that there is a process of selection that determines which patients with COPD receive aggressive care is the reason why a model needs to be developed in the first place. As highlighted above such selection is actively recommended by the COPD NICE guidelines[4]. However this means that there is an inevitable danger of selection bias in the patients who are actually recruited to the study. It might be thought that the way to deal with this would be to develop the outcome model on all patients with COPD, whether they were selected as candidates for aggressive care or not. Such a strategy poses major logistical problems. Patients not selected as candidates for aggressive care are scattered all over the hospital, whereas those selected are brought to the critical care area where data collection can be concentrated. In addition, and more importantly, the whole point of the model is not to provide an answer to the general question "what is the probability of survival of a patient with a severe exacerbation of obstructive airways disease", but to provide an answer to the question "what is the probability of survival of a patient with a severe exacerbation of obstructive airways disease who receives all treatment up to and possibly including intubation". This emphasises Altman's point that outcome prediction models cannot ignore treatment[17]. The strategy used in this study to deal with selection bias was to recruit patients from a large number of different units so that all patient types who might be appropriate for active treatment would be likely to be selected somewhere. The success of this approach in overcoming selection bias depends upon clinicians being unable to operate a consistent admitting strategy across the 95 units in the study. As long as such inconsistency exists, all the patient types who might be considered for aggressive therapy will be likely to be included in the sample. This will

allow the model to be applicable to all the patients who might be considered for aggressive therapy in the real world. There is evidence to suggest that even when prescriptive guidelines exist about which patients should receive which treatments, the guidelines are followed inconsistently and patients either receive treatment that they should not receive or do not receive treatment that is appropriate. For example, Hemmingway showed that patients with ischemic heart disease were both over and under treated[31].

2.6 Select an appropriate statistical modelling technique

Since the outcome of interest, survival at 180 days is binary, logistic regression is an appropriate technique to develop a model predicting 180-day survival.

2.7 Adopt a systematic strategy to handle missing values for risk factors

The recruitment of sufficient patients to develop robust prognostic models is expensive and time consuming. Statistical techniques such as logistic regression will omit cases if there are data missing in even one of the risk factors that are being evaluated. For this reason it is crucial that every effort is made to limit the amount of missing data. Data are rarely missing completely at random and this means that imputation of missing values may introduce bias. The methods employed in this study to minimise missing data are outlined in section 4.10 below. Harrell has suggested that straight-forward imputational strategies can be used for missing data with little detriment to the model as long as less than 5% of live subjects are affected[32]. Under these circumstances imputation using the mean or median value for all the subjects with data present can be appropriate, and when there is a good correlation of missing variables with other non-missing variables imputation of correlated means or medians may offer some advantage. However Harrell points out that such simple strategies are inadequate once the proportion of missing data exceeds around 5%.

When it comes to developing a parsimonious bedside model the frequency of missing data can be useful in identifying variables that are difficult to collect and might be inappropriate for use in a busy clinical setting. Also any information about variables

vulnerable to error can inform final variable selection for the model. The information collected during the study that highlighted problems of data collection is outlined in Chapter 8.

2.8 Adopt a systematic strategy to select a final set of risk factors

2.8.1 Methodological issues the selection of the variables in the final model

The strategy used to select a final set of risk factors for model building requires great care because attempting to fit too many predictors in a sample with too few events will produce an unstable model that is likely to contain false positive associations (over fitting) and is unlikely to predict well in future data. This is particularly important in the case of the CAOS model because even with a multi-centre study the number of patients recruited will be limited. As outlined in section 2.5.3 around 10 deaths per risk factor level are required for model stability[30] but the greater the number of deaths the lower the chance of overfitting. Harrell suggests that adequate model validation requires at least 100 deaths in the validation sample[33]. To achieve this for COPD would require data collection in most of the units in England for a year. It is important that the rigorous requirements of external validation studies are understood otherwise a well developed model may appear to perform poorly simply because the external validation study has been inadequately powered. External validation is discussed further in section 2.10.2 below.

There is therefore an argument for carrying out as much risk factor selection as possible before beginning the model development process. One method of achieving this is to collect information about the ease and likely reliability of candidate variables and use this information to produce a short list of variables to take forward to model development (Section 2.8.2 below).

The most important bias in variable selection occurs when variables are selected using the outcome observed in the data set that is used for modelling. Harrell suggests that clinical knowledge should guide the selection of candidate predictors, and that "early

deletion of those (factors) with little chance of being predictive or of being measured reliably will result in models with less overfitting and greater generalisability" [21]. Strategies that can be used to reduce candidate risk factors before any analysis with outcome are briefly listed below and summarised in Figure 2.8.1.

2.8.2 Strategies used to select variables for modelling independent of patient outcome

i. Literature review

Critical appraisal of existing literature sources can allow risk factors to be classified into those with evidence of a robust relationship with outcome and those where the relationship appears less well established or has only been suggested in studies of poor methodological quality.

ii. Practicality and simplicity of measurement

If a model is intended to be used in a busy clinical environment and there are two possible methods of collecting information about a single domain the simplest acceptable method should be chosen. In the CAOS study the functional score and Katz activities of daily living score were both calculated from information about the patients' independence prior to hospitalisation. If data collectors found that both were practical then the shortest and simplest might be chosen if prognostic performance was similar.

iii. Accuracy in measurement

Efforts should be made to identify risk factors that are measured accurately and reliably.

iv. Frequency of missing data

Variables that are frequently missing are often difficult to collect and are rarely missing at random. Unless complicated strategies are used variables with more than 5% missing cannot be imputed without the risk of introducing major bias.

Figure 2.8.1 Summary of strategies used to reduce the list of candidate variables before any modelling occurred

Literature review
Identify risk factors with an association with mortality
Critical appraisal
Stratify risk factors into those with a robust relationship with outcome on the basis of a consistent relationship demonstrated in numerous studies and studies of high quality.
Practicality of measurement and simplicity
Ask units about how easy they found it to collect variables
Accuracy in measurement
During the data collection process data collectors were asked about problems encountered and out-of-range or unreasonable values were identified
Magnitude of missing values
Drop variables with more than 5% missing values
Subjectivity
Consider the degree of subjectivity
Correlated variables
Explore the correlations between all variables and if values are highly correlated consider will be given to dropping one of them
Alternative method for measuring a single domain
Use data driven methods only if good evidence exists for different measures of a single domain and all else was equal data driven methods were used to choose between them at the last moment
Variables thought to be associated with selection bias
Identified any absolute contraindications to ICU admission in some units and drop such variables prior to modelling e.g. home oxygen

v. Subjectivity

Variables that are subjective are a potential source of bias particularly when they are collected from proxies i.e. carers and friends rather than the patients themselves. Proxy ratings are most accurate when they describe concrete observable domains such as those

comprising the functional score or activities of daily living, and least reliable when describing subjective domains such as patients' global ratings of their quality of life[34].

vi. Strong correlation with another variable

If two variables are strongly correlated, incorporation of both can introduce instability into the model. Also in some cases correlations occur because variables measure the same domain, in which case including both may add little to the model but increase its complexity.

vii. Possible selection bias

If a variable is seen as a virtual contraindication to intubation in many units the patients with that characteristic who are admitted to ICU may be selected because they are "super fit" in other respects. If there are sufficient numbers of these patients, the variable may be retained in a final model with a coefficient that would be wholly inappropriate if applied to the patients who do not reach critical care. Selection bias is of course a potential problem for all the variables in the data set, but for the majority there is likely to be inconsistency in the way that such bias operates between units. Selection bias should only be grounds for excluding a variable if the impression is that the bias has been strong and widespread.

2.8.3 Composite physiology scores

Risk adjustment models for hospitalised patients typically measure a number of biochemical and physiological variables to assess the magnitude of the homeostatic derangements as a marker of the severity of the acute illness. Examples include the acute physiology score (APS) in APACHE II [35] and APACHE III[36]. The SUPPORT study developed a score specifically for COPD patients. This used the APS from APACHE III but gave additional weight to albumin and PaO_2/FiO_2, indicating that disease-specific acute physiology scores can be more useful than generic scores[12]. Developing a composite score to weight and select the 17 or so biochemical and physiological variables that are available during the assessment of a patient with COPD would require at least 170 deaths even if all the risk factors were modelled as

continuous variables. Generic or COPD acute physiology scores developed in the USA may be poorly calibrated for the UK[13 37]. In order to deal with this problem it was decided to develop a disease specific acute physiology score for the UK using data from the UK Case Mix Programme. This allowed acute physiological variables to be weighted in a dataset containing over 8000 COPD patients admitted to ICU (Chapter 8). As a consequence the acute physiological variables collected in the CAOS study could then be used without the risk of data driven weighting that would occur if the acute physiological variables were weighted and selected within the much smaller CAOS data set. Though this is not a perfect strategy since the acute physiology from patients in the case mix programme would be measured following admission to ICU, it is likely to be the best strategy available given the limitations of the alternatives.

2.9 Moving from a logistic regression model to a useable score

Once a model has been produced it is often useful to transform it into an integer scoring system. This allows users to easily calculate a total risk score once the patients' characteristics are known without the need to carry out complex mathematical calculations. The production of an integer score involves the multiplication of the model coefficients by a number that converts them to whole numbers. This will require that some coefficients have to be rounded up or down. It is sensible to carry out this process before any validation or adjustment for overfitting is carried out so that the reported performance of the model takes into account any drop off in performance produced by the transformation and rounding.

2.10 Validating the model

Harrell points out that "only with appropriate model validation can an apparently accurate model be shown to be inaccurate"[21]. In this section the various strategies that can be used for model validation are briefly reviewed followed by a description of the bootstrap approach used for the CAOS model.

2.10.1 Internal Validation

i. Data splitting

In this method, a portion of the data, e.g. 2/3rds, is used for model development. The model is then tested on the remainder of the data. The area under the receiver operating curve (ROC) is calculated to determine discrimination and a measure of calibration is estimated.

An advantage of this is that it may be possible to make a split with respect to geography or time so that the validation is more stringent in demonstrating generalisability.

However this method is wasteful of data since only a portion of the data is used to produce the final model. Also different ways of splitting the data will produce different answers.

ii. Cross-validation

Cross-validation is repeated data splitting. Multiple models are developed and tested with the results averaged over multiple repetitions. In a sample of say 1000 patients the model might be developed 400 times leaving out a random 50 patients each time. It has been suggested that to produce accurate estimates more than 200 models may need to be developed[38].

Cross-validation is similar to data splitting, but it has the advantage that a) the training sample can use a much greater proportion of the data since less data is discarded from the training set and b) cross-validation does not rely on a single data split.

The disadvantage is that there is a tendency to get different estimates of validity when the process is repeated (though this is nowhere near as bad as the variation seen with simple split sample validation).

iii. Bootstrapping

Bootstrapping is an alternative form of internal validation that depends upon the generation of large numbers of 'bootstrap' samples. Patients are dropped randomly from the model development sample and replaced by including other patients more than once.

This results in a population of patients with a slightly different spread of severity than that seen in the original sample. This can be automated and carried out hundreds of times with the model developed and tested in each sample. Thus if the original sample contained 600 patients the bootstrap sample still contains 600 patients but spread of severity will have been altered by the random replacement and replication process[38]. Bootstrapping strategies are described in more detail in section 2.11.

2.10.2 External validation

External validation involves testing the model in a completely new population of patients. It has the advantage of providing an estimate of the model's performance in the "real world" and may for example give insight into the effect of secular trends on predictions made by the model.

In order for the validation to be meaningful Harrell suggests the sample needs to contain around 100 events[33]. In England, this would be likely to require 95 units collecting data for 9 months, or 48 units collecting data for 18 months. A large well designed validation study would also allow researchers to investigate the possibility that the results of CAOS had altered admitting behaviour so that for example clinicians had started to admit sicker patients. If such a change in behaviour had occurred the CAOS model might have the potential to be recalibrated. Ideally prognostic scores should be seen as tools that need to be continually validated and updated to take account of changing practice. This area holds great potential for methodological advances that would make prognostic scores more trusted and therefore useful. This area is discussed in more detail in chapter 12.

2.11 Bootstrapping strategies to take account of overfitting

2.11.1 Bootstrapping to modify model coefficients to adjust for over fitting

The intercept and coefficients from the model produced in a certain set of data will tend to fit that data well and be influenced by the range of the values of the variables in that data. If the variables measure disease severity the model fit will be influenced by the spread of severity in that sample. If the model is subsequently used in another sample of patients where the range of severity is different, the model fitting the range of severity

in the original sample may tend to predict less well in the new population. However bootstrapping can be used to adjust the intercept and coefficient in the final model to take account of the potential heterogeneity in future patient samples by using multiple bootstrap samples to drop and replace patients from the original sample. This procedure mimics the heterogeneity of future patient populations and alters the calibration of the final model so that the calibration performance will be more robust. The usefulness of this procedure depends upon the original sample having recruited the types of patients likely to be encountered in the future. As in any application of trial data to future patients, external validity requires that the original study population are similar to the population in which one wishes to extrapolate the findings. If the original sample was biased and totally excluded an important subset of patients bootstrapping will be unable to remedy the situation.

A typical approach would involve the generation of 500 bootstrap samples. The new intercepts and coefficients fitted would differ from those in the original model by a magnitude that reflected the original model's lack of fit in the new bootstrap samples. The average of the new intercept and coefficients could then be used to produce a new model that had a coefficient and intercept that produced less good fit in any individual sample, but performed better on average in samples of patients with varying distributions of severity.

2.11.2 Bootstrapping to estimate the performance of the model in future samples

In this use of bootstrapping the variables selected in the final model are fitted in a large number of bootstrap samples and then tested in the original patient sample. This allows an almost unbiased estimate of the expected discrimination of the final model in future populations. This is expressed in terms of an adjustment to the area under the receiver operator characteristic (ROC) curve that describes the estimate of the model's discrimination in future patient populations.

2.12 Model calibration

2.12.1 Calibration curves

Calibration curves are useful ways of describing the predictive performance of prognostic models. Patients are placed in a number of equally sized groups and the mean predicted probability of mortality for each group is plotted against the observed proportion of that group that actually do die. A clear understanding of the calibration of predictions is crucial to understanding how predictions can be used to guide patient management. For example in Chapter 1, Figure 1.4.2 shows the calibration curve for the COPD SUPPORT model and the unaided American clinicians. It showed that clinicians tended to be pessimistic for most patients except those with the highest probability of survival, while the model tends to be pessimistic for patients with a moderate probability of survival (around 70%) and optimistic for patients with an 80% probability of survival, but is otherwise well calibrated.

2.13 Conclusions

The development of a robust model for the prognosis of COPD patients has been achieved in the United States using a group of patients with 330 deaths at 180 days[12]. This nine-variable model out-performed clinicians in terms of both discrimination and calibration The technique of bootstrapping[38] was not used in the US model, but this permits more efficient use of data and holds out the prospect of producing a more robust model in a sample of equivalent size. Nevertheless model development must be carried out with great care in order to avoid data driven overfitting, and Omar[22] has suggested a schema to guide model development. A crucial step in avoiding overfitting is to ensure that only variables that have a robust relationship with outcome are used in model development. The next chapter outlines the systematic review that was carried out in order understand the risk factors associated with outcome in COPD.

Chapter 3 Systematic review of intubation studies for patients with COPD

3.1 Identifying relevant publications

Systematic reviews aim to identify and evaluate all the relevant studies in order to avoid the biases inherent in merely selecting the latest or best known studies, and aim to provide a comprehensive summary of the available evidence. There is no consensus about the best search strategy for finding studies that identify prognostic factors[28]. The search strategy used was developed from the sensitive search strategy for prognostic studies outlined for Medline by McKibbon et al[39] and used in Embase using the CASP filters modification (Appendix 1). The same strategy was used to search the grey literature using the SIGLE database. The bibliographies of the identified studies were searched and in addition Web of Science was used to carry out a citation search on the papers identified as describing the outcomes of COPD patients with acute respiratory failure. Papers were selected for further review if the abstract suggested that: (1) the study reported the outcome of COPD patients intubated for the treatment of acute respiratory failure and (2) data were available on the outcome of intubated patients. Data were extracted if the study reported the outcome of more than 10 COPD patients as a distinct group. Twenty nine studies were identified that reported outcomes of more than 10 COPD patients admitted as emergencies and intubated and these studies are reviewed in more detail below.

3.2 Studies reporting outcomes for more than 10 intubated patients

Twenty nine studies reported outcomes for more than 10 intubated COPD patients. Many of these studies also attempted to identify patient characteristics that have prognostic value in predicting survival. Altman has recently described the problems of systematically summarising studies of prognostic variables[17 28]. Table 3.2.1 below summarises the problems that Altman highlights and illustrates them with examples from the COPD literature with the strategies used in this study to address the problem if relevant.

As Table 3.2.1 illustrates, the pitfalls encountered in producing high quality prognostic studies are legion and consequently very few studies that set out to identify prognostic factors are sufficiently rigorous to produce evidence that is likely to be accurate and generalisable[40]. In addition the methodological heterogeneity of study design means that meta-analysis of results is likely to be difficult and lack precision. A recent workshop on the meta-analysis of observational studies emphasised that these have much more potential for bias than randomised controlled trials, and as a result reporting single summary estimates of outcome will often be misleading[41]. It is for this reason that the results of the studies identified in the systematic search will be presented in a narrative descriptive format describing the mortality attending intubated COPD patients and the factors that have been explored as predictors of this mortality. In view of the marked heterogeneity in study design, aggregate mortality figures should be interpreted with caution, and where possible the mortality of relevant subgroups will be presented.

3.3 Mortality following intubation for COPD

Table 3.3.1 displays the reported mortality in Intensive Care Unit (ICU), hospital or post hospital) for the intubated COPD patients in the 29 studies identified by the literature search. The heterogeneity in mortality is shown in Figure 3.3.1, in which the results of the 24 studies that report hospital mortality are plotted along with the 95% confidence intervals.

The heterogeneity of survival in the different studies partly reflects the small size of many of the studies and also arises because of a number of the factors that Altman has highlighted as barriers to meaningful meta-analysis of prognostic studies[17], such as differences in inclusion criteria.

Table 3.2.1 Problems with systematic reviews of prognostic studies (modified from Altman[17])

Problem identified by Altman	Example relevant to Intubated COPD outcomes
Difficulty in identifying all studies in the literature	A multifaceted approach was used in which a sensitive strategy designed to identify prognostic studies was used along with bibliography and citation searches.
Negative (non-significant) results may not be reported (publication bias)	Only one of the studies[12] had published a prior analysis strategy[42], so it is impossible to tell whether a study has reported negative results. In addition negative studies may never have been published. This makes it difficult to know if associations noted in one study were found to be negative in other studies and not reported.
Inadequate reporting of methods	Data driven associations are prone to false positive findings and most of the studies did not report how the analyses were planned and how many comparisons were made.
Variation in study design	In the SUPPORT study[12] the acute physiology data used to build the outcome model are collected on the third day of hospital admission. In the APACHE III study[43] the worst value recorded in the first 24 hours after critical care entry is used.
Most studies are retrospective	This often means that the data used are those available in existing data bases and are often generic e.g. APACHE II scores rather than COPD disease specific.
Variation in inclusion criteria	In some studies only COPD patients with a clear chest x-ray are included. In others all COPD exacerbations are included.
Differing methods of handling continuous variables (some dependent on data)	In many studies continuous variables are categorised and risk ratios presented for the grouped categories. This makes comparison between studies difficult. It is also likely that categorisation decisions will have been data driven.
Different statistical methods of adjustment	Many studies simply report univariate associations between risk factors and outcome. In addition some studies explore associations with critical care mortality, others hospital mortality and others 180-day or even 365-day mortality.
Adjustment for differing sets of variables	When multivariate associations are reported it is not always clear what the other risk factors were that were adjusted for and no two studies adjust for the same set of variables.
Inadequate reporting of quantitative information on outcome	It is not always clear when mortality is reported how many patients have been lost to follow-up.
Variation in presentation of results (for example survival at different time points)	In some American hospitals hospital mortality is reported when a large proportion of patients are discharged back to chronic care facilities where they may die soon afterwards. Reporting mortality at fixed time points e.g. 30-day is more informative.
Different assays or measuring techniques	For example: FEV_1- post bronchodilator in period of stability is most accurate, but frequently not stated
Variation in methods of analysis	Some studies use logistic regression, others use Cox proportional hazards, others use chi-square tests.
Lack of recognised criteria for quality assessment	Whereas published randomised controlled trials should be published in accordance with the CONSORT statement[16], there is no such agreed convention adopted for prognostic studies.

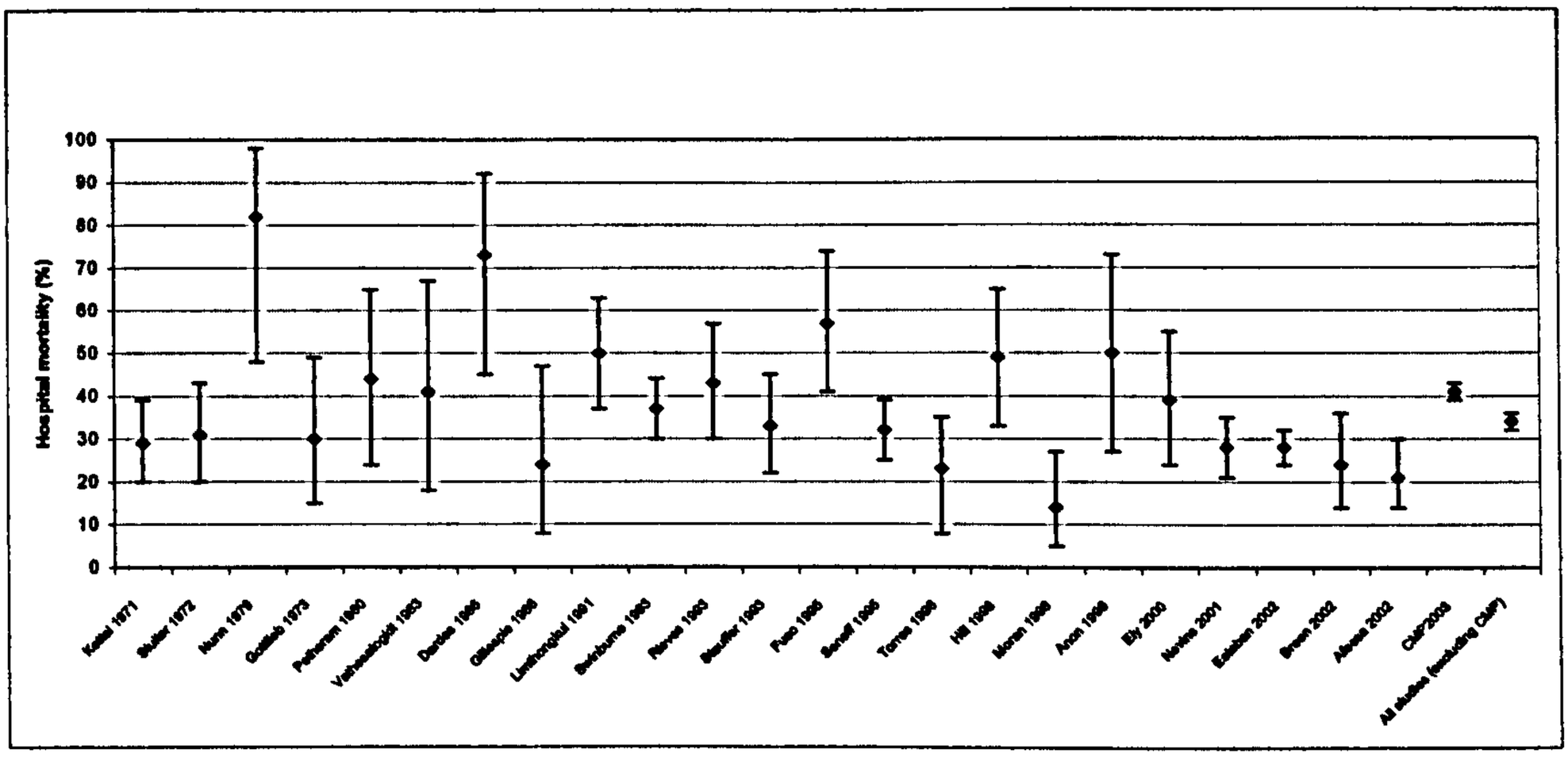
3.3.1 Variations in mortality due to case-mix

The difficulty in establishing a clear understanding of the meaning of the differences in mortality can be illustrated by a comparison between the studies where some information was available on the case mix of the included patients using measures such as APACHE II score, aetiology of the exacerbation or the age of the population (Table 3.3.1 below). It can be seen that for many studies the age and case mix measures for the intubated patients are not specifically reported but grouped with the non-intubated patients, making comparisons difficult. In addition it can be seen that for the majority of these studies the 95% confidence intervals around the hospital mortality figures are similar (Table 3.3.1.1 and 3.3.1.2). In studies with higher mortality there are typically differences in case mix. Either the patients are older, or the sample has included patients with pneumonia, or the APACHE score is higher. For example in the Seneff study[43] the 170 intubated patients had a mean (SD) APACHE III score of 63 (24.9) which was lower than the mean (SD) APACHE III score of 67.8 (22.9) for the definitely/probably intubated patients in the Wildman study[27]. However there are studies from single centres which appear to represent outliers. For example the Moran study from Australia[44] has low hospital mortality despite APACHE II scores and patient ages that were comparable with other studies. However it did not include patients with pneumonia.

3.3.2 Variations in mortality due to poorly defined outcome time point

Though almost all studies report hospital mortality, measures such as 30 or 60-day mortality are more robust for comparison purposes because the definition of hospital mortality may be influenced by local discharge practices. Nevins reported[45] the comparatively low hospital mortality of 27.7% (95% CI 21.1-35.2) in 166 intubated COPD patients from one US centre in which 38% of patients were transferred to chronic care facilities. When patients are transferred to chronic care facilities the hospital mortality is difficult to interpret.

Figure 3.3.1 All studies reporting hospital mortality for 10 or more intubated patients



The low mortality found by Nevins was accompanied by a relatively low case mix score, in this case APACHE II, mean (SD) score 15(6) vs. mean (SD) APACHE II 19.7 (6.4) in the Wildman study[27] and once again the Nevins study did not include patients with pneumonia and heart failure. In the Wildman study intubated patients had a mortality of 35.9% (95% CI 34.1 – 37.6%) in the hospital housing the CMP unit, but an ultimate hospital mortality of 40.6% (95% CI 38.8 – 42.4%). Ely reports a hospital mortality of 38.6% (95% CI 24.4 – 54.5) for 44 intubated COPD patients from a US academic centre in which patients had a mean (SD) APACHE II of 19.4 (5) [46] which is similar to that observed in the Case Mix Programme study. In the Esteban study [47] the 522 patients with COPD receiving mechanical ventilation in 361 ICUs in 20 countries had a hospital mortality of 28% (95% CI 24 – 32) and a Median IQR SAPS II of 38 (31 – 49). This compares to a median (IQR) SAPS II of 42 (35- 52) for the intubated patients in the CMP study.

Table 3.3.1.1 29 studies reporting outcomes for more than 10 intubated COPD patients: ICU and hospital survival

Author publication year	Country	Number intubated	Intubated Critical care mortality	Intubated hospital mortality	Other mortality period
Kettel 1971[48]	USA	35	NA	11 (28.7%) (19.5-39.4)	NA
Sluiter 1972[49]	Holland	45	NA	21 (30.9%) (20.2-43.3)	NA
Nunn 1979[50]	UK	11	NA	9 (81.8%) (48.2-97.7)	NA
Gottlieb 1973[51]	USA	30	NA	9 (30%) (14.7-49.4)	2 year 20 (66.7%) (47.2-82.7)
Petheram 1980[52]	UK	25	NA	11 (44%) (24.4-65.1)	1 year 15 (60%) (38.7- 78.9)
Vathesatogkit 1983[53]	Thailand	17	NA	7 (41.2%) (18.4-67.1)	NA
Dardes 1986 [54]	Italy	15	NA	11 (73.3%) (44.9-92.2)	NA
Gillespie 1986[55]	USA	21	NA	5 (23.8%) (8.2-47.2)	1 year 12 (57.1%) (34.0-78.2)
Kaelin 1987[56]	Switzerland	39	NA	NA	180 -day 15 (38.5%) (23.4-55.4)
Menzies 1989[57]	Canada	95	20 (21.1%) (13.4-30.6)	NA	1 year 59 (62.1%) (51.6-71.9)
Limthongkul 1991[58]	Thailand	66	NA	33 (50%) (37.4-62.6)	NA
Swinburne 1993[59]	USA	200	NA	74 (37.0%) (30.3-44.1)	NA
Rieves 1993[60]	USA	58	NA	25 (43.1%) (30.2-56.8)	1 year 37 (71.2%) (56.9-82.9)
Stauffer 1993[61]	USA	67	18 (26.9%) (16.8-39.1)	22 (32.8%) (21.8-45.4)	1 year 38 (56.7%) (44.0-68.8)
Esteban 1994[47]	Spain	59	20 (33.9%) (22.1-47.4)	NA	NA
Fuso 1995[62]	Italy	37	NA	21 (56.8%) (39.5-72.9)	NA
Seneff 1995[43]	USA	170	NA	54 (31.8%) (24.8- 39.3)	NA
Torres 1996[63]	Spain	22	5 (22.7%) (7.8-45.4)	5 (22.7%) (7.8-45.4)	NA
Connors 1996[12]	USA	358	NA	NA	180-day 150 (43%) (37.8-48.5)
Hill 1998[64]	UK	41	12/41 (29.3 %) (16.1-45.5)	20 (48.8%) (32.9 - 64.9)	1 year 24 (59%) (42.1 - 73.7)
Moran 1998[44]	Australia	43	NA	6 (14%) (5.3-27.9)	
Anon 1999[65]	Spain	20	7 (35%) (15.4-59.2)	10 (50%) (27.2-72.8)	1 year 15 (75%) (50.9-91.3)
Hoo 2000[66]	USA	74	NA	NA	30 -day 7 (12.5%) (5.2-24.1)
Ely 2000[46]	USA	44	NA	17 (38.6%) (24.4-54.5)	NA
Nevins 2001[45]	USA	166	NA	46 (27.7%) (21.1-35.2)	NA
Esteban 2002[47]	World	459	109 (23.7%) (19.9-27.9)	128 (28%) (23.8-32.2)	NA
Afessa 2002[67]	USA	113**	NA	24 (21.2%) (14.1-29.9)	NA
Breen 2002[68]	Australia	63	10 (15.9%) (7.9-27.3)	15 (23.8%) (14 0-36.2)	NA
§Wildman 2003[27]	UK	3052	757/3052 (24.8%) (23.3-26.4)	1187/2927 (40.6%) (38.8-42.4)	NA

Mortality given as number (%) 95% CI. These are the patients intubated within 24 hours, we don't know about patients intubated beyond 24 hours, the denominator for hospital mortality is only 2927 because of missing data.

** In the Afessa paper some patients were intubated after failing NIV, the 113 reported in this table are the patients who were intubated from the outset.

§ It should be noted that the Wildman 2003 study is based on patients admitted to ICU prior to the period during which the CAOS study was carried out.

Table 3.3.1.2 Studies published since 1995 reporting hospital mortality for 10 or more intubated COPD patients in which the case mix data are reported

Study, year & country	Number of centers	Number of Intubated patients/ total in study	Hospital mortality for intubated patients % (95% CI)	APACHE III Mean (SD)	APACHE II Mean (SD)	Age Mean (SD)	Pneumonia included
Seneff 1995 [43] (USA)	40	170/362	31.8% (24.8 – 39.3)	63 (24.9)	NA	†66	No
Torres 1996 [63] Spain	8	22/124	23% (7.8- 45.4)	NA	NA	†67 (11)	Yes
Moran 1998[44] Australia	1	43/100	13.9% (5.3 – 27.9)	NA	†18 (5)	†68.5 (7)	No
Hill 1998[64] UK	1	41/41	49% (32.9 – 64.9)	NA	NA	NA	Yes
Ely 2000[46] USA	1	44/44	38.6% (24.4-54.5)	NA	All intubated 19.4 (5)	65 (12)	Unclear
Nevins 2001[45] USA	1	166/166	27.7% (21.1 – 35.2)	NA	All intubated 15 (6)	67 (13)	NO
Afessa 2002[67] USA	1	153/250	20.3% (14.2 – 27.5%)	NA	†19.0 (7.3)	†63.1 (8.9)	Yes
Breen 2002[68] Australia	1	63/74	23.8% (14 0 – 36.2%)	NA	†22 (7)	†65.5 (9.0)	No
Wildman 2003[27] UK	128	3052/3752	40.6% (38.8- 42.3)	67.8 (22.9)	†19.0 (6.7)	†Median 67.8 (IQR 60.5- 73.6)	Yes

† In these studies the case mix data is not available separately for the intubated patients and the value presented includes both intubated and non-intubated patients.

The authors of this international study found the 30-day mortality of the ventilated COPD patients to be 19.5% (95% CI 16.2 – 23.2) (Personal communication F. Frutos), such that only 2/3rds of deaths occurred within 30-days, a proportion which was considerably lower than the 35.7% (95% CI 33.9 – 37.4) 30-day mortality calculated in the CMP study which comprised around 90% of hospital deaths.

3.3.3 Overall mortality from studies reporting outcomes for intubated COPD patients

It can be seen from the foregoing discussion that the observed variation in mortality between studies reflects both the heterogeneity of the studied populations and imprecision in definitions such as hospital mortality. As a result any summary mortality figure that incorporates data from all the studies must be treated with caution. In addition the UK CMP study is by far the biggest and of the studies and therefore has a dominant influence on the overall figure. Figure 3.3.3 below displays the overall mortality at discharge 180 days and 1 year for all the studies, and it can be seen that around 40% die in hospital (based on 4675 patients), around 43% die by 180 days (based on 387 patients) and around 60% die by 1 year (based on 327 patients).

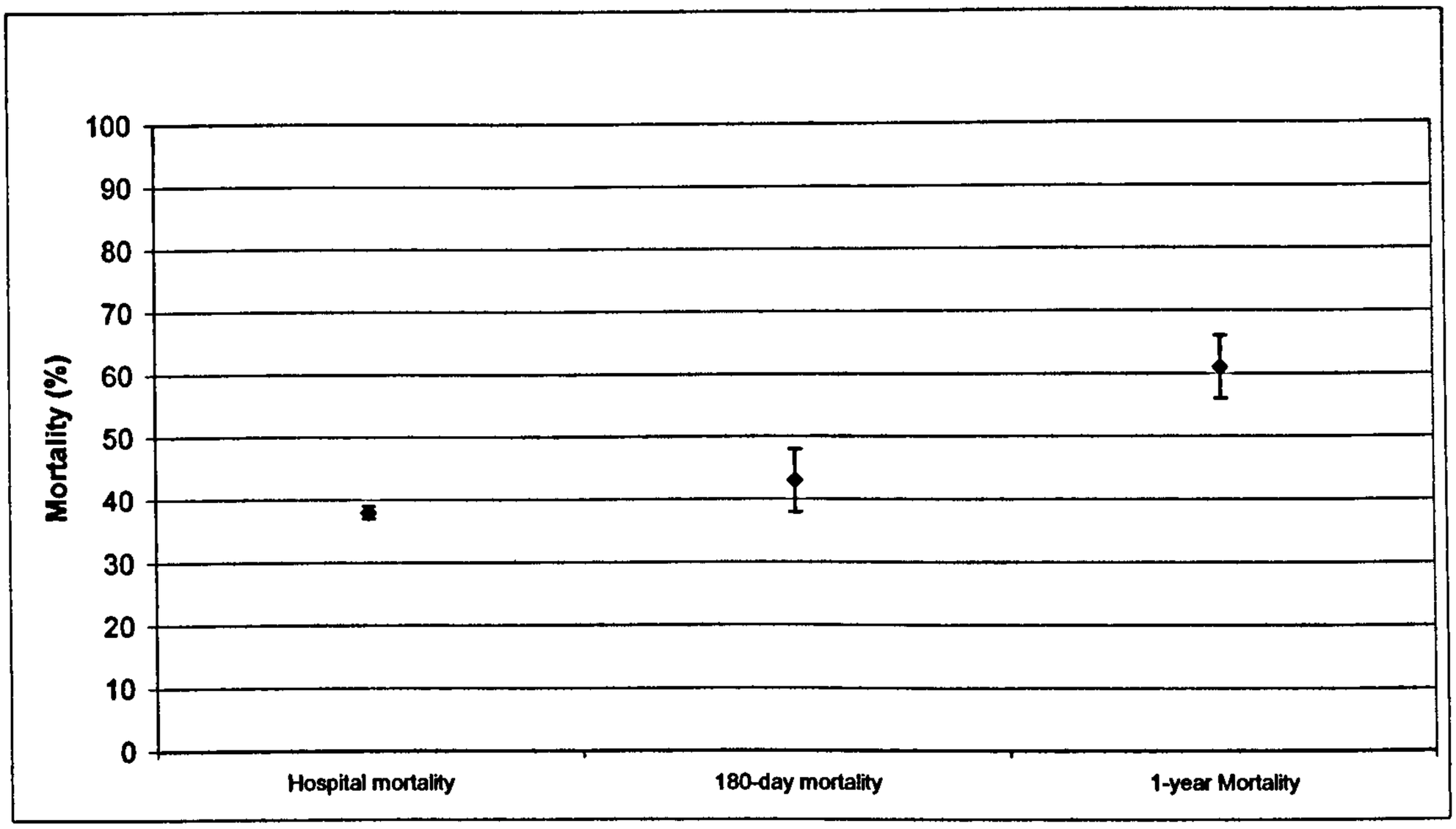
3.4 Risk factors associated with mortality

Risk factors associated with the outcome of intubation for patients with COPD can be classified into two main groups; those which describe the patient's characteristics in the period of stability prior to the exacerbation, and the clinical findings and results of investigations that become available during the emergency admission. The evidence from the literature will be reviewed below.

3.4.1 Age

Age has an important association with mortality since people are more likely to die at 80 years of age than at 20 years of age. In prognostic models which take account of some of the other factors that increase with age such as comorbidity, age may become less important when patients are compared over a smaller age range. However it is often the case that age retains an important association with mortality simply because studies cannot measure every risk factor and may measure some risk factors imperfectly.

Figure 3.3.3 All studies reporting outcomes for 10 or more intubated patients (combined outcomes for all studied patients).



Hospital mortality draws on 24 of the 29 studies with 1771 deaths out of 4675 patients studied (mortality 37.9%, 95% CI 36.5-39.3).
180-day mortality only draws on 2 studies with 165 deaths in 387 patients (mortality 42.6%, 95% CI 37.7 – 47.7%).
1-year mortality draws on 7 studies with 200 deaths in 327 patients studied (mortality 61.2%, 95% CI 55.6- 66.5%).

On occasions age will appear to have no relationship with mortality. For example age may not be associated with mortality in patients admitted to critical care following a cardiac arrest, and this will often be because rigorous selection pressures have only allowed the fittest of the elderly to be admitted to ICU. Table 3.4.1.1 below summarises the ages of the COPD patients in the studies where there was no analysis of age with outcome and Table 3.4.1.2 summarises the studies where some analysis of the relationship with age and outcome was carried out.

Twenty one of the 29 studies identified in the systematic search reported data on age of the included COPD patients. The mean age in the majority of studies was in the mid-sixties. The largest study from the UK included just under 4000 patients of which 80% were intubated, and reported a median (IQR) age of 67.7 (60.4 – 73.5).

Table 3.4.1.1 Studies in which the age of patients was summarised but no analysis with outcome performed

Study	Age (Years)	Analysis
Sluiter 1972 [49]	Mean 61.2	Summary statistics only
Gottlieb 1973[51]	Mean 57 (range 27-75)	Summary statistics only
Petheram 1980[52]	Bronchitis survivors mean 62.3, non-survivors mean 65.3 Emphysema survivors mean 54, non-survivors mean 59.2	Summary statistics only
Dardes1986 [54]	Mean (SD) 69(8)	Summary statistics only
Torres 1996 [63]	Mean (SD) 67(11)	Summary statistics only
Ely 2000 [46]	Mean (SD) 65(12)	Summary statistics only

Six of the 21 studies report summary statistics only. In keeping with much of the COPD outcome results analysis tends to be based on end-points such as hospital mortality rather than more robust outcomes such as 30-day survival or 60-day survival. Eight studies found age not to be significantly associated with mortality. In four of the negative studies the numbers of deaths were small with 20 or fewer deaths in each study[56 64 65 68]. In one of the negative studies with only 39 episodes in total, the analysis of outcome predictors was carried out after the sample had been stratified by FEV_1, which is likely to reduce the impact of age in such a small sample[60]. Three studies had larger numbers of patients and reported no association between age and outcome[45 57 67]. In one of these studies the age of 36 1-year survivors and 59 non-survivors was compared but formal survival analysis to 1-year was not carried out[57]. In another of the negative studies the age of 120 hospital survivors was compared with 46 non-survivors in a sample where 45 patients were discharged to chronic care facilities[45]. In the final study finding age to be non-predictive of survival 250 episodes were analysed in 180

patients and a univariate comparison was made with hospital survival, though the numbers being discharged to chronic care facilities was not reported[67]

Seven studies reported an association between age and outcome. In one of the positive studies which included patients with respiratory failure due to both COPD and other causes, though the age of the COPD patients was reported separately the survival was analysed for the group as a whole[61]. Two of the positive studies contained large numbers of hospitalised patients of whom only a small proportion were intubated[58 62]. Two studies that reported only on critical care patients also found increasing age to be significantly associated with hospital mortality. The Seneff study[43] included 362 patients with COPD identified from the APACHE III development data set, and the larger Wildman study[27] included just under 4000 patients of whom 80% were intubated. The Wildman study reported univariate and multivariate odds ratios for hospital mortality for 10 year age increments, with an OR (95% CI) univariate of 1.59 (1.46 – 1.73), and a multivariate OR of 1.58 (1.44 – 1.73). Only two studies carried out formal survival analysis[12 44]. One was small with only 8 hospital deaths[44], but found that age was associated with mortality beyond hospital. The other larger study that included 1016 COPD patients[12] reported a significant association between age in 10 year bands and mortality in both univariate and multivariate analysis, with univariate hazard ratio (95% CI) 1.30 (1.14 – 1.47), and multivariate 1.22 (1.05 – 1.41).

Though the data from studies looking at the association between age and outcome conflict (8 studies reporting no association between age and mortality, 7 reporting increasing mortality with increasing age) it is likely that 4 of the negative studies were too small to show any effect. Of the 4 remaining negative studies none used formal survival analysis. In one study hospital outcome may have been a poor measure because around 27% of patients were discharged to chronic care facilities[45], and in another study analysis was by episode rather than by patient[67]. Of the positive studies two used formal survival analysis[12 44].

Table 3.4.1.2 Studies in which there was investigation of relationship between age and outcome

Study	Age (Years)	Analysis	Findings	Comment
Kaelin 1987[56]	Mean (SD) 64.0 (7.5) 180day survivors, 67.6 (8.1) non-survivors.	Univariate analysis by 180-day survival	No significant association with survival	All 39 patients intubated and 15 lived less than 180 days
Menzies 1989[57]	Mean (SD) 69.6 (9.3)	Univariate analysis by 1-year survival. Analysis: independent T test, X^2	No significant association with survival, 36 survivors mean age of 67, non-survivors 71 years.	36 1-year survivors, 59 non-survivors
Limthongkul 1991[58]	Total group mean (SD) 68.4 (0.5)	Univariate analysis by hospital survival	Survivors mean (SD) 67.6 (10.1); non-survivors 72.2 (8.5) P<0.001	Study includes 400 episodes of which 66 involved intubation. Analysis is for total group.
Swinburne 1993[59]	181 COPD patients aged <80 years and 19 patients aged ≥ 80 years mean (SD) not presented		Hospital survival: % (95%CI) 64.6% (57.2 – 71.6) of patients aged <80, 47.4% (24.4 – 71.1) patients aged ≥ 80 years	181 COPD patients aged <80 years and 19 patients aged ≥ 80 years
Rieves 1993[60]	Mean age of whole group not reported.	Univariate/multivariate analysis in groups defined by FEV_1	Age not a significant predictor either as a univariate or a multivariate	39 episodes analysed in 33 patients, so numbers small and stratifying by FEV_1 likely to reduce impact of age.
Stauffer 1993[61]	Mean (range) in 67 COPD patients 64.6 (48-93)	Univariate estimate of odds of hospital and 1 year death for whole 383 patients per 5-year increase in age	OR (95%CI) hospital death 1.60 (1.28-2.00), 1 year death assuming survival from hospital 1.20 (1.02 – 1.43)	67 out of the total 383 men in this study had COPD but age was analysed in total group
Fuso 1995[62]	Mean (SD) total group 67.9 (10.2)	Univariate analysis by hospital survival	Hospital survivors 66.3 (10) vs. 73.1 (8.4) non-survivors p<0.001	Note that the sample contained 590 patients of whom 37 were intubated.
Seneff 1995[43]	Mean (SD) All n=362, age 66 (9.6) Intubated n=170, age 66 (9.5) Not intubated n=192, age 66 (9.7)	Multiple regression analysis	Increasing age significantly associated with hospital mortality.	
Connors 1996[12]	Median (IQR) 70 (63 – 77)	Univariate and multivariate Cox proportional hazards for mortality up to 180-days	Hazard ratio (95%CI) per 10 year age increase. Univariate 1.30 (1.14 – 1.47), Multivariate 1.22 (1.05 – 1.41)	
Hill 1998[64]	Median (range) 21 hospital survivors 67 (59.5 – 72.0) 69.5 20 non-survivors median 69.5 (64 – 72.8)	Univariate analysis by hospital survival	No significant difference	

Table 3.4.1.2 Studies in which there was investigation of relationship between age and outcome *continued*.

Study	Age (Years)	Analysis	Findings	Comment
Moran 1998[44]	Total group mean (SD) 68.5 (7)	Univariate & multivariate Cox proportional hazards analysis of ICU & hospital length of stay hospital and beyond hospital, survival. The analysis was on total cohort not just intubated patients.	Age was reported as significant univariate predictor of survival beyond hospital discharge only, but not hospital discharge and was not a multivariate outcome predictor	Of the 75 patients only 43 were mechanically ventilated. The hospital mortality was 11% i.e. 8 patients and the 180-day mortality was 25% i.e. 19 patients. Hence little power to determine associations with hospital mortality.
Anon 1999[65]	Mean 64 years (median 64) (range 44-77)	Univariate analysis with ICU survival	Mean (SD) ICU survivors 61 (8.9) non-survivors 68 (7.1) p=0.06	20 intubated patients with 7 deaths in ICU and 10 deaths in hospital
Nevins 2001[45]	Mean (SD) 67 (13)	Univariate comparison with hospital survival	Hospital survivors 67.4 (11.9) Non-survivors 66.3 (14.)0 p=0.64	166 intubated patients with 46 hospital deaths. Note 45 patients were transferred to a chronic care facility.
Afessa 2002[67]	Mean (SD) 63.1 (8.9)	Univariate comparison by hospital survival.	Hospital survivors 62.5 (8.6) non-survivors 63.9 (8.3) p=0.34	213 survivors and 37 non-survivors. Analysis was by episode with 250 episodes in 180-patients. Number discharged to chronic care facilities not reported.
Breen 2002[68]	Mean (SD) 65.5 (9.0) median (range) 65 (46-85)	Univariate comparison by hospital survival and 6 month survival	Age not associated with outcome	Only 15 hospital deaths, and 30 deaths at 180-days
Wildman 2003[27]	Median (IQR) 67.7 (60.4 – 73.5)	Univariate and multivariate comparison by hospital survival	OR (95% CI) hospital mortality per 10 year age increase UMnivariate 1.59 (1.46 – 1.73) multivariate 1.58 (1.44 – 1.73)	

The two largest studies that included almost 5000 patients in total showed broadly similar odds of death per 10 year increase in age, with the SUPPORT study that contained a lower proportion of intubated patients having the lower unadjusted hazard of death 1.30 (1.14 – 1.47) and the Wildman study an unadjusted odds of death of 1.59 (1.46 – 1.73). Given the agreement of the largest studies and the methodological problems of the negative studies it would be reasonable to conclude that age is an important risk factor for mortality, a conclusion that would be consistent with outcome

in most critically ill patients since age takes account of much unmeasured confounding in terms of physiological reserve.

3.4.2 Sex

The majority of the studies did not investigate sex as a predictor of outcome and in a number of studies [60 61] all the patients were male. The eight studies that did investigate the relationship between sex and outcome are shown in Table 3.4.2. It can be seen that only the UK case mix programme study found sex to be associated with outcome, with males having a univariate increased risk of mortality that was lost when multiple factors were adjusted for. The message from the systematic review regarding sex is unclear. The negative studies are relatively small and the finding of a univariate association between male sex and mortality that loses significance with adjustment for other risk factors in the large UK study raises the possibility that male sex may be a marker for other risk factors and therefore might have a role in a parsimonious model where all possible risk factors are not measured. It is of interest to note that a recent paper from Spain looking at 135 consecutive COPD patients admitted to hospital found women to have an increased mortality compared to men, but in this study the women were significantly older than the men (women mean (SD) age 79.4 (8.96) men 72.2 (9.3)[69].

3.4.3 Lung function

i. As an indicator of prognosis in stable outpatients

As highlighted in Chapter 1 (Section 1.1 above) COPD involves lung damage which reduces lung function, and the forced expiratory volume that the patient can blow out in one second (FEV_1) has been used in the classification of the severity of disease[70]. Much of the work investigating the relationship between FEV_1 and prognosis has been carried out in stable outpatients. The FEV_1 cut-offs demarcating severity vary around the world. The British Thoracic Society classifies patients into mild: FEV_1 60 – 80% predicted, moderate: FEV_1 40 – 59% predicted and severe: FEV_1 <40% predicted[2].

Table 3.4.2 Sex and mortality for intubated COPD patients

Study	Number (%) male	Analysis	Findings	Comment
Menzies 1989[57]	50/95 (52.6%)	Univariate comparison between survivors & non-survivors	No significant difference between men and women	
Seneff 1995[43]	203/362 (54%)	Unclear but probably univariate	No significant difference between men and women	
Hill 1998[64]	21/41 (51.2%)	Univariate comparison with hospital mortality	No significant difference	
Nevins 2001[45]	103/166 (62%)	Univariate comparison with hospital mortality	No significant difference	
Afessa 2002[67]	147/250 58.8%	Univariate comparison with hospital mortality	No significant difference	
Breen 2002[68]	44/74 59.5%	Univariate comparison with hospital mortality	No significant difference	
Wildman 2003[27]	1869/3611 51.8%	Univariate & multivariate comparison with hospital mortality	Univariate male 1.19 (1.03-1.39) multivariate 1.04 (0.88-1.22)	Males at increased risk which becomes non-significant when all other factors taken into account†

† In this case the multivariate analysis involved age, comorbidity, length of stay prior to ICU, CPR pre-ICU, acute physiology, organ failures.

Note in SUPPORT 523 (51.5%) were male and only factors that had been previously identified as likely to be associated with mortality were analysed with mortality

The European Respiratory Society use slightly different cut-offs of mild: ≥70%, moderate: 50-69%, and severe:, <50%[71]. The American Thoracic Society classify COPD into 3 stages, with patients in stage I having FEV_1 ≥50% predicted, stage II 35-49% predicted and stage III <35% predicted[72]. The cut-offs reflect the fact that studies have found that low FEV_1 identifies patients with a poor prognosis. The post-

bronchodilator FEV_1 was considered to be the best measure of FEV_1 since it was thought to measure the fixed impairment[73]. Though FEV_1 and age are correlated Anthonisen[74] found that post-bronchodilator FEV_1 was still a significant predictor of mortality when age was taken into account. Anthonisen also attempted to find a threshold at which FEV_1 began to be associated with poor prognosis. He found that patients with a FEV_1 <30% predicted had a significantly higher mortality than those with an FEV_1 lying between 30 to 39%, but that patients with an FEV_1 between 40 to 49% did not differ from those with an FEV_1 >50%, who in turn did not differ from normal smokers. Clearly, as the proportion of deaths decreases, the sample size needed to find important differences in mortality will need to increase. Nevertheless, the message of higher mortality associated with lower FEV_1 was borne out in the majority of studies and the data from Traver[73] are useful in this regard as shown in Table 3.4.3.1.

Table 3.4.3.1 Survival rates in COPD according to % predicted post bronchodilator FEV_1 ($PBFEV_1$) in patients ≤ 65 years of age (Traver[73])

	Cumulative survival rate (%)				
Initial Post bronchodilator FEV_1 (% Predicted)	Number	At 2 years	At 5 years	At 10 years	At 15 years
<20	9	44	11	11	0
20 – 29	40	65	30	10	3
30 – 39	43	83	47	21	7
40 - 49	26	92	89	39	30
50 - 59	21	95	95	57	32
60+	9	100	89	89	67

Hodgkin[75] points out that an important limitation in some of the studies that found FEV_1 to be a poor predictor of mortality was a lack of spread of FEV_1s and the Postma study[76] illustrated this with the FEV_1 of the 129 study patients lying between 0.35L and 0.91 litres. An understanding of the contribution that a variable makes to outcome requires

patients to be distributed along a continuum from mild to severe. Even the best FEV_1 of 0.91 in the Postma study reflects marked impairment of airflow.

Hodgkin also highlights the variability in prognosis that persist despite patients having similar lung function, drawing attention to comment by Traver[73] that "perhaps the most important point to be made from the overall study, and one often ignored in previous reports, is the very wide variability in survival of individual patients whose initial findings appear similar." In a growing recognition of the limited predictive power of FEV_1 in isolation, more recent studies have tended to look at a number of patient characteristics to predict outcome. Celli and co-workers have recently published work investigating a multidimensional grading system (the BODE index) that consists of four factors: body mass index, dyspnoea (Modified MRC dyspnoea score) and exercise capacity (using the 6 minute walk) in addition to FEV_1 in a single index[77].This index was developed in 859 outpatients with COPD and had an area under the ROC curve of 0.74 in comparison to 0.65 if the FEV_1 % predicted was used alone. In this study a mortality of 80% at 52 months was observed for those patients in the highest quartile of the BODE score.

ii. As a predictor of hospital outcome

The literature investigating the usefulness of FEV_1 in predicting mortality in intubated patients is less clear in its messages than that in stable patients. Fifteen of the 28 studies identified in the systematic review report lung function and these are summarised in Table 3.4.3.2.1 (studies where FEV_1 was analysed with outcome) and Table 3.4.3.2.2 (studies where FEV_1 was reported but not analysed with outcome) below.

In 13 of the studies the absolute FEV_1 was reported and in 9 of these the mean or median FEV_1 of the group was less than 1L. Four studies reported FEV_1 percent predicted. The FEV_1 percent predicted was reported separately for survivors and non-survivors by Kaelin[56] and Nevins[45] with survivors having mean (SD) FEV_1 percent predicted of 36.6% (14.5) and 47% (20) respectively, and non-survivors 30% (15.7) and 54% (25) respectively (NS). Three studies reported the mean FEV_1 % predicted for the whole group which was 40% in a population with COPD and pneumonia[63], and 35%[57]

and 23%[46] in two studies with unselected COPD exacerbations. Of the 15 studies 8 did not report analysis of the relationship between lung function and outcome. In 2 of the 8 studies without outcome analysis, though FEV_1 was sought, it was available in less than 40% of the patients[12 46]. In the 7 studies in which analysis was carried out to investigate a possible association between FEV_1 and survival, 4 studies found no significant relationship between FEV_1 and survival. However in 2 of these studies there were fewer than 15 hospital deaths[44 68]. Of the other 2 negative studies one included only 39 patients[56] and the other only identified lung function in 56 patients which was 34% of the total sample[45].

This systematic review demonstrates that the majority of COPD patients intubated in critical care have fairly similar lung function with an FEV_1 of less than 1L. It is likely that relatively large studies would be required to explore differential outcomes in a population with such narrowly distributed lung function and none of the negative studies would be considered large. In two of the studies reporting associations between lung function and outcome the association is described without a clear presentation of statistical significance. Menzies[57] describes survival curves for patients with differing FEV_1 % predicted and Rieves[60] reported that as the FEV_1 of patients rose the mortality ratio fell. One study reports a significant univariate association between FEV_1 and both hospital and 1-year survival with survivors having better lung function[65]. This is also a small study but it differs somewhat from the others in that the patients were selected to be homogeneous, all being on long term oxygen therapy prescribed by a chest physician.

It should be remembered that lung function is just one determinant of outcome in COPD, and that whilst patients with very poor lung function may require only mild intercurrent illness to precipitate ICU admission, patients with better lung function may frequently require a more major insult such as pneumonia to require intubation. It is noteworthy in this respect that whereas Ely's[46] patients with heterogeneous causes of respiratory failure had a mean FEV_1 of 23% predicted, the patients reported by Torres[63] with COPD and community acquired pneumonia had a mean FEV_1 of 40% predicted. In the Nevins[45] study patients with respiratory failure and a clear x-ray had a mean (SD)

FEV_1 of 0.99 (0.40) and those with other causes of respiratory failure had a mean (SD) FEV_1 of 1.39 (0.62) p=0.006. It seems likely that on average patients with better preserved lung function require a greater insult to end up requiring intubation than those with greater lung function impairment. The SUPPORT study[12] demonstrated the importance of acute physiological derangement as an independent outcome predictor and the CMP data[27] demonstrated the independent prognostic significance of organ failures. Patients with fairly good lung function and pneumonia are more likely to have other organ failures than patients with extremely poor lung function whose deterioration has been precipitated by a mild exacerbation. This possibility along with the association of age with declining lung function makes it clear that an understanding of the contribution of lung function to survival requires large studies in which potential confounders are explored in an adequately powered multivariate analysis. It would seem fair to conclude that though the majority of the studies do not confirm a relationship between FEV_1 and outcome in intubated COPD patients, the literature might be considered inadequate to inform an assessment of the predictive significance of FEV_1. That is to say there is an absence of evidence of a relationship rather than evidence of lack of a relationship.

3.4.4 Functional capacity

i. Mortality in stable outpatients with COPD

Advanced COPD is associated with a progressive decline in patients' functional capacity and increasing shortness of breath on exertion. It might be expected that functional impairment and increasing dyspnoea would be associated with an increased risk of mortality and this has been shown in a number of studies of stable outpatients. In a study of 227 COPD patients enrolled in a 5-year prospective study Nishimura et al[78] found a five point dyspnoea scale[79] (similar to the ATS dyspnoea scale) to be better able to identify patients at different risk of dying over 5 years than a classification of patients into categories of severity using FEV_1. (Using a Cox proportional hazards analysis, grade II dyspnoea was taken as the reference group, and the relative risk for

death (95% CI) for worsening dyspnoea was grade III 2.21 (0.93 – 5.27), grade IV 8.31 (3.41 – 20.27), and grade V 61.3 (13.2 – 285.4)).

Table 3.4.3.2.1 Lung function in studies investigating intubated patients: analysis with outcome

Study	FEV_1 (absolute and or % predicted)	Analysis	Findings	Comment
Kaelin 1987[56]	Mean (SD) % predicted 36 6% predicted (14.5) 180 day survivors; 30 0% predicted (15.7) 180 day non-survivors	Comparison of mean FEV_1 % predicted between 180-day survivors/non-survivors	No significant difference	Only 39 patients.
Menzies 1989[57]	FEV_1 mean (SD) 0 80 (0.38) FEV_1 (% predicted) mean (SD) 35% (15) 75% of patients had FEV_1 < 45% predicted, 50% of patients had FEV_1< 30% predicted	Univariate analysis comparing survivors to non-survivors. Model constructed containing FEV_1 (% predicted), functional score, albumin, cor pulmonale, LVF	FEV_1 % predicted significantly higher in survivors than non-survivors 40% vs. 31% Survival curves constructed for FEV_1 (% predicted) >40%, 25-40%, <20%- no significance tests of curves presented.	Data were available on 79/95 patients. The risk ratios associated with specific levels of FEV_1 were not presented and the model produced was not validated in a test set of new patients.
Rieves 1993[60]	39 episodes in patients with FEV_1<1l mean 0.75. 19 episodes FEV_1>1l mean 1.56	Analysis looked for predictors of mortality in patients with FEV_1 >1 or <1l Another analysis found that as FEV_1 in the whole group fell the mortality ratio rose.	FEV_1 % predicted was not a significant mortality predictor in the patients analysed in FEV_1 > or < 1l. Infiltrates predicted mortality in patients with FEV_1 < 1l but not >1l	FEV_1 % predicted was analysed in the patients already classified by FEV_1. There were 26 comparisons in total only 58 subjects.
Moran 1998[44]	0.7 (0.34) mean (SD)	Univariate comparison for hospital mortality	FEV_1 not a significant predictor of hospital mortality	Less than 10 hospital deaths
Anon 1999[65]	FEV_1 total group median (range) 0 83 (0.48-1.07)	Univariate comparison survivors vs. non-survivors	Mean (SD) FEV_1 ICU non survivors 0 68 (0.3) vs. ICU survivors 1.0 (0.34) p=0 089 FEV_1 was reported as significant for hospital death and death within 1 year as a univariate association p=0.03 Hospital, p=0 05 1 year	Only 20 patients in the sample. All on Long term oxygen therapy.
Nevins 2001[45]	Entire group 1.24 (0.58), COPD clear chest x-ray 0 99 (0.40), others 1.39 (0 62)	Univariate comparison hospital survivors vs. non-survivors	Survivors mean (SD) 1.23 (0.54), % predicted 47% (20) vs. Non-survivors 1.26 (0.7) 54% (25) p=ns	FEV_1 data only available for 56 pts i.e. 34%. .
Breen 2002 [68]	Whole group mean (SD) median (range) 0.74 (0.34) 0.68 (0.2-1.9)	Multivariate logistic regression	Reported as not a significant predictor of hospital mortality	Only 15 hospital deaths.

Table 3.4.3.2.2 Lung function in studies investigating intubated patients: descriptive studies

Study	FEV_1 (absolute and or % predicted)	Analysis	Findings	Comment
Sluiter 1972 [49]	0.75L non-intubated 0.67L delayed intubated 0.85L immediate intubated	Descriptive only		No outcome analysis
Gottlieb 1973 [51]	Mean 1.15L (range 0.5-1.9)	Descriptive only		No outcome analysis
Petheram 1980[52]	Mean 1.13L survivors vs. 0.78L died bronchitis, Mean 0.8 survived vs. 0.48 emphysema	Descriptive only	Note the dying emphysema patients had a mean age of 59.2 compared to 54 in survivors.	No outcome analysis
Limthongkul 1991[58]	FEV_1 0.58 (0.39) mean (SD)	Descriptive only		No outcome analysis
Torres 1996[63]	Mean FEV_1 % predicted 40%	Descriptive only		No outcome analysis
Connors 1996[12]	0.80 (0.58-1.20) median (IQR)	Descriptive only		FEV_1 sought on all patients, but only available in 27% so no analysis carried out.
Hoo 2000[66]	FEV_1 total group 0.79(0.4)	Descriptive only		74 out of 138 patients intubated, but total group lung function presented
Ely 2000[46]	FEV_1 0.67(0.27) % predicted 23.13% (7.8%) mean (SD)	Descriptive only		FEV_1 available for 16 pts (36%)

In a study of 158 COPD patients recruited in pulmonary rehabilitation who were followed up for 40 months patients with a low 12 minute walking distance were at significantly increased risk of mortality in a multivariate logistic model that included age, FEV_1 and BMI[80].

ii. As a predictor of outcome in patients with COPD hospitalised with exacerbations

Ten of the 29 studies identified in the systematic search collected data on functional capacity and/or dyspnoea. In three of the studies there was no clear investigation of the

relationship between functional capacity and outcome (Table 3.4.4.2.1 below) and in seven studies some analysis with outcome was carried out (Table 3.4.4.2.2 below).

Table 3.4.4.2.1 Studies of hospitalised COPD patients reporting functional capacity but not analysing with outcome

Study	Measure of exercise capacity	Analysis	Findings	Comment
Sluiter[49]	26/68 Patients graded as capable of light work. 32 graded as having severe capacity	No analysis with outcome		
Gottlieb[51]	20/30 Patients were breathless after walking about 100 yards or a few minutes on the level . 10/30 were bedridden or confined to the house	No analysis with outcome		These 30 patients with their first episode of respiratory failure due to COPD
Moran[44]	Pre-morbid exercise capacity; 23% able to walk long distance, 33% able to walk 100m own pace, 44% housebound.	No analysis with outcome.		It was not clear from the study report whether exercise capacity was tested as an outcome predictor.

Ten studies reported functional capacity or dyspnoea and all reported a high proportion of patients to be unable to carry out at least one activity of daily living. Two studies presented descriptive data only[49 51] and in one study it was unclear whether functional capacity had been explored as an outcome predictor[44].

Two of the seven studies investigating the association between functional capacity or dyspnoea and outcome did not find a significant association; both were small (25 patients[52] and 58 patients[60]) and in the study with 58 patients analysis was stratified by FEV_1 making the strata more homogeneous. Five studies showed a significant association between functional capacity or dyspnoea and outcome. Two studies[57 68] used the functional score (lifestyle score) and found more severe impairment to be associated with post discharge mortality. One of the studies did not report any analysis with hospital mortality[57] and the other reported that an analysis had taken place but that no association with hospital mortality had been found[68].

Table 3.4.4.2.2 Studies of hospitalised COPD patients reporting functional capacity in which there is some analysis with outcome

Study	Measure of exercise capacity	Analysis	Findings	Comment
Petheram[32]	Exercise tolerance was graded as: "normal"- able to walk long distances at own pace, "intermediate"- able to walk 100 yards on flat and "housebound":	Univariate analysis with hospital mortality.	"Exercise tolerance unhelpful in predicting outcome in 7 patients with emphysema" "Survivors tended to have better exercise tolerance in 18 patients with chronic bronchitis"	Small numbers.
Menzies[57]	Functional score† ATS Dyspnoea score[81]‡	Univariate analysis with 180-day mortality. Also Kaplan- Meir type survival curve showed that patients grouped by function were different p<0.1 group (0+1) vs. (2) vs. (3+4)	Univariate comparison mean functional score survivors 1.9 vs. 2.8 non-survivors p<0 001 Dyspnoea score survivors 3.1 vs. 3 8 non-survivors p<0.01	
Rieves[60]	Activity score 0=performs vigorous activity, 1= Independent, limited exercise capacity, 2= Independent, severely limited exercise ability, 3=performs self-care cannot live alone, 4= bed or chair bound	Separate univariate analysis by hospital mortality with patients stratified by FEV_1>1L or <1L	Activity score did not predict hospital mortality-mean (SD) FEV_1<1L: survivors 2.86 (0 89) vs. 3.12(0 86) non-survivors, FEV_1 > 1L survivors 1.82 (0.75) vs. 1.75 (1.04) non-survivors	The two groups stratified by FEV_1 were small and relatively homogeneous.
Seneff[43]	Activity score ¥ Patients dichotomised for analysis into those with functional limits vs. no functional limits.	Univariate and multivariate analysis of patients with functional limits vs. no functional limits to all time points	Functional limits only significantly associated with 1-year mortality. Mortality 69% in patients with functional limits, 50% without functional limits p=0 01	Note they only had post discharge outcome data on patients 65 years or older and of these 216 they had 1 year outcome data on 167
Connors [12]	Katz ADL[82] and Duke Activity Score Index (DASI)[83] in period of stability 2 weeks prior to exacerbation. Total population median (IQR) ADL 1 (0-2) DASI 17 (15-20)	Univariate and multivariate Cox proportional hazards analysis to 180-days	Hazard ratio (95% CI) ADL 1 point change Univariate 1 24 (1.14 – 1.34) , multivariate 1.14 (1.03 – 1.26) DASI 5 point fall; univariate 1 04 (1.01-1.07) multivariate 1.07 (0.90 -1.29)	A 1-point change in ADL indicates increasing disability. A fall in DASI indicates poorer exercise tolerance
Breen [68]	Functional score† used with grade 0 and 1 amalgamated. 40.5% of patients housebound (Functional score grade 3 or 4)	Univariate analysis by hospital mortality and survival to three years	Functional score was not associated with hospital mortality or longer-term survival.	Only 15 hospital deaths and 47 deaths at 3-years
Wildman[27]	34.9% of admissions had severe respiratory disease as measured by APACHE II [35]severe respiratory disease definition when stable¶	Univariate and multivariate analysis by hospital survival.	Odds ratio (95%CI) for hospital mortality patients with severe respiratory disease versus those without Univariate 1.15 (0 98 – 1.34) multivariate 1.20 (1 01- 1.42)	

Notes: †Menzies Functional score (Lifestyle score)[27] : 0 = working, 1= Independent- fully ambulatory and living without any assistance, 2= Restricted- able to live on their own and get out of their homes to do basic necessities, but severely limited in exercise ability. 3= Housebound- cannot get out of the house unassisted or get out of the house rarely; able to perform self-care but unable to do heavy chores such as housecleaning; cannot live alone; may be institutionalised. 4= Bed or chair bound.

‡ATS dyspnoea score[81]. (1) Are you troubled by shortness of breath when hurrying on the level or walking up a slight hill? (2) Do you have to walk slower than people of your own age on the level because of breathlessness? (3) Do you ever stop for breath when walking at your own pace on the level? (4) Do you ever have to stop for breath after walking about 100 yards (or after a few minutes) on the level? (5) Are you too breathless to leave the house or breathless on dressing or undressing?

¥Seneff[43]. (1) Severe limits: Short of breath at rest or did not perform any activities of daily living (ADL[82]) or both . (2) Moderate limits: Short of breath with light activity and unable to work and perform two or more ADLs. (3) No limits: No reported dyspnoea and no more than 1 limitation in ADLs.

¶ APACHE II definition of severe respiratory disease: " Patient has 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 such as walking 20 metres on level ground, walking slowly in the house, climbing one flight of stairs , dressing or standing.

Both studies were relatively small. Two studies used data routinely collected for APACHE scoring to dichotomise patients into those with functional limits versus those

without functional limits[27 43]. The APACHE III dataset study found that functional limits were only associated with 1-year mortality, but not with hospital mortality[43]. The UK study using APACHE II found that though the functional impairment group had a non-significantly increased univariate risk of hospital mortality (OR (95%CI) for death 1.15 (0.98 – 1.34)), the risk was marginally significant in the multivariate analysis (OR (95% CI for death) 1.20 (1.01 – 1.42))[27]. The SUPPORT study[12] using Katz's Activities of daily living score (ADLS)[82] and the Duke Activity Score index (DASI)[83], found that ADLs had a significant association with hospital mortality in both univariate and multivariate analysis, but found an association with mortality only in the univariate analysis using the DASI. It should be noted however that the multivariate model also contained Katz's ADLS and there was likely to be some co-linearity between ADLs and DASI.

iii. Why is functional capacity not a better predictor of outcome in acutely ill COPD patients?

The above studies suggest that functional capacity does have a relationship with mortality in acutely ill patients but the relationship appears less robust than in out-patients followed up over longer periods, with performance in a 12 minute walk showing a particularly strong association with outcome in the outpatient setting[80]. There may be a number of explanations for this finding. It is known that when a risk factor is measured with non-differential error any risk ratios will tend towards the null[84]. COPD patients requiring intensive care will often be too ill to give a clear account of their functional capacity and this information will often need to be collected via a proxy such as the next of kin. This method of data collection has important limitations. Various authors have reviewed the reliability of proxy data in describing quality of life domains[34 85 86]. Exploration of the reliability of proxy report classically involves comparison with the patients self report which is taken as the gold standard. Sprangers[85] points out that though reviews of the literature generally show a relatively low concordance between proxies and patients some of the low concordance may arise

because of methodological difficulties in measuring concordance rather than being a real measure of disagreement.

There are three main methodological issues. Firstly the dimension that is being explored and the way it is categorised will impact upon concordance. The more visible and concrete a construct, the higher the concordance. Concordance in determining affective states is likely to be lower than in determining visible functional attributes. For example asking proxies whether a patient is happy or sad will be less reliable than asking if the patient can feed themselves or not. In addition questions that dichotomise an attribute as present or absent are likely to show greater concordance than when questions require responders to judge the degree or frequency of participation in an activity. Secondly the statistical tests used to measure agreement are influenced by the range and variability of responses. If there is little variability in scores, correlations will be low simply because of lack of score variability. Sneeuw demonstrated this phenomenon in a study exploring proxy reports of quality of life in patients with brain cancer[87]. Thirdly neither the patient nor the observer will be entirely reliable in reporting the underlying construct described. In this regard Magaziner has shown that patients can differ in their description of their functional capacity when that description is compared with observation of patients actual performance in the tasks reported[86]. Sprangers[85] draws upon Nunnally[88] and Bland[89] to point out that this potential for unreliability is important since the correlation between two scores can never exceed the square root of the product of the scores' reliability. A recent study highlighted the issue that patients and proxies may not agree because patients may report their function in a biased way. In this study a number of patients who were only able to carry out light physical activities reported that they had a high level of physical fitness[90].

Certain aspects of the research on proxy ratings have particular relevance for understanding the results of studies that have used functional capacity in predicting outcome. The literature suggests that there is a tendency for proxies to report greater disability than subjects self-report[91 92], though this bias can be lessened if questions about function are modified to refer to "explicitly defined and observable behaviors"[86]. Since proxy ratings are most reliable when they relate to concrete and observable

domains and least reliable when they relate to subjective experiences such as anxiety or pain, measures such as Katz's ADLs[82] are likely to be relatively robust since they ask whether the patient is or is not independent in an ADL. It might be expected that proxy ratings of breathlessness would be intermediate between dichotomised descriptions of observed function and proxy ratings of subjective mental states such as anxiety. The definition of severe respiratory disease used in the UK CMP study[27] is open to some interpretation in that it asks whether the patient has "permanent shortness of breath with light activities"[35]. If a disability rating tended to encourage proxies to over report disability one would expect more patients to be categorised in the lowest functional group than occupy that group in reality, thus diluting the prognostic significance of maximally impaired function. In routinely collected data such as that used in the CMP study and the APACHE III study there is also the possibility of failing to collect data and if these data were missed at random it would again dilute the predictive ability of function.

iv. Summary: Functional capacity and outcome in COPD

In conclusion, the evidence reviewed suggests that in COPD outpatients measures of function do predict outcome[80]. In the acute setting, errors in collecting true descriptions of patients function may limit the predictive ability of functional information, but complete collection of dichotomised attributes are likely to be the most reliable. This speculation is borne out by the observation that the best predictor of outcome in the studies described is Katz's ADLS, a dichotomised description of function that is likely to have been completely collected since the SUPPORT study was a very well funded study with high standards of data monitoring and general data completeness[12].

3.4.5 Self-rated quality of life

Some studies have used patients' self-rated quality of life as a way of capturing patients' overall views of the impact of disease on their life. Lynn found that in hospitalized patients with COPD those patients with self-rated quality of life that was excellent or very good had better survival rates than those with poor quality of life [93]. The difficulty with self-rated quality of life is that it is a subjective non-observable patient attribute that is likely to be unreliable if collected via proxies[86].

3.4.6 Co-morbidity

COPD is mainly caused by smoking and in the recent summary of the results of 50 years of follow up of British doctors Doll listed 10 broad categories of disease associated with cigarette smoking in addition to COPD[94]. With cigarette smoking associated with disease in so many body systems it might be expected that comorbidity would be an important problem in patients with COPD.

3.4.6.1 Methodological issues in comorbidity measurement

Elixhauser[95] provides a useful categorisation of the entire burden of disease of a patient admitted to hospital in the following 5 categories 1) The primary reason for hospitalisation, as reflected in the principal diagnosis, 2) The severity of the principal diagnosis, 3) Complications that result from the process of care, 4) Unimportant comorbidities or other conditions present on admission that have a trivial impact on resource use and outcomes and, 5) Important comorbidities or conditions present on admission that are not related directly to the main reason for hospitalisation, but that increase the intensity of resources used or increase the likelihood of a poor outcome. Elixhauser considered a secondary diagnosis to be a comorbidity only when it did not relate directly to the primary diagnosis, on the basis that comorbidity related to the primary diagnosis might in reality be a marker of the severity of the original disease rather than a distinct comorbidity.

The evidence outlining the contribution of comorbidity to outcome prediction in COPD is limited and what evidence there is might be taken to suggest a relatively minor role in

hospital mortality. In the SUPPORT study[12] comorbidity data were collected by nurses using the 42 comorbidity classes defined in the APACHE III prognostic system[36]. Seventy five percent of COPD patients in SUPPORT had 2 to 3 comorbidities[93]. The contribution of comorbidity to mortality was explored by using the total number of comorbidities as an explanatory variable in the regression model and this did not have a significant hazard ratio for death (univariate hazard ratio (95%CI) for each additional co-morbidity 1.09 (0.98-1.21), multivariate hazard ratio 1.13 (0.99-1.28). Elixhauser makes the point that counting the number of comorbidities can produce spurious results. This is illustrated by Elixhauser's finding that studies have shown that minor comorbidities such as hypertension may seem "protective" because they are coded in patients who have no other comorbidities but missed in patients with many comorbidities. Hence hypertension only appears in the otherwise healthy patients since though it may well be present it is not coded in the sickest patients. In Elixhauser's study[95] this finding was confirmed in that hypertension decreased the odds of in-hospital death by 40% Elixhauser points out that "a seriously ill patient may have so many medical problems that hypertension though detected was not abstracted for the discharge record."- hence hypertension only gets abstracted in the non-sick patients. It is unclear whether this process of "under abstraction" might contribute to the poor predictive performance of the total number of comorbidities in SUPPORT.

Elixhauser's study also provides compelling evidence for disease specific weighting of comorbidities by demonstrating significantly different disease specific weightings in data derived from 1779167 medical admissions in California. Unfortunately disease specific weightings are not presented for COPD and personal communication with the author confirms that these were not calculated. Nevertheless the fact that different comorbidities do bear different weights depending upon the primary diagnosis suggests that a more sophisticated approach to comorbidities other than simple counting them is likely to discriminate better. In keeping with this work Incalzi[96] collected comorbidities in COPD patients using the Charlson index[97] and showed that though the weighted Charlson index did not add useful explanatory power to models predicting mortality, individual comorbidities (specifically chronic renal failure and previous myocardial

infarction) were predictive. The Incalzi study was relatively small (270 patients recruited at hospital discharge) but showed that collecting comorbidities in a more detailed way did increase their predictive power. (A history of myocardial infarction in Charlson was not predictive, whereas specific ECG changes were). This suggests that increasingly sophisticated ways of collecting comorbidity data might yield greater discrimination. It should be noted however that some studies that have used very sophisticated and time consuming measures of comorbidity have shown only modest increases in the capability of comorbidity measures to predict increased risk[98].

3.4.6.2 Comorbidity in studies identified in the systematic literature search

Ten of the 29 studies identified in the systematic search reported comorbidities for the included COPD patients[12 27 43-45 57 62 63 65] and these are summarised in Table 3.4.6.2.1 and Table 3.4.6.2.2. Most of these studies used different non-validated measures of comorbidity making comparisons difficult. However the APACHE II comorbidity classification was used by both the Nevins study[45] that included 166 intubated patients from a critical care unit in the USA and the CMP study[27] that included 3752 patients from 128 UK critical care units. Patients admitted to the USA study had a 10-fold increased prevalence of comorbidity compared to the UK study (42% USA versus 3.8% UK). Though it is impossible to exclude coding differences, as a cause for these differences it is noteworthy that the USA has many more critical care beds than the UK and the differences may reflect UK gatekeeping policies which tend to exclude COPD patients with comorbidity.

Of the nine studies seven explored the relationship between comorbidity and survival. Four found no significant association[43 44 57 65]. In two of the negative studies there were less than 20 deaths[44 65]. In the Menzies study[57] there were only 95 patients and there was a non-significant trend towards both cor pulmonale and a history of left ventricular failure being commoner in non-survivors. In the other non-significant study[43] it is unclear how comorbidities were analysed and the author states that "comorbidity was a non-significant determinant of hospital mortality once severity of illness was taken into account". Of the three studies identifying comorbidities as being associated with

outcome, each used different classification systems. Fuso[62] looked at individual comorbidities as defined for his study and found atrial fibrillation, previous myocardial infarction and ventricular arrhythmias to have a univariate relationship with survival, and atrial fibrillation and ventricular arrhythmias to have a multivariate relationship with survival. Nevins[45] used the APACHE II comorbidity classification system and found that patients with any comorbidity had significantly lower survival than those without. Analysis of individual comorbidities found only active malignancy to have a significantly poorer survival, but numbers were small. Connors[12] used the APACHE III comorbidity classification system and found that though single additional comorbidities did not quite convey significantly poorer prognosis, differences of greater than one comorbidity did .

Table 3.4.6.2.1 Studies describing comorbidity but not exploring association with outcome

Study	Measure of comorbidity	Analysis
Rieves [60]	Stable angina 36 4%, congestive cardiac failure 30.3%, hypertension 30.3%, diabetes 21.2%	Association between chronic health problems and outcome not reported. 33 patients described, but total % exceeds 100% since some patients had more than 1 comorbidity
Torres[63]	No comorbidities in 31%, cardiovascular comorbidity in 28%, diabetes in 6%, neurological in 4%, surgery in 8%, others in 23%.	Association with outcome not explored.
Wildman[27]	Comorbidity was presence of APACHE II defined illness with <4% of cohort having comorbidity 0.2% cirrhosis, 0 8 % immunosuppression, 0.3% chronic renal failure, 0.2% active malignancy and 2.3% cardiovascular disease	Numbers too small to allow individual exploration of comorbidity with hospital mortality

3.4.6.3 Comorbidity measurement in COPD: Conclusions

The foregoing suggests that measuring comorbidities is difficult. There is a tension between finding a validated measure that is easy to use and the fact that simplistic descriptions of comorbidity may fail to identify those patients at greatest risk. For example the fact that a patient has had a myocardial infarction is nowhere near as useful as knowing the patient's cardiac ejection fraction[99].

Table 3.4.6.2.2 Studies exploring association between comorbidity and outcome in hospitalized patients with COPD

Study	Measure of comorbidity	Analysis	Findings	Comment
Menzies [57]	History of left ventricular failure in 19% Cor pulmonale on ECG† in 41% of sample History of myocardial infarction - distribution not reported	Univariate analysis with 180-day survival	Cor pulmonale present in 31% survivors vs. 56% non-survivors .05<p<0 1 History LVF present in 11% survivors vs. 24% non-survivors. MI not associated with outcome.	
Fuso [62]	Of the 590 patients. 23.7% hypertension, 11.0% diabetes, 7.6% chronic renal failure, 5..3% ischaemic heart disease, 3.7% chronic liver disease, 3.2% previous myocardial infarction, 0.7% valvular heart disease, 18 8% ventricular arrhythmias, 14 9% ST segment & T wave changes, 14.4% right bundle branch block, 8.5% atrial fibrillation, 6.1%previous myocardial necrosis, 4 1% previous myocardial necrosis.	Univariate and multivariate analysis of individual comorbidities with hospital mortality	Significant univariate association with hospital death OR (95% CI) atrial fibrillation 3.95 (1.99 – 7 80), previous myocardial infarction 3.69 (1.26 – 10.5), ventricular arrhythmias 2.48 (1.43 – 4.28) and multivariate atrial fibrillation 2.27 (1.14 – 4.51) and ventricular arrhythmias 1 91 (1.10 – 3.31)	
Seneff [43]	Distribution of comorbidity not described	Not explicitly stated, though textual description suggests multivariate analysis including acute physiology.	Text reports that comorbidity was a non-significant determinant of hospital mortality once severity of illness taken into account.	
Connors[12]	Proportion of population with number of comorbidities: 0=2.7%, 1=19.2%, 2=34.5%, 3=23.2%, 4=12.8%, >4=7.6% Congestive cardiac failure as cause of exacerbation and cor pulmonale both associated with lower mortality in univariate and multivariate analysis	Univariate and multivariate association with mortality to 180-days explored with Cox proportional hazards analysis	Hazard ratio (95% CI) per 1 comorbidity increase: Univariate 1.09 (0 98 – 1 21), Multivariate 1.13 (0 99 – 1.28). Though the presence of a single additional comorbidity did not identify patients at significantly increased hospital mortality additional comorbidities did and comorbidity was included in the outcome model.	Comorbidities classified using the 42 categories used in APACHE III [36]
Moran[44]	Proportion of population with comorbidities: Cor pulmonale 32%, congestive cardiac failure 35%, ischaemic heart disease 28%, hypertension 17%	Univariate exploration of comorbidities in association with hospital and post discharge mortality	No association of comorbidity and outcome.	Only 8 hospital deaths and 19 180-day deaths
Anon [65]	Comorbidity present in 40% of patients: 20% hypertension, 10% diabetes, 10% atrial fibrillation, 20% ischemic heart disease, 60% had ECG signs of right ventricular hypertrophy.	Univariate association between right ventricular hypertrophy and ICU mortality investigate.	7 out of 12 patients with right ventricular hypertrophy died but this was not statistically significant.	Note only 20 patients in this study.
Nevins [45]	Comorbidity was presence of APACHE II defined illness with 42% of cohort having comorbidity. 3 6% cirrhosis, 17.7% immunosuppression, 4.2% chronic renal failure, 21.7% active malignancy	Univariate comparison with hospital mortality, any comorbidity and cancer significant. Others non-significant.	Any versus no comorbidity survivors vs. non-survivors 37% vs. 54% p=0.04. Active malignancy present / absent survivors vs. non-survivors 14% vs. 41% p<0.001	

† P pulmonale defined as any one of , (1) p pulmonale, (2) right ventricular failure, (3) right axis deviation, according to Marriot criteria.[100]

The results from the case mix programme database in which comorbidity was present in only 4% of over 3000 COPD patients admitted to critical care raises the possibility that in the UK patients with COPD and comorbidity tend not to be admitted to critical care[27]. Of the validated comorbidity measures the Charlson[101] is one of the simplest and the possibility of individual weightings of comorbidities holds promise for greater discrimination. In addition certain comorbidities such as atrial fibrillation[62] are easy to collect and have been shown in some studies to have value.

3.4.7 Body mass index

The normal range of BMI is 20 – 25kg/m^2 [102]. BMI does not distinguish between depletion of fat and protein stores, but in general terms patients with a BMI less than 20kg/m^2 may be at risk of nutritional depletion.

Table 3.4.7 BMI in UK adults [103]

BMI (kg/m^2)	Interpretation
>40	Grade III obesity
30-40	Grade II obesity
25-30	Grade I obesity
17-20	Underweight
<17	Severely underweight

3.4.7.1 Body mass index in stable outpatients with COPD

The association between low body mass index and poor prognosis has been studied by Landbo et al in COPD patients identified from the Copenhagen City Heart Study[104]. In this study of over 2000 patients with obstructive spirometry (FEV_1 to FVC ratio <0.7) multivariate Cox regression was used to identify risk factors for mortality occurring over 17 years. In mild to moderate COPD there was a nonsignificant U-shaped relationship between BMI and mortality, with the lowest risk in normal-weight to overweight subjects, whereas in severe COPD the relative risk for low versus high BMI was 7.11 (95% CI 2.97 to 17.05). The risk ratios were adjusted for age, ventilatory function and smoking habits. Schols studied the relationship between BMI and outcome

using a Cox proportional hazards model including age, sex, spirometry, blood gases and smoking in a population of 400 COPD patients enrolled in a pulmonary rehabilitation scheme and suggested a threshold value of 25kg/m^2 below which mortality was clearly increased[105]. Schols also carried out a post hoc survival analysis of a randomised controlled trial of nutritional support and though the intervention group did not differ from the non-intervention group response in terms of overall survival, those patients who demonstrated a weight gain of >2kg in eight weeks did show significantly increased survival. More recently Celli has demonstrated BMI to be an important contributor to a multidimensional BODE index (see section 3.4.3) in predicting mortality in COPD patients[77].

3.4.7.2 Body mass index and outcome in acutely ill patients with COPD

Only two of the studies identified in the systematic search investigated the role of body weight and mortality, a weakness possibly related to the retrospective nature of the majority of the studies which often depended on routinely collected data. The two studies are summarised in the table 3.4.7.2 below.

Table 3.4.7.2 Body mass index and outcome in acutely ill patients with COPD

Study	BMI in study population	Analysis	Findings	Comment
Kaelin[56]	Mean (SD) ideal body weight was reported for 180-day survivors vs. non-survivors	Univariate comparison	No significant difference between 180-days survivors vs. non-survivors. Mean (SD) 180-day survivors 87 (15) vs. non-survivors 88 (17)	Very small sample n=39
Connors [12]	Summary statistics not presented.	Cox proportional Hazards for 180-day survival, univariate and multivariate	Hazard ratio (95%CI) BMI 5 Kg/m^2 fall, Univariate 1.33 (1.20 –1.49), Multivariate 1.33 (1.17 – 1.49)	

The only study to investigate body mass index in COPD patients with acute respiratory failure found it to be significantly associated with outcome in a well designed prospective study using Cox proportional hazards[12]. The only other study that investigated body weight did not report body mass index and studied only 39 patients in total[56].

3.4.7.3 Problems with measuring body mass index in acutely ill patients

The SUPPORT study demonstrated a robust relationship between BMI and outcome in acutely ill COPD patients, which is consistent with the observations in stable outpatients[12]. However, though the number of patients with missing BMI is not reported there was clearly a problem with missing data since the final outcome model contained a dummy variable for those patients where the BMI was missing. This was despite the study only recruiting in five centres and having full time data collectors in each centre.

3.4.7.4 Mid-upper arm circumference

Collins demonstrated that the mid-upper arm circumference (MAC) had a good correlation with BMI in 98 severely malnourished adults in a feeding centre in Sudan, the correlation between the two being 0.88 (95% CI 0.82-0.92 $p<0.001$)[106]. A French study identified MAC to be significantly associated with 180-day mortality in a population of 116 consecutive patients aged 70 years or older admitted for various reasons to a single French critical care unit and intubated for at least 24 hours [107]. In this study a MAC under the 10th percentile for the older French population in good health was used as a threshold value and reported to have an odds ratio of 3.43 for mortality compared to patients with a MAC greater than this level. They report that this threshold had a sensitivity and specificity for 180-day mortality of 35% and 89% and a positive predictive value of 78% and a negative predictive value of 56%. The analysis involved a data driven exploration of several variables with outcome. The patients who survived 180-days had a mean (SD) MAC cm 30.2 (4.6) cm and the patients who died within 180-days had a mean (SD) MAC of 27.5 (3.5).

MAC is easy to measure and does not require expensive equipment like the more sophisticated mid-upper arm muscle circumference which requires a skin fold calliper, and as such it provides a potential way of estimating BMI in patients who are acutely ill with COPD although up to now, this has not been explored in this context.

3.4.8 Acute physiology as a predictor of outcome

The APACHE score[108] has found widespread acceptance as a method of measuring the risk of death for patients admitted to critical care and is now in its third version[36]. It has components that take account of the chronic health of the patient, the primary diagnosis and the acute physiological impact of the illness (acute physiology score (APS). The APS gives weights to the various biochemical and physiological derangements associated with acute illness. The APACHE score is a generic acute physiology score and when the SUPPORT study[12] produced an outcome prediction model for patients with COPD, albumin and the PaO_2/FiO_2 ratio added explanatory power to a model that already contained the generic APS from APACHE III (which already takes account of albumin and oxygenation). This suggests that a disease specific APS might be useful. A number of the studies identified in the systematic search investigated individual acute physiological factors and these are highlighted below. Section 2.5.3 above discussed the need for at least 10 deaths per level of a risk factor. This makes it clear that many of the studies were too small to systematically investigate the significance of acute physiological factors.

3.4.9 Albumin

Albumin has been noted to be an important predictor of outcome in a wide range of hospitalised patients. In 509 male patients identified because they were inpatients in a Veterans Affairs Hospital with any diagnosis and selected for the study because of the finding of an albumin less than 34g/L, there was a linear relationship between 30 day mortality and serum albumin. For the 50 patients with an albumin less than 20g/L the 30-day mortality was 62% (95% CI 47.2 – 75.3)[109]. Albumin is included in the generic severity scores APACHE II[35] and APACHE III[36]. In the SUPPORT[12] COPD model, albumin was retained in the mortality prediction model that already contained albumin as a component of the acute physiology score from APACHE III. A 10g/L fall in albumin was associated with an independent relative hazard of death of 1.37 (95% CI 1.02- 1.82). Hypoalbuminaemia may reflect poor hepatic synthetic function, acute inflammatory response or malnutrition. It seems likely that the prognostic importance of

albumin in COPD patients will reflect both the impact of malnutrition and the impact of the acute inflammatory response. The acute inflammatory response reduces albumin by four mechanisms; (1) haemodilution, (2) leakage into the extra vascular space due to increased vascular permeability, (3) increased albumin consumption by cells and (4) decreased albumin synthesis by direct inhibition by cytokines. Though albumin has a half-life of approximately 20 days with around 4% being degraded daily, the falls associated with the acute inflammatory response may be relatively rapid. Nevertheless the long half-life of albumin may partly explain its marked importance in the SUPPORT model that used day 3 acute physiology allowing more time for the effects of the acute illness to impact upon the albumin.

Table 3.4.9.1 below shows the relationship between albumin and outcome reported by the studies identified in the systematic search. Nine of the 28 studies reported albumin levels in the studied COPD patients, five studies carried out univariate analysis and three studies carried out multivariate analysis. Many of the studies were small and had limited numbers of deaths. Only the Kaelin study[56] found that albumin levels were the same in patients who lived or died but this was a small study (n=39). In the studies using univariate analysis, one study reported lower albumin in ICU non-survivors compared to survivors[65] and two studies reported lower albumin levels in patients dying in hospital compared to survivors[45 60], though in the Rieves study where the analysis was stratified by FEV_1, there were few events and the difference between survivors and non-survivors did not reach statistical significance. One study using univariate analysis found the albumin on hospital admission to be significantly lower in patients who died before one year than one year survivors[57]. Of the three studies reporting multivariate analysis[12 27 44] two studies used an explicit a priori analysis plan[12 27] and both these studies showed albumin to be significantly associated with mortality. In the SUPPORT study[12] 1016 COPD patients were studied of whom 348 were intubated and albumin was found to have an independent relative hazard of death of 1.36 (1.02- 1.8) in a multivariate analysis that also contained body mass index and age. In the CMP study[27] in a multivariate analysis of 3752 patients of whom 3052 were intubated comparing hospital survivors and non-survivors in which patients with an

albumin greater than 25g/L were used as the reference group, patients with an albumin <20g/L had an OR (95%CI) for hospital mortality of 1.94 (1.46 – 2.58) and patients with an albumin 20 – 24g/L had an OR (95% CI) of 1.28 (1.01 – 1.61) for hospital mortality. This multivariate analysis did not contain body mass index but did contain age. Though once again many of the studies are small there is a consistent message that albumin is an important predictor of outcome. This is confirmed in the bigger studies where albumin is shown to be an independent predictor of outcome, even in the SUPPORT study that also included body mass index.

3.4.10 Acidosis.

Acid-base balance is an important aspect of homeostasis and blood pH, (the negative logarithm of the hydrogen ion concentration), is closely controlled in the range 7.35 to 7.45. In COPD patients, acute type II respiratory failure (PaO_2<8kPa, $PaCO_2$ >6.5kPa), will cause a respiratory acidosis. Metabolic acidosis will reflect developing failure of other organs, for example acute renal failure will cause metabolic acidosis, as would cardiac failure that might result in circulatory shock.

Acidosis is an important marker for the severity of the acute illness and contributes to the acute physiology score of both APACHE II and APACHE III. PH has been identified as a risk factor for mortality in hospitalised COPD patients with respiratory failure[110 111] and this is partly because it identifies those patients who will require intubation. Sluiter[49] reported intubation rates of 85% in patients with a pH <7.20 and 63% in patients with a pH between 7.21 and 7.40 and Hoo[66] described an intubation rate of 70% in patients with a pH <7.20 and 50% in those with a pH >7.25. However there are no hard and fast rules about intubation though the decision will often be driven by the pH. Table 3.4.10.1 below shows those studies identified in the systematic review that have reported pH and Table 3.4.10.2 those that analysed pH with outcome.

Twelve studies report the pH of the included COPD patients. However only 8 analyse the association between pH and mortality. In two of the studies[12 62] that report no association between pH and mortality the reported pH is close to the normal range. In SUPPORT[12] the day three pH is analysed (median (IQR) 7.36 (7.30 – 7.40) and in the

Fuso study[62] the mean (SD) pH in both survivors and non-survivors is in the normal range at 7.35 (0.07) and 7.35 (0.09) respectively. The three other studies reporting no association between pH and mortality include data from acidotic patients but carry out the analysis using the pH at the time of intubation[45 64 68]. PH values at the time of intubation measure the pH before aggressive treatment has started and reflect process of care factors such as oxygen management, whereas pH measured once aggressive care has been established may reflect poor response to therapy which may be more associated with outcome.

In a study of 983 patients with COPD presenting in casualty, Plant showed that 20% of patients with acidosis improved with initial simple treatments and that the pH was inversely correlated with arterial oxygen tension[112]. This highlights the impact of oxygen management on pH in spontaneously breathing COPD patients. Of the studies finding no relationship between pH and survival two were small, with the Hill study[64] including only 20 hospital deaths and the Breen study[68] only 15 deaths. A further negative study included 166 patients with 46 hospital deaths with the mean (SD) pH in survivors 7.27 (0.12) compared to the mean (SD) in non-survivors 7.25 (0.12) p=0.6.

Of the three studies showing a significant association between pH and hospital mortality one included a large proportion of non-intubated patients and used the pH at hospital admission[58]. The other two positive studies, which include over 4000 patients in total, used the pH from ICU [27 67] and in the CMP study which was the largest of these studies the pH used was selected as the lowest in the first 24 hours in ICU. The CMP study included just less than 3000 intubated patients and found significant increased odds of hospital mortality with increasing acidosis in both univariate and multivariate analysis.

Table 3.4.9.1 Albumin and outcome in hospitalised COPD patients

Study	Albumin level	Analysis	Findings	Comment
Kaelin[56] (albumin closest to intubation)	Mean (SD) 34 (8) g/L in 180-day deaths, 34 (6)g/L in 180-day survivors.	Univariate. 15 patients dying before 180 days were compared to 24 patients surviving more than 180-days	Early mortality group mean (SD) albumin was 34(8)g/L and in survivors beyond 180-days was 34(6)g/L	There are small numbers of patients with a small number of events.
Menzies[57] (albumin on hospital admission)	Mean in survivors 32g/l in non-s 29g/l	Univariate analysis for 1 year survival	Mean in survivors 32g/l in non-survivors 29g/l p<0.05	95 patients with 59 deaths at 1 year.
Rieves[60] (Albumin within 24 hours of intubation)	Mean (SD) FEV_1<1L hospital survivors albumin 34.1(5 1) g/L, non-survivors albumin 30.2 (0.71) g/L p=0 056 FEV_1>1L hospital survivors albumin 36.5(8.2) g/L, non-survivors albumin 32.2(8 9)g/L p=0.26	Univariate analysis by hospital survival	A lower albumin (borderline significant) was observed in the 39 episodes in the pts with FEV_1<1l and in those with FEV_1> 1L, patients who died had a lower albumin but numbers were small	There were half as many deaths in those patients with FEV_1> 1L, (lack of power explaining the lack of statistical significance) but overall the study supports albumin as a univariate outcome predictor.
Torres[63] (Albumin measured on admission)	Mean (SD) albumin for population 31(7) g/L	No analysis		Given that these patients all had pneumonia the effect of acute phase might be expected to produce a low mean albumin.
Connors[12] (Reported albumin measured at day 3)	Distribution in cohort not reported	Cox proportional hazards model. Multivariate and univariate analysis of time to death	Hazard ratio (95% CI) 1.78 (1.35-2.38) - increased risk of death for every 10g/l fall in albumin univariate and 1.36 (1 02- 1.8) multivariate	Multivariate analysis included both intubated and non-intubated patients and both body mass index and acute physiology score that already includes albumin.
Moran [44] (Albumin at ICU admission)	38 (SD 6) (range 18-49)	Multivariate analysis investigating 2 year mortality with model containing age, ICU admission and plasma albumin	Albumin taken at ICU admission predicted long term 2-year survival in a multivariate p<0.01.	Albumin did not predict hospital mortality but only 8 hospital deaths.
Anon[65] (Albumin at ICU admission)	Median range total group 29.5 (23-38)	Univariate comparison between ICU survivors and non-survivors	Mean (SD) ICU survivors 30 6 (0.34) non survivors 27.8 (0 18), p=0.05	
Nevins[45] (Lowest albumin in 1st 24 hours in ICU)	Distribution in total group not reported	Univariate comparison between hospital survivors and non-survivors	Hospital survivors mean (SD) 30g/l (6) non-survivors 26 (6) p=0 01	
Wildman CMP (Lowest albumin in 1st 24 hours in ICU)	Median (IQR) in total group 28 (23 – 33) > = 25 or not recorded	Univariate and multivariate comparison between hospital survivors and non-survivors, relative to patients with albumin	Albumin <20 g/L univariate OR (95% CI) 2.73 (2.11 – 3.54), multivariate OR (95% CI) 1 94 (1.46 – 2.58) Albumin 20 – 24 g/L univariate OR (95% CI) 1.49 (1.20 – 1.84), multivariate 1.28 (1 01 – 1 61)	

Table 3.4.10.1 Studies reporting but not analysing pH with outcome

Study	pH of included patients	Analysis	Findings	Comment
Gottlieb[51]	Mean pH 7.3 range (6.95- 7.47), on air	None done		Includes intubated and non-intubated patients.
Moran[44] (Pre-ICU admission pH)	Mean (SD) 7.24 (0.11) for 100 patients in total group, 7.21 (0.12) in 43 intubated patients	None done		Study includes intubated and none intubated.
Anon[65] (In first 24 hours in ICU)	Median (range) whole group 7.2 (7.0-7.34)	No analysis of pH done instead APACHE II analysed		All patients were intubated.
Hoo[66] (pH on hospital admission)	Intubated pH mean (range) 7.26 (0.07), range (6.96-7.35); not intubated pH 7.28 (0.06), range (7.04-7.35)	No analysis of pH in association with survival	Intubation rate 70% in patients with pH< 7.20, 50% in those with pH >7.25	

Table 3.4.10.2 Studies that have investigated the association of pH and outcome

Study	pH of included patients	Analysis	Findings	Comment
Limthongkul 1991[38] (pH at hospital admission)	Group mean not reported	Univariate comparison of hospital survivors versus non-survivors	Mean (SD) pH survivors 7.37 (0.8) vs7.29 (0 015) non-survivors p<0.001	Includes intubated and non-intubated patients.
Fuso 1995[62] (pH at hospital admission)	Group mean not reported	Univariate comparison of hospital survivors versus non-survivors	Mean (SD) pH survivors 7.35 (0.07) 7.35 (0.09) non-survivors p=ns	Includes intubated and non-intubated patients with 85 deaths from 590 patients
Connors 1996[12] (lowest pH day 3)	Group median (IQR) 7.36 (7.30-7.40)	Univariate and multivariate Cox proportional hazards analysis for 180-day mortality	pH was neither a significant univariate nor a multivariate predictor of 180-day mortality	Includes 1016 COPD patients of whom 348 were intubated.
Hill 1998[64] (H^+ immediately prior to intubation)	Group median not reported	Univariate comparison of hospital survivors versus non-survivors	Median (range) hydrogen ion concentration 69.2 (57.1 - 91.2) died 62 8 (49.4 - 91) not significant	All patients intubated. 20 deaths and 21 survivors and paradoxically the survivors were more acidotic, though not significantly so.
Nevins 2001[45] (pH at time of intubation)	pH 7.26 (0.12)	Univariate comparison of hospital survivors versus non survivors	Mean (SD) 7.27 (0.12) hospital survivors 7.25 (0.13) non-survivors p=0 6	All patients intubated.
Afessa 2002[67] (pH in ICU)	Group mean not reported	Univariate comparison between hospital survivors and non-survivors	Mean (SD) Hospital survivors 7.25 (0.1); non-survivors 7.21 (0.12) p=0.0408	250 admissions in 180 patients of whom 153 episodes involved intubation
Breen 2002[68] (pH directly before intubation or on ICU admission)	Mean (SD) for 54 intubated patients 7.13 (0.13)	Multivariate analysis including intubated and non-intubated for hospital mortality	pH reported as non-significant.	Analysis included intubated and non-intubated patients with 15 hospital deaths.
Wildman 2003[27] (lowest pH in first 24 hours in ICU)	Median (IQR) 7.26 (7.18 – 7.33)	Univariate and multivariate analysis for hospital mortality	OR (95%CI) per 0.1 decrease in pH Univariate 1.31 (1.23 – 1 40) Multivariate 1.25 (1.15 – 1.23)	Analysis included intubated and non intubated patients, though 80% of samples were definitely or probably intubated in first 24 hours in ICU.

3.4.10.1 Acidosis: conclusions

In summary, of the eight studies investigating the relationship between pH and mortality five found no significant relationship and three found that patients who were more acidotic had a higher mortality. It is likely that the relationship between pH and mortality is complicated by the fact that a respiratory acidosis soon after hospital admission occurring due to uncontrolled oxygen therapy is likely to have a very different significance to a metabolic acidosis that may indicate additional organ failures.

3.4.11 Oxygenation

As COPD progresses patients become increasingly hypoxic so that hypoxia is a marker of how advanced the COPD is. In addition acute illnesses such as pneumonia will worsen hypoxia with greater hypoxia reflecting greater severity. For these reasons it might be expected that worsening hypoxia would be associated with worsening outcome. Typically hypoxia is measured by analysis of the oxygen in the blood and because the oxygen in the blood can be corrected by supplemental inspired oxygen it is important to correct for supplemental oxygen if the arterial oxygen concentration is to be used as a marker of severity.

3.4.11.1 Alveolar-arterial oxygen gradient

The Alveolar–arterial oxygen gradient is a relatively complicated way of taking into account the influence of both the inspired oxygen concentration and the level of the alveolar carbon dioxide concentration and the equation is given below.

$$\text{A-a gradient} = FiO_2 \times (pAtm - pH_20) - (paCO_2/R) + [paCO_2 \times FiO_2 \times (1-R)/R] - PaO_2$$

Where pAtm = 760mmHg x exp – (altitude in Metres/7000)

And pH20 = 47mmHg x exp ((Temp in centigrade – 37)/18.4)

R = respiratory quotient

Normal A-a gradients have not been established but they tend to increase with age. One study produced a predictive equation based on 80 patients breathing room air and suggested that a normal 60 year old breathing room air might be expected to have an A-

a gradient of 2kPa[113]. Pathological processes that impair gas exchange will lead to increases in the A-a gradient.

3.4.11.2 PaO_2/FiO_2 ratio

The PaO_2/FiO_2 ratio is often used clinically in place of the A-a gradient because though it takes account of the inspired oxygen concentration it is much easier to calculate. Here the PaO_2 is the arterial oxygen concentration and the FiO_2 is the inspired oxygen concentration which will be 0.21 for individuals breathing air. The equation is:

$$PaO_2 \text{ (kPa)} \div FiO_2$$

So for a patient breathing air the FiO_2 would be 0.21, whilst for a patient breathing 40% oxygen it would be 0.40. Covelli [114] has suggested that the normal range of PaO_2/FiO_2 is 41kPa to 68kPa with a value <34kPa indicating clinically significant impairment of gas exchange. Esteban[47] showed that in 5183 patients ventilated for respiratory failure of various aetiologies in 361 ICUs from around the world ICU mortality had a significant univariate and multivariate relationship with PaO_2/FiO_2 ratio such that compared to patients with a PaO_2/FiO_2 ratio of >40KPa, the univariate odds ratio (95% CI) for ICU mortality were, (a) $PaO_2/FiO2$ 26.7 – 40.0 kPa OR 1.10 (0.92 – 1.33), (b) PaO_2/FiO_2 20-26.69 kPa OR 1.36 (1.16 –1.61), (c) PaO_2/FiO_2 13.3 – 19.99 kPa OR 2.29 (2.26 –3.54), (d) PaO_2/FiO_2 <13.3kPa OR 15.73 (10.45 – 23.69).

Sixteen of the 28 studies identified by the systematic search strategy report at least some data about oxygenation and these data are summarised in Tables 3.4.11.1 and 3.4.11.2. In three studies[51 54 66] there was no investigation of the association with mortality. In one study oxygenation was grouped with other respiratory aspects of the acute physiology score and reported to predict 180-day survival better than hospital survival though the reporting lacks detail[43]. Six studies report the PaO_2 without taking into account the FiO_2 and all these show no significant relationship with mortality[45 52 56 64 65 68]. One study reported the PaO_2 on air in a period of stability, but the results are dichotomised as above or below 7.3kPa and the cut-point of 7.3kPa is unrelated to 12 month survival[57]. One study reported the Alveolar-arterial (A-a gradient) oxygen gradient two hours after starting therapy in a sample of 590 hospitalised COPD patients of whom 37 were

intubated, and found that though univariate analysis did not show the A-a gradient to be associated with mortality, the multivariate analysis found an A-a gradient >6kPa to be associated with increased odds of hospital death [62]. It is possible that this was a data driven cut-off.

Four studies reported PaO_2/FiO_2 ratios[12 27 44 67]. In one study it is not clear what analyses were carried out[44]. Of the three remaining studies two[12 27] showed both a univariate and a multivariate relationship with hospital mortality and one did not. The study that did not show a significant association between PaO_2/FiO_2 and mortality analysed 250 episodes in 180 patients and included 153 intubated episodes. Although the PaO_2/FiO_2 ratio was higher in non-survivors it did not reach statistical significance[67]. It was unclear which gases were selected for analysis. Of the two studies that showed a multivariate relationship with mortality, one study used logistic regression to investigate hospital mortality and found an odds ratio (95% CI) for hospital death of 1.13 (1.04 – 1.23) per 10kPa decease in PaO_2/FiO_2[27] and the other study used Cox proportional hazards and included deaths to 180 days and found a hazard ratio (95% CI) of 1.28 (1.05 – 1.54) per 13.2 kPa fall in PaO_2/FiO_2[12].

Table 3.4.11.1 Studies reporting oxygenation but not analysing with outcome

Study (Time oxygenation measured)	Oxygenation patients	Analysis	Findings	Comment
Gottlieb 1973[51] (PaO_2: breathing air on hospital admission)	Mean (range) PaO_2 6.4kPa (3.9-10.9)	No analysis with outcome		
Dardes 1986[54] (PaO_2 on hospital admission)	Mean (SD) of total group PaO_2 5.2kPa (1.1)	No analysis with outcome		Sample included 152 patients only 15 were intubated
Moran 1998[44] (PaO_2/FiO_2 at time points quoted for 43 intubated patients)	Mean (SD) kPa PaO_2/FiO_2 for 43 intubated patients Pre-ICU 24.7 (10.3) On ICU admission 29.2 (10.5) 24hrs post ICU admission 31.5 (13.6)	Unclear whether PaO_2/FiO_2 was analysed with outcome		It is not explicitly stated what factors were investigated in association with hospital mortality.
Hoo 2000[66] (PaO_2/FiO_2 on hospital admission)	Mean (SD) kPa PaO_2/FiO_2 Intubated patients 30.0 (13.9) kPa	No analysis of outcome predictors		

Table 3.4.11.2 Studies investigating the association between oxygenation and outcome

Study (Time oxygenation measured)	Oxygenation patients	Analysis	Findings	Comment
Petheram 1980 [52] (PaO_2: immediately prior to intubation)	Mean PaO_2 5.15kPa in hospital survivors vs. 7.53kPa in non-survivors	Univariate analysis hospital survivors versus non-survivors	The PaO_2 in non-survivors was lower but statistically insignificant though only 18 patients in the sample.	Inspired oxygen not specified, but the non-survivors with the higher PaO_2 also had higher $PaCO_2$ i e. 8 5 kPa in survivors, 10.23 kPa in non-survivors.
Kaelin 1987[56] (PaO_2 :in period of stability)	Mean (SD) in 180-day survivors PaO_2 7.4 (1.9) PaO_2 8 1 (2.5) in 180 day non-survivors	Univariate comparison of 180-day survivors with non-survivors	The PaO_2 in non-survivors was lower but statistically insignificant. Only 39 patients in the sample and only 15 deaths before 180-days.	Inspired oxygen not specified, but the non-survivors with the higher PaO_2 also had higher $PaCO_2$ i.e. 6.02 (1.3) kPa in survivors 6.5 (1.1) kPa non-survivors.
Menzies 1989 [57] (PaO_2: in period of clinical stability)	49% of the 95 study patients had PaO_2<7.3	The PaO_2 in a period of stability was dichotomised into hypoxic and non-hypoxic and used the binary variable in univariate analysis.	A PaO_2 in period of stability <7.3 was present in 49% of patients who died before 12 months and 50% of survivors.	The dichotomising of the PaO_2 looses information about the mean PaO_2 in living and dying populations
Fuso 1995 [62] (A-a gradient: 2 hours after starting oxygen therapy)	Mean (SD) Alveolar arterial (A-a) oxygen gradient in surviving vs. dying 6.1 (2.8) kPa vs.7 6 (3 8) kPa PaO_2 in survivors 7.5 (1.7) vs. 7.4 (2.2) kPa	Univariate and multivariate analyses for hospital survival	Univariate comparison showed that non-survivors were more hypoxic though this did not reach statistical significance. In Multivariate logistic regression a A-a gradient of > 6 kPa was associated with OR (95% CI) of death 2.33 (1.39 – 3.90)	The multivariate model used factors found to be significant in the univariate analysis and contained age, A-a gradient, atrial fibrillation and ventricular arrhythmias. Note that the sample contained 590 patients of whom 37 were intubated.
Seneff 1995 [43] (Worst value in first 24 hours in ICU)	Not reported	Not analysed alone.		Arterial oxygenation was not reported separately, but along with the other respiratory components of the APACHE III score was reported to predict 180-day mortality better than hospital mortality.
Connors 1996[13] (PaO_2/FiO_2): third day of admission)	Median (IQR) 28 13 (22 8-35.59) kPa	Multivariate and univariate Cox proportional hazards for mortality to 180-days	13.2kPa decrease in ratio associated with a univariate Hazard ratio (95%CI) for death of 1.28 (1.06 – 1.54) and multivariate 1.28 (1.05- 1.54)	The Hazard ratio assumes a constant relationship to deaths occurring throughout the 180-day period
Hill 1998 [64] (PaO_2 : immediately prior to intubation)	Median (range) 9.3kPa (6 1 - 12.4) in survivors, 6.7kPa (5.5 - 11.5) in non-survivors	Univariate analysis	No significant difference.	No adjustment for FiO_2
Anon 1999 [65] (PaO_2 in first 24 hours in ICU for 20 intubated patients)	Median (range) kPa PaO_2 5.73 (3 47 – 8.13)kPa	Univariate comparison of PaO_2 in ICU survivors and non-survivors	No significant difference	

Table 3.4.11.2 Studies investigating the association between oxygenation and outcome *continued*

Study (Time oxygenation measured)	Oxygenation patients	Analysis	Findings	Comment
Nevins 2001[45] (PaO_2 prior to intubation)	Mean (SD) PaO_2 12.3(9.1) kPa hospital survivors 10 4(5 3) kPa non-survivors	Univariate comparison of hospital survival	No significant difference (p=0.3)	
Afessa 2002[67] (PaO_2/FIO_2 in ICU)	Mean (SD) PaO_2/FIO_2 Hospital survivors 28 0 (14 1) kPa non-survivors 27.2 (14.8) kPa		No significant difference (p=0.72)	Includes both 153 intubated patients and 97 not intubated. The study analysed 250 episodes in 180 patients, though the PaO_2 is measured in ICU it is not clear how the value was selected
Breen 2002[68] (PaO_2 :on admission to ICU or immediately prior to intubation)	Whole group Mean(SD) 12 8 (9 7) kPa Median (range) 9 6(4.5-62.4) kPa	Multivariate logistic regression	PaO_2 did not predict hospital mortality on multivariate logistic regression	74 patients in sample and 63 were intubated. Small numbers of deaths.
Wildman 2003 [27] (PaO_2/FIO_2 from ABG with lowest PaO_2 in first 24 hours in ICU)	Whole group Median (IQR) 23 0 (17.2 – 29 7) kPa	Univariate and Multivariate logistic regression in relation to hospital mortality	OR (95% CI) per 10 kPa decrease in PaO_2/FIO_2 Univariate 1.17 (1.09-1.26) Multivariate 1.13 (1 04 – 1 23)	Analysis carried out on all 3439 patients with data of which 80% were intubated

3.4.11.3 Conclusion oxygenation and outcome

The larger studies support the suggestion that gas exchange is a risk factor for mortality but confirm that the association is best shown when the arterial oxygen concentration takes account of the inspired oxygen concentration.

3.4.12 Carbon Dioxide

As COPD progresses hypercapnia may occur with exacerbations and in more advanced disease hypercapnia may become present between exacerbations. Hypercapnia is usually defined as a $PaCO_2$ > 6kPa. In a 5-year prospective study of 85 patients admitted with COPD exacerbations, patients who became hypercapnic during the exacerbation and those who remained eucapnic had a similar prognosis with 28% and 33% 5-years survival respectively. However patients who remained hypercapnic had a 5-year survival of only 11% [115]. In COPD patients who are intubated the $PaCO_2$ may be influenced by ventilatory strategies such as low tidal volume ventilation which is

employed to minimise ventilator-associated lung damage. For these reasons it might be expected that the $PaCO_2$ level measured once patients were intubated would not be an important predictor of mortality in COPD patients intubated with respiratory failure. Table 3.4.12.1, 3.4.12.2 and 3.4.12.3 below shows the studies identified in the systematic review that described carbon dioxide levels.

Fifteen of the 29 studies identified in the systematic search reported data on carbon dioxide levels. Four studies presented summary statistics without analysis by outcome[44 51 65 66]. Two studies investigated the association between outcome and the $PaCO_2$ in the period of stability[56 57]. Both found the steady state $PaCO_2$ to be higher in patients dying within 180 days or 1 year after admission compared to survivors, and though neither of these small studies reached statistical significance they raise the possibility that adequately powered studies might be consistent with the findings of Costello who showed that patients with hypercarbia in periods of stability had lower survival[115].

Nine studies reported the results of analysis of the association between $PaCO_2$ measured during hospital admission and outcome, and eight of the nine failed to find an association[12 27 45 52 62 64 67 68]. In the largest of the studies analysis included over 3000 patients of whom 80% were intubated and used the most acidic blood gas in the first 24 hours in ICU[27]. The one study that found an association between $PaCO_2$ and outcome showed similar survival at hospital discharge but significantly increased mortality at 1 year in patients 65 years and older with a $PaCO_2 \geq 6.7$kPa compared to patients with a $PaCO_2$ lower than this value[43]. The other large study with outcomes to 180 days was the Connors study[12] and in this study patients with a $PaCO_2$ less than 6.7kPa were explicitly excluded.

The studies identified in the systematic review suggest that the level of the $PaCO_2$ in the acute setting does not predict hospital outcome, though it should be remembered that some studies will have required a raised $PaCO_2$ as part of the inclusion criteria. The Seneff study[43] suggests that when patients with only mildly raised $PaCO_2$ are included and outcomes over a prolonged period are compared, significant differences emerge at 1 year. It may well be that the group with a $PaCO_2 < 6.7$ kPa will include a greater

proportion of patients who have a normal CO_2 when stable than patients with a $PaCO_2 \geq$ 6.7kPa. An understanding of the natural history of respiratory failure in patients with COPD leads to the expectation that patients with hypercarbia in the stable state represent a prognostically distinct group, though the numbers of patients in the systematically identified studies that had had $PaCO_2$ measured in the period of stability were small.

Table 3.4.12.1 Studies in which $PaCO_2$ was measured in period of stability pre-exacerbation

Study (Time measured)	$PaCO_2$ included patients	Analysis	Findings	Comment
Kaelin 1987[56] (In period of stability)	Mean (SD) 6.0 (1.3) kPa 180day survivors 6.5 (1.1) kPa Non-survivors	Univariate comparison by 180-day mortality	No significant difference	All 39 patients intubated and 15 lived less than 180 days
Menzies 1989 [57] (In period of clinical stability)	Summary statistic not presented, $PaCO_2 > 6kPa$ was present in 39% of those who survived 12 months and 56% of those who died by 12 months	Comparison of proportion of patients with $PaCO_2 > 6kPa$ between 1 year survivors and non-survivors	No significant difference	95 intubated patients with 59 deaths at 1-year. The analysis loses power by dichotomising $PaCO_2$ into >< 6.0kPa

3.4.12.1 $PaCO_2$ and outcome conclusions

None of the studies demonstrated a convincing relationship between the $PaCO_2$ measured during the exacerbation and survival. Though there are studies which do not concentrate on intubated patients that suggest that the $PaCO_2$ measured in the period of stability might predict outcome, only two studies from the systematic search used the $PaCO_2$ from the period of stability and both were small and neither found a significant association. It seems likely that the most promising way to use $PaCO_2$ to predict outcome would be using $PaCO_2$ from the period of stability but this is likely to be unavailable in the acute setting.

Table 3.4.12.2 Studies in which $PaCO_2$ was measured in critical care and/or the relationship of $PaCO_2$ to intubation status is unclear

Study (Time measured)	$PaCO_2$ included patients	Analysis	Findings	Comment
Connors 1996 [12] ($PaCO_2$ measured on day 3)	Whole group median (IQR) 7.46 (6.67-8.66) kPa	Univariate and multivariate Cox proportional hazards for mortality up to 180-days	No significant association with survival.	Sample contained 1016 patients selected if they had $PaCO_2 \geq 6.67$kPa of whom 348 were intubated
Hoo 2000 [66] ($PaCO_2$ measured on hospital admission)	74 Intubated patients mean (SD) $PaCO_2$, 9.73 (1.9) kPa	Summary statistics only No analysis of $PaCO_2$ with mortality		
Afessa 2002 [67] ($PaCO_2$ measured in ICU)	Mean (SD) 8.1 (2.7) kPa Hospital survivors 7.54 (2.3) kPa non-survivors	Univariate comparison by hospital outcome.	No significant association with survival	Includes both 153 intubated patients and 97 not intubated. The study analysed 250 episodes in 180 patients, though the $PaCO_2$ is measured in ICU it is not clear how the value was selected.
Wildman 2003 [27] ($PaCO_2$ from blood gas with lowest pH in first 24 hours in ICU)	Whole group median (IQR) 8.7 (6.9 – 10.7)	Univariate and multivariate comparison of $PaCO_2$ levels in 10kPa increments by hospital outcome	No association with hospital mortality either in univariate or multivariate analysis	Analysis carried out on all 3439 patients with data of which 80% were intubated

3.4.13 Composite acute physiology scores

Three studies[12 43 45] reported the association between the weighted acute physiology scores from APACHE II and APACHE III and outcome. In all three studies there was a significant association between the higher scores and outcome. No studies reported a lack of association between a composite acute physiology score and outcome. The three studies are outlined in table 3.4.13.

Table 3.4.12.3 Studies in which $PaCO_2$ was measured prior to critical care admission or documented as prior to intubation

Study (Time measured)	$PaCO_2$ included patients	Analysis	Findings	Comment
Gottlieb[51] (On hospital admission on air)	Mean(range) $PaCO_2$ 9.6 (6.4-13.3)kPa,	Summary statistics only		
Petheram[52] (Immediately prior to intubation)	Mean 8.5 kPa hospital survivors vs. 10.2 kPa non-survivors	Univariate comparison by hospital mortality	No significant difference	In 18 intubated patients with chronic bronchitis 12 survived to 1 year.
Fuso[62] (2 hours after starting oxygen therapy)	Mean (SD) 7.5 (2.2) kPa hospital survivors; 7.45(2.6) kPa non-survivors.	Univariate comparison of hospital survival	No significant difference. (Mean in survivors non-significantly higher than non-survivors)	Note that the sample contained 590 patients of whom 37 were intubated.
Hill[64] ($PaCO_2$ measured immediately prior to intubation)	Median (range) 20 patients dying in hospital 9.7 (6.6 – 11.7) kPa, 21 survivors 11.2 (8.7 – 13.1) kPa	Univariate comparison by hospital survival	No significant association with survival.	
Moran[44] ($PaCO_2$ measured pre-ICU admission)	Mean (SD) for 43 intubated patients 12 (4) kPa	Univariate and multivariate analysis were those with univariate p value <0.01	No significant association with survival	$PaCO_2$ was not a significant predictor, but it looks like it was investigated & rejected.
Hoo [66] ($PaCO_2$ measured on hospital admission)	74 Intubated patients Mean (SD) $PaCO_2$, 9.73 (1.9) kPa	Summary statistics only No analysis of $PaCO_2$ with mortality		
[65] ($PaCO_2$ measured on ICU admission)	Median range for all 20 intubated patients. 11.3 (5.9-17.7) kPa	Summary statistics only. No analysis of $PaCO_2$ with mortality		
Nevins[45] ($PaCO_2$ measured immediately prior to intubation)	Mean(SD) Hospital survivors 9.1(3.9) kPa Non-survivors 9.3(3.7) kPa	Univariate comparison by hospital outcome.	No significant association with survival. p=0.7	All patients intubated
Breen[68] ($PaCO_2$:on admission to ICU or immediately prior to intubation)	Whole group mean (SD) 12.0 (3.1)kPa median (range) 11.9 (5.5-20.3)kPa	Multivariate comparison by hospital outcome	PaO_2 did not predict hospital mortality on multivariate logistic regression	74 patients in sample and 63 were intubated

Table 3.4.13 Acute physiology score and outcome

Study	Acute Physiology Score (APS) / Time measured	Analysis	Findings	Comment
Seneff 1995 [43]	APS III 1st 24 hours in ICU	Multivariate analysis	Respiratory components more strongly predictive of 180-day outcome, non-respiratory organ dysfunction more strongly predictive of hospital mortality	
Connors 1996 [12]	APS III Day 3 of hospital admission	Multivariate analysis	10 point change in APS associated with Hazard ratio for death over 180-days of 1.32 (1.20-1.45)	
Nevins 2001 [45]	APS II 6 hours after onset of mechanical ventilation	Multivariate analysis	Mean (SD) APS in survivors 7(5) vs. non-survivors 11(6) $p<0.001$	

APSIII acute physiology score from APACHE III

APS II acute physiology score from APACHE II

3.4.14 Aetiology of exacerbation

In studies which have included patients for whom the disease process leading to intubation has included causes other than COPD e.g. Adult Respiratory Distress Syndrome (ARDS) following sepsis, the aetiology of respiratory failure identifies patients with distinct outcomes. In a prospective international study of 361 intensive care units 5183 intubated patients were studied with an overall ICU mortality of 30.7%[47]. Patients intubated because of ARDS had an ICU mortality of 52% (95% CI 45%-59%), patients with pneumonia an ICU mortality of 38% (95% CI 35 – 42), and patients intubated because of COPD exacerbation had an ICU mortality of 22% (95% CI 19-26). In this study only patients intubated because of asthma (with an ICU mortality of 11% (95% CI 6 – 21)) and neuromuscular disease (with an ICU mortality of 15% (95% CI 9 – 24)) had lower ICU mortality than the COPD patients. Studies reporting the aetiology of the exacerbation are summarised in Table 3.4.14.

Table 3.4.14 Table outlining the aetiology of the exacerbation in hospitalised COPD patients.

Study	Aetiology of exacerbation	Analysis	Findings	Comment
Kaelin 1987 [56]	Pneumonia in 59% of total sample of 39 patients: 54 2% of 180-day survivors 66.7% non-survivors	Chi-square comparison 180- day survival	Pneumonia less common in 180-day survivors $p<0.05$	Pneumonia described as "clear-cut" diagnostic criteria not provided.
Menzies 1989[57]	Exacerbation of COPD 49%, pneumonia 20%, LVF 7%, surgery 11%, other 13%	Comparison of aetiology by 1-year outcome	Cause of respiratory failure not significantly associated with 180 outcome	Pneumonia- new airspace shadowing on CXR plus ≥ raised white cell count, fever, positive blood culture, and CXR response to antibiotics.
Rieves 1993[60] (survival defined as spontaneous ventilation for >72 hours)	Exacerbation of COPD 47%, COPD with CXR infiltrates 53%	Comparison of presence of infiltrates by 72 hour survival stratified by FEV_1	FEV_1< 1L (n=39) Pulmonary infiltrates 9% survivors vs. 94% non-survivors $p< 0.001$ FEV_1> 1L (n=19) Pulmonary infiltrates 54% survivors vs. 88% non-survivors $p=0.127$	(1) Pneumonia: CXR infiltrates plus any 3 of: fever, positive blood cultures, raised white count, pathogenic sputum culture. (2) Congestive cardiac failure: lung infiltrates plus elevated wedge pressure, (3) Exacerbation COPD: no other cause for deterioration. Note. Analysis by episode 39 episodes in 33 patients with FEV_1 < 1l and 19 episodes in patients with FEV_1 >1L
Fuso 1995[62]	LVF in 26% CXR inflammatory exudates 9%	Univariate analysis	CXR findings of pneumonia or LVF not associated with mortality	(590 in sample only x intubated)
Seneff 1995[43]	This sample only included COPD patients without pneumonia or LVF	No analysis of aetiology by outcome, but the study probably identifies the outcome of patients without pneumonia or left ventricular failure i.e. a clear CXR	Hospital mortality in intubated patients 31.8% (24 8 – 39.3)	The study inclusion criteria suggest that included patients will have COPD and a clear CXR in that patients with COPD and pneumonia or LVF would be coded as pneumonia or LVF and not included
Torres 1996 [63]	124 patients in total. Sample only included COPD patients with proven pneumonia. Note that mean (SD) FEV_1 40% (11)		22 patients intubated with hospital mortality of 23% (95% CI 8 – 45)	Patients had relatively good lung function.
Connors1996 [12]	"Infection as a cause" Congestive cardiac failure (CCF) as cause Cor pulmonale	Univariate and multivariate Cox survival analysis	Infection as cause of acute deterioration not associated with survival CCF as cause protective Hazard ratio (95% CI) univariate 0 67 (0 47 – 0.94) multivariate 0.66 (0.45- 0.97). Cor pulmonale protective univariate 0 64 (0.44- 0.93), multivariate 0.67 (0.45 – 0 99)	Respiratory infection as a cause was reported in 47.4% of the 1016 patients however the definition is not reported.

Table 3.4.14 Table outlining the aetiology of the exacerbation in hospitalised COPD patients *continued.*

Study	Aetiology of exacerbation	Analysis	Findings	Comment
Hill 1998[64]	Consolidation on CXR in 44%	Univariate analysis by hospital survival	Consolidation on CXR in 33% of survivors and 55% of non-survivors non-significant	
Moran 1998[44]	Excluded all patients with pneumonia or heart failure	No analysis of aetiology by outcome, but the study probably identifies the outcome of patients without pneumonia or left ventricular failure i.e. a clear CXR	Hospital mortality in intubated patients 14% (5..3 – 27.9)	
Hoo 2000[66]	138 patients in group , 20% had CXR infiltrates	Univariate comparison of presence of CXR infiltrates by success of conservative management	Proportion of patients with CXR infiltrates in patients intubated % (95% CI) 27% (17- 39) in patients successfully managed conservatively 13% (6 – 23) p=0.06	A greater proportion of patients admitted to hospital with hypercapnic failure who needed intubation had CXR infiltrates, but the difference failed to reach statistical significance.
Nevins 2001[45]	COPD exacerbation 23%, pneumonia 43%, ARDS 9%, unstable angina/MI 12%, congestive heart failure 24%, sepsis 11%, encephalopathy 7%	Univariate comparison of cause of deterioration in COPD patient by survival	% Survivors with aetiological factor vs. non-survivors: COPD exacerbation survivors 28% vs. non-survivors 13%, p= 0.049 Congestive heart failure Survivors 26% vs. non-survivors 20% p=0.40 Pneumonia survivors 39% vs. 50% non-survivors p=0.40 Other survivors 13% vs. non-survivors 24% p= 0.10	All 166 of these patients were intubated.
Afessa 2002 [67]	Acute COPD exacerbation 58%, pneumonia 23%, cardiac 10%, sedatives 3%, pneumothorax 2%, sepsis or ARDS 1%, other 4%	No analysis of outcome by aetiology		
Wildman 2003 [27]	†Pneumonia 20 8%, right ventricular failure 4%, left ventricular failure 3.8%, COPD alone or plus other secondary diagnosis 71%	Multivariate analysis of diagnostic group versus patients with COPD alone	Adjusted OR (95% CI) Pneumonia 1.04 (0 85 – 1.26) Right ventricular failure 1.60 (1.07 – 2.38) Left ventricular failure 0.79 (0.52 – 1.20)	

†Patients were assigned to one of the three subgroups of COPD (pneumonia in a patient with COPD, right ventricular failure in a patient with COPD or left ventricular failure in a patient with COPD) if the first or second cause of admission was pneumonia, right ventricular failure or left ventricular failure in a patient in whom the other cause of admission was COPD, exacerbation of COPD or emphysema.

Of the 29 studies identified in the systematic search, 13 provide information on the aetiology of the respiratory failure. However the criteria used to classify the aetiology varied between studies and were not always explicit. In four studies the cause of the respiratory failure was described but there was no analysis of outcome[43 44 63 67]. In two of these studies patients with pneumonia or heart failure were excluded[43 44] and one study confined itself entirely to patients with COPD patients presenting with pneumonia[63].

3.4.14.1 Pneumonia

Eight studies identified patients with pneumonia or pulmonary infiltrates and explored the association with outcome[27 45 56 57 60 62 64 66]. Seven of these studies carried out univariate comparisons of the frequency of patients with pneumonia/pulmonary infiltrates in survivors and non-survivors. Of the studies employing univariate comparisons two studies reported that there was no association between pneumonia and survival but do not report figures[57 62]. Two studies[45 64] report greater numbers of patients with pneumonia amongst non-survivors than survivors (Nevins non-survivors 50% pneumonia vs. survivors 39% pneumonia, Hill non-survivors pneumonia 55% vs. 33% survivors) but both studies failed to reach statistical significance. In the Hoo[66] study 27% of patients with pulmonary infiltrates required intubation compared to 13% of patients without infiltrates though again the difference did not reach statistical significance ($p=0.06$). Two studies report that pneumonia/pulmonary infiltrates were significantly commoner in non-survivors than survivors[56 60]. The Kaelin study does not report the proportions. In the Rieves study where the analysis was stratified by lung function, of 39 patients with an FEV_1 <1L, 94% of non-survivors had pulmonary infiltrates compared to 9% of survivors ($p<0.001$). In the 19 patients with an FEV_1>1L pulmonary infiltrates were present in 88% of non-survivors compared to 54% of survivors $p=0.127$. In the CMP study[27] pneumonia was not associated with hospital mortality in an analysis adjusted for case-mix that included careful adjustment for the severity of disease within the first 24 hours in critical care. The Connors study[12] carried out both a univariate and multivariate analysis to identify factors associated with

survival and investigated the role of "infection as a cause" of the respiratory failure. The diagnostic group "infection as a cause" was not associated with increased mortality but it is unclear what proportion of patients in this group would have had pulmonary infiltrates and what proportion would have had an infective exacerbation of COPD with a clear chest x-ray.

It is likely that the relationship between pulmonary infiltrates and outcome is complicated because of confounding related to lung function and severity of illness. On the whole patients with well-preserved lung function will require a substantial additional burden of illness in order to develop respiratory failure that requires intubation and ventilation. Many of these patients are likely to have pneumonia accompanied by additional organ failures. The SUPPORT study showed that mortality in COPD patients has an independent association with increased physiological derangement[12] and the CMP study showed an independent association between organ failures and mortality[27]. Patients with advanced COPD and very poor lung function will develop respiratory failure of sufficient severity to require critical care with relatively little additional illness burden. There is some support for this hypothesis from the Nevins study in which COPD patients intubated in ICU with a clear CXR had a mean(SD) FEV_1 of 0.99 (0.40) compared to the whole group FEV_1 1.24 (0.58)[45]. In the Ely study[46] that included COPD patients intubated for exacerbations the FEV_1 % predicted was mean 23%, whereas in the Torres study[63] that included only COPD patients with pneumonia the FEV_1 % predicted was mean 40%.

When studies simply compare COPD patients in critical care with and without pneumonia, it is likely that the group of patients with pneumonia will contain relatively more patients with well preserved lung function and a severe acute illness, and on average the patients without pneumonia will have a relatively minor acute illness and markedly impaired lung function. Thus in order to understand the role of pneumonia, studies need to adjust for the patients functional capacity, carefully define pneumonia clearly and measure the severity of illness in terms of an acute physiology score or organ failure score. One reasonable interpretation of the available evidence is that at any given level of lung function patients will have a worse outcome with more severe

physiological derangement, and since pneumonia often has widespread adverse physiological consequences patients with pneumonia will have a worse outcome. However in comparisons of outcome if the acute physiology is adequately controlled for chest x-ray shadowing alone may be relatively unimportant.

3.4.14.2 Cor pulmonale and congestive cardiac failure

Cor pulmonale is effectively right heart failure where the aetiology is attributed to lung pathology, whereas congestive cardiac failure may be due to a primary cardiac problem. The Connors study[12] and the CMP study[27] investigated the association of heart failure with outcome. In the Connors study cor pulmonale was found to have an association with improved outcome (adjusted hazard ratio for survival over 180 days 0.67 (0.45 – 0.99)) and in the CMP study right ventricular failure had an association with increased hospital mortality (adjusted OR (95% CI) 1.60 (1.07 – 2.38)). In the Connors study congestive cardiac failure was also associated with improved survival (adjusted hazard ratio 0.67 (0.47 – 0.94)). It is interesting that the Connors study reports almost identical hazard ratios for both congestive cardiac failure and cor pulmonale, and in fact the study definitions for the two conditions are quite similar so that clinicians may have found it difficult to differentiate the groups.

3.4.15 Length of stay in hospital prior to critical care

Lead time can have important implications for prognostic models. Seneff reported an association between length of stay before ICU admission and death in COPD patients admitted to US critical care units but did not report the magnitude of risk[43]. The SUPPORT prognostic model for functional capacity after critical care estimated that the independent odds ratio (95% CI) for severe dysfunction following critical care was 1.04 (1.02 – 1.06) per day in hospital pre-critical care[116]. Analysis of 3400 patients admitted to UK critical care units with COPD estimated an independent odds ratio (95% CI) for hospital mortality of 1.02 (1.01 – 1.03) per one day increase in hospital length of stay prior to critical care[27].

3.4.16 Long term oxygen therapy

There is some evidence that some clinicians consider long term oxygen therapy (LTOT) to be a contraindication to intubation[6]. However since patients with hypoxia on long term oxygen survive longer than those not on oxygen it might be supposed that all else being equal in terms of baseline hypoxia those patients on LTOT might be expected to have a better prognosis if intubated [117 118]. No studies provide a comparison of intubated patients with and without LTOT. Only the Anon study considers patients with LTOT and in a group of 20 such patients 35% died in ICU, 50% in hospital and 75% in one year[65].In a study from Spain that looked at 135 consecutive hospitalised COPD patients (but did not specifically report outcomes for intubated patients) patients on long term oxygen therapy had higher death rates after 2 years' follow-up[69]. It is possible that a study including all hospitalised patients may include patients with a wider spread of severity than a critical care study, and LTOT use may identify a frailer subgroup. LTOT was not included in a multivariate analysis.

3.4.17 Non-invasive ventilation use prior to intubation

Systematic reviews have suggested that non-invasive ventilation (NIV) is the optimal first line treatment for patients with exacerbations of COPD and patients treated with NIV had a decreased need for intubation and a lower hospital mortality than those treated with conventional therapy [3 119 120]. However there are some limitations to the generalisability of these results because in all of these studies patients who required immediate intubation were excluded prior to randomisation.

It is likely that the survival benefit of using NIV first line documented in the RCTs partly results from NIV patients avoiding the additional risks of intubation. Chastre suggested that ventilator associated pneumonia occurred in 8 to 28% of intubated patients[121]. Some information about outcomes of patients intubated following NIV is available from an observational study in a single ICU in which 212 COPD patients were treated with either intubation first line (n=113) or NIV first line (n=99), followed by intubation in patients in whom NIV failed. Eighty nine of the 113 patients intubated

first line survived (79%, 95% CI 70-86%), 47 of the patients treated with NIV first line failed and 40 were intubated of whom 30 survived (75%, 95% CI 59% - 87%)[67].

3.4.18 Previous intubation

A single study found that patients who had survived a previous intubation were at lower risk than patients who were intubated for the first time[45].

3.4.19 Repeated hospitalisations

In the SUPPORT study patients with repeated admissions in the period following the index admission in which study recruitment occurred had an increased mortality, but there were no studies which explored the association with information available at the time of index admission and outcome[12]. A study from Spain that included 135 hospitalised COPD patients did not explicitly report the outcome for intubated patients but found that patients who had been admitted to hospital in the previous year had increased univariate odds of mortality of 2.28 (95% CI 1.36-3.82) compared to patients who had not had multiple admissions[69].

3.5 Quality of life after intensive care admission

The duration of time that has elapsed after ICU is likely to be important in determining patients' health status. Patients will want to know how long it will take before the effects of ICU have worn off and their functional capacity has reached a plateau. However the data on the trajectory of patient's health status following ICU are limited. In a patient who was previously well and suffers an injury, the trajectory of recovery simply takes account of the recovery from a single insult against a background of full function. In patients with chronic disease, there is the need to consider the recovery from the acute exacerbation that resulted in ICU admission, but there is also the impact that the exacerbation and critical care admission will have on the trajectory of a chronic disease that may well have a progressive component. There have been no studies that have explicitly addressed this question in COPD patients admitted to ICU.

Probably the most useful data relating to COPD patients comes from the SUPPORT study. In 1016 patients with COPD[12 93], 11% died in hospital, 20% by 60 days, 33% by 180 days, 43% by 1 year and 49% by 2 years. The SUPPORT study also provides data on perceived quality of life at 6 months[12] and 12 months[93]. Only group comparisons are available and some patients who report quality of life at 6 months will not have survived to 12 months. At 6 months 518 patients provided data on self-rated quality of life and 600 at 12 months.

Table 3.5 Quality of life after hospital admission in COPD patients from the SUPPORT study

Quality of life rating	6-months n=518	12 months n=600
Very good or excellent	21.1%	10%
Good	30.1%	21%
Fair	28.4%	53%
Poor	20.1%	16%

Interpretation of these data is complicated by there being only 518 respondents at 6 months but 600 respondents at 12 months, and it is unclear how far differential response of patients with better quality of life at 6 months accounts for the better quality of life at that time point. Nevertheless there were 109 patients describing their quality of life as excellent or very good at 6 months when there was incomplete response and only 61 at 12 months with complete response, so that whatever group the 6 month non-responders belonged to, there had been some decrease in the number of patients rating their quality of life as good or very good by 12 months. If poor quality of life at follow-up was largely due to the reversible effects of an index acute illness it might be expected that these effects would lessen over time so that patients' quality of life would be worse at 6 months than it was at 12 months. That there are less patients with excellent or very good quality of life at 12 months than 6 months is consistent with the possibility that there are

aspects of progression of the chronic disease that are causing patients' health to deteriorate.

In 101 patients with COPD studied primarily in the outpatient setting, 75% had peak expiratory flow values that had recovered to baseline by 35 days, and only 7% of patients had not recovered their baseline peak expiratory flow rate by 91 days[122]. These data suggest that the time course of recovery of COPD exacerbations is relatively short and might be expected to be complete by 180 days, though how applicable this is to a patient with a critical care admission is unclear. It is known that as COPD becomes more severe, exacerbations become more frequent and that exacerbations are associated with deterioration in quality of life. In an earlier paper involving 70 COPD patients Seemungal reported that over 1 year some patients had three or more exacerbations, and that quality of life measured using the St Georges Respiratory Questionnaire was significantly worse in the frequently exacerbated[123]. These data suggest that measuring quality of life at 180 days in CAOS provides a reasonable estimate of the recovery that might be expected after ICU, but that in patients having frequent exacerbations these might be expected to result in ongoing decline in quality of life.

3.6 Summary and conclusions

The systematic review has shown that there are number of risk factors associated with outcome in COPD patients. The quality and number of the studies that have identified associations varies from risk factor to risk factor. The risk factors have been organised into tables (Tables 3.6.1, 3.6.2 and 3.6.3 below) that summarise the findings of the systematic review with a brief comment about the strength of evidence supporting the association of each risk factor with outcome. The risk factors are organised into those that describe the patients' characteristics in the period of stability pre-exacerbation, and those that describe the patients' characteristics after hospital admission and before critical care admission. These tables were used to guide the choice of data to collect. The weight of evidence supporting the various risk factors helped to inform the selection of variables used in the final model as outlined in chapter 10 below.

Table 3.6.1 Patient characteristics available in the period of stability pre-exacerbation that have been shown to be associated with outcome

Variable	Association with outcome	Strength of evidence/comment
Age	Most studies show age to be associated with increased mortality	Evidence mainly consistent. However occasional studies showed no increased mortality with age, but this was usual in small studies or where there was a suggestion of selection bias so that only the fittest of the old were selected.
Sex	Only a few studies examine the relationship with sex. The case mix programme study with over 3000 patients found a univariate increased risk of death in males[27]	The association between sex and mortality that disappears after adjustment for other risk factors in a large data set raises the possibility that being male is a marker for other risk factors. As such in a parsimonious model male sex may be a useful predictor if the model does not adequately take into account all the other risk factors that are associated with male sex
FEV_1	Studies in the outpatient setting find FEV_1 to be associated with mortality. Inadequate data in the acute setting.	Likely to have an association with outcome as long as there is a great enough range of values in the patients ending up requiring intubation. Many studies have found that FEV_1 is unavailable in the acute setting.
Exercise tolerance in the period of stability	Many studies have found some relationship between functional capacity and outcome. Useful scores included Katz ADL score and the functional score and the Duke activity score index.	Strength of relationship is perhaps weaker than expected which may reflect under and over-estimation by both patients and proxies.
Self-rated prior quality of life	Single study found an association with mortality [93]	A single study found an association, but self-rated quality of life is likely to be difficult from proxies.
Comorbidity	Some studies found an association	Co-morbidity is difficult to measure adequately and counting comorbidities may be biased by mild comorbidities being recorded in fit patients and ignored in patients with multiple problems. Probably the most effective way of taking account of comorbidities is to weight them individually depending on the patient's primary disease.
Long term oxygen	No evidence about relationship with outcome for intubated patients	A univariate association with 2 year mortality found in 135 hospitalised patients. It is unclear whether LTOT was a marker of the sickest subgroup since multivariate analysis not carried out[69].
Previous intubation	One study suggested prior intubation associated with survival[45]	
Previous admissions	One study identified patients who survived index admission and were readmitted had worse survival[12].	A study from Spain that didn't explicitly report intubation outcomes identified that admissions in the past year had a univariate and multivariate association with 2 year mortality[69].

Table 3.6.2 Patient characteristics available in the 24 hours after hospital admission and prior to critical care admission and outcome

Variable	Association with outcome	Strength of evidence/comment
Body mass index	Body mass index (BMI) had a multivariate association with outcome in the SUPPORT study[12].	Body mass index was also identified in studies in outpatients and the relationship appears robust. However the SUPPORT study found it difficult to measure BMI in all its patients and had to use a dummy variable in the final model for patients with a missing BMI.
Mid-arm circumference	A French ICU study found mid-arm circumference to be associated with survival in older patients with heterogeneous reasons for intubation[107].	Mid-arm circumference may be easier to measure than BMI in acutely ill patients.
Recent weight loss	No studies reported this.	Lynn [93] suggested that recent weight loss might be an important predictor of mortality after observing that BMI was so important in SUPPORT.
Length of stay pre-critical care	Quantified small but significant multivariate association in two studies[27] [124] and reported but not quantified in a third [43]	Likely to have a small but important effect
Atrial fibrillation		An easy to measure comorbidity identified in 1 study.
Chest x-ray		Part of the UK folklore in which acute changes are thought to identify a group of patients with a reversible component who will benefit from ICU. Only 1 study small study provides any data and suggests that acute chest x-ray changes identify a group at higher risk of mortality.
Congestive cardiac failure	The SUPPORT study suggested that congestive cardiac failure was associated with improved outcomes.	

Table 3.6.3 Acute physiology and outcome

Variable	Association with outcome	Strength of evidence/comment
Acute physiology	Acute physiology scores show a consistent association with outcome.	The finding in SUPPORT that albumin and PaO_2/FiO_2 added explanatory power to the acute physiology score from APACHE III suggested that a COPD specific acute physiology score might well perform better than a generic score.

Chapter 4 Methods

4.1 Introduction

In Chapter 1 it was argued that there was a need to produce a prognostic model to estimate the probability of survival of COPD patients admitted to Intensive Care Units (ICU), with the prognostic information most useful in informing intubation decisions. The introduction also argued that it was important to understand whether patients rated their quality of life after ICU as worth living. Chapter 2 set out the methodological challenges that must be overcome to make the development of a successful model a possibility and emphasised the need for careful collection of data on risk factors on a large number of patients with minimal missing data. Chapter 3 indicated what those variables should be. In this methods section the practical steps that were taken to make the development of a COPD risk model a reality are outlined.

4.2 Study setting and overview

The CAOS study was carried out in collaboration with the Intensive Care National Audit and Research Centre (ICNARC) and the ICUs contributing to the ICNARC Case Mix Programme (CMP). The CMP is a national audit that collects case mix and outcome data on consecutive admissions to ICUs in England, Wales and Northern Ireland. The units that contribute to the CMP have experience of ongoing case mix data collection, and most units have individuals trained in data collection, with time set aside for this task. The CMP data are generic case mix data that are collected once a patient has been admitted to ICU. However clinicians making the decisions to admit patients to ICU will necessarily use the data available prior to ICU and will typically seek out information specific to the patient's presenting condition in addition to more generic data about severity of illness. CAOS captured both the disease specific and generic severity data that would be available to the gatekeeping clinician prior to ICU admission. Nesting CAOS within the CMP infrastructure allowed the pre-ICU data to be collected by experienced data collectors with an ongoing commitment to data collection for these patients.

4.3 Unit recruitment

In November 2001 a letter was sent from Dr Kathy Rowan, the Director of ICNARC, to all the 178 units in the Case Mix Programme (Appendix 2). The letter briefly outlined the purpose of the study and invited units to express an interest in participating. Units expressing an interest were then invited to a launch meeting on 26th April 2002 in Birmingham. At the launch meeting, the background to the study and data collection methods were outlined, and units who wished to take part were provided with a CAOS box that contained all the relevant data collection booklets and patient information sheets.

4.4 Unit visits and training

Dr Wildman visited units that were unable to attend the launch meeting but wanted to take part in the study. During the unit visit the background to the study was explained and the nominated data collectors were instructed in the data collection process.

4.5 Respiratory High Dependency Units

In some hospitals much of the care for COPD patients with respiratory failure is carried out on Respiratory High Dependency Units (RHDUs). These units do not take part in the CMP. In order to gain some understanding of how the case mix data collected in the CMP units could be applied to patients treated in the RHDU environment three such units were recruited, two from Leeds and one from the West Midlands. These units were able to collect the CAOS data but did not collect the CMP data from the first 24 hours in ICU. 180 day follow-up was carried out in the same way as for the CMP units. RHDUs have been set up in an ad hoc fashion around the country and there are no centralized data that allow comparison with the units recruited.

4.6 Patients inclusion criteria

The objective was to recruit consecutive patients, aged 45 years or older, admitted to ICU with breathlessness, respiratory failure or changes in mental status, due to an exacerbation of COPD or asthma as the major reason for admission.

4.7 Patient exclusion criteria

Patients were excluded if they had had surgery in the past ten days or had been transferred from another hospital. Surgical patients were excluded because patients who have had surgery, particularly if the surgery involved abdominal wounds, were likely to have a different prognosis to patients with respiratory failure unrelated to surgery. Patients from other hospitals were excluded because the pilot study suggested that patients were likely to have missing data if treatment had been started in another institution.

4.8 Patient classification

It can be difficult to distinguish between patients with COPD and patients with asthma, and clinicians were asked to use clinical judgment to categorise the patient as having COPD, asthma or a mixture of COPD and asthma.

4.9 Data collection

4.9.1 The CAOS data collection booklet

The CAOS data collection booklet collected information on the risk factors identified in the systematic review as being associated with outcome (Chapter 3 above). These data related to the patients' characteristics in the period of stability prior to hospital admission, to the severity of illness after hospital admission but prior to ICU admission, and descriptive of the respiratory support strategies employed in ICU (Appendix 3).

4.9.2 Development of CAOS data collection booklet

The data collection booklet was prepared in draft form in November 2001 and piloted in two units in the West Midlands in November and December 2001. The final version was produced in January 2002.

4.9.3 Layout of CAOS data collection booklet

The inpatient data collection booklet (Appendix 3) combined data collection sheets with instructions. This ensured that the instructions for data collection would always be

available when and where they were needed. Also an overall summary of the study was provided on the inside of the booklet cover. The sixth sheet illustrates particularly well how facing pages contain guidance notes to support data collection. In this case guidance notes give additional detail about steroid inhalers to assist completion of question 17, and clarify exactly what is meant by home oxygen to clarify question 18. A diagram and instructions were provided to standardise the measurement of the mid-arm circumference, and every data collection booklet was provided with an attached paper tape measure.

Each data collection booklet had a unique identification number that was used to identify the patients concerned, allowing all other identifiers to be removed from electronically stored data. The booklet contained seven blue sheets and one yellow sheet. The blue sheets were for data that would be available within the first 24 hours in ICU and the yellow sheets for data on the treatment received whilst the patient was in ICU.

4.9.4 The instruments in the data collection booklet

A copy of the data collection sheet is included in the pocket inside the cover of the thesis. The first blue sheet (page 1) incorporated inclusion and exclusion criteria, date and time of admission, demographics, and patient and General Practitioner contact details.

The second blue sheet (page 3) was the only one that had to be completed by medical staff, and was for data about:

- the presence or absence of atrial fibrillation and congestive cardiac failure;
- the appearance of the pre-ICU chest x-ray; and
- the admitting clinician's estimates of the probabilities of the patient's surviving until leaving the ICU, leaving the hospital, and until 180 days after admission to the ICU.

Clinicians were also asked to predict the patient's self-rated quality of life at 180 days if they were to survive, using a thermometer scale bounded between best imaginable health state corresponding to a score of 100 and worst imaginable health state

corresponding to a score of zero. The thermometer scale was the same as that used in the EuroQol questionnaire that surviving patients received at 180 days [125]. The date and time of the prediction were noted along with the grade and specialty of the clinician making the prediction.

The third blue sheet (page 5) covered function and the patient's self-rated quality of life in the period of stability two weeks prior to admission to hospital. The functional score had originally been used with five levels that included whether the patient was working. This category was omitted in this study as the majority of patients would be beyond retirement age[57] and the scale simply started with what had been level 2 in the original version i.e. "Fully mobile and living without assistance". The data collector was asked to indicate the information source for the data, ticking all categories that applied. Possible sources included the clinical record, the patient or another witness.

The fourth blue sheet (page 7) was again for information on the patient in the period of stability two weeks prior to admission to hospital. It involved the Katz classification of activities of daily living[82] which was found to have a significant association with survival in the SUPPORT study[12]

The fifth blue sheet (page 9) was for on the patient's co-morbidity, using the Charlson index. This has been used extensively to investigate the relationship between co-morbidity and length of stay[101]

The sixth blue sheet (page 11) was for other aspects of medical history that have been shown to be associated with mortality, including treatment with inhaled steroids[126], home oxygen treatment via a prescribed oxygen concentrator[65], prior intubation[45], and number of hospital admissions in the past 6 months[12]. This sheet also covered smoking history in terms of pack years, with the aim of identifying never smokers as patients who were likely to have simple asthma. Data were also collected on the patient's weight and height. Pilot studies for CAOS indicated that nursing staff found it difficult to weigh and measure acutely ill patients and three methods were used to assess BMI. Data collectors were asked to:

- rate patients' weight on a five point scale running from very underweight to very overweight;
- provide the patient's weight and height and to state whether this was estimated or measured; and
- measure the mid-arm circumference.

The seventh blue sheet (page 13) was for acute physiology recorded in the 24 hours prior to ICU admission. This was to help characterise the severity of illness at that time. These data included: the most acidic gases in the 24 hours prior to critical care admission, the paired systolic and diastolic blood pressure measurements from the blood pressure with the lowest diastolic, the highest and lowest central temperature, non-central temperature, heart rate, respiratory rate, haematocrit, haemoglobin, white cell count, serum sodium, serum potassium, serum creatinine, serum urea, serum albumin, serum bilirubin, serum glucose and the Glasgow Coma Scale.

Page 15 was the only yellow sheet in the booklet and contained questions that determined the type of respiratory support that the patient received in ICU. Question 32.1 determined the date and time of intubation and its duration, defined as ending once the patient had ceased to receive pressure support via a tracheostomy or endotracheal tube. The date and time of a tracheostomy was recorded. Data were also collected that identified those patients who only received non-invasive therapy, with question 31.2.1 determining whether patients only receiving non-invasive ventilation would have been intubated if the non-invasive ventilation had failed.

4.9.5 Hospital outcome

For patients surviving to leave critical care, the duration of the hospital stay following ICU and the patients' vital status were sought at weekly intervals following receipt of the yellow sheet. The cause of death was sought for all hospital deaths, and units were asked whether there had been a decision to withdraw treatment.

4.10 Strategies for minimising missing data

Every effort was made to ensure that missing data were identified and chased on a day by day basis. The blue sheets (for data that described the patient prior to ICU admission) were faxed to the CAOS co-coordinating centre within 24 hours of ICU admission. This allowed inconsistencies to be resolved before the patient left ICU, after which it was unlikely that the data would be readily available.

4.11 A qualitative understanding of feasibility of data collection on risk factors

Ongoing dialogue with units about the verification of out-of-range values and chasing of missing data provided an opportunity to identify the variables that were difficult to collect. This information was to be used in the final selection of variables during prognostic model development.

4.12 180-day follow-up

Data describing patient's quality of life after ICU discharge were collected by postal questionnaire at 180 days (Appendix 4). The 180 day questionnaire consisted of a single sheet of paper folded to produce a booklet (Appendix 4). This format was chosen so that all the questions to be completed were easily seen. A covering letter was included with the questionnaire. The questionnaire contained two well-validated health status instruments: the EuroQol and the AQ-20.

4.12.1 The EuroQol

The EuroQol is a generic quality of life measure for collecting information about a patient's level of function in 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression[125]. For each domain the patient is asked to indicate their level of function, e.g. for mobility patients are asked to choose from three options: 'I have no problems walking about", "I have some problems walking about" or "I am confined to bed". With 5 domains and 3 levels in each domain there are 243 possible health states or combinations. The developers of the EuroQol used a representative sample of the general population to value these health states using time

trade-offs, so that for any possible health state there was a valuation between 1.0 (perfect health) and -0.59 (a state worse than death). The population derived value for the health state is called the EQ-5D. In addition the EuroQol questionnaire contains a visual analogue scale which asks the patient to record their health state on the day of the data collection, on a scale from 100, corresponding to the best imaginable health state to 0, corresponding to the worst possible health state. (This visual analogue scale was also incorporated into the data collection booklet used at ICU admission to collect clinicians' predictions of the patients' quality of life at follow-up.)

4.12.2 The AQ-20

The AQ20 questionnaire[127] is a disease-specific health status measure for patients with airways disease developed from the St Georges Respiratory Questionnaire (SGRQ)[128]. The AQ20 was used in preference to the SGRQ because it contains only 20 questions in contrast to the 50 in the SGRQ. The booklet also contained the modified functional score that was part of the inpatient dataset[57]. In addition patients were asked:

- whether they would choose intensive care treatment again under similar circumstances; and
- how their current health status compared to how they were when well prior to hospitalisation 6 months ago, on a five point scale running from much worse to much better.

4.13 Strategy to identify patients who died after leaving hospital

In order to avoid causing distress by sending questionnaires to bereaved relatives, steps were taken to identify patients who died prior to the time of follow-up. Hospital outcome was obtained as part of the in-patient data collection protocol. Two weeks prior to sending the follow-up questionnaire a letter (Appendix 5) was sent to the patient's GP and this was followed up with a phone call to the GP's receptionist to confirm that the patient was still alive.

4.14 Outcomes for non-responders and patients lost to follow-up

Patients who were lost to follow-up were traced through the Office of National Statistics (ONS), who provided a date and cause of death for those patients who had died. In the case of patients who were lost to follow-up because they had moved GP, the ONS identified the Health Authority of the patient's new GP. The GP's identity was obtained from the Health Authority, and the practice was contacted to obtain the patient's new address and to confirm that they were alive.

4.15 Strategies for improving the 180 day response rate

Strategies to improve the response rate to postal questionnaires have been studied and reported in a recent Cochrane review[129]. Where practical, these strategies were incorporated into the questionnaire design and mailing strategy. Table 4.15 shows the strategies used to improve response and the odds ratio (95% CI) associated with these strategies that were calculated in the Cochrane systematic review. Great care was taken to make the questionnaire short and user-friendly. The questionnaire was printed on high quality paper with coloured ink. An unconditional incentive was provided in the form of a biro and the questionnaire was personalised with a hand-written post-it note asking the patient to answer questions that involved unfolding the questionnaire. In addition, the questionnaire was sent out by recorded delivery. A return, stamped envelope was enclosed. Patients received three mailings, the first two by recorded delivery and the third by normal post. The final mailing by normal post was in case patients were unable to answer the door to sign for a recorded delivery. In patients in whom the response was very delayed the GPs were contacted again to confirm that the patient was still alive, and to ensure that the GP did not know of a reason why the patients should not be contacted. If the study team had a phone number available these patients were contacted by phone.

4.16 Causes of death

Death certificates were sought for all patients from the ONS at the end of the study in spring 2004. This meant that causes of death were obtained for all patients who had died

Table 4.15 Strategies to improve postal questionnaire response rate

Strategy	*Application in CAOS*	*Odds ratio (95% CI) for response rate with strategy vs. without*
Non-monetary incentive with questionnaire	All questionnaires contained a biro	1.19 (1.11-1.28)
Shorter vs. longer questionnaire	Questionnaire kept as short as possible	1.86 (1.55 – 2.24)
Coloured ink vs. standard	Coloured inks used	1.39 (1.16 – 1.67)
Folder or booklet vs. stapled pages	Fold out booklet format used	1.17 (0.94-1.45)
More personalised vs. less personalised	Hand written post-it notes naming the recipient highlighted the need to answer all parts of questionnaire	1.16 (1.06 – 1.28)
Recorded delivery vs. standard	Recorded delivery used	2.21 (1.51 – 3.25)
Stamped return envelope vs. business reply	Hand written stamped return envelopes included	1.26 (1.13-1.41)

within 180 days of admission to ICU. In addition, in those patients who had entered the study early, deaths beyond 180 days were identified.

4.17 Identification of missing patients via the Case Mix Programme database

In order to identify patients who were eligible for admission to CAOS, but had been missed by individual units, the CMP database that covered the period when the unit was taking part in CAOS was searched to identify eligible COPD patients. The CMP coding system was used to identify patients who had not had recent surgery and who had a primary reason for admission of COPD, exacerbation of COPD, emphysema or asthma,

or any of these four reasons for admission as the second cause when pneumonia, right ventricular failure or left ventricular failure were the primary cause.

4.18 Maintenance of study momentum

As soon as a unit recruited their first patient they were sent a CAOS mug with a thank-you note to celebrate. Each time a patient's details were faxed to the CAOS coordinating centre the unit was contacted by phone the same day and thanked, and any details that were missing or ambiguous were checked. Follow-up of the hospital outcomes maintained regular contact between the CAOS coordinating centre and individual units. In addition, newsletters were produced updating units on study recruitment (Appendix 6). The newsletters had an ongoing themed section called "Voices from the Trenches" where unit data collectors gave tips describing successful methods for avoiding missing patients. The units who provided the "Voices from the Trenches" received a box of CAOS biscuits decorated with the CAOS logo, as did units recruiting the 100th, 200th etc. patient. It was hoped that the brightly coloured biscuit boxes decorated to resemble the unit CAOS boxes also maintained the study profile in individual units. CAOS post-its were provided to units and carried the study logo and inclusion criteria, and were designed to be attached to unit admission packs, so that each time a patient was admitted to ICU, they would be considered for inclusion in the study. Posters were also provided (Appendix 7). The CAOS study was also presented at Annual Case Mix Programme meetings in January 2002 and 2003, and was on the ICNARC stand at National Intensive Care Society meetings. A description of the study was also carried in the British Thoracic Society Newsletter.

4.19 Data management and analysis

All data were entered using Epi-Info 2000, with data entry fields set up to mirror the data collection questionnaires. Epi-Info stores data in Access. The data entry programme contained range checks so that out of range values were not accepted. In addition the data entry programme calculated derived variables such as age, the number of days after hospital admission that ICU entry occurred, and the length of stay in hospital. This served to highlight illogical data entry such as patients having a negative

length of stay. The study database was registered through the hospital data protection officer.

Data were converted from the Epi-info Access format to Stata by Stat-transfer and all analysis was carried out in Stata 7.0.

4.20 Data protection

Though the CAOS inpatient data booklet contained the patient's name and address only, the patient's CAOS number was entered into the CAOS database. Once the data were entered, the first page of the data booklet, the only sheet containing patient identifiers, was removed and locked away. At this point, the follow-up dates for the patient were noted and the remainder of the data booklet was filed.

4.21 Multi-centre Research Ethics and Research and Development approval

The study received Multi-Centre Research Ethics Committee (MREC) approval (Appendix 8). Since the study was observational and did not involve altering patient treatment the Local Research Ethical Committees were not required to give additional approval but were all informed of the study and provided with patient information sheets and protocol. In addition approval was obtained from the Research and Development (R & D) departments in each participating hospital.

4.22 Patient information and consent

Patients were provided with an information sheet on leaving ICU that explained the study and informed them that they would be contacted after 180 days to determine their health status. The patient information sheet contained a sentence approved by the ONS, explaining that ONS data sources would be used to determine their survival up till that point. Patients were asked to sign a form confirming that they had received the information sheet. In discussion with the MREC it was felt that patients who had just left intensive care might find taking in this kind of information difficult and should be provided with written information, with contact details, which enabled them to opt out of the study at any point in the future. At 180 days the patients received a second

information sheet and completed a consent form. The MREC felt that it would be impossible to obtain the consent of patients who entered ICU unconscious and then died on the unit, and considered that including these patients without formal consent was acceptable. All the patient information sheets were approved by the MREC. Information sheets were produced in Welsh, Gujarati, Punjabi, Urdu and Bengali. Information sheets are included in the appendix (Appendix 9). As recruitment proceeded it was found that patients entering the study were able to speak English or had a carer who could speak English and as a consequence the 180 day follow-up questionnaire was not translated.

4.23 Study steering group

A steering group was formed to oversee the study and to provide guidance and support in the development of the PhD. The members of the group were Dr Colin Sanderson (Reader in Health Services Research), Dr Barney Reeves (Senior Lecturer in Epidemiology) and Dr Martin Wildman (MRC Training Fellow in Health Services Research and study coordinator) all from the London School of Hygiene and Tropical Medicine, Professor Jon Ayres (Professor of Respiratory Medicine, Birmingham Heartlands Hospital), Dr Kathy Rowan (Scientific Director of ICNARC), Dr Duncan Young (Senior Lecturer, Nuffield Department of Anesthetics, Oxford) and Mrs. Jayne Groves (Research Nurse, Birmingham Heartlands Hospital).

4.24 Dissemination

The recruitment rate and study progress were given a high priority during the conduct of the study, with an emphasis on regular contact with individual units, and the production and dissemination of CAOS newsletters.

The results for individual units will be fed back to the collaborating units along with the anonymised data from the whole study. In addition the results of the study will be published in articles submitted to peer review medical journals.

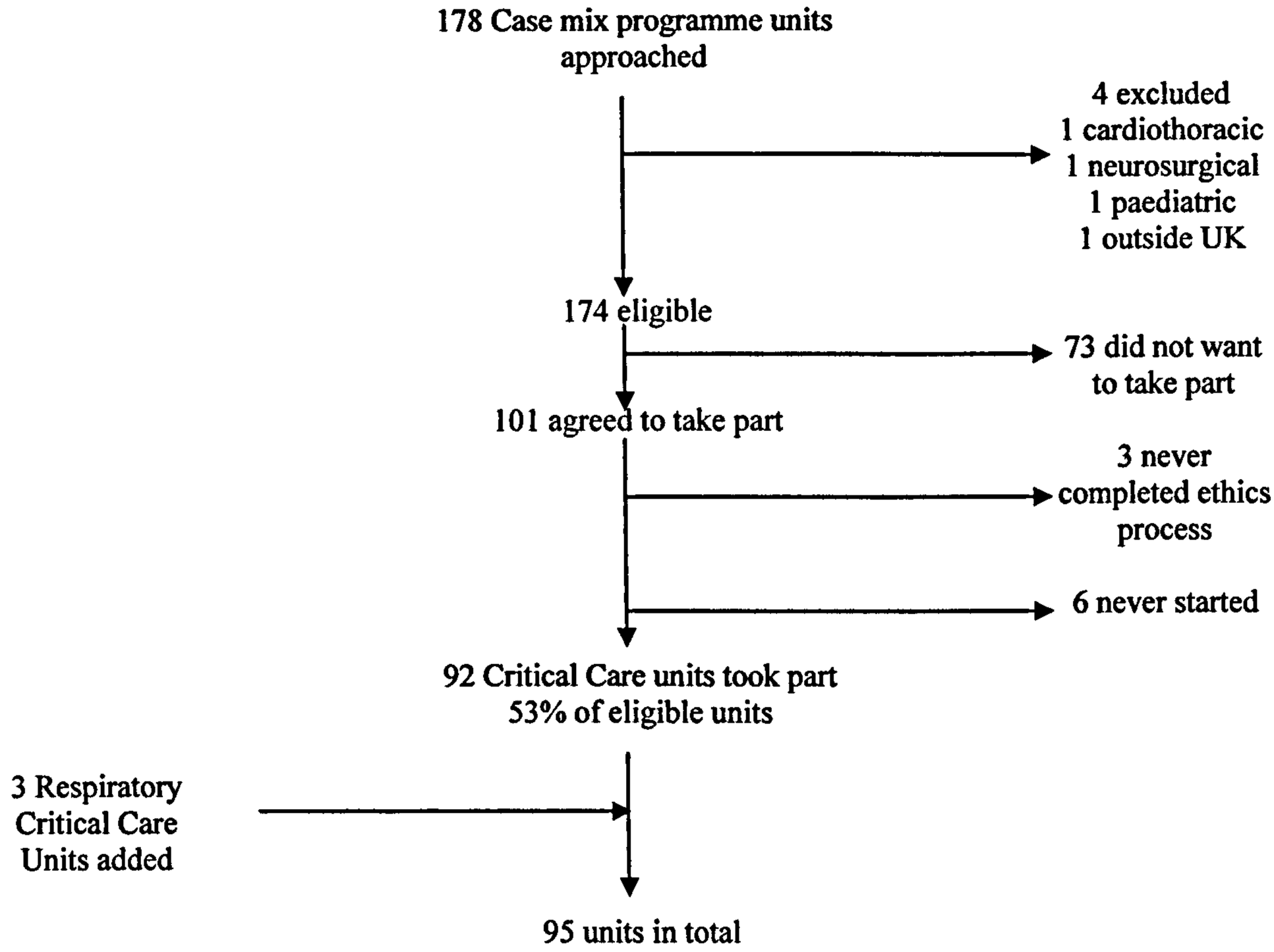
Chapter 5 Units and patients

5.1 Unit recruitment

5.1.1 Intensive Care Unit Recruitment

In January 2002 the 178 ICUs in the case mix programme were invited to take part in CAOS. Four units were ineligible; three were specialist units that did not admit COPD patients and one unit was located outside the UK. Seventy-three units indicated that they did not want to take part. A hundred and one units agreed to take part, and of these, three never received Caldicott approval and six never started to collect data. This left 92 ICUs that collected data, 53% of those eligible to take part (Figure 5.1.1 below).

Figure 5.1.1 Units taking part in the CAOS study



5.1.2 Comparisons between participating and non-participating units

For 170 of the 174 eligible units there were data that allowed comparison of the characteristics of units that participated and units that did not participate (Table 5.1.2). The table draws upon the data in the CMP database for the end of CAOS study period in August 2004. It can be seen that CAOS units were broadly similar to the non-participating units. In particular the percentage of admission diagnoses likely to fulfil the CAOS inclusion criteria was 3.6% for both groups of units, and the mean COPD acute physiology scores were almost identical (CAOS ICUs 30.6, non-CAOS ICUs 30.7). Slightly fewer University hospitals took part in CAOS, but taken together, University and University-affiliated hospitals made up 32.2 % of CAOS units and 32.5% of non-participating units.

5.1.3 Respiratory High Dependency Unit recruitment

Three RHDUs participated. There is no directory of hospitals with RHDUs, and those that took part were known to the author and had the infrastructure and commitment to collect data. The units recruited 35, 45 and 28 patients respectively. In addition 6 were admitted to RHDU but were transferred to Critical Care. The RHDUs had relatively large proportions of patients with treatment limitation decisions, with 18/35 (51%), 12/45 (27%) and 21/28 (75%) designated not for intubation respectively.

5.2 Patient recruitment

The number of patients recruited was 832. Of these, 108 were recruited to RHDU. Of the 724 patients admitted to ICUs, case mix programme data were available for the period corresponding to the admission for 684 (94.5%).

5.3 Identifying missed patients via the Case Mix Programme

CAOS relied on staff in participating units to identify and then recruit patients who met the inclusion criteria. Typically units had one or two staff who were the study champions and did most of the data collection.

Table 5.1.2 CAOS and non-participating CMP units compared

		In CAOS	*Not in CAOS*
Number of Units (%)		90 (52.9)	80 (47.1)
Total number of admissions in CMPD, number (%)		158,226 (57.2)	118,505 (42.8)
Admissions potentially eligible for CAOS, number (%)		5,726 (3.6)	4,281 (3.6)
COPD acute physiology score, mean (SD)		30.6 (14.4)	30.7 (14.6)
Hospital Type, number of units (%)	University	12 (13.3)	18 (22.5)
	University Affiliated	17 (18.9)	8 (10.0)
	Non-university	61 (67.8)	54 (67.5)
ICU Type, number if units (%)	ICU	39 (43.3)	32 (42.1)
	ICU\CCU	3 (3.3)	4 (5.3)
	ICU\HDU	43 (47.8)	38 (50.0)
	ICU\HDU\CCU	5 (5.6)	1 (1.3)
	HDU	0 (0.0)	1 (1.3)
Number of beds, number of units (%)	2 – 4	21 (23.3)	21 (26.6)
	5 – 6	39 (43.3)	26 (32.9)
	7 – 9	20 (22.2)	18 (22.8)
	10 – 13	7 (7.8)	12 (15.2)
	14 – 22	3 (3.4)	2 (2.5)

Since a data collector would usually only be in the unit for 40 hours per week this left 128 hours each week when they would not be available. It seemed likely that patients would be missed.

The CMP dataset allowed the patients admitted to ICU that were recruited to CAOS to be compared to those who satisfied the inclusion criteria for CAOS but were not recruited (Section 4.17). 1873 CAOS eligible patients were identified through the CMP data set and of these 684 were recruited to CAOS and 1189 were missed. The total of recruited patients is less than the total of patients recruited to CAOS because CMP data were not collected in the RHDU, so RHDU patients are not included in the comparisons of included and missed patients.

5.3.1 Missed patients and ICU mortality

Patients who died quickly might be expected to have a greater risk of being missed, in which case missed patients would have higher ICU mortality. Table 5.3.1 shows the ICU mortality in the 1189 missed and 684 recruited patients. There was no significant increase in the risk of ICU mortality in the missed patients.

Table 5.3.1 ICU mortality for missed and recruited patients

Recruited to CAOS	*Died in ICU (%)*	*Survived ICU (%)*	*Total*
No	246 (20.7%)	943 (79.3%)	1189
Yes	130 (19.0%)	554 (81.0%)	684

Relative risk of dying in ICU in patients not recruited to CAOS compared to CAOS patients was 1.09 (95%CI 0.9-1.32) chi-square 0.77 p=0.38

5.3.2 Missed patients and severity

As is explained in Chapters 10 and 11 below, the study led to the development of a CAOS score that allowed individual patients' risk of death at 180-days to be calculated. This score used patients' characteristics prior to ICU admission, with aspects of their physiological status used to produce a severity measure, the COPD acute physiology score (CAPS) (Chapter 8 below). Some components of the CAOS score were missing for patients admitted to critical care but not recruited to CAOS. However the CMP data contained all the variables required to calculate the CAOS acute physiology score (CAPS). Table 5.3.2 shows the CAPS for missed and admitted patients. There was no difference in acute severity between recruited and missed patients.

Table 5.3.2 COPD Acute Physiology Score for missed and recruited patients

Recruited	*Mean APS (SD)*	*95% Confidence interval*
No	28.9 (13.8)	(28.1-29.7)
Yes	28.9 (10.9)	(28.1-29.7)

Independent samples t-test p=0.96

5.3.3 Missed patients and age

There was no difference in mean age between the missed and recruited patients (Table 5.3.3).

Table 5.3.3 Age for missed and recruited patients

Recruited	*Mean age in years (SD)*	*95% Confidence interval*
No	66.3 (9.8)	(65.9-66.8)
Yes	66.4 (9.6)	(65.7-67.1)

Independent samples t-test p=0.49

5.3.4 Missed patients and sex

Of the 832 patients recruited, 47.7% (44.3-51.2%) were male. This was slightly lower than in other published series in which males typically comprised just over 50%, though the 95% confidence intervals suggest that the difference could have been due to chance. Table 5.3.4 shows that though there was a very slightly higher proportion of males amongst the missed patients, but the difference does not reach statistical significance.

Table 5.3.4 Sex amongst missed and recruited patients

Recruited	*Male (%)*	*Female (%)*
No	583 (49.0%)	606 (51.0%)
Yes	333 (48.3%)	356 (51.7%)

Pearson Chi-square 0.09 p=0.77

5.3.5 Missed patients and day of critical care admission

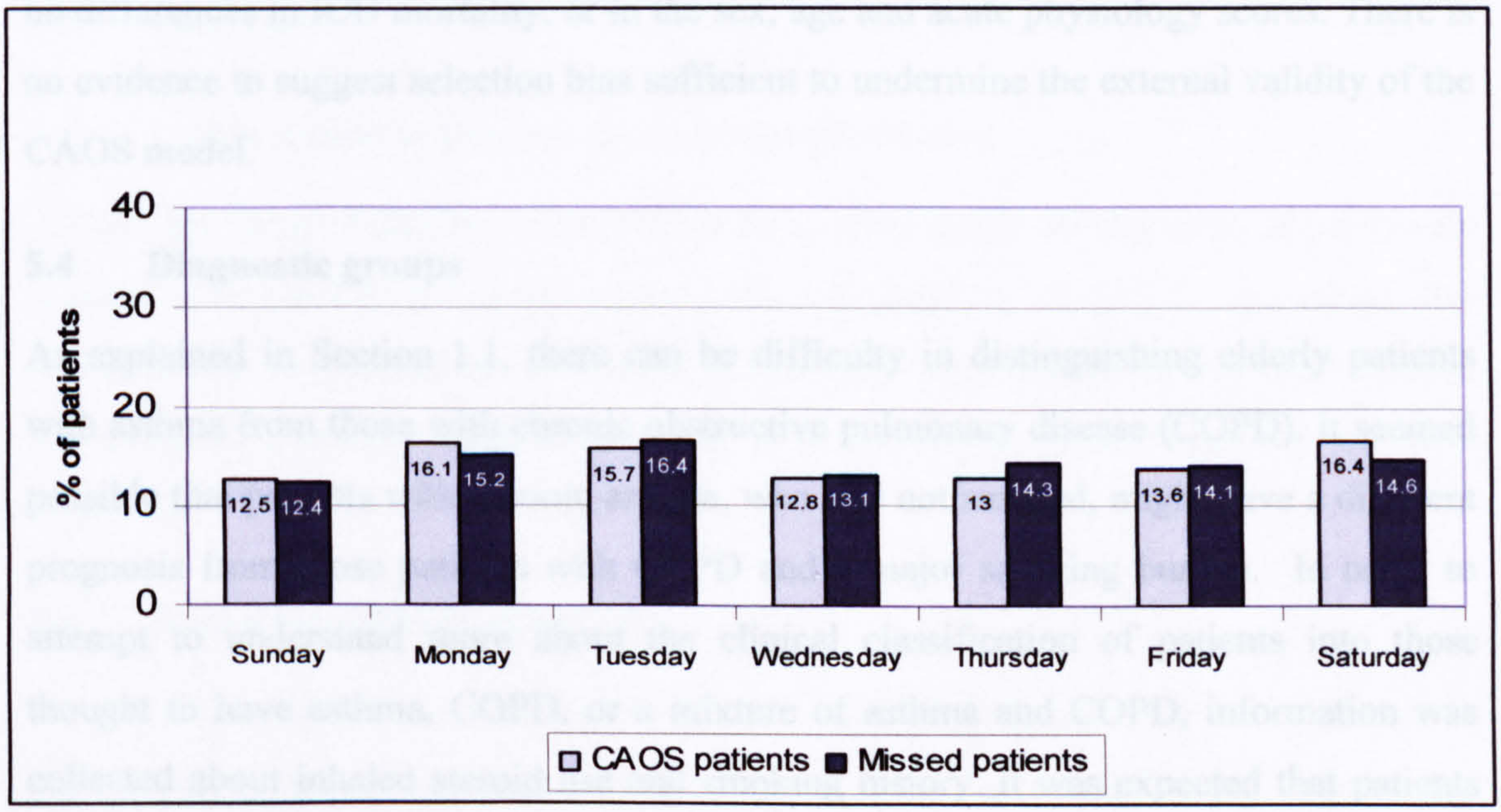
It might be the case that patients would be more likely to be missed if admitted at the weekend. Table 5.3.5 shows that there was no evidence for a difference between recruited and missed patients in the percentages of patients admitted at weekends. Figure 5.3.5 below shows the day of week on which included and missed patients were admitted.

Table 5.3.5 Weekend vs. non-weekend admissions in missed & recruited patients

Recruited	*Weekend (%)*	*Weekday (%)*
No	320 (26.9%)	869 (73.1%)
Yes	196 (28.7)	488 (71.3)

Pearson Chi-square 0.81 p=0.32

Figure 5.3.5 Day of week admitted to critical care in CAOS patients and missed patients



5.3.6 Missed patients and the working day

Patients admitted out of hours might be more likely to be missed. Table 5.3.6 shows patients grouped by whether they were admitted between 0800hrs and 1759hrs or between 1800hr and 0759 hrs. There was no significant difference between the proportions of missed patients between the time periods.

Table 5.3.6 Patients recruited and missed during working day and out of hours

Recruited	*Working day (%)*	*Out of hours (%)*	*Total*
No	545 (45.9%)	642 (54.1%)	1189
Yes	341 (49.4%)	349 (50.6%)	684

Pearson Chi-square =2.15 p=0.14

5.3.7 Conclusion: missing patients in CAOS

Although the objective of consecutive series was not achieved, there was no evidence of any systematic differences in the characteristics of patients recruited to CAOS compared with those who were not. Of particular relevance was the fact that there were no differences in ICU mortality, or in the sex, age and acute physiology scores. There is no evidence to suggest selection bias sufficient to undermine the external validity of the CAOS model.

5.4 Diagnostic groups

As explained in Section 1.1, there can be difficulty in distinguishing elderly patients with asthma from those with chronic obstructive pulmonary disease (COPD). It seemed possible that patients with chronic asthma, who had not smoked, might have a different prognosis from those patients with COPD and a major smoking burden. In order to attempt to understand more about the clinical classification of patients into those thought to have asthma, COPD, or a mixture of asthma and COPD, information was collected about inhaled steroid use and smoking history. It was expected that patients with asthma would take more inhaled steroids and would have smoked less than patients with COPD. Patients with a clinical diagnosis of a mixture of asthma and

COPD might be intermediate. It should be remembered that any association may have occurred because clinicians use the smoking and inhaled steroid history in their classification decisions.

5.4.1 Inhaled steroid use

Five hundred and forty three patients (65.3%) were taking inhaled steroids. Of patients with a diagnosis of asthma, 79.4% were reported to be taking steroids, while the figure for the patients considered to have a mixture of asthma and COPD was 72.2%. These were in contrast to the rate of 63.5% for patients considered to have COPD alone. The distribution of inhaled steroid use supports the diagnostic classification.

5.4.2 Smoking status

A patient with asthma is more likely never to have smoked than a patient with COPD. Figure 5.4.2 shows the proportion of patients in each of the three diagnostic groups, together with the accumulated smoking burden in pack years, grouped by smoking status. It can be seen that the "pure" asthmatics comprise the largest diagnostic group in the never smokers (48%) but the smallest group among current and ex-smokers (5% and 10% respectively).

5.5 Classification of patients by treatment limitation

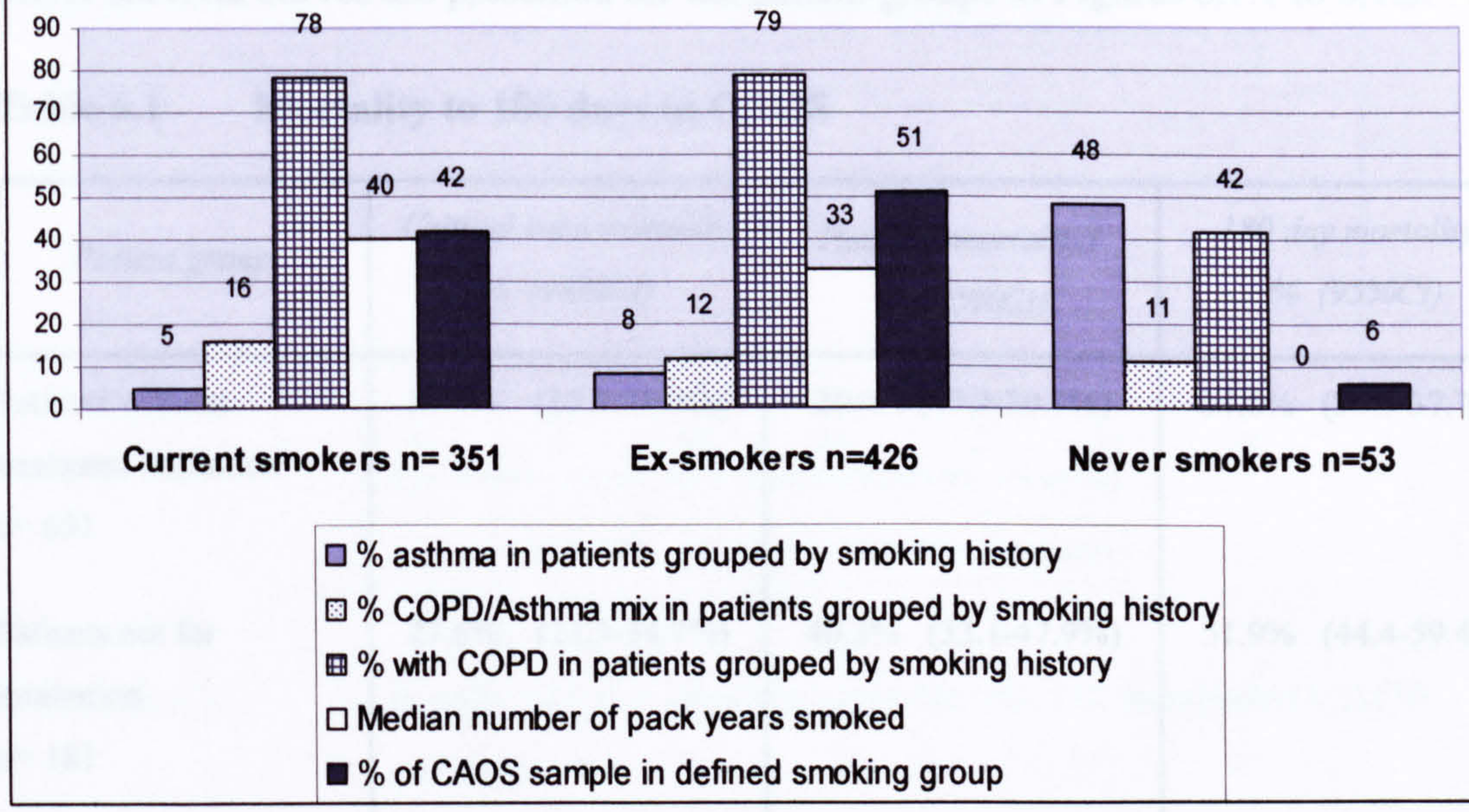
Altman has stressed that treatment cannot be ignored in the development of prognostic models[17] (section 2.5.4). For this reason units were asked to identify those patients who would not be considered for intubation if less aggressive treatment was unsuccessful. The prognostic model was developed only in those patients without recorded treatment limitation.

5.6 Recruited patients summary

In total 832 patients were recruited to CAOS, and in 181 the decision was made not to intubate the patient if less aggressive treatment failed. The remaining 651 patients had no treatment limitations. The available data comparing patients recruited with patients

missed suggested that the patients recruited to CAOS were representative of eligible patients admitted to UK ICUs.

Figure 5.4.2 Smoking in the CAOS diagnostic groups



Chapter 6 Mortality

6.1 Overall mortality rate

Table 6.1 shows the mortality in ICU, in hospital and at 180 days after ICU admission for all the patients recruited to CAOS and for the patients classified by treatment limitation. In addition the mortality of the 450 intubated patients is shown. Kaplan-Meier survival curves are presented for the patient groups in Figures 6.1.1 to 6.1.3.

Table 6.1 Mortality to 180 days in CAOS

Patient group	*Critical care mortality % (95%CI)*	*Hospital mortality† % (95%CI)*	*180 day mortality* % (95%CI)*
Patients without treatment limitation n= 651	16.4% (13.7-19.5%)	26.6% (23.2-30.1%)	34.0% (30.3-37.7%)
Patients not for intubation n= 181	27.6% (21.3-34.7%)	40.3% (33.1-47.9%)	51.9% (44.4-59.4%)
Intubated patients n=450	23.3% (19.5-27.5%)	35.8% (31.3-40.4%)	41.6% (37.0-46.2%)
All patients n=832	18.9% (16.3-21.7%)	29.6% (26.5-32.8%)	37.9% (34.6-41.3%)

† The hospital mortality includes those patients dying in critical care.

*180 day mortality includes critical care, hospital and 180 day deaths.

6.2 Causes of death in CAOS

There were 315 deaths during 180 days from ICU admission, and a further 80 deaths in those patients with longer follow-up. Figure 6.2 shows the causes of death found in the study.

Figure 6.1. **Kaplan-Meier survival plot for all 832 CAOS patients**

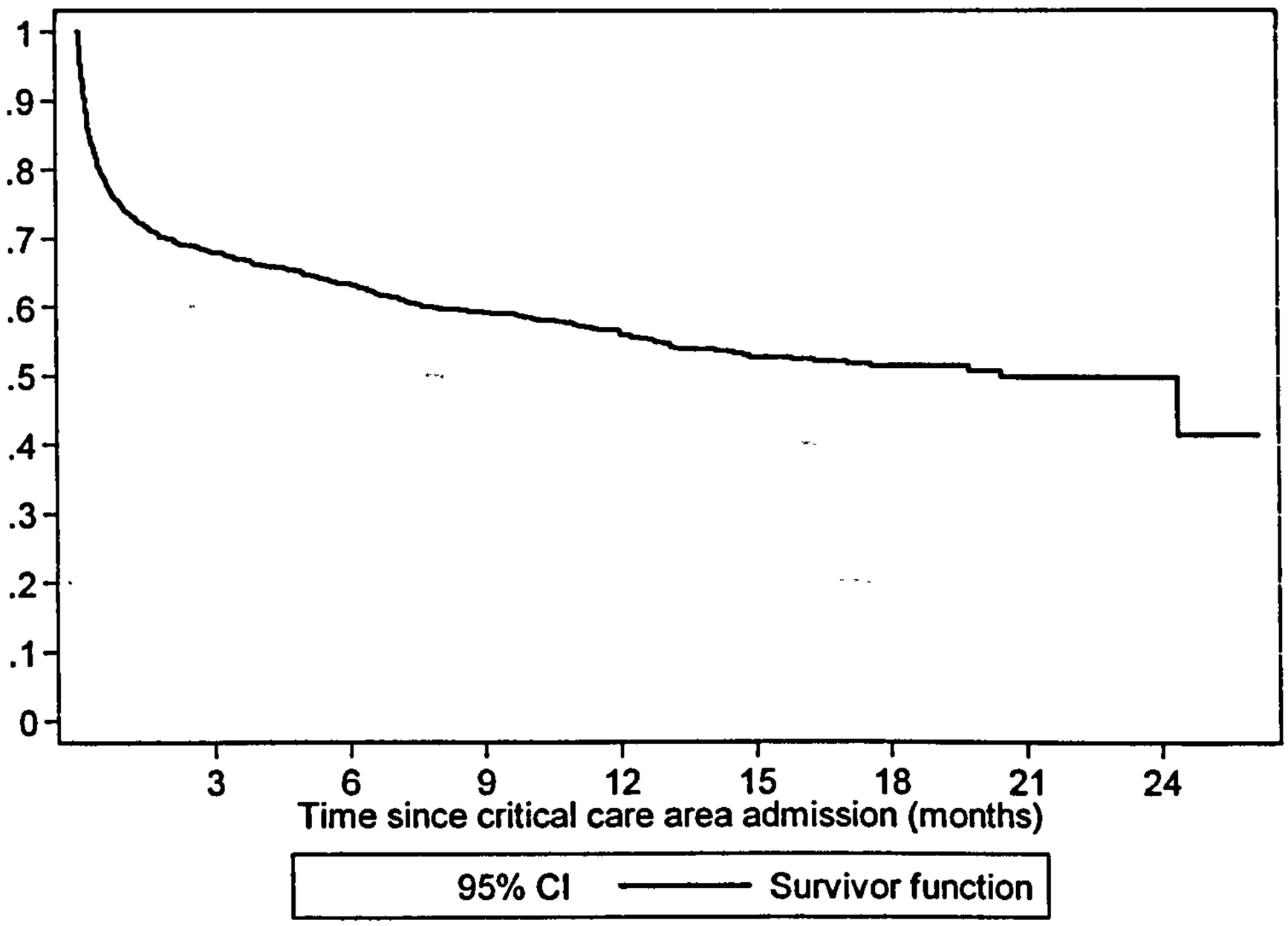


Figure 6.1.2 **Kaplan-Meier survival plot for the 450 intubated CAOS patients**

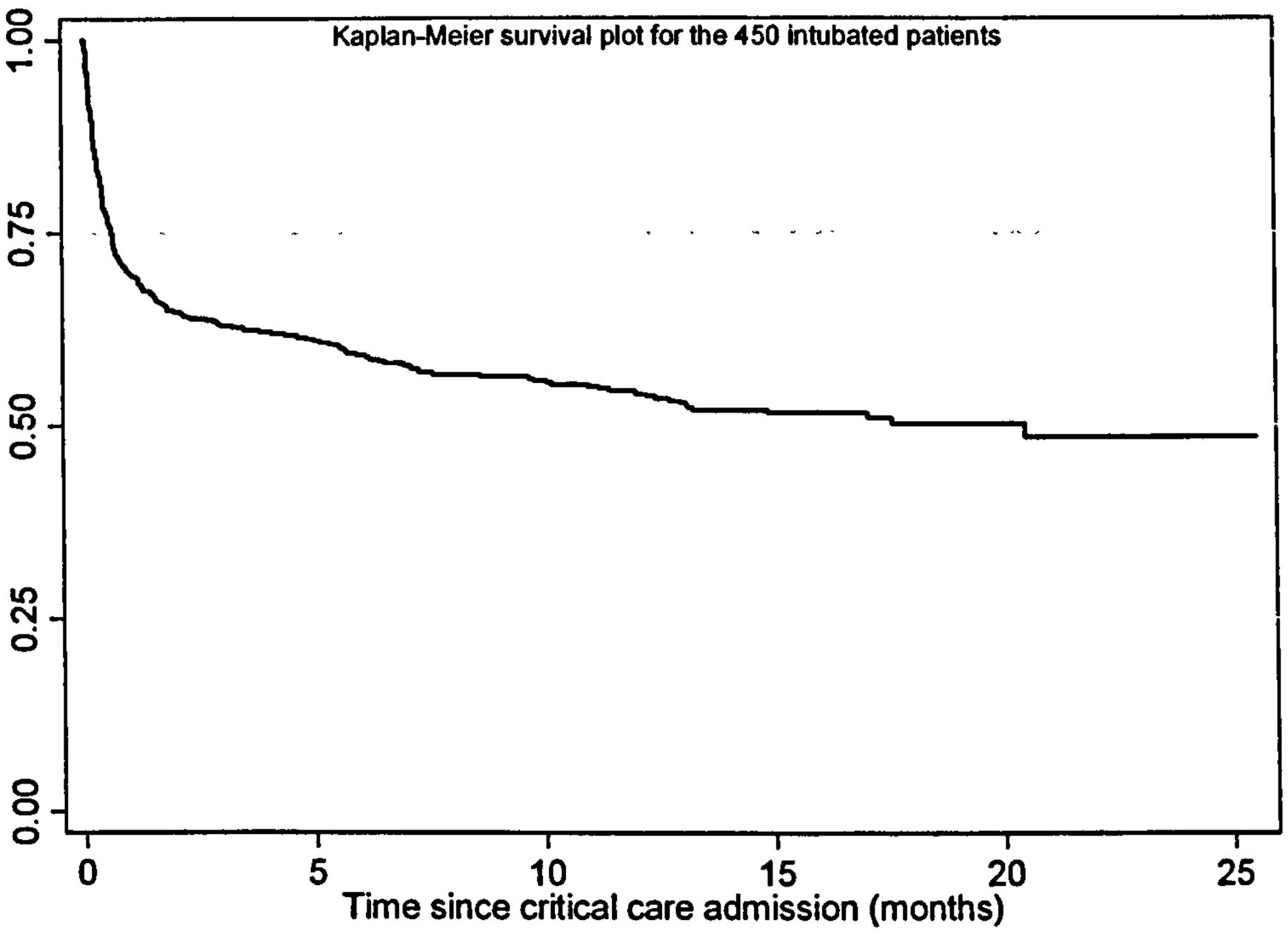
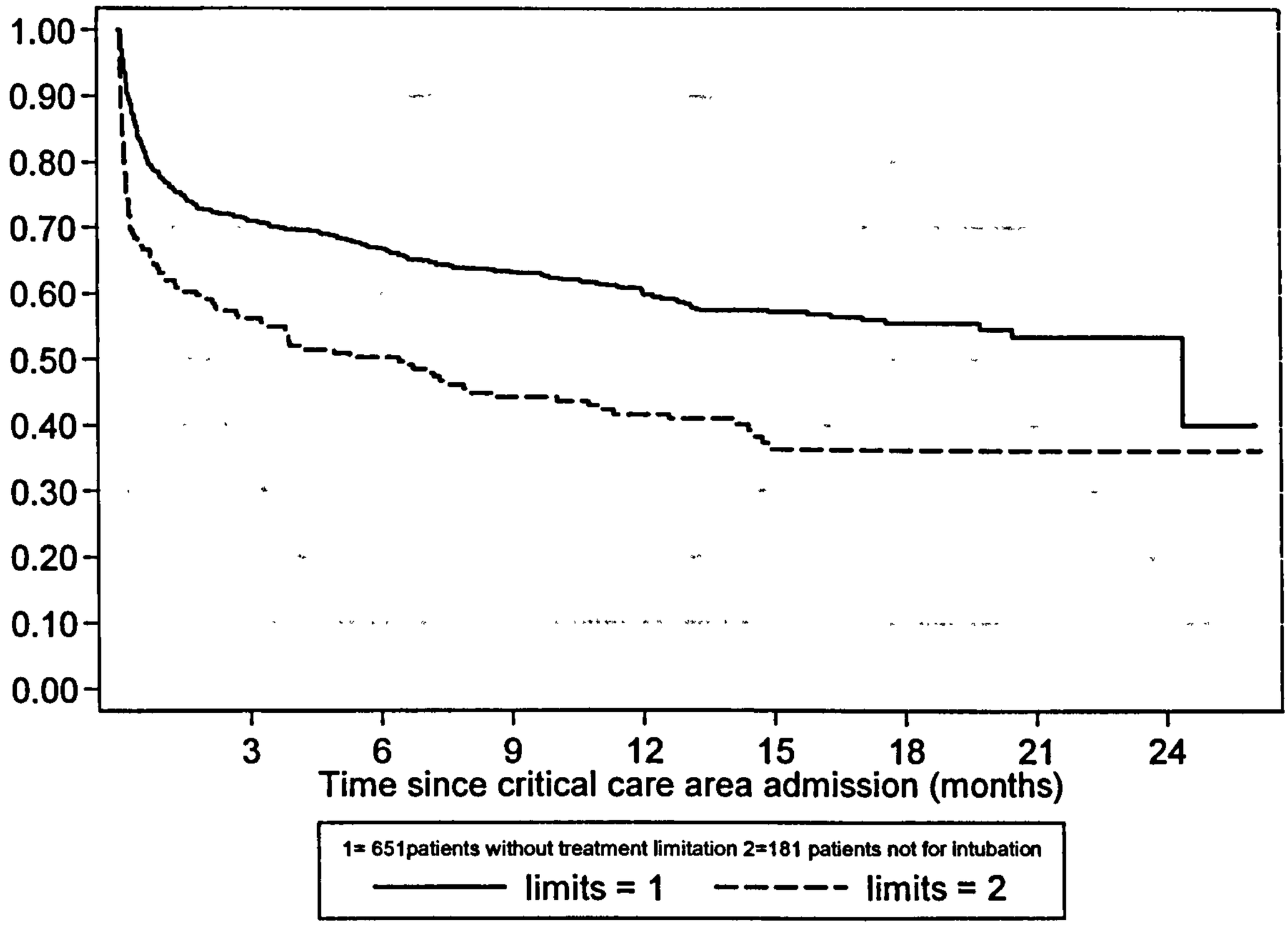


Figure 6.1.3 **Kaplan-Meier survival plot comparing CAOS patients with and without treatment limitation**

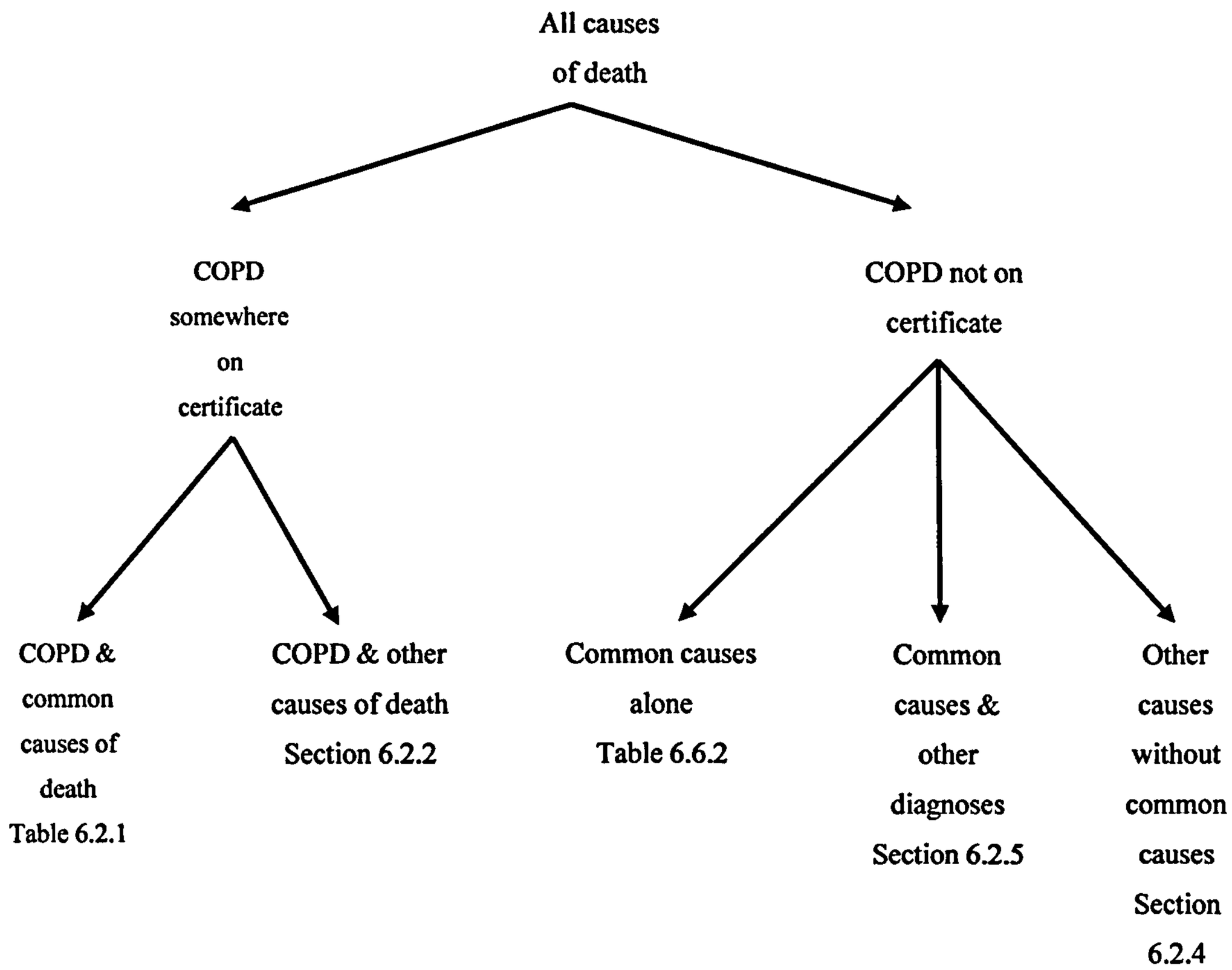


Log rank test for equality of survival functions Chi-square =26.6 p<0.0001

6.2.1 Deaths with COPD on the death certificate

Of the 395 deaths during the total period of follow-up, 256 (64.8%) had COPD somewhere on the death certificate. Table 6.2.1 shows the causes of death in these patients. It can be seen that in most cases the certificates included other causes of death as well as COPD, and the more frequently occurring causes are listed individually in the table.

Figure 6.2 Schema used to summarize causes of death in CAOS



The common causes of death were those that occurred frequently with COPD or with other diagnoses and comprised the following: (i) respiratory failure, (ii) bronchopneumonia, (iii) cardiovascular disease, (iv) organ failure and sepsis, (v) renal failure, (vi) asthma, (vii) carcinoma of the lung and (viii) cor pulmonale.

Table 6.2.1 Certified causes of death

Cause	*ICU death* *n= 157*	*In hospital after ICU discharge* *n=89*	*After discharge up to 180 days* *n=69*	*>180 days after ICU onset* *n=80*	*Total number of deaths with COPD on certificate*	*Total number of deaths in 180 days* *n=315*
COPD anywhere on certificate	84 (53.5%)	60 (67.4%)	52 (75.4%)	60 (75%)	256	196 (62.0%)
COPD alone	31 (19.7%)	19 (21.3%)	21 (30.4%)	11 (13.8%)	82 (32.2%)	71 (26.0%)
COPD & respiratory failure	13 (8.3%)	11 (12.4%)	17 (24.6%)	0	41 (16.1%)	41 (13.0%)
COPD & pneumonia	18 (11.5%)	6 (6.7%)	1 (1.4%)	0	25 (9.8%)	25 (7.9%)
COPD & bronchopneumonia	9 (22.0%)	7 (17.1%)	10 (14.5%)	15 (12.5%)	41 (16.1%)	41 (13.0%)
COPD & cardiovascular dis.	13 (8.3%)	16 (18.0%)	8 (11.6%)	18 (22.5%)	55 (21.5%)	37 (11.7%)
COPD & organ failure/sepsis	4 (2.5%)	1 (1.1%)	0	1 (1.25%)	6 (2.7%)	5 (1.6%)
COPD & renal failure	3 (1.9%)	1 (1.1%)	0	1 (1.25%)	5 (2.0%)	4 (1.3%)
COPD & Asthma	0	0	0	1 (1.25%)	1 (0.4%)	0
COPD & carcinoma of lung	1 (0.6%)	1 (1.1%)	0	3 (3.75%)	5 (2.0%)	2 (1.6%)
COPD & cor pulmonale	2 (1.3%)	0	2 (2.9%)	3 (3.8%)	7 (2.7%)	4 (2.2%)
§COPD & other	6 (3.8%)	16 (18.0%)	8 (11.6%)	14 (17.5%)	44 (17.2%)	30 (9.5%)

Note column totals will exceed 100% because some patients have more that 2 diagnoses e.g. COPD and ischaemic heart disease and bronchopneumonia and other etc. § Diagnoses in "other" category listed in section 6.2.2 below

6.2.2 Other cause of death given with COPD

There were 44 causes of death that made up the 'COPD and others' category in Table 6.2.1 above: i) hyperkaleamia, ii) schizophrenia, iii) cigarette smoking (x3), iv) urinary tract infection, v) obstructive sleep apnoea, vi) osteoporosis, vii) fractured femur (x3), viii) acute myeloid leukaemia (x2), ix) autonomic neuropathy, x) pulmonary hypertension, xi) diverticular abscess, xii) paraproteinaemia (x2), xiii) hypercalcaemia (1), xiv) gastrointestinal bleed, xv) pulmonary fibrosis, xvi) hypertension, xvii) coal workers pneumoconiosis, xviii) non insulin dependent diabetes mellitus (NIDDM), xviv) acute large bowel obstruction, xx) korsakoff syndrome & depression, xxi) liver metastasis, xxii) cerebrovascular accident (x3), xxiii) atrial fibrillation, xxiv) old age, xxv) obesity induced hypoventilation, xxvi) PE (x2), xxvii) alcoholic, xxviii) bronchiectasis, xxviv) cardiac arrest (x4), xxx) allergic broncho-pulmonary aspergillosis, xxxi) alpha-1 antitrypsin deficiency, xxxii) peritonitis, xxxiii) osteoarthritis, xxxiv) lung metastasis with unknown primary.

6.2.3 CAOS deaths with cardiovascular, respiratory or renal causes without COPD

Table 6.2.2 shows the cause of death for patients where COPD did not appear on the certificate but where the cause given was one commonly found to accompany COPD in certificates where COPD does appear (i.e. the categories specified in table 6.2.1 excluding "other"). 'Miscellaneous' was far the largest group.

6.2.4 Miscellaneous causes of death given without COPD or from Table 6.2.2

Other causes of death that appeared on certificates without COPD or any of the common causes in table 6.2.2 included a range of conditions that are listed below. Some of these occurred more than once. This group corresponds to the "Other causes of death not including COPD or the causes above" category in table 6.2.2 were: a) terminal lung disease, b) metastatic breast cancer, c) gall stone pancreatitis, d) peritoneal bleed, e) massive pulmonary embolus & gastrointestinal bleed, f) metastatic cancer with unknown primary, g) end stage lung disease, h) old age, i) abdominal compartment syndrome following perforated viscus, j) pulmonary hypertension & leukaemia, k)

alcoholic cirrhosis, l) bowel perforation, m) cardiac or respiratory arrest, n) cerebrovascular accident, o) peritonitis, p) gastrointestinal bleed, q) pulmonary fibrosis.

Table 6.2.2 Cardiovascular, respiratory or renal deaths without COPD

Cause	*Number (%) of total ICU deaths* *n= 157*	*Number (%) of total hospital deaths (post ICU discharge)* *n =89*	*Number (%) of total deaths after hospital discharge up to 180 days* *n=69*	*Number (%) of total deaths >180days after ICU onset* *n=80*	*Number (%) of total 180 day deaths* *n =315*
Respiratory failure alone	12 (7.6%)	9 (10.1%)	2 (2.9%)	0	23 (7.3%)
Pneumonia alone	6 (3.8%)	0	1 (1.4%)	2 (2.5%)	7 (2.2%)
Bronchopneumonia alone	1 (0.6%)	4 (4.5%)	1 (1.4%)	1 (1.3%)	6 (2.2%)
Cardiovascular disease alone	4 (2.5%)	1 (1.1%)	3 (4.3%)	3 (3.8%)	8 (2.5%)
Organ failure & sepsis alone	5 (3.2%)	0	0		5 (1.6%)
Renal failure alone	0	0	0	0	0
Asthma alone	1 (0.6%)	0	0	1 (1.3%)	1 (0.3%)
Carcinoma of lung alone	0	1 (1.1%)	1 (1.4%)	0	2 (0.6%)
Cor pulmonale alone	1 (0.6%)	0	0	0	1 (0.3%)
†Miscellaneous causes of death not including COPD or the causes above	43 (27%)	14 (16%)	9 (13%)	13 (16%)	66 (21%)
Column total (% of all deaths in time period)	73 (47%)	29 (33%)	17 (25%)	20 (25%)	119 (38%)

† These are the patients who had causes of death that did not include COPD and did not include one of the commoner causes explicitly named in the other rows of this table. The causes of death making up this group are listed in section 6.2.5 below.

6.2.5 Common causes of death in Table 6.2.2 appearing with diseases other than COPD

This section provides the list of other diagnoses that appear with the common causes of death in which the common cause does not appear with COPD and does not occur alone. The accompanying diagnoses are as follows:

i) renal failure: (1) clostridium difficile. *ii)* bronchopneumonia: ischaemic colon, gastric cancer, rheumatoid lung & cigarette smoker. *iii)* Respiratory failure: (2) pneumothorax, hypertension, NIDDM, obesity, *iv)* Pneumonia: bronchiectasis, (pneumothorax & pneumonia & surgical emphysema), respiratory failure, kyphoscoliosis, atrial fibrillation, *v)* Cardiovascular disease: liver failure; *vi)* Multi-organ failure and morbid obesity.

6.3 Discussion

6.3.1 Mortality

Hospital mortality is difficult to compare between studies because of differences in case mix (section 3.3.1). Restricting the comparison to intubated patients is one way of ensuring relatively homogeneous groups of patients, although differences in inclusion criteria and also in the definitions of outcome (e.g. hospital mortality rather than 30-day mortality) may remain problems. Nonetheless comparing hospital mortality for the intubated patients it can be seen that the rate in the CAOS patients, 35.8% (95% CI 31.3–40.4%) is close to that observed in systematic review 37.9% (1771/4675) (95% CI 36.5-39.3%), chi-square 0.77 p=0.38. Mortality at 180 days was available for fewer intubated patients in the systematic review, but the 165 deaths in 387 patients again gave a similar rate, 42.6% (95% CI 37.7-47.7%) compared to 41.6% for CAOS (95% CI 37.0-46.2%), chi-square 0.10 p=0.75. The similarity of these rates supports the contention that the patients included in CAOS are representative of intubated COPD patients in general.

6.3.2 Causes of death

It has been suggested that the accuracy of death certificates is greatest in young people and deteriorates with increasing age and increasing numbers of coexistent diseases[130]. Studies of causes of death in airways disease have tended to concentrate on the misclassification of asthma as COPD, particularly in the elderly[130-132]. A study from Finland[133] followed 2,237 patients identified from hospital episode data as having COPD as the primary reason for admission, and determined the causes of death in 1,070 patients who died over the subsequent 10 years. They found that coronary heart disease was the most frequent, comprising 37% of deaths, and the second most common was COPD in 30.2% of deaths. Lung cancer accounted for 12.1%. A study from the UK that used the records of the ONS to identify all death certificates that mentioned COPD or asthma found that a disease of the circulatory system was listed as a frequent underlying cause of death, as was a neoplasm[134]. In CAOS, the proportion of all deaths in study patients attributed to COPD was 53.3% for within ICU mortality, and 75% for 180 day mortality. This increase in the percentage of patients with COPD with length of follow-up may be because many patients who die in ICU develop complications such as gastrointestinal bleeding and peritonitis, and the doctors providing the death certificate may give these as the immediate cause of death, having lost sight of the fact that the patient was admitted to critical care with an exacerbation of COPD. It is interesting that these percentages certified as COPD are higher than in the Finnish study. It might be that COPD patients recruited to CAOS and dying soon after hospital discharge had severe COPD.

Chapter 7 Quality of life after intensive care

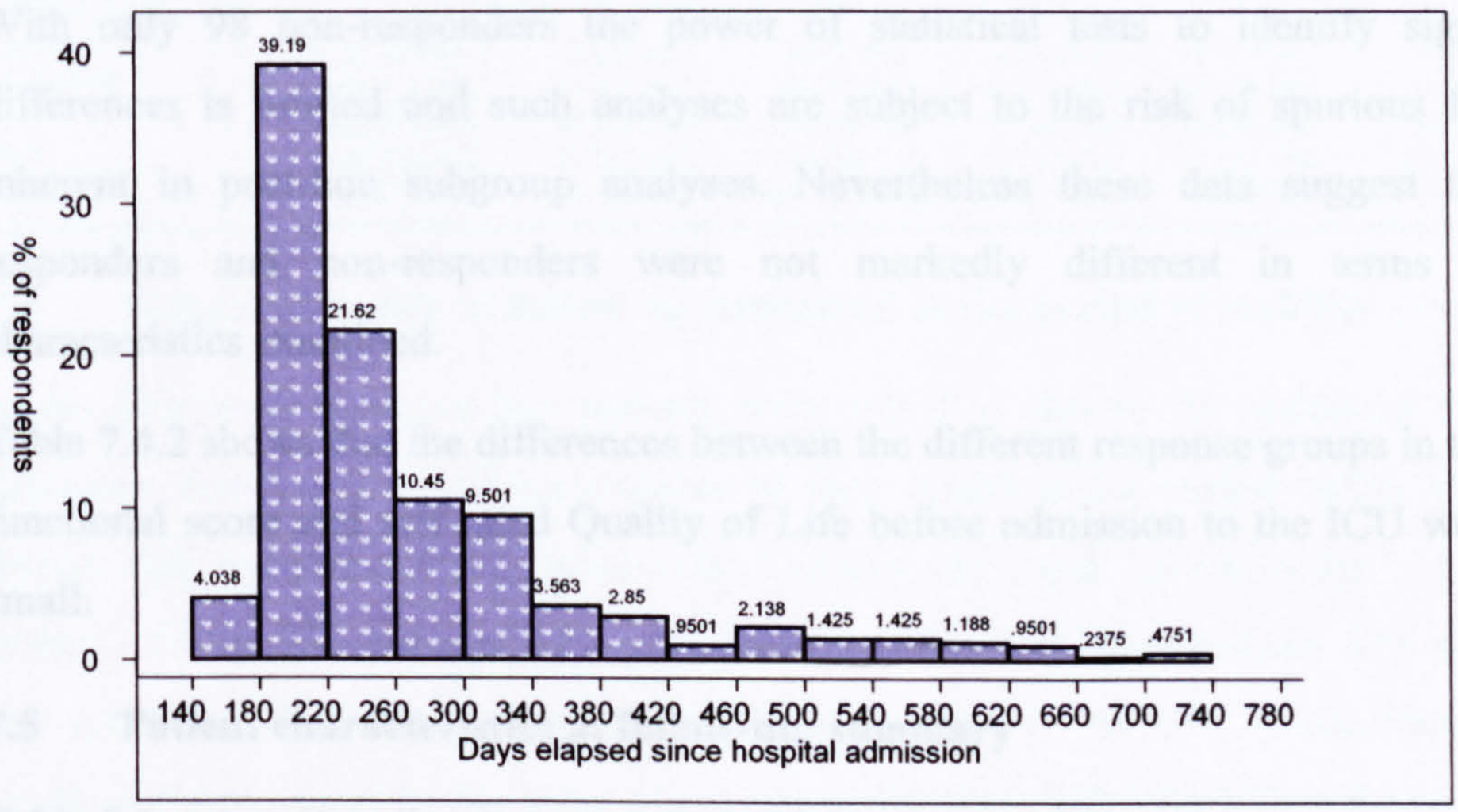
7.1 Introduction

A major concern for clinicians admitting COPD patients to critical care is that the treatment provided will merely prolong the process of dying, and that survivors will be left with such poor quality of life that they will regret having been treated aggressively. The 180-day follow-up questionnaire was designed to collect data that would enable clinicians to understand the likely health status and views about aggressive treatment of survivors.

7.2 Response rate

Four hundred and twenty of the 518 (81.1%) 180-day survivors provided answers to the follow-up questionnaire. Figure 7.2 below shows the number of days after ICU admission at which responders returned the 180-day questionnaire. The mean (SD) and median (IQR) number of days elapsed between hospital admission and questionnaire return was 268 (104), 231 (200-299).

Figure 7.2 Time elapsed after ICU admission until questionnaire completed



7.3 The implications of non-response

Non-response is an important threat to the conclusions that can be drawn from quality of life questionnaires, because non-responders may differ systematically from responders. Three strategies were used to gain insight into the effects that non-response might have had on the follow-up in this study. First, responders were compared with non-responders in terms of data collected while both groups were in hospital. Second, very late responders would have been non-responders had the study closed earlier and may give some insight into the characteristics of non-responders. For this reason, in analyses of hospital and follow-up data, responders have been classified as prompt (up to and including patients who responded within 220 days after ICU admission), delayed (221 days to 364 days) and very delayed (>365 days). Quality of life measures were presented for each response group. Third, sensitivity analyses were carried out to investigate the outcomes if all non-responders had had the most favourable response and if they all had had the most unfavourable response.

7.4 Responders vs. non-responders: hospital data

The non-responders were older, more of them were male, and more had been intubated (Table 7.4.1). These differences were small and did not reach statistical significance. With only 98 non-responders the power of statistical tests to identify significant differences is limited and such analyses are subject to the risk of spurious findings inherent in post-hoc subgroup analyses. Nevertheless these data suggest that the responders and non-responders were not markedly different in terms of the characteristics examined.

Table 7.4.2 shows that the differences between the different response groups in terms of functional score and self-rated Quality of Life before admission to the ICU were also small.

7.5 Patient characteristics at follow-up: summary

Table 7.5 summarises the characteristics of the patients at follow-up.

Table 7.4.1 Characteristics of responders and non-responders

	Total cohort n=832	*Surviving non-responders n=98*	*All responders n= 420*	*Prompt n=184*	*Delayed n= 179*	*Very delayed n=57*
Admission data						
Age						
n mean (SD)	67.0 (9.7)	65.4 (9.6)	65.2 (9.5)	65.7 (9.6)	65.4 (9.1)	63.0 (9.9)
n median (IQR)	68.0 (60-75)	66.0 (58-73)	65.0 (59-72)	66 (58-73)	66 (59-72)	61.5 (57.5-71.5)
Male n %	397 (47.7%)	46 (47.4%)	187 (44.4%)	81 (43.8%)	87 (48.3%)	19 (33.9%)
Intubated n (%)	450 (54.1%)	52 (53.6%)	212 (50.4%)	86 (46.5%)	95 (52.8%)	31 (55.4%)

Table 7.4.2 Pre-ICU functional score and QoL by response delay

	Total cohort n=832	*Surviving non-responders n=98*	*All responders n= 420*	*Prompt n=184*	*Delayed n= 179*	*Very delayed n=57*
Functional Score						
Fully mobile n (%)	207 (24.9%)	25 (24.7%)	130(30.9%)	56 (30.3%)	53 (29.4%)	21 (37.5%)
Independent n (%)	308 (37.0%)	34 (35.1%)	160 (38.2%)	71 (38.9%)	71 (40.0%)	17 (30.4%)
Housebound n (%)	280 (33.7%)	35 (36.1%)	121 (28.7%)	52 (28.1%)	53 (29.4%)	16 (28.6%)
Bed/chair bound n (%)	37 (4.5%)	4 (4.1%)	9 (2.1%)	5 (2.7%)	2 (1.1%)	2 (3.6%)
Self-rated QoL						
Excellent	21 (2.5%)	2 (2.1%)	14 (3.3%)	6 (3.2%)	6 (3.3%)	2 (3.6%)
Very good	142 (17.1%)	17 (17.5%)	88 (20.9%)	37 (20.0%)	40 (22.8%)	10 (17.9%)
Fair	361 (43.4%)	47 (48.5%)	169 (40.2%)	77 (42.2%)	70 (38.9%)	22 (39.3%)
Poor	248 (29.8%)	30 (29.9%)	118 (28.1%)	51 (27.6%)	47 (26.1%)	20 (35.7%)
Very poor	60 (7.2%)	2 (2.1%)	31 (7.4%)	13 (7.0%)	16 (8.9%)	2 (3.6%)

7.6 Self-rated health at follow-up compared to the period of stability pre-ICU

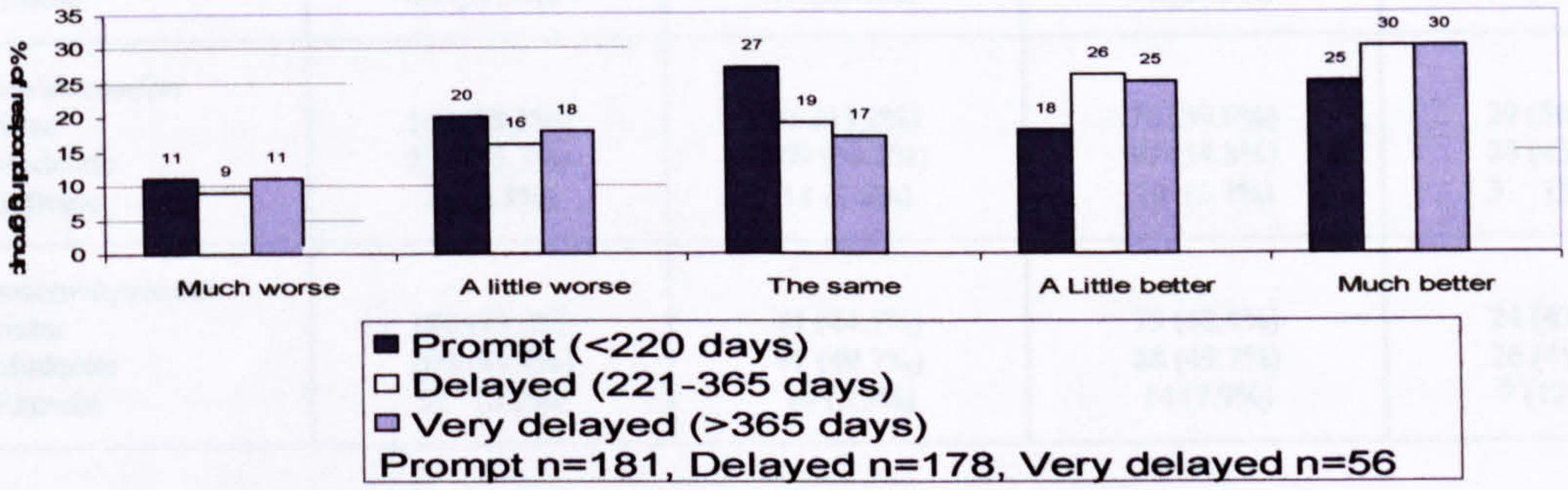
In the follow-up questionnaire patients were asked to choose the statement that best described their current health compared to their health in the period before the acute illness that resulted in ICU admission. Options ran from "much worse" to "much better". Of the 420 patients who completed the follow-up questionnaire 415 answered this question. Seventy-two percent (302/415), (95% CI 68.2-77.0) considered their health at follow-up to be the same or better and 27.2% (113/415),(95% CI 23.0-31.8%) considered their health to be worse. If all the non-responders are considered to have

quality of life that is worse than prior to ICU 59% (306/518), (95% CI 55-63) would have a quality of life 180-days after ICU that was the same or better than prior to ICU. The proportions are almost identical if just the intubated patients are considered. Of the 450 intubated patients 263 (58.4%) survived to 180-days and 166 (78%), (95%CI 72-84%) of responders considered their quality of life at 180-days to be the same or better than prior to ICU. If all non-responders are considered to have worse quality of life than pre-ICU 166/263 intubated patients would have quality of life that was the same or better than prior to ICU (63%, 95% CI 57-69%).

Figure 7.6.1 and Table 7.6.1 show the responses of patients grouped by promptness of response, and it can be seen that there was no significant difference in quality of life between prompt and delayed respondents. Again this is a post-hoc analysis and the numbers are relatively small but there is adequate power to detect a major difference. For example, if 30% of delayed responders had a worse quality of life compared to 15% of prompt responders, a study with a sample size of 280 (140 early responders and 140 late) would detect such a difference as significant at the 5% level with a probability of 85%.

If the very delayed responders are taken as giving some insight into non-responders there is no evidence to suggest that non-response has mainly occurred in patients with the worst quality of survival.

Figure 7.6.1 Current compared to pre-admission quality of life, by response delay.



†Missing responses to the health state transition question.

Prompt group 4 missing responses, delayed 2 missing responses, very delayed no missing responses.

Table 7.5 Patient characteristics at follow-up

Mean(SD) *Median (IQR)*	*All responders* *n= 420*	*Prompt* *n=184*	*Delayed* *n=179*	*Very delayed* *n=57*
Health status measure				
Prior health Much worse Little worse Same Little better Much better	 41 (9.8%) 72 (17.2%) 80 (19.1%) 102 (24.3%) 124 (29.6%)	 19 (10.3%) 33 (17.9%) 30 (16.3%) 45 (24.5%) 57 (30.9%)	 16 (9.0%) 28 (15.7%) 34 (19.1%) 47(26.4%) 53 (29.8%)	 6 (10.5%) 11 (19.3%) 16 (28.1%) 10 (17.5%) 14 (24.6%)
ICU again Yes No	 400 (96.4%) 15 (3.6%)	 174 (94.5%) 7 (3.9%)	 169 (96.0%) 8 (4.5%)	 57 (100%) 0 (0%)
Functional score Fully mobile Independent Housebound Bed/chair bound	 91 (21.7%) 141 (33.6%) 171 (40.7%) 17 (4.1%)	 40 (21.7%) 62 (33.7%) 70 (38.0%) 12 (6.5%)	 38 (21.2%) 59 (33.0%) 79 (44.1%) 3 (1.7%)	 13 (22.8%) 20 (35.1%) 22 (38.6%) 2 (3.5%)
AQ20 score	11.2 (4.7) 12 (8-15)	11.1 (4.7) 12 (8-15)	11.2 (4.8) 12 (8-15)	11.7 (4.2) 13 (9-14)
EQ-5D	54.6 (31.0) 62 (35-74)	53.3 (32.3) 62 (29-74)	56.2 (29.8) 62 (52-74)	53.8 (31.0) 62 (38-74)
Thermometer score	54.9 (19.5) 50 (40-70)	54.1 (20.8) 50.5 (40-70)	55.5 (17.7) 50 (45-70)	55.1 (20.6) 55 (50-70)
Mobility No problems Some problems Bed bound	 72 (17.2%) 341 (81.6%) 5 (1.2%)	 37 (20.1%) 145 (78.8%) 2 (1.1%)	 26 (14.7%) 150 (84.8%) 1 (0.6%)	 9 (15.8%) 46 (80.7%) 2 (3.5%)
Self-care No Problems Some problems Unable wash/dress	 211 (50.5%) 183 (43.8%) 24 (5.7%)	 92 (50%) 83 (45.1%) 9 (4.9%)	 94 (53.1%) 73 (41.2%) 10 (5.6%)	 25 (43.9%) 27 (47.4%) 5 (8.8%)
Usual activities No problems Some problems Unable	 78 (18.7%) 250 (59.8%) 90 (21.5%0	 35 (19.0%) 104 (56.5%) 45 (24.5%)	 36 (20.3%) 105 (59.3%) 36 (20.3%)	 7 (12.3%) 41 (71.9%) 9 (15.8%)
Pain/discomfort None Moderate Extreme	 160 (38.3%) 231 (55.3%) 27 (6.5%)	 61 (33.2%) 109 (59.2%) 14 (7.6%)	 70 (39.6%) 97 (54.8%) 10 (5.7%)	 29 (50.9%) 25 (43.9%) 3 (5.3%)
Anxiety/depression None Moderate Extreme	 180 (43.2%) 205 (49.2%) 31 (0.2%)	 81 (44.3%) 91 (49.7%) 10 (5.5%)	 75 (42.4%) 88 (49.7%) 14 (7.9%)	 24 (42.1%) 26 (45.6%) 7 (12.3%)

If all the 98 non-responders had worse quality of life at follow-up than in the period prior to ICU the proportion of 180-day survivors with the same or better quality of life would be 58.3% (302/518). If all non-responders had better quality of life than in the period of stability prior to ICU the proportion of 180-day survivors with the same or better quality of life would be 77.2% (400/518).

Table 7.6.1 Current compared to pre-admission quality of life, by response delay

	Worse quality of life than in period stability pre-ICU	*Same or better quality of life than in period of stability pre-ICU*	*Total patients in response group*	*Prompt vs. delayed* *Chi-square P value*	*Prompt vs. very delayed* *Chi- square P value*
Prompt Responders	52 29%	129 71%	181		
Delayed responders	44 25%	134 75%	178	ChiSq=0.74 P=0.39	
Very delayed responders	17 30%	39 70%	56		ChiSq=0.05 P=0.81
†Overall: all responders	113/415 27.2%	302/415 72.8%	415		

† The denominator of 415 is used in this table since this makes no assumptions about the views of non-responders and the sensitivity analysis below explores the impact of non-responders

7.7 Preference for admission to ICU again

Overall 96.4% of the responders (400/415) would be willing to undergo ICU again under circumstances similar to the original admission. If all non-responders are assumed to not want ICU again the overall preference for entering ICU again under similar circumstances would fall to 77.2% (400/518). Of the 450 intubated patients 263 (58%) survived to 180-days and 212 (81%) responded to the question about ICU. Of these 204/212 would want ICU again under similar circumstances (96.2%). If all of the intubated non-responders are assumed to not want ICU again the proportion of all survivors who would want ICU again would be 204/263 (78%).

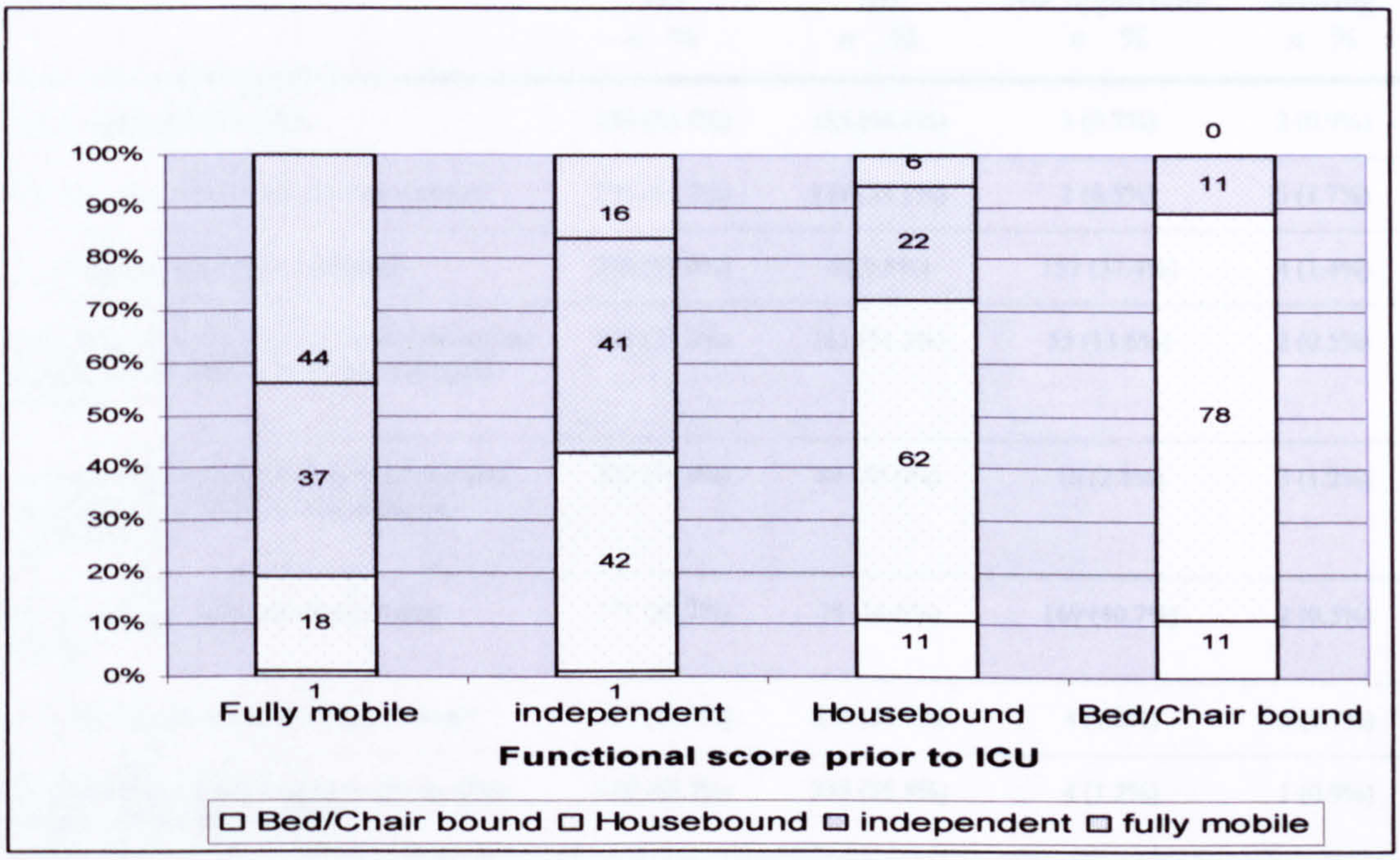
7.8 Functional score at follow-up compared to the period of stability pre-ICU

The functional score that described patients exercise tolerance was collected at ICU admission (to describe the patients' functional capacity in the period of stability prior to critical care admission) and also at follow-up (to describe the functional capacity on the day that they completed the follow-up questionnaire). In Figure 7.8.1 the functional score at follow-up is shown for patients grouped by their pre-ICU functional score. Table 7.8.1 shows the numbers that correspond to the percentages shown in the figure. Of the 420 patients with functional score data both before ICU and at follow-up 198 (47.1%) had the same level of function at follow-up, 129 (31%) had dropped by one level and 26 (6.2%) had dropped by 2 levels and 41 (9.8%) had improved by one or more levels.

Table 7.8.1 Functional capacity before and 180-days after ICU admission

Functional capacity 180-days After ICU onset	Functional capacity in period of stability prior to ICU admission			
	Fully mobile n=131	Independent n=160	Housebound n=120	Bed/Chair bound n=9
Fully mobile	44.3%	16.3%	5.8%	0%
Independent	37.4%	41.0%	21.7%	11.1%
Housebound	18%	41.9%	61.7%	77.8%
Bed/Chair bound	0.8%	1.3%	10.8%	11.1%

Figure 7.8.1 Functional score at follow-up for patients classified by functional score in the period of stability prior to ICU.



7.9 AQ-20 Questionnaire

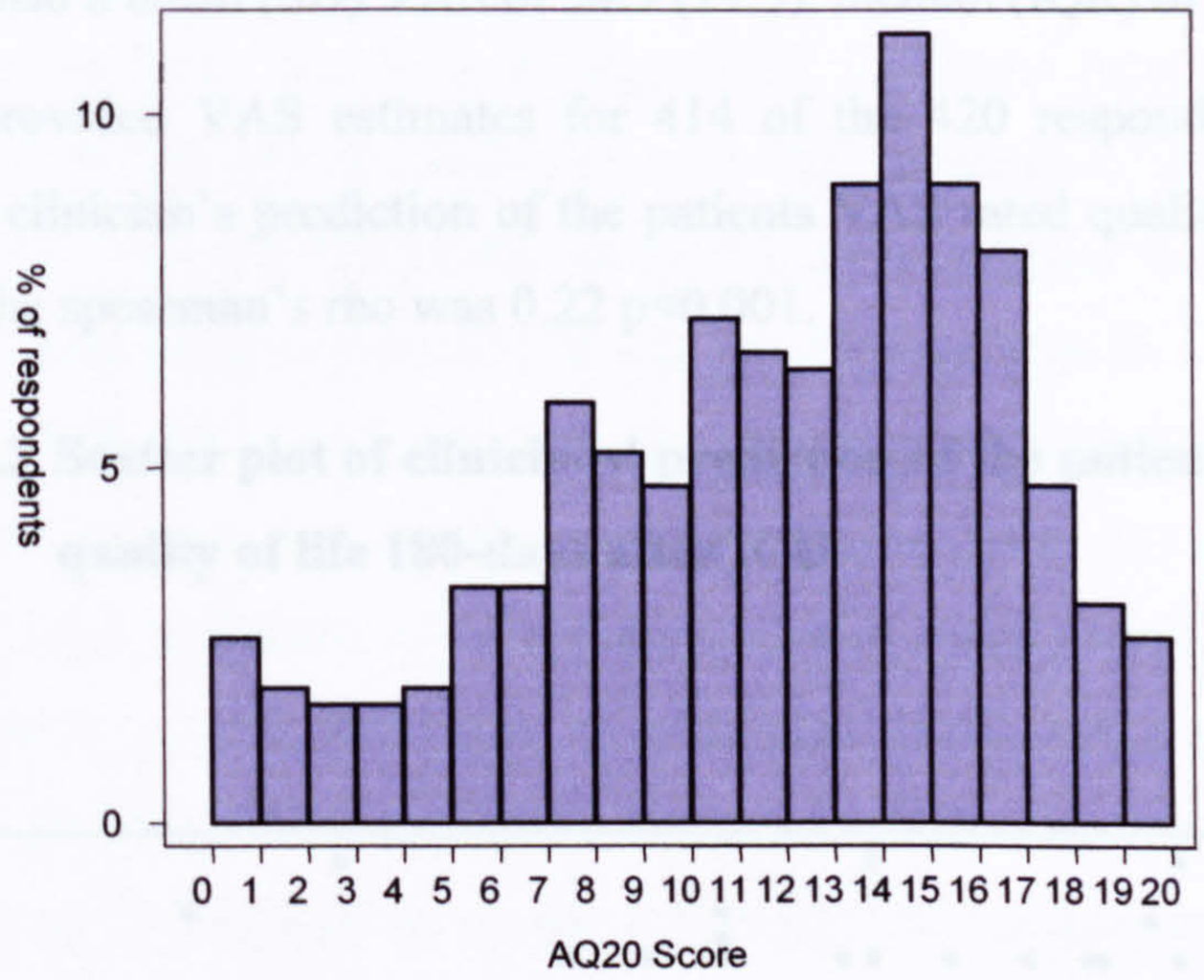
In the AQ-20 questionnaire patients we asked about symptoms associated with airways disease. Table 7.9 summarises the data from the 420 respondents.

The AQ20 has a maximum score of 20 and a minimum score of zero. The mean (SD), and median (IQR) scores were 11.2 (4.7), 12 (8-15). Figure 7.9 displays the distribution of scores in the CAOS respondents. 42.7% of CAOS respondents report feeling breathless when trying to get to sleep and 82.3% considering that the fullness of their lives is limited by their chest trouble.

Table 7.9 AQ-20 responses

Question	*Yes* *n %*	*No* *n %*	*Not applicable* *n %*	*Missing* *n %*
Do you cough during the day?	230 (54.8%)	185 (44.1%)	3 (0.7%)	2 (0.9%)
Does your chest often make you feel restless?	274 (65.2%)	139 (33.1%)	2 (0.5%)	5 (1.7%)
Does gardening make you breathless?	218 (51.9%)	41(9.8%)	157 (37.4%)	4 (1.4%)
Do you worry when going to a friend's house that there might be something there that will upset your chest?	148 (35.2%)	215 (51.2%)	55 (13.6%)	2 (0.5%)
Do you get chest problems when you come into contact with strong smells, exhaust fumes, perfumes etc?	323 (76.9%)	84 (20.0%)	10 (2.4%)	3 (1.2%)
Does your partner find your chest trouble upsetting?	171 (40.7%)	78 (18.6%)	169 (40.7%)	2 (0.5%)
Do you feel breathless when trying to sleep?	179 (42.7%)	230 (54.9%)	4 (1.2%)	6 (1.7%)
Do you worry about the long term effects of the drugs you take for chest trouble?	179 (42.7%)	233 (55.5%)	4 (1.2%)	1 (0.9%)
Does emotional upset make your chest trouble worse?	286 (68.1%)	118 (28.1%)	11 (2.6%)	5 (1.7%)
Are there times when you have difficulty getting around the house because of your chest trouble?	303 (72.1%)	109 (26.0%)	5 (1.4%)	3 (0.9%)
Does your chest problem make you breathless when you do things at work? (paid employment)	33 (7.9%)	26 (6.2%)	358 (85.5%)	3 (0.9%)
Does walking upstairs make you breathless?	313 (74.5%)	58 (13.8%)	47 (11.7%)	2 (0.5%)
Do you get breathless doing housework?	265 (63.3%)	55 (13.1%)	96 (23.4%)	3 (0.75%)
Does your chest trouble make you go home sooner than others after a night out?	158 (37.6%)	92 (21.9%)	164 (39.5%)	6 (1.4%)
Do you suffer from breathlessness when you laugh?	186 (44.3%)	223 (53.1%)	6 (1.7%)	5 (1.4%)
Does your chest trouble make you feel impatient?	292 (69.5%)	123 (29.3%)	2 (0.7%)	3 (0.9%)
Do you think the fullness of your life is limited by your chest trouble?	345 (82.3%)	69 (16.5%)	2 (0.7%)	3 (0.9%)
Do you feel drained after a cold because of your chest trouble?	334 (79.5%)	55 (13.1%)	28 (6.9%)	3 (0.9%)
Do you have a feeling of chest heaviness?	257 (61.2%)	156 (37.1%)	3 (0.7%)	4 (1.4%)
Do you worry a lot about your chest trouble?	250 (59.5%)	163 (38.8%)	3 (0.7%)	6 (1.9%)

Figure 7.9 The distribution of AQ-20 scores in questionnaire responders

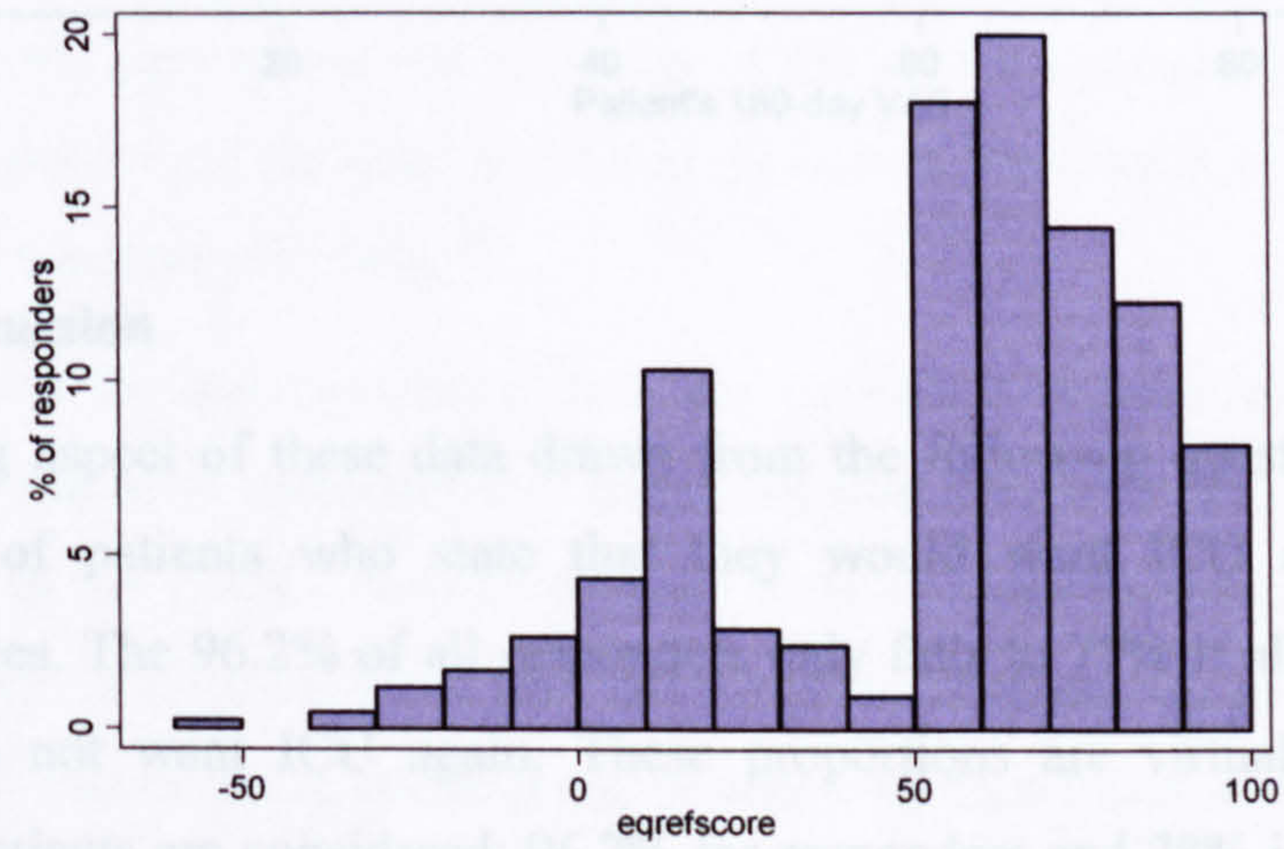


7.10 EuroQol

7.10.1 EQ-5D values in the CAOS responders

Responders had a mean (SD) EQ-5D of 54.6 (31.0) and median (IQR) of 62.0 (35-74). The distribution of the EQ-5D in the responders is shown in Figure 7.10.1. The distribution of patients between the individual domains is shown in Table 7.5 above.

Figure 7.10.1 EQ-5D values for the CAOS population.

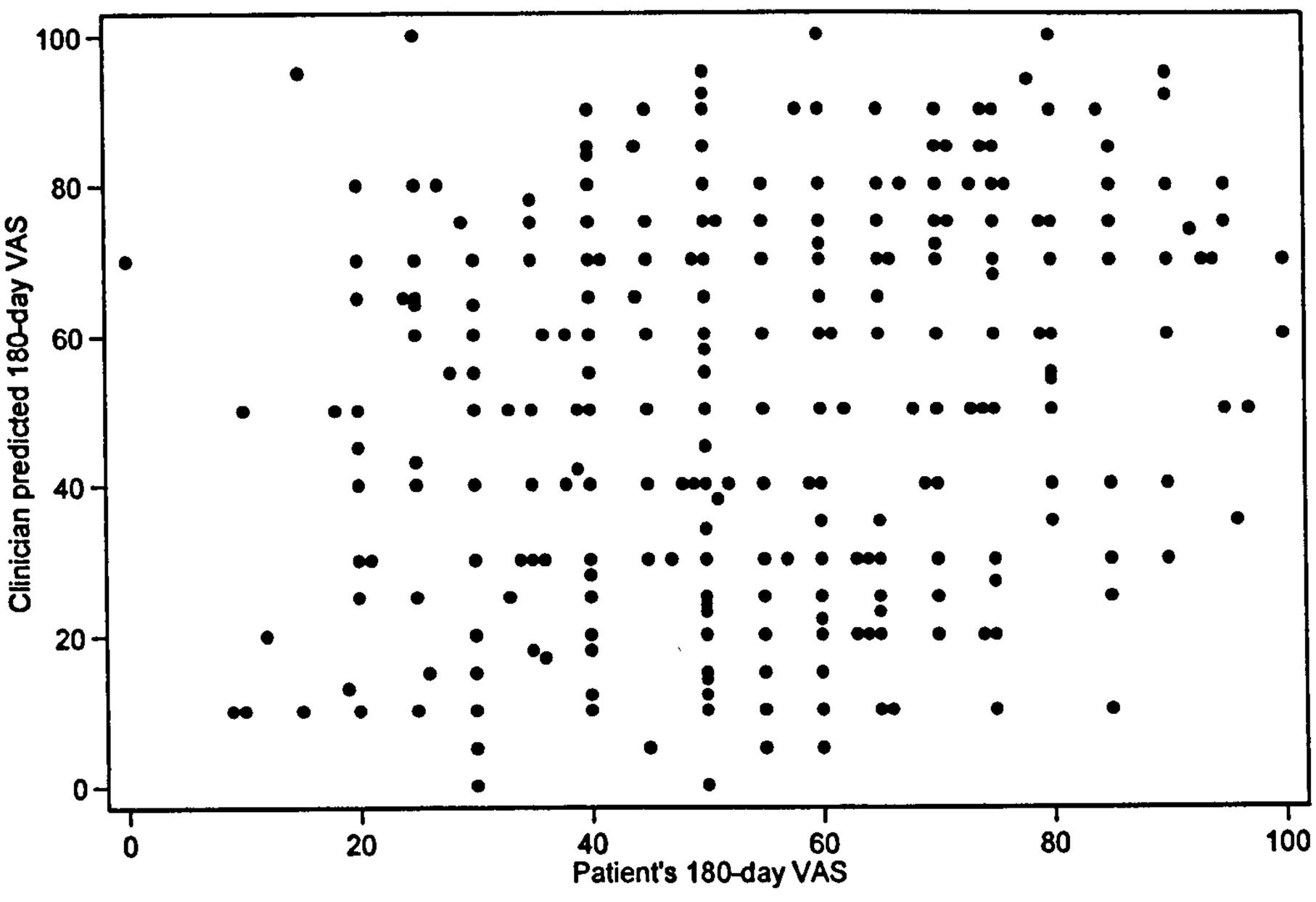


7.10.2 EuroQol visual analogue score (VAS)

Responders had a mean (SD) VAS of 54.9 (19.5), median (IQR) of 50 (40-70).

Clinicians provided VAS estimates for 414 of the 420 respondents. Figure 7.10.2 displays the clinician's prediction of the patients VAS rated quality of life at 180-days after ICU. The spearman's rho was 0.22 p<0.001.

Figure 7.10.2 Scatter plot of clinicians' prediction of the patients VAS rated quality of life 180-days after ICU



7.11 Discussion

The striking aspect of these data drawn from the follow-up questionnaire is the high proportion of patients who state that they would want ICU again under similar circumstances. The 96.2% of all responders only falls to 77% if all non-responders are assumed to not want ICU again. These proportions are virtually the same if just intubated patients are considered: 96.2% for responders and 78% if non-responders are

all assumed not to want ICU again. This figure is similar to that observed in a group of 84 US medical ICU patients interviewed at 1 year after ICU[135] The majority of survivors also consider that their quality of life is similar to the quality of life they experienced in the period of stability prior to ICU admission. This finding reproduces the observation from the SUPPORT study that the functional capacity in the 2 weeks prior to ICU best predicted quality of life at 180-days after ICU. This is despite the actual level of disability and symptom burden being considerable. The AQ-20 scores show just how many symptoms the patients had and the severity of symptoms in the CAOS population is illustrated by comparison with a population of 165 stable COPD outpatients with a mean (SD) age of 69.0 (6.8) years and a mean (SD) FEV_1 % predicted of 39.8% (16.5%) studied in Japan using Japanese translations of the AQ20 where the mean (SD) AQ20 score was 5.9 (4.6)[136] in comparison to the mean CAOS score of 11.2 (4.7). It is interesting however that when the patients make a global assessment of their quality of life using the EuroQol VAS responders had a mean (SD) VAS of 54.9 (19.5), median (IQR) of 50 (40-70). This was similar to the VAS in stable UK COPD outpatients, who had a mean (SD) VAS of 50.9 (16.4) and a median of 50.0[137]. The EQ-5D values in the CAOS responders [mean (SD) EQ-5D of 54.6 (31.0) and median (IQR) of 62.0 (35-74)] were also similar to 125 outpatients with COPD recruited in a UK chest clinic for whom the mean (SD) EQ-5D was 52.4 (15.7) and the median was 53.1[137].

The scatter plot comparing clinicians predictions of the patient's quality of life compared to the patients self-rated quality of life serves to emphasise that clinicians are not good at predicting patients' self-rated quality of life after ICU, an observation that has been documented elswhere[138].

A weakness of the questionnaire data is that patients may have tended to give positive responses because of concerns that responses that seemed negative might undermine future care. In the CAOS study though the patient information sheet that accompanied the questionnaire explained that the data would be anonymous, patients may have still been worried that negative opinions might influence their future care.

7.12 Conclusion

The questionnaire data are useful for decision making and for informing conversations with patients when used alongside survival predictions. Patients are likely to find it helpful to know that if they do survive that by 180-days or so after ICU admission they will have between at least a 77% chance and probably nearer to 96% chance of being willing to undergo ICU again under similar circumstances, information that suggests that they will not regret the decision to go ahead with ICU if they survive. It is also helpful to know that between 60 to 73% of survivors will consider the quality of life if they survive to be the same or better than in the period of stability prior to ICU admission. Given the poor correlation between clinicians' estimates of patients self-rated quality of life and patients actual rating, clinicians will perhaps be best to simply explain to patients that if patients do survive the best predictor of their quality of life at 180-days or so after ICU will be their quality of life in the period of stability prior to ICU.

Chapter 8 An acute physiology score for UK COPD patients

8.1 Introduction

As explained in section 2.5.3, investigation of the independent effects of a 20 potential acute physiological variables would require at least 200 deaths in the study, even if the effect of each variable was simply assumed to be linear. The drawbacks of generic acute physiology scores are highlighted in section 2.8.3, and it was felt that the best approach would be to develop a UK COPD-specific acute physiology score (CAPS).

In this chapter the CAOS data on each of the physiological variables are first examined for suitability for inclusion in a prognostic index. This is mainly based on the amounts of missing data. The distributions of each variable are also reported to permit comparison with other studies and populations.

The intercorrelations between the different physiological variables in the CAOS dataset are presented. Then the development of a new acute physiology score for UK COPD patients, using data from all the participants in the CMP over the period from December 1995 to January 2004 (with admissions to units participating in CAOS during the time period of the study excluded) is described. The analysis of the CMP data was carried out by Dr David Harrison, the chief statistician at the Intensive Care National Audit and Research Centre, using data on 8527 patients aged 45 years and older admitted to critical care with obstructive lung disease.

The relationships between the new CAPS score and each of its component parts, and with 180–day mortality is described.

The chapter concludes with a discussion of the findings.

8.2 Blood gases

Table 8.2 shows the distribution of blood gas measurements in the CAOS population. The aim of the study was to identify patients with respiratory failure due to obstructive lung disease, and such patients would be expected to have Type II respiratory failure characterised by a $PaCO_2 > 6.0$kPa and respiratory acidosis with a $pH < 7.35$. The

results show that the majority of patients were indeed hypercarbic with a median (IQR) $PaCO_2$ of 10.4 kPa (8.1-13.3) and acidotic with a median (IQR) pH of 7.2 (7.1-7.3).

Table 8.2 Blood gases

Variable	*All patients n=832*		*Patients for all Treatment n=651*		*Patients not for intubation N=181*	
	Number (%)	*Mean SD Median (IQR)*	*Number (%)*	*Mean SD Median (IQR)*	*Number (%)*	*Mean SD Median (IQR)*
pH		7.2 (0.1) 7.2 (7.1-7.3)		7.2 (0.1) 7.2 (7.1-7.3)		7.2 (0.1) 7.3 (7.2-7.3)
Missing	0		0		0	
FiO_2 (%)		48.1 (26.2) 35.0 (28.0-60.0)		50.7 (26.9) 40.0 (28.0-77.5)		38.7 (21.1) 28.0 (25.0-40.0)
Missing	3 (0.4%)		3 (0.5%)		0	
PaO_2 (kPa)		12.7 (10.1) 9.6 (7.2-13.9)		13.3 (10.9) 9.7 (7.3-14.8)		10.7 (6.2) 8.9 (6.7-12.0)
Missing	0		0			
$PaCO_2$ (kPa)		11.0 (4.2) 10.4 (8.1-13.3)		11.0 (4.3) 10.5 (8.0-13.3)		10.9 (3.9) 10.1 (8.5-13.1)
Missing	0		0			
PaO_2/FiO_2		29.3 (16.9) 26.3 (17.4-37.1)		28.7 (16.6) 25.8 (16.9-36.8)		31.4 (17.8) 27.4 (19.7-38.6)
Missing	3 (0.4%)		0	3 (0.5%)	0	

8.2.1 PaO_2/FiO_2 ratio

Most of the units found it difficult to determine the FiO_2 measurements that took place outside critical care. Though blood gases were well recorded in the notes the FiO_2 was poorly recorded and certain units expressed the concern that the FiO_2 recorded was often incorrect. Collecting FiO_2 data often required repeated contact with the units to check values that did not correspond to possible values according to the accepted

performance of the various delivery devices. For this reason the PaO_2/FiO_2 ratio was considered likely to be unreliable in clinical practice.

8.3 Other acute physiology

Table 8.3 displays the distribution of the other acute physiological variables measured in CAOS. If we consider the median values we can see that though patients were tachycardic (median (IQR) heart rate 120 (101 – 132)) and tachypnoeic (median (IQR) respiratory rate 30 (25-37)) with a raised $PaCO_2$ (Median (IQR) 10.4 kPa (8.1-13.3)) indicating respiratory failure, the other measures of acute physiology were not markedly deranged suggesting that the majority of patients had single organ respiratory failure.

8.3.1 Non-ventilated respiratory rate

Non-ventilated respiratory rate had 47 missing values, which at 5.6% is one of the highest for missing data. Respiratory rate is notoriously poorly collected in the medical notes. However 41 of the 47 patients with a missing respiratory rate were intubated and this may in part explain the high number of data unavailable.

8.4 Correlations among physiological variables

The significant correlations are indicated in bold face in Table 8.4.1. Those which arose because the same (or closely related) variables were involved in calculating both indicators (matrix 1 PaO_2 and PaO_2/FiO_2, matrix 1 systolic and diastolic blood pressure and mean arterial pressure) are not discussed further. Correlations arising because of known associations for example between a high $PaCO_2$ and a low pH or between creatinine and urea and potassium are also not discussed further.

8.4.1 Correlations with the Glasgow Coma Scale

There is a correlation between falling GCS and rising FiO_2, PaO_2 and $PaCO_2$ (Table 8.4.1). This is likely to reflect the fact that as the $PaCO_2$ rises the patients develop CO_2 narcosis and the GCS falls.

Table 8.3 Other acute physiology

Variable	*All patients n=832*		*Patients for all Treatment n=651*		*Patients not for intubation n=181*	
	n (%)	*Mean SD Median (IQR)*	*n (%)*	*Mean SD Median (IQR)*	*n (%)*	*Mean SD Median (IQR)*
Systolic blood pressure (mmHg)		130 8 (33.7) 130 (106-152)		130 9 (34 6) 130.(105-154)		130.5 (30 1) 130 (110-150)
Missing	2 (0.2%)		1 (0.2%)		1 (0 6%)	
Diastolic blood pressure (mmHg)		69 0 (20 7) 68 (55-80)		68.8 (21.2) 68.0 (55-80)		69 6 (19 0) 69 (57-82)
Missing	3 (0.4%)		2 (0 4%)		1 (0 6%)	
Mean arterial pressure (mmHg)		89.6 (23.2) 88.3(73.3-104.3)		89 5 (23.9) 88 3 (73 3-103.7)		89 9 (20 6) 89 5(75.5-104.8)
Missing	3 (0 4%)		2 (0.4%)		1 (0 6%)	
Central temperature ^{O}C		37.0 (1.3) 37.1(36 1-37.9)		37.0 (1.3) 37.1 (36 1-37 8)		37 0 (1.2) 36 9 (36.2-38.0)
Missing	5 (0 6%)		5 (0 8%)		0	
Heart rate (bpm)		118 0 (25.7) 120 (101-132)		119 1 (26.1) 120 (104-135)		114 2 (23.7) 115 (99-128)
Missing	1(0.1%)		1(0.2%)		0	
Non-ventilated respiratory rate (bpm)		30.2 (10.2) 30 (25-37)		30.1 (10 6) 30 (24-38)		30.5 (8 7) 30 (25-36)
Missing	47 (5.6%)		46 (7.1%)		1(0 6%)	
Haemoglobin (g/dl)		13.8 (2.4) 14 0 (12.3-15.4)		13 8 (2.4) 14 0 (12.2-15 4)		13 8 (2.3) 14 0 (12.4-15.4)
Missing	0		0		0	
White Cell Count (x10^9/L)		15.6 (14 8) 13.3 (10.0-18.4)		15.7 (15.1) 13.5 (10 4-18 6)		15.2 (13.8) 12.1 (9.0-17.6)
Missing	0		0		0	
Sodium (mmol/L)		137.0 (5.4) 138 (134-140)		137.1 (5.5) 138 (135-140)		136 8 (5.2) 138 (134 -140)
Missing	0		0		0	
Potassium (mmol/L)		4.5 (0 8) 4.4 (4 0-4.9)		4.5 (0.8) 4 4 (3.9-4.9)		4.5 (0.7) 4 4 (4 1-4 9)
Missing	2 (0 2%)		0		0	
Creatinine (mmol/L)		109.4 (68.3) 93 (74-122)		111.1 (71.0) 94 (75-121)		105 8 (57.5) 92 (72-124)
Missing	0		0		0	
Urea (mmol/L)		9.3 (6.5) 7.5 (5.1-11.2)		9 2 (6.5) 7.5 (5.0-10 8)		9.6 (6 6) 7.8 (5.2-12.5)
Missing	0		0		0	
Albumin g/L		34 5 (7 3) 35 (30-40)		34 2 (7.6) 35(29-40)		35 4 (5.7) 35 (32-40)
Missing	3 (0.4%)		2(0 4%)		1 (0 6%)	
Bilirubin µmol/L		11.5 (10 0) 9.(6-14)		11.3 (8.1) 9 (6-14)		12.3 (15.0) 10 (7-13)
Missing	15 (1.8%)		9 (1.4%)		6 (3.3%)	
Glucose (mmol/L)		9.2 (4.0) 8 1 (6 4-10 6)		9 5 (4 2) 8 3 (6.5 -11.1)		8 0 (2.7) 7.6 (6 1-9.1)
Missing	14 (1.7%)		8 (1.2%)		6 (3 3%)	
Glasgow coma scale		12.1 (4.2) 15 (9-15)		11.8 (4.3) 14.0 (9-15)		12.9 (3.7) 15 (13-15)
Missing	3 (0.4%)		3 (0.5%)		0	

The fact that the FiO_2 and PaO_2 rise in parallel with this may be because uncontrolled oxygen is causing the rise in $PaCO_2$, or that once the $PaCO_2$ rises and the GCS falls patients are given uncontrolled oxygen in preparation for intubation. In addition patients with a low GCS have a low respiratory rate. As the Glasgow Coma Scale (GCS) improved, the pH and respiratory rate also rose.

There is a correlation between diastolic and mean arterial pressure and albumin. The reason for this is unclear. One possibility is that patients with low blood pressure received more additional fluids that cause the measured serum albumin to fall.

There is a correlation between glucose and $PaCO_2$. The reason for this correlation is unclear and it may have arisen by chance.

8.5 Use of acute physiology to calculate the COPD acute physiology score

In view of the problems with measurement of FiO_2 outlined in section 8.3.3, PaO_2 and PaO_2/FiO_2 ratio were not investigated in the CMP data set. Also since many of the patients in the CMP data set were intubated the respiratory rate was not used. GCS was dropped because it correlated with many of the factors associated with intubation such as pH and in any case is often used as a prompt to intubate. This left 13 variables from the case mix programme data set (Table 8.5). Mean arterial pressure was found to discriminate better than either diastolic or systolic blood pressure and was therefore used in preference to either component alone.

Each variable was inspected on a univariate basis and divided into a number of categories developed in part from normal ranges. Adjacent categories were combined if the difference in mortality was not significant at 10%. All the variables were then put into a multiple logistic regression model in a development sample of 2/3 of admissions (5513 patients from 2/3rds of units) and removed one by one in a stepwise manner, with measures of model fit, calibration and discrimination observed at each step in the validation sample of 1/3 of admissions (3014 patients in $1/3^{rd}$ of the units).

Table 8.4 Acute physiology correlation matrix

	pH	*FIO₂*	*PaO₂kPa*	*PaCO₂kPa*	*PaO₂FIO₂*	*sbp*	*dbp*	*map1*	*tempap2*	*HRI*	*RRI*	*Hbl*	*WBCl*	*Nal*	*Kl*	*creatl*	*ureal*	*albl*	*billl*	*glcl*
FIO_2	-0.323	1.000																		
	0.000																			
PaO_2kPa	-0.242	0.440	1.000																	
	0.000	0.000																		
$PaCO_2kPa$	-0.732	0.204	0.137	1.000																
	0.000	0.000	0.000																	
PaO_2FIO_2	-0.035	-0.311	0.605	0.018	1.000															
	0.308	0.000	0.000	0.604																
sbp	-0.046	-0.011	0.080	0.095	0.079	1.000														
	0.188	0.754	0.022	0.006	0.024															
dbp	-0.096	-0.015	0.100	0.118	0.117	0.719	1.000													
	0.006	0.662	0.004	0.001	0.001	0.000														
map1	-0.079	-0.014	0.098	0.116	0.107	0.911	0.942	1.000												
	0.023	0.680	0.005	0.001	0.002	0.000	0.000													
tempap2	0.177	-0.116	-0.159	-0.153	-0.077	0.017	0.019	0.019	1.000											
	0.000	0.001	0.000	0.000	0.027	0.620	0.593	0.577												
HRI	-0.129	0.029	-0.011	-0.011	-0.004	0.079	0.118	0.108	0.041	1.000										
	0.000	0.405	0.758	0.756	0.901	0.023	0.001	0.002	0.237											
RRI	0.114	-0.116	-0.142	-0.111	-0.006	0.103	0.074	0.094	0.049	0.216	1.000									
	0.001	0.001	0.000	0.002	0.864	0.004	0.039	0.009	0.174	0.000										
Hbl	-0.073	-0.065	-0.057	0.149	-0.001	0.096	0.191	0.160	0.050	0.039	0.054	1.000								
	0.036	0.061	0.099	0.000	0.989	0.006	0.000	0.000	0.155	0.265	0.133									
WBCl	-0.062	0.033	0.030	-0.003	0.014	-0.031	-0.072	-0.058	-0.023	0.067	0.029	-0.075	1.000							
	0.075	0.342	0.381	0.929	0.688	0.367	0.038	0.095	0.518	0.053	0.424	0.031								
Nal	-0.044	0.009	0.034	0.022	0.031	0.048	0.054	0.055	0.000	0.034	-0.025	-0.034	-0.024	1.000						
	0.201	0.790	0.323	0.519	0.378	0.167	0.119	0.111	0.993	0.335	0.485	0.335	0.490							
Kl	-0.210	-0.037	0.012	0.164	0.079	0.003	0.025	0.016	-0.072	-0.056	-0.018	0.148	0.014	-0.101	1.000					
	0.000	0.283	0.721	0.000	0.023	0.922	0.480	0.640	0.038	0.105	0.621	0.000	0.686	0.004						
creatl	-0.020	-0.001	-0.027	-0.113	-0.002	-0.102	-0.144	-0.135	0.048	-0.090	-0.038	-0.150	0.062	0.050	0.191	1.000				
	0.564	0.973	0.446	0.001	0.961	0.003	0.000	0.000	0.169	0.010	0.283	0.000	0.072	0.153	0.000					
ureal	0.085	-0.035	-0.065	-0.103	-0.017	-0.177	-0.241	-0.229	0.032	-0.151	-0.002	-0.127	0.032	-0.027	0.220	0.666	1.000			
	0.014	0.320	0.062	0.003	0.629	0.000	0.000	0.000	0.359	0.000	0.959	0.000	0.353	0.431	0.000	0.000				
albl	-0.134	-0.060	0.049	0.152	0.121	0.233	0.245	0.258	0.003	0.104	-0.008	0.359	-0.005	0.071	0.107	-0.144	-0.229	1.000		
	0.000	0.084	0.155	0.000	0.001	0.000	0.000	0.000	0.927	0.003	0.822	0.000	0.887	0.040	0.002	0.000	0.000			
billl	0.059	0.021	-0.066	-0.012	-0.062	-0.123	-0.098	-0.118	0.037	-0.048	-0.019	0.112	0.018	-0.090	-0.002	0.111	0.132	-0.097	1.000	
	0.093	0.554	0.058	0.727	0.077	0.000	0.006	0.001	0.287	0.168	0.595	0.001	0.613	0.010	0.964	0.001	0.000	0.006		
glcl	-0.338	0.156	0.131	0.222	0.040	0.003	0.024	0.016	-0.148	0.157	-0.030	0.049	0.067	0.005	0.012	0.003	-0.058	0.041	-0.042	1.000
	0.000	0.000	0.000	0.000	0.260	0.937	0.494	0.656	0.000	0.000	0.411	0.166	0.056	0.896	0.743	0.933	0.099	0.240	0.239	
GCS	0.461	-0.308	-0.219	-0.446	0.019	0.003	0.001	0.002	0.079	0.041	0.207	0.014	0.001	-0.002	-0.062	-0.038	-0.028	0.049	-0.012	-0.205
	0.000	0.000	0.000	0.000	0.590	0.938	0.975	0.956	0.024	0.237	0.000	0.682	0.977	0.949	0.076	0.277	0.420	0.157	0.743	0.000

The "best" model was then selected based on a combination of performance and parsimony. Five variables were dropped because they had a minimal impact on discrimination or calibration. These were potassium, temperature, $PaCO_2$, glucose and bilirubin (Table 8.5.1). This gave an acute physiology score containing the following eight variables: heart rate, white count, sodium, pH, creatinine, albumin, mean arterial pressure and urea. An integer score on the log-odds scale was then constructed by re-estimating coefficients for the final model on all available data, and multiplying all coefficients in the model by a constant that allowed the acute physiology score to range from 0 to 100. The score is shown in Table 8.5.2.

The Hosmer-Lemeshow chi-squared goodness of fit statistic gives an estimate of the impact of removing variables on the goodness of fit i.e. on the model's calibration (whereas the area under the curve gives a measure of discrimination). The higher the HL chi-square the poorer the calibration, though the absolute magnitude will depend upon the degrees of freedom. (That is why the model with just urea, mean arterial blood pressure (MAP) and albumin has a lower HL chi-square than a model with more variables.)

8.6 COPD acute physiology components and 180 day mortality

Table 8.6.1 shows odds ratios for 180 day mortality for each of the acute physiological variables used to develop the COPD-specific APS. The variables have been grouped according to the intervals used in the score. In general the individual variables show the expected relationships with mortality. The relationships of heart rate and mortality are inconsistent though, and this may reflect error of measurement outside ICU.

Table 8.6.2 shows the odds ratios for the variables not used in the COPD physiology score. None of them show a significant association with mortality.

Table 8.5.1 COPD acute physiology model: variable selection

Variables dropped	Variables	Parameters	AUC	HL χ^2 *
None	13	47	0.7341	11.46
Potassium	12	45	0.7350	11.50
Temperature	11	42	0.7345	16.50
$PaCO_2$	10	40	0.7339	12.79
Glucose	9	38	0.7334	14.39
Bilirubin	**8**	**35**	**0.7314**	**15.30**
Heart rate	7	30	0.7271	15.27
Sodium	6	27	0.7260	13.51
pH	5	23	0.7230	19.63
WBC	4	19	0.7205	16.70
Creatinine	3	16	0.7092	13.78
Albumin	2	11	0.6962	15.49
MAP	1	5	0.6557	---
Urea	0	1	0.5000	---

The variables in bold were retained in the final APS score. This table shows their impact when dropped during model development.

AUC: Area Under the (ROC) Curve; HL: Hosmer-Lemeshow goodness-of-fit statistic on 10 degrees of freedom. Values over 18.30 indicate a significant lack of fit at the 5% significance level; WBC: White Blood Count; MAP: Mean Arterial Pressure

Table 8.5.2 The CAOS Acute Physiology Score

Heart rate	bpm	< 80	80 – 109	110 – 129	130 – 149	150 – 169	≥ 170
	score	*3*	*0*	*2*	*3*	*5*	*7*
MAP	mmHg	< 40	40 – 49	50 – 59	60 – 69	70 – 89	90 – 99	≥ 100
	score	*19*	*12*	*9*	*6*	*3*	*0*	*4*
pH	pH	< 7.00	7.00 – 7.09	7.10 – 7.19	7.20 – 7.24	≥ 7.25
	score	*9*	*6*	*3*	*1*	*0*
Sodium	mmol/l	< 130	130 – 134	135 – 144	≥ 145
	score	*6*	*2*	*0*	*2*
Urea	mmol/l	< 2.5	2.5 – 6.7	6.8 – 11.9	12.0 – 17.9	≥ 18.0
	score	*0*	*8*	*16*	*22*	*24*
Creatinine	µmol/l	< 150	150 – 199	≥ 200
	score	*0*	*5*	*8*
Albumin	g/l	< 15	15 – 19.9	20 – 24.9	25 – 29.9	30 – 34.9	≥ 35
	score	*20*	*14*	*8*	*6*	*4*	*0*
WBC	$\times 10^9$/l	< 4	4 – 14.9	15 – 19.9	20 – 24.9	≥ 25
	score	*7*	*0*	*1*	*4*	*7*

MAP: Mean Arterial Pressure; WBC: White Blood Count

Table 8.6.1 **COPD acute physiology score components and 180 day outcome**

Variable	*All patients n=832*		*Patients for all Treatment n=651*		*Patients not for intubation N=181*	
	number dead/n (%)	*OR (95%CI)*	*number dead/n(%)*	*OR (95%CI)*	*number dead/n (%)*	*OR(95%CI)*
Albumin						
≥ 35g/L	153/441 (34.7%)	1	105/338 (31.1%)	1	48/103 (46.6%)	1
30-34.9g/L	70/197 (35.5%)	1.04 (0.73-1.47)	42/145 (29.0%)	0.90 (0.59-1.39)	28/52 (53.9%)	1.34 (0.68-2.60)
25-29.9g/L	50/119 (42.0%)	1.36 (0.90-2.06)	38/101 (37.6%)	1.34 (0.84-2.13)	12/18 (66.7%)	2.29 (0.80-6.57)
20-24.9g/L	22/47 (46.8%)	1.65 (0.90-3.06)	16/39 (41.0%)	1.54 (0.78-3.04)	6/8 (75%)	3.43 (0.66-17.84)
15-19.9g/L	13/21 (61.9%)	3.05 (1.24-7.54)	13/21 (61.9%)	3.61 (1.45-8.96)		
< 15g/L	7/7 (100%)	†	7/7 (100%)	†		
Creatinine						
<150µmol/L	249/724 (34.4%)	1	174/571 (30.5%)	1	75/153 (49.0%)	1
150-199µmol/L	34/58 (58.6%)	2.70 (1.57-4.66)	19/37 (51.4%)	2.41 (1.23-4.70)	15/21 (71.4%)	2.6 (0.96-7.06)
≥200 µmol/L	32/50 (64.0%)	3.39 (1.87-6.16)	28/43 (65.1%)	4.26 (2.22-8.17)	4/7 (57.1%)	1.39 (0.30-6.40)
Urea						
<2.5 mmol/L	8/25 (32.0%)	1	5/18 (27.8%)	1	3/7 (42.9%)	1
2.5-6.7 mmol/L	93/338 (27.5%)	0.81 (0.34-1.93)	64/272 (23.5%)	0.80 (0.27-2.33)	29/66 (43.9%)	1.05 (0.22-5.04)
6.8-11.9 mmol/L	115/282 (40.8%)	1.46 (0.61-3.50)	84/226 (37.2%)	1.54 (0.53-4.47)	31/56 (55.4%)	1.65 (0.34-8.08)
12.0-17.9 mmol/L	57/113 (50.4%)	2.16 (0.86-5.41)	35/75 (46.7%)	2.28 (0.74-7.02)	22/38 (57.9%)	1.83 (0.36-9.35)
≥ 18.0 mmol/L	42/74 (56.8%)	2.79 (1.07-7.27)	33/60 (55.0%)	3.18 (1.00-10.04)	9/14 (62.3%)	2.4 (0.38-15.32)
Sodium						
≥ 145mmol/L	15/41 (36.6%)	1.00 (0.52-1.92)	10/31 (32.3%)	0.94 (0.60-1.45)	5/10 (50.0%)	1.03 (0.28-3.75)
135-144mmol/L	213/581 (36.7%)	1	306/459 (33.3%)	1	60/122 (49.2%)	1
130-134 mmol/L	53/144 (36.8%)	1.01 (0.69-1.47)	36/113 (31.9%)	0.95 (0.44-2.07)	17/31 (58.8%)	1.25 (0.57-2.77)
<130mmol/L	34/66 (51.5%)	1.84 (1.10-3.06)	22/48 (45.8%)	1.69 (0.93-3.08)	12/18 (66.7%)	2.07 (0.73-5.86)
pH						
≥ 7.25	129/341 (37.8%)	1	77/248 (31.1%)	1	52/93 (55.9%)	1
7.20-7.24	43/109 (39.5%)	1.07 (0.69-1.67)	31/84 (36.9%)	1.30 (0.77-2.18)	12/25 (48.0%)	0.73 (0.30-1.76)
7.10-7.19	88/217 (40.6%)	1.12 (0.79-1.59)	64/172 (37.2%)	1.32 (0.87-1.98)	24/45 (53.3%)	0.90 (0.44-1.84)
7.00-7.09	38/99 (38.4%)	1.02 (0.65-1.62)	33/85 (38.8%)	1.41 (0.84-2.35)	5/14 (35.7%)	0.44 (0.14-1.41)
<7.00	17/66 (25.8%)	0.57 (0.31-1.03)	16/62 (25.8%)	0.77 (0.41-1.45)	1/4 (25%)	0.26 (0.03-2.62)

† OR cannot be calculated since 100% of patients in this category died.

Table 8.6.1 *continued*: COPD acute physiology score components and 180 day outcome.

Variable	*All patients n=832*		*Patients for all treatment n=651*		*Patients not for intubation n=181*	
	number dead/n (%)	*OR (95%CI)*	*number dead/ n (%)*	*OR (95%CI)*	*number dead/n (%)*	*OR (95%CI)*
Mean arterial pressure						
≥ 100 mmHg	88/274 (32.1%)	1.14 (0.72-1.80)	61/218 (28.0%)	1.25 (0.71-2.20)	27/56 (48.2%)	1.12 (0.47-2.65)
90-99 mmHg	37/126 (29.4%)	1	22/93 (23.7%)	1	15/33 (45.5%)	1
70-89 mmHg	111/270 (41.1%)	1.68 (1.07-2.64)	75/206 (36.4%)	1.85 (1.06-3.22)	36/64 (56.3%)	1.54 (0.66-3.59)
60-69 mmHg	39/84 (46.4%)	2.08 (1.17-3.71)	29/66 (43.9%)	2.53 (1.28-5.00)	10/18 (55.6%)	1.50 (0.47-4.76)
50-59 mmHg	28/57 (49.1%)	2.32 (1.22-4.43)	24/50 (48.0%)	2.98 (1.43-6.20)	4/7 (57.1%)	1.60 (0.31-8.30)
40-49 mmHg	6/14 (42.9%)	1.80 (0.59-5.56)	5/12 (41.7%)	2.31 (0.66-7.99)	1/2 (50%)	1.2 (0.07-20.85)
< 40 mmHg	6/7 (85.7%)	14.43 (1.68-124.07)	5/6 (83.3%)	16.14 (1.79-145.58)	1/1 (100%)	†
White cell count						
<4 x 10^9/L	4/8 (50%)	1.80 (0.44-7.27)	3/7 (42.9%)	1.57 (0.35-7.13)	1/1 (100%)	†
4-14.9 x 10^9/L	172/481 (35.8%)	1	117/362 (32.2%)	1	55/119 (46.2%)	1
15 -19.9 x 10^9/L	68/173 (39.3%)	1.16 (0.81-1.66)	53/144 (36.8%)	1.22 (0.81-1.83)	15/29 (51.7%)	1.25 (0.55-2.81)
20-24.9 x 10^9/L	42/102 (41.2%)	1.26 (0.81-1.95)	29/87 (33.3%)	1.05 (0.64-1.72)	13/15 (86.7%)	7.56 (1.64-34.99)
≥ 25 x 10^9/L	29/68 (42.7%)	1.34 (0.80-2.24)	19/51 (37.3%)	1.24 (0.68-2.29)	10/17 (58.8%)	1.66 (0.59-4.66)
Heart rate (beats per minute)						
<80	18/38 (47.4%)	1.55 (0.78-3.09)	13/29 (44.8%)	1.67 (0.75-3.70)	5/9 (55.6%)	1.38 (0.34- 5.60)
80-109	87/237 (36.7%)	1	57/174 (32.8%)	1	30/63 (47.6%)	1
110-129	109/290 (37.6%)	1.04 (0.73-1.48)	71/222 (32.0%)	0.97 (0.63-1.47)	38/68 (55.9%)	1.39 (0.70-2.77)
130-149	68/180 (37.8%)	1.05 (0.70-1.56)	56/153 (36.6%)	1.19 (0.75-1.87)	12/27 (44.4%)	0.88 (0.36-2.18)
150-169	22/64 (34.4%)	0.90 (0.51-1.61)	15/55 (27.3%)	0.77 (0.39-1.51)	7/9 (77.8%)	3.85 (0.74-20.00)
≥ 170	11/23 (47.8%)	1.58 (0.67-3.73)	9/18 (50%)	2.05 (0.77-5.45)	2/5 (40.0%)	0.73 (0.11-4.69)
Acute physiology score						
0-19.9	44/180 (24.4%)	1	24/110 (17.9%)	1	20/46 (43.5%)	1
20-39.9	195/531 (36.7%)	1.79 (1.22-2.63)	134/414 (32.4%)	2.19 (1.35-3.57)	61/117 (52.1%)	1.42 (0.71-2.81)
40-59.9	68/111 (61.3%)	4.89 (2.93-8.15)	56/94 (59.6%)	6.75 (3.69-12.36)	12/17 (70.6%)	3.12 (0.94-10.31)
60-79.9	8/10 (80%)	12.36 (2.53-60.41)	7/9 (77.8%)	16.04 (3.14-82.07)	1/1 (100%)	†
80-100						

† OR cannot be calculated since 100% of patients in this category died.

Table 8.6.2 **Acute physiology and 180 day outcome for variables not included in COPD acute physiology model**

Variable	*All patients n=832*		*Patients for all treatment n=651*		*Patients not for intubation n=181*	
	number dead/n (%)	*OR (95%CI)*	*number dead/n (%)*	*OR (95%CI)*	*number dead/n (%)*	*OR (95%CI)*
PaO_2/FiO_2						
≥26.6kPa	144/407 (35.4%)	1	100/308 (32.5%)	1	44/99 (44.4%)	1
13.3-26.59kPa	119/302 (39.4%)	1.19 (0.87-1.62)	82/235 (34.9%)	1.11 (0.78-1.60)	37/67 (55.2%)	1.54 (0.83-2.88)
<13.3Kpa	51/120 (42.5%)	1.35 (0.89-2.04)	38/105 (36.2%)	1.18 (0.74-1.88)	13/15 (86.7%)	8.12 (1.74-37.92)
Potassium						
<5mmol/L	239/643 (37.2%)	1	160/501 (31.9%)	1	79/142 (55.6%)	1
5-5.9mmol/L	64/160 (40.0%)	1.13 (0.79-1.61)	50/123 (40.7%)	1.46 (0.97-2.19)	14/37 (37.8%)	0.49 (0.23-1.02)
≥6mmol/L	12/27 (44.4%)	1.35 (0.62-2.94)	11/25 (44.0%)	1.67 (0.74-3.77)	1/2 (50%)	0.80 (0.05-13.0)
Temperature						
<35°C	15/31 (48.4%)	1.63 (0.79-3.38)	14/27 (51.9%)	2.35 (1.07-5.16)	1/4 (25.0%)	0.28 (0.03-2.74)
35-36.9°C	49/118 (41.5%)	1.24 (0.82-1.86)	33/93 (35.5%)	1.20 (0.75-1.93)	16/25 (64.0%)	1.47 (0.60-3.63)
36-37.9°C	178/488 (36.5%)	1	120/382 (31.4%)	1	58/106 (54.7%)	1
≥38°C	71/190 (37.4%)	1.04 (0.73-1.47)	52/144 (36.1%)	1.23 (0.82-1.85)	19/46 (41.3%)	0.58 (0.29-1.17)
$PaCO_2$						
<12kPa	213/539 (39.5%)	1	150/420 (35.7%)	1	63/119 (52.9%)	1
12-17.9kPa	84/234 (35.9%)	0.86 (0.62-1.18)	54/180 (30.0%)	0.77 (0.53-1.12)	30/54 (55.6%)	1.11 (0.58-2.12)
>18Kpa	18/59 (30.5%)	0.67 (0.38-1.20)	17/51 (33.3%)	0.90 (0.49-1.67)	1/8 (12.5%)	0.13 (0.02-1.06)
Glucose						
<5mmol/L	16/44 (36.4%)	1	11/34 (32.4%)	1	5/10 (50%)	1
5-19.9mmol/L	287/760 (37.8%)	1.06 (0.56-2.00)	202/595 (34.0%)	1.07 (0.51-2.25)	85/165 (51.5%)	1.06 (0.30-3.81)
≥ 20mmol/L	8/14 (57.1%)	2.33 (0.69-7.93)	8/14 (34.4%)	2.79 (0.78-10.02)		
Bilirubin						
<15 µmol/L	226/632 (35.8%)	1	157/491 (32.0%)	1	69/141 (48.9%)	1
15-19.9µmol/L	40/98 (40.8%)	1.24 (0.80-1.91)	31/84 (36.9%)	1.24 (0.77-2.02)	9/14 (64.3%)	1.88 (0.60-5.88)
20.0-29.9µmol/L	24/49 (49.0%)	1.72 (0.96-3.10)	15/36 (41.7%)	1.52 (0.76-3.03)	9/13 (69.2%)	2.35 (0.69-8.00)
≥30 µmol/L	19/38 (50%)	1.80 (0.93-3.46)	15/31 (48.4%)	2.00 (0.96-4.13)	4/7 (57.1%)	1.39 (0.30-6.44)

8.7 Discussion

The blood gas results indicate that the CAOS population had more severe respiratory failure than the patients recruited to the SUPPORT study where the median (IQR) $PaCO_2$ was 7.47 kPa (6.67-8.67) and the median (IQR) pH was 7.36 (7.30-7.40)[12]. The CAOS population was probably more severely ill because they were all admitted to ICU, whereas in SUPPORT only 53% of patients entered ICU.

8.7.1 PaO_2/FiO_2 ratio

There is good evidence that the PaO_2/FiO_2 ratio is associated with mortality in patients with COPD, including data from the American SUPPORT study[12] and from the UK Case Mix programme[27]. However the reliability of the PaO_2/FiO_2 ratio is crucially dependent on accurate measurement of the inspired oxygen concentration (FiO_2). It is well known that in the UK there are difficulties in prescribing defined oxygen concentrations, and for this reason the CAOS data collection booklets contained a table that described the FiO_2 delivered by the various oxygen delivery devices. Nonetheless, during data collection it became clear that units were finding it difficult to determine accurately the FiO_2 corresponding to the most acidic blood gases measured in the 24 hours prior to ICU. Once the patients were admitted to ICU, accurate FiO_2 measurement was straightforward. However the blood gases after ICU admission would not be the ones used to make the decision to admit. Discussions with the units led us to conclude that inaccurate calculation of the FiO_2 was sufficiently widespread outside ICU that incorporating the PaO_2/FiO_2 ratio into the model would be accompanied by frequent errors. For this reason it was dropped as a candidate variable.. Interestingly the PaO_2/FiO_2 ratio in CAOS was, with median (IQR) 26.3 (17.4-37.1), similar to that in the SUPPORT[12] (28.1 (22.8 – 35.6). It should be remembered however that the data eventually recorded in CAOS often involved quite a lot of checking and double checking of results that had initially been received at the CAOS co-ordinating centre and considered unlikely. In addition it should be remembered that the critical care staff recording the FiO_2 data had the data collection booklet charts and day to day experience of calculating FiO_2.

8.7.2 Conclusion

The UK COPD Acute Physiology Score (CAPS) allows the acute physiology collected in the CAOS study to be weighted for use in the outcome model. In an ideal study sufficient data would have been collected to have enabled the development of the acute physiology score using the acute physiology available prior to ICU collected in the CAOS study. However assuming the need for a minimum of 10 deaths for each level in the model at least 410 deaths would have been required to develop the acute physiology score. Thus the study would not have had adequate power to weight the acute physiology and take into account other aspects of the patients. Clearly though the APS score has been developed using data from ICUs, at least these are patients over the age of 45 years admitted to UK ICUs with chronic obstructive airways disease. This is likely to be a better measure of the severity of disease than to have used, for example, the acute physiology score from APACHE III that was developed on all types of ICU patients in the US healthcare system, and included a measure of oxygenation which had to be excluded from the UK model because of problems with the data (feedback from the units indicated that estimates of the FIO_2 outside ICU was unreliable).

Chapter 9 Predictors of outcome

9.1 Introduction

This chapter is concerned with the non-physiological variables found in the systematic review to be associated with survival following critical care admission with an exacerbation of COPD. These include: age and sex; data relating to the period of stability before the exacerbation, (including function and quality of life, comorbidity and previous use of health care); and data relating to the 24 hours before admission to ICU (including diagnosis, length of stay and prior intubation). Data are presented for all 832 patients recruited to CAOS, for the 651 patients without treatment limitation, and for the 181 with treatment limitation, i.e. those who would not have been intubated if more conservative treatment had been unsuccessful.

Information gained through contact with units during the data collection process is presented where it informs an understanding of the reliability of a variable or ease of collection.

Then the distribution of each variable is described, to allow comparison of the CAOS patients with those in other studies and populations.

In section 9.5 the intercorrelations of these variables are considered, and in section 9.6 the relationship of each of variable with 180 day mortality is described.

9.2 Age and sex

9.2.1 Age

As Table 9.2 shows, the mean (SD) age was 67.0 (9.7) years and the median (IQR) was 68.0 (60-75). Overall the patients considered suitable for intubation were slightly younger that those who were not.

9.2.2 Sex.

There were about 48% men and 52% women in both the 'all treatment' and 'no intubation' groups.

Table 9.2 Data about patients in the period of stability pre-exacerbation

Variable	*Patients for 'All treatment' n=651*		*Patients for 'No intubation' n=181*		*All patients n=832*	
	Number (%)	*Mean SD Med (IQR)*	*Number (%)*	*Mean SD Med (IQR)*	*Number (%)*	*Mean SD Med (IQR)*
Age		66.1 (9.5) 67.0 (59-73)		70.3 (9.4) 72.0 (63-77)		67.0 (9.7) 68 (60-75)
Missing	0		0		0	
Sex						
Female	340 (52.2%)		95 (52.5%)		435 (52.3%)	
Male	311 (47.8%)		86 (47.5%)		397 (47.7%)	
Missing	0		0		0	
FEV_1		1.1 (0.7) 0.9 (0.6-1.4)		0.7 (0.3) 0.6 (0.5 – 0.9)		1.0 (0.6) 0.8 (0.6-1.3)
Missing	437 (67.1%)		104 (57.5%)		514 (61.8%)	
Functional score						
Fully mobile	189 (29.0%)		18 (9.9%)		207 (24.9%)	
Out of house	267 (41.0%)		41 (22.7%)		308 (37.0%)	
Housebound	176 (27.0%)		104 (57.5%)		280 (33.7%)	
Bed/chair bound	19 (2.9%)		18 (9.9%)		37 (4.5%)	
Missing	*0*		*0*		0	
Prior quality of life						
Excellent	17 (2.6%)		4 (2.2%)		21 (2.5%)	
Very good	122 (18.8%)		16 (8.9%)		138 (16.6%)	
Fair	286 (44.0%)		71 (39.4%)		357 (43.0%)	
Poor	178 (27.4%)		69 (38.3%)		247 (29.8%)	
Very Poor	41 (6.3%)		19 (10.6%)		60 (7.2%)	
Missing	7 (1.1%)		2 (1.1%)		9 (1.1%)	
Activities of daily living		0.6 (1.2) 0 (0-1.0)		1.5 (1.7) 1.0 (0.0-3.0)		0.8 (1.4) 0 (0.0 – 1.0)
Missing	0		4 (2.2%)		4 (0.5%)	
Comorbidity		0.8(1.0) 1.0 (0.0-1.0)		1.0 (1.1) 1.0 (0.0-1.0)		0.8 (1.0) 1.0 (0.0-1.0)
Missing	0		0		0	
Long term Oxygen						
No	582 (89.4%)		112 (61.9%)		694 (83.4%)	
Yes	69 (10.6%)		69 (38.1%)		138 (16.6%)	
Missing	0		0		0	
Previous Intubation						
No	575 (88.3%)		160 (88.4%)		735 (88.3%)	
Yes	76 (11.7%)		21 (11.6%)		97 (11.7%)	
Missing	0		0		0	
Admissions in past 6 months		0.7 (1.4) 0.0 (0.0-1.0)		1.0 (1.4) 0.0 (0.0-1.0)		0.8 (1.4) 0.0 (0.0-1.0)
Missing	1 (0.2%)		0		1 (0.1%)	

9.3 Data about the period of stability pre-exacerbation

9.3.1 FEV_1

Lung function was only available in 38.2% of patients and of these around half had to be obtained from old notes. This could often take a number of days. At hospital admission patients were often too unwell to perform the FEV_1 manoeuvre. In the 318 patients in whom FEV_1 was available the mean (SD) FEV_1 was 1L (0.63), median (IQR) 0.8 (0.6-1.3).

9.3.2 Functional score

In 321 patients (38.6%), the patients described their own function in the period of stability. Otherwise the information came from other sources. Overall only 37 patients (4.5%) were bed- or chair-bound, and this fell to 19 (2.9%) of the 651 in the 'all treatment' in contrast to 18 (9.9%) in the 'no intubation' group.

The proportion of patients who were 'housebound or worse' in the patients in the 'all treatment' group was 29.9% compared to 67.4%, in those who were not, suggesting that the functional capacity may be used to select patients for the level of treatment offered.

9.3.3 Prior quality of life

In 358 patients (43%) the information regarding self-rated quality of life came directly from the patient themselves in the other 57% it came from others. Table 9.3.3 shows the proportions of patients with each quality of life rating according to whether the state was self-rated or reported by a proxy.

Investigation of how proxy assessments of quality of life might differ from self-report is only possible where data exist for both types of source. In this study only one rating of prior quality of life was available for any given patient. Some data collectors mentioned that this was a fairly subjective item to collect. However the spreads of the ratings of quality of life provided by proxies and patients were similar. This seems likely to be because patients who were unable to give quality of life ratings were similar in this respect in the period of stability prior to ICU to those in whom the rating came from a

proxy. An alternative explanation is that they were worse, but that proxies tended to give unduly favourable assessments, and so this conclusion should be treated with caution.

Table 9.3.3 Prior quality of life: patient and proxy ratings compared.

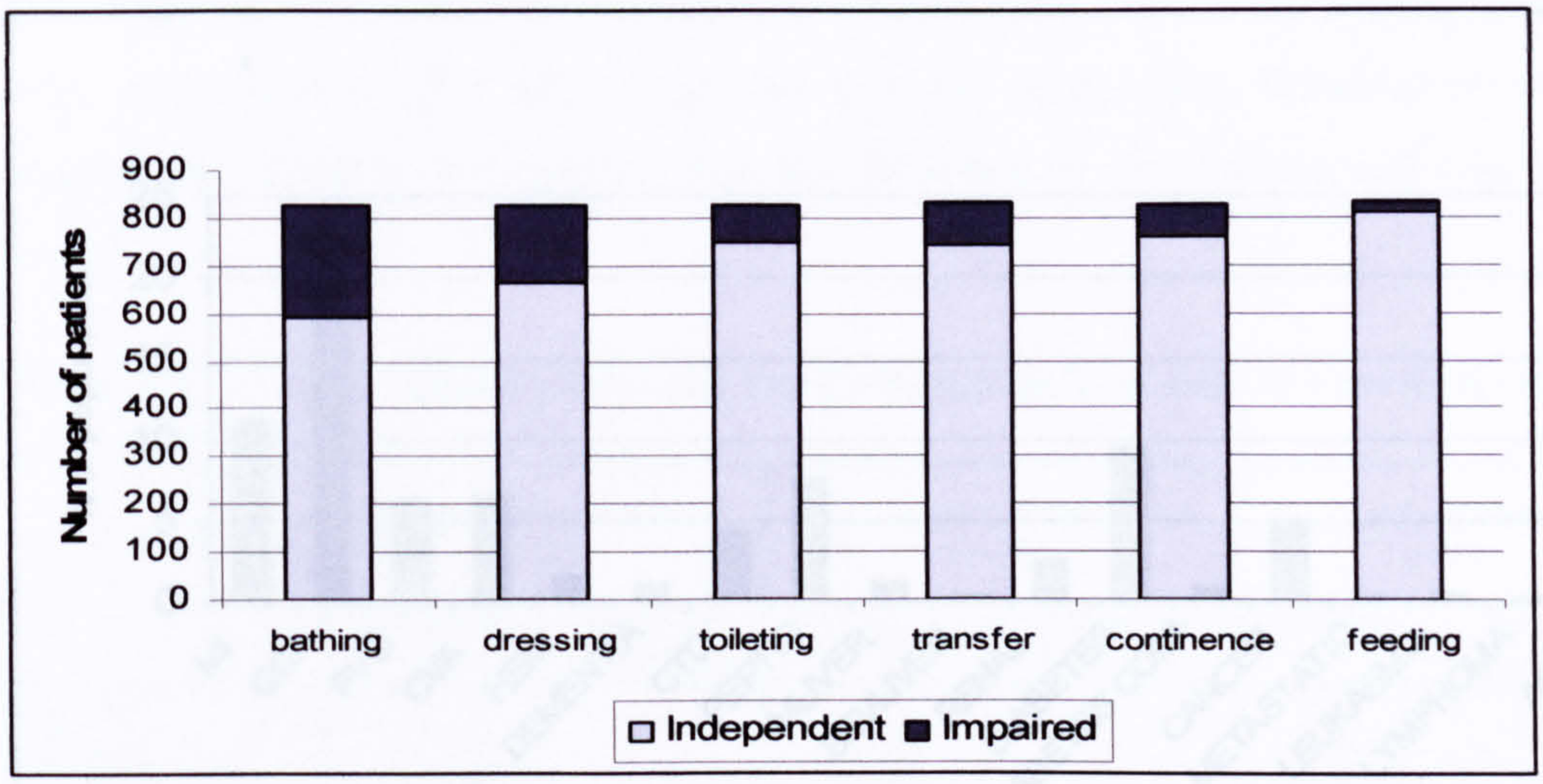
Prior quality of life	*Patient rated (n = 358)* n % (95%CI)	*Proxy rated (n = 464)* n % (95%CI)
Excellent	15 4.2% (2.4-6.8)	6 1.3% (0.5-2.8)
Very good	57 15.9% (12.3-20.1)	81 17.4% (14.1-21.8)
Fair	162 45.3% (40.0-50.6)	195 41.9% (37.4-46.6)
Poor	100 27.9% (23.3-32.9)	147 31.6% (27.4-36.1)
Very poor	24 6.7% (4.3-9.8)	36 7.7% (5.5-10.6)

Chi-square = 8.66 on 4 degrees of freedom and the p = 0.0701

9.3.4 Activities of daily living

In 354 patients (42.5%) the data about activities of daily living (ADLs) came from patients and in 476 (57.2%) it came from proxies. Figure 9.3.4 shows the number of patients with each type of impairment and it can be seen that bathing caused the most problems and feeding the least.

Figure 9.3.4 Activities of daily living in CAOS population.



9.3.5 Comorbidity

One patient had 6 comorbidities, 5 had 5 comorbidities, 10 had 4 and 39 patients had 3. Patients with three or more comorbidities were amalgamated into one group for analysis. The commonest comorbidity was congestive cardiac failure (23% of those in the study). This was followed by previous myocardial infarction (11%) and uncomplicated diabetes (9.5%). The percentages of patients with specific comorbidities are shown in Figure 9.3.5.

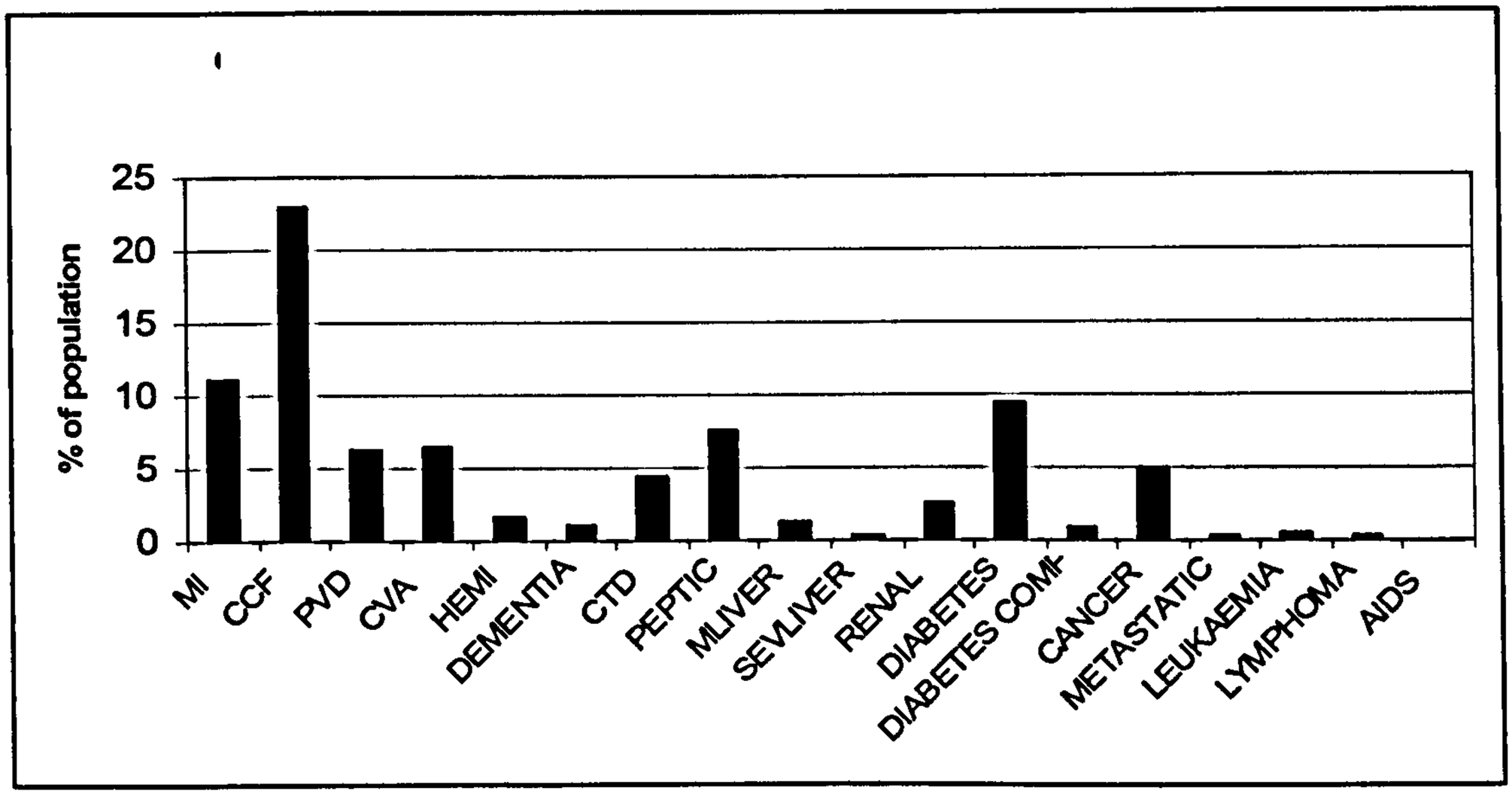
9.3.6 Long term oxygen therapy (LTOT)

There were 136 patients in the total sample on LTOT. The observation that 38.1% of the 'no intubation' group were on long term oxygen, compared to only 10.6% of the 'all treatment' group suggests that LTOT may have been a clinical indication for treatment limitation.

9.4 Patient characteristics in 24 hours before critical care and intubation

Table 9.4 summarises patient characteristics in the 24 hours prior to critical care admission and intubation status. Each variable will be discussed in turn.

Figure 9.3.5 Comorbidities in the CAOS population



Key

MI: Myocardial infarction
CCF: congestive cardiac failure
PVD: peripheral vascular disease
CVA: cerebrovascular disease
HEMI: hemiplegia
CTD: connective tissue disease
PEPTIC: peptic ulcer disease
Cancer: non-metastatic
Metastatic: metastatic cancer
AIDS: aids.
Mliver: mild liver disease
Sevliver: moderate or severe liver disease
Renal: moderate or severe renal disease
Diabetes: diabetes without complications
Diabcomp: with end organ damage

9.4.1 Diagnostic groups

The vast majority of patients recruited (76.3%) were considered to have COPD alone; 14.1% were considered to have a mixture of COPD and asthma, and 9.6% to have asthma alone.

9.4.2 Length of stay before admission to critical care

As figure 9.4.2 shows, most patients (452, 54%) were admitted to critical care on the day of admission to hospital. However there were some patients with a very long length of stay prior to critical care entry.

A Lowess Smoothing Plot (Figure 9.4.3) was produced to explore whether outliers were distorting the relationship between the number of days in hospital prior to critical care entry and outcome. The plot suggested that the relationship between outcome and hospital stay prior to critical care was not distorted by the outliers and was relatively linear[139].

Table 9.4 Data about patient in the 24 hours before critical care/intubation

Variable	*Patients for all treatment n=651*		*Patients not for intubation n=181*		*All patients n=832*	
	Number (%)	*Mean SD Med (IQR)*	*Number (%)*	*Mean SD Med (IQR)*	*Number (%)*	*Mean SD Med (IQR)*
Diagnosis						
Asthma	78 (12.0%)		2 (1.1%)		80 (9 6%)	
COPD/Asthma mix	104 (16.0%)		13 (7.2%)		117 (14.1%)	
COPD	469 (72.0%)		166 (91.7%)		635 76.3%	
Missing					0	
Length of stay pre-Critical care	651	2 1 (9 3) 0 0(0 0-1 0)	181	1 6 (3.5) 0 0 (0 0-1 0)	832	2 0 (8 4) 0 0 (0 0-1 0)
Missing					0	
Atrial fibrillation						
No	587 (90 2%)		142 (78 5%)		729 (87.6%)	
Yes	64 (9.8%)		39 (21.6%)		103 (12 4%)	
Missing					0	
Chest X-ray						
No acute changes	278 (42.7%)		69 (38.1%)		347 (42%)	
Acute Changes	367 (56 4%)		109 (60.2%)		476 (57 2%)	
Missing	6 (0.9%)		3 (1.7%)		9 (1.1%)	
Congestive cardiac failure as cause						
No	520 (80 0%)		125 (69.1%)		645 (77.6%)	
Yes	130 (20.0%)		55 (30.4%)		185 (22.3%)	
Missing	1 (0.1%)		1 (0.1%)		2 (0.2%)	
Ankle oedema						
No	492 (75 8%)		121 (66.9%)		613 (73.9%)	
Yes	156 (24.0%)		60 (33.2%)		216 (26.0%)	
Missing	2 (0.3%)		0		2 (0.2%)	
Intubated						
No	201 (30 9%)			181 (100%)	382 (45.9%)	
Yes	450 (69 1%)			0	450 (54.1%)	
Missing					0	

9.4.3 Atrial fibrillation

Atrial fibrillation occurred in only 12.4% of the group as a whole but was more common (21.6%) in those patients designated 'no intubation'.

Figure 9.4.2 Length of stay pre-critical care

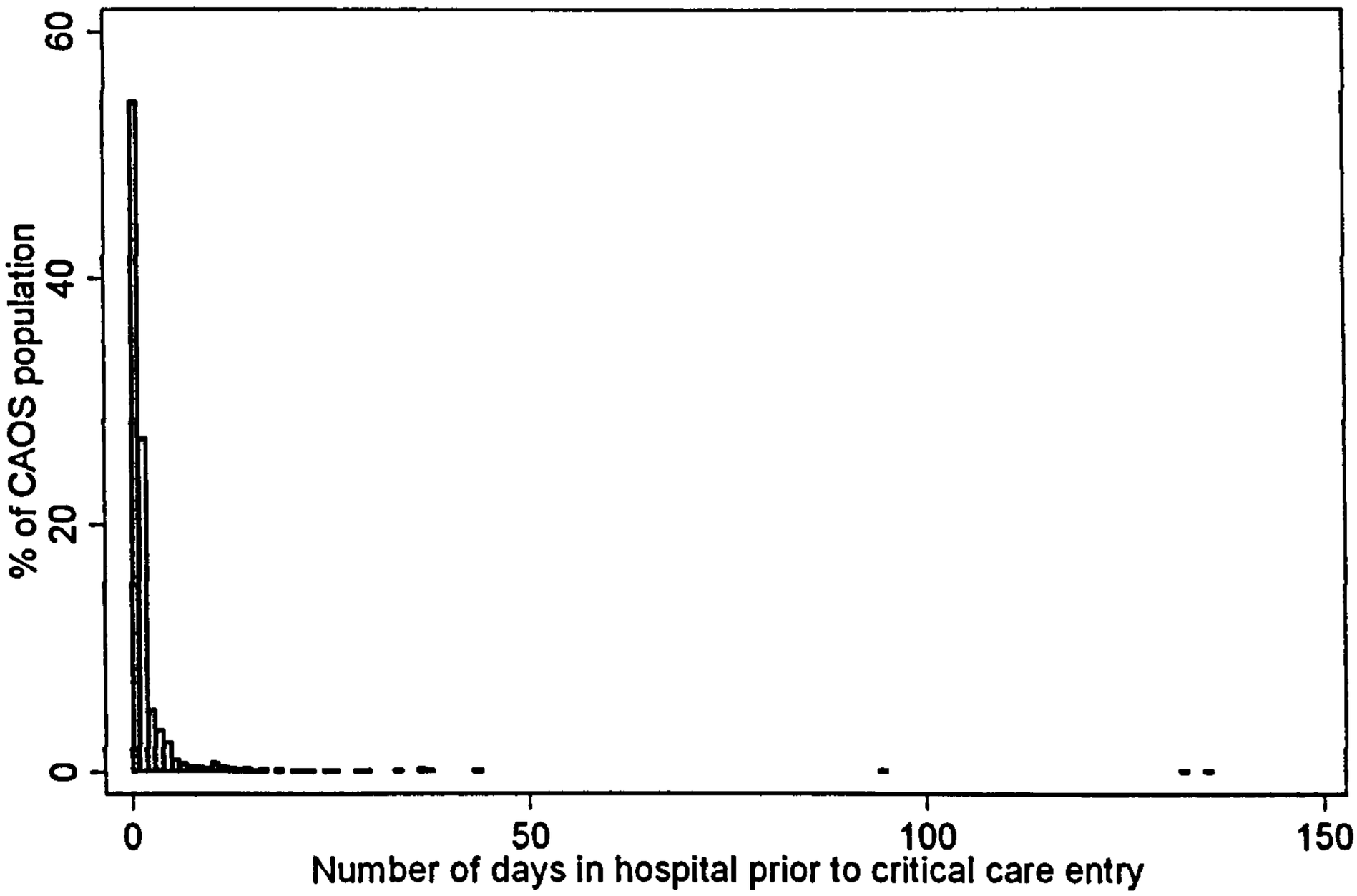
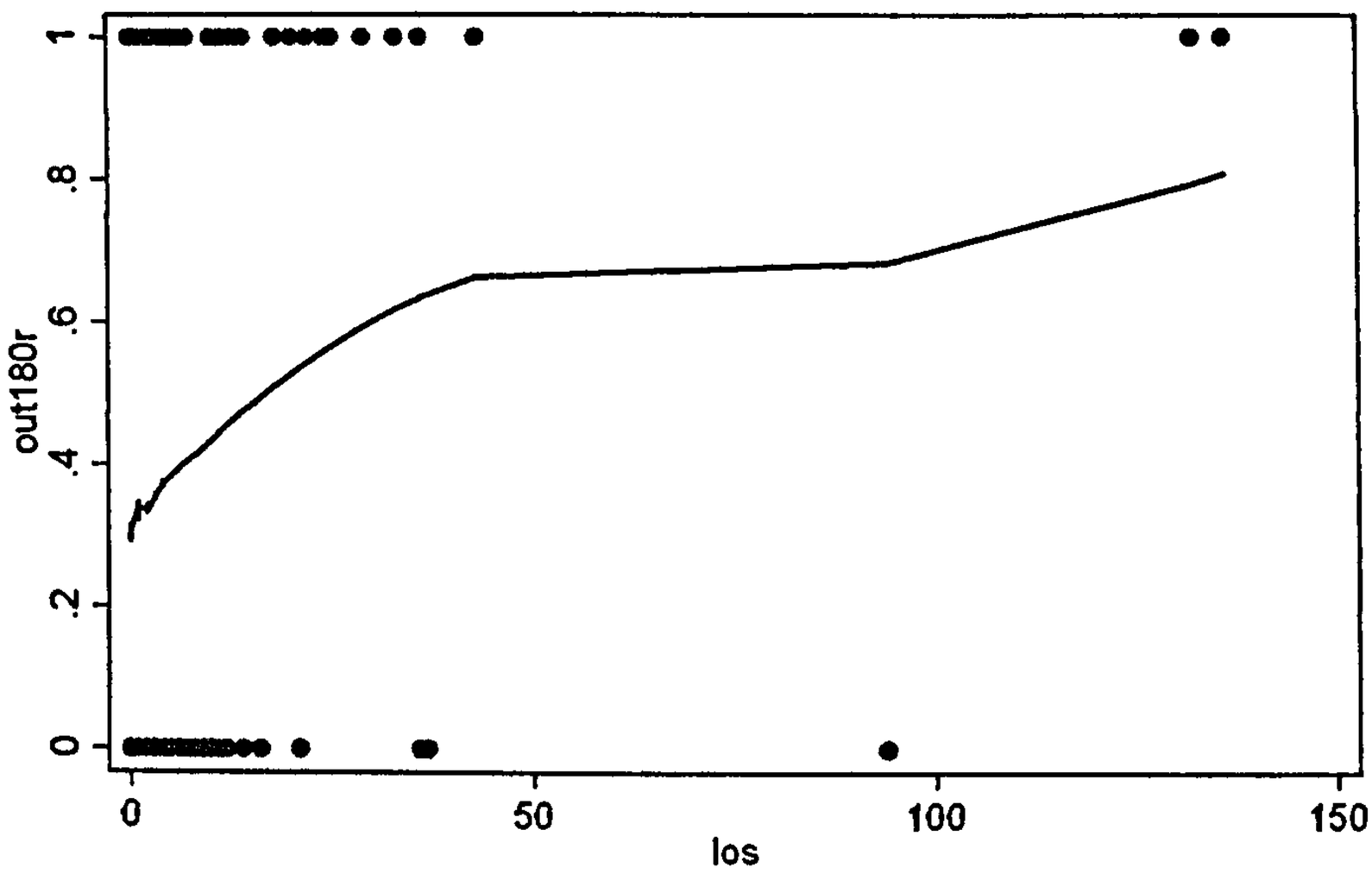


Figure 9.4.3 Lowess Smoother Plot exploring number of days in hospital pre-ICU and outcome



The y axis shows the proportion surviving at 180-days and the x-axis shows the length of stay prior to ICU

9.4.4 Chest x-ray changes

On admission to critical care, clinicians rated the chest x-ray as having abnormal shadowing or not. Abnormal shadowing was found in 507 (61%). In 9 patients (1.1%) there were missing data. Of patients with abnormal shadowing 43 were classified as 'other' and a free text description was recorded. The free text was examined and 31 of the entries described chronic changes such as old TB calcification or pleural plaques or old scarring. These patients were then classified as 'chronic changes'. Of the remaining 11 patients three had pneumothoraces, 4 had probable cancer, and one each had pulmonary infarction, pleural effusion, collapsed lung, and unknown. One patient had infection and was recoded as such.

The classification of x-rays for analysis was guided by the *a priori* questions that the study set out to answer. There is a common belief amongst clinicians that the prognosis is worse in patients without an acute abnormality on the x-ray because there is nothing reversible. In addition there is a suggestion that of the reversible processes, pure heart failure is particularly readily reversed and has a fairly good prognosis. For this reason patients were classified into two groups: (1) 'No acute changes' which included patients with a clear chest x-ray or old chronic changes, or (2) 'Acute changes' which included isolated heart failure and other miscellaneous acute changes including patients with infection or heart failure plus infection and also the patients with pneumothoraces or lung collapse.

Table 9.4.4 summarises the chest x-ray appearances in the two groups. Missing data were imputed as most common category i.e. acute changes present as infection.

9.4.5 Congestive cardiac failure as a cause and ankle oedema

Congestive cardiac failure as a cause was difficult to distinguish from cor pulmonale on clinical grounds. It was also noted that patients with ankle oedema included both patients with congestive cardiac failure and those with cor pulmonale

Table 9.4.4 Chest x-ray appearances

Acute changes (n = 485) *n (% of total population)*			*No acute changes (n = 347)* *n (% of total population)*		
Heart failure alone	34	(4.1%)	Chest x-ray clear	316	(38%)
Infection	326	(39%)	Chronic changes	31	(3.7%)
Combined failure/infection	105	(12.6%)			
Pneumothorax	3	(0.6%)			
Miscellaneous	8	(1.6%)			
Missing	9	(1.1%)			

9.4.6 Measurement of body mass

Table 9.4.6 summarises the measures used to estimate patients' body mass index (BMI).

i) Body weight Lickert scale

All patients had their body weights estimated using the Lickert scale and though the data collectors found the scale subjective they said it was easy to use.

ii) Body mass index estimation

Even though each data collection booklet had a tape measure attached to it, only 284 (34.6%) of patients had their heights measured. The rest were estimated, the majority (586 70.4%) in feet and inches. It was mentioned by a few units that using the tape measure to determine a patient's height gave the impression that the patient was being measured up for a coffin. Only 195 (23.4%) patients were actually weighed; weights were estimated in metric units in 60.7% of cases.

The information from units suggested that deriving a body mass index would be difficult. It would often involve estimates of weight and height, conversion from imperial to metric units, and finally the calculation itself.

iii) Mid-arm circumference

Mid-arm circumference (MAC) had one of the highest frequencies of missing data (22, 2.6%). It seems likely that these values were not missing at random in that of the 22 patients with missing values 18 (81.8% of those missing) died within 180 days. Discussion with the units with missing MACs revealed that often where the MAC was not recorded the patient had died before the nurses on the critical care unit had had chance to measure it. This problem arose in CAOS because data collection was centralised in ICU.

MAC has a close relationship with the Lickert scoring of body weight with a correlation coefficient of 0.7563 P<0.0001. (Figure 9.4.6 shows a scatter plot of MAC and the body weight Lickert scale for those patients with both measurements). All the patients with missing MACs had full data for the Lickert score of body weight. For this reason it was decided to impute values for MAC based on the mean MAC corresponding to the Lickert scores. Of the 18 patients with missing MAC who died before 180 days 3 were described as very underweight, 2 described as mildly underweight, 6 as normal, 6 as overweight and 1 as very overweight. For the 4 patients who survived 180 days with missing MAC 2 were rated as mildly underweight, 1 as normal weight and 1 as mildly overweight (Table 9.4.6 below). Imputing the MAC from the Lickert rating of weight would be an alternative strategy since it is independent of outcome as long as there are differences in measured MAC for each of the classifications of body weight using the Lickert.

9.5 Correlation between predictors

Correlations between predictors were explored (Table 9.5). The key to the abbreviations used are summarised at the foot of the matrix.

Correlation coefficients greater than 0.2 at a significance level p<0.00001 are discussed. A conservative significance level has been chosen since the correlation matrix contains several hundred correlations so there is a high risk of correlations appearing simply by the play of chance.

Table 9.4.6 Measurements of body mass index

Variable	*Patients for all treatment n=651*		*No intubation n =181*		*All patients n=832*	
	Number (%)	*Mean SD Med (IQR)*	*Number (%)*	*Mean SD Med (IQR)*	*Number (%)*	*Mean SD Med (IQR)*
Body wt Lickert						
Very under	39 (6.0%)		25 (13.8%)		64 (7.7%)	
Mildly under	131 (20.1%)		41 (22.7%)		172 (20.7%)	
Normal wt	218 (33.5%)		61 (33.7%)		279 (33.5%)	
Mildly over	185 (28.4%)		30 (16.6%)		215 (25.8%)	
Very over	78 (12.0%)		24 (13.3%)		102 (12.3%)	
Missing					0	
Weight loss in 6m						
No	471 (72.7%)		114 (63.0%)		585 (70.6%)	
Yes	168 (25.9%)		66 (36.5%)		234 (28.2%)	
Missing	12 (1.8%)		1 (0.6%)		13 (1.6%)	
Mid-arm circumference		28.8 (5.3) 29 (25-32)		27.4 (5.9) 27 (23-31)		28.5 (5.4) 28 (25-32)
<30cm	271 (42.7%)		58 (33.1%)		329 (40.6%)	
25-29.9cm	228 (35.9%)		51 (29.1%)		279 (34.4%)	
20-24.9cm	115 (18.1%)		57 (32.6%)		172 (21.2%)	
<20cm	21 (3.3%)		9 (5.1%)		30 (3.7%)	
Missing	16 (2.5%)		6 (3.3%)		22 (2.6%)	
Body Mass Index		25.8 (7.9) 24.9 (21.4-29)		25.0 (8.9) 23 (19.4-28.6)		25.6 (8.1) 24.8 (20.8-28.9)
Missing	7 (1.1%)		2 (1.1%)		9 (1.1%)	

Figure 9.4.6 Scatter plot of MAC and the Lickert scale

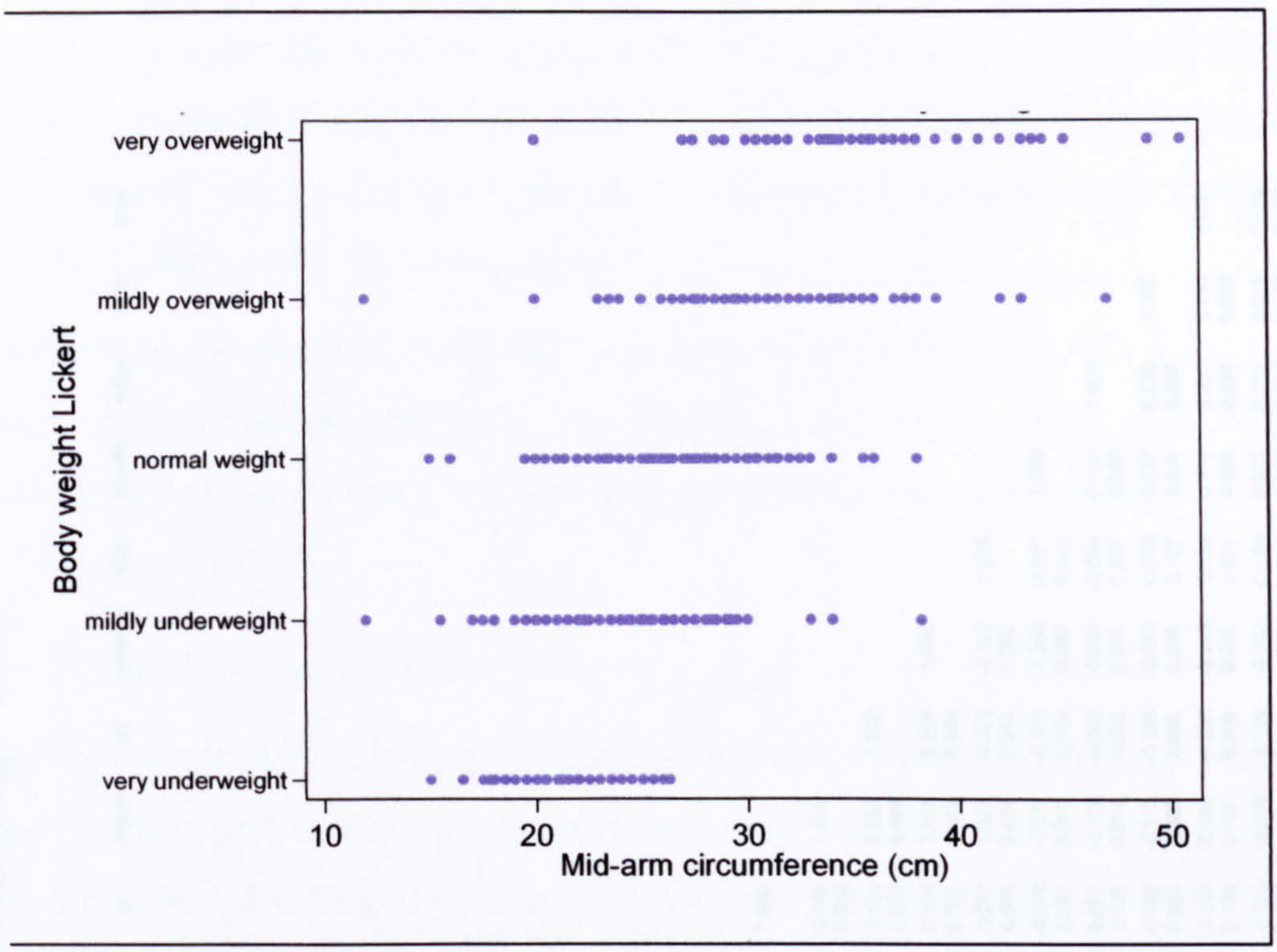


Table 9.4.6i Lickert Body weight rating and mean MAC measurement

Lickert rating	*MAC measurement* mean (SD) cm
Very underweight	21.2 (2.6)
Mildly underweight	24.3 (3.4)
Normal weight	27.7 (3.3)
Mildly overweight	31.5 (3.7)
Very overweight	35.8 (4.7)

Table 9.5 Correlation matrix for other variables with COPD Acute Physiology Score

	age	sex	fev1	funsc	prqol	totadl	totcomob	ltot	intprev	adm6m	diag	los	af	shdxrl	ccf	oedema	intcc	bdwtlik	wtls6	bmir	mac
sex	-0.036 0.298	1																			
fev1	-0.155 0.006	-0.175 0 002	1.000																		
funsc	0.132 0.000	0.119 0.001	-0.282 **0.000**	1.000																	
prqol	-0.032 0.360	0.066 0.056	-0 174 0 002	0.491 **0.000**	1.000																
totadl	0 045 0.193	0.045 0 197	-0.044 0 431	0.566 **0.000**	0.377 **0.000**	1.000															
totcomob	0 197 0.000	-0.030 0 381	-0.027 0.635	0.190 0.000	0.127 0.000	0.161 0 000	1.000														
ltot	-0.025 0.475	0.085 0 014	0.228 **0.000**	-0.274 **0.000**	-0.149 0.000	-0.193 0.000	-0 054 0.118	1.000													
intprev	0.167 0.000	0.043 0 217	0.003 0 955	0.014 0.692	0.002 0.957	-0.009 0 789	0.034 0.324	0 090 0 010	1.000												
adm6m	-0.057 0.101	-0.020 0.556	-0.108 0.055	0 241 **0.000**	0.164 0.000	0.156 0 000	0 059 0.089	-0 234 **0.000**	-0 056 0.104	1.000											
diag	-0.163 0.000	0.063 0.069	0.277 0.000	-0.169 0.000	-0.101 0.004	-0.118 0.001	-0.089 0.010	0 095 0.006	0 034 0.321	-0.033 0.340	1.000										
los	0.049 0.162	-0.034 0 322	-0.104 0.064	-0 027 0 443	0 031 0.370	-0.030 0.382	0.002 0.948	0.030 0.387	-0.034 0 330	-0.031 0 371	-0.065 0.060	1.000									
af	-0.222 **0.000**	-0 016 0.651	0.075 0.182	-0.093 0 007	-0.013 0.707	-0.052 0.131	-0.115 0.001	0 019 0.588	-0.034 0.324	-0.002 0.962	0.045 0.194	-0.014 0.691	1 000								
shdxrl	-0.150 0 000	0.125 0 000	0 004 0.945	-0.061 0.080	-0.007 0.831	-0.023 0.505	-0.165 0.000	0 023 0.502	-0.080 0.021	0.095 0.006	0.143 0.000	-0.069 0 047	0.148 0.000	1.000							
ccf	-0.169 0.000	0 033 0.340	0.069 0.222	-0.133 0.000	-0 081 0.020	-0.053 0.130	-0.342 **0.000**	0 034 0 334	-0 014 0 684	0.049 0.160	0.100 0 004	0.033 0 347	0.124 0.000	0.253 **0.000**	1.000						
oedema	-0.023 0.511	-0.022 0.520	0.195 0.001	-0.150 0.000	-0.129 0 000	-0.065 0.061	-0.148 0 000	0.031 0.376	-0.044 0.202	0.024 0.489	0.086 0.013	0.007 0 833	0.144 0.000	0.151 0.000	0.264 **0.000**	1.000					
intcc	0.142 0.000	0.011 0.752	-0.091 0 104	0.219 **0.000**	0.090 0.010	0.207 **0.000**	0.091 0.008	-0.199 0 000	0.034 0.326	0 107 0.002	-0 155 0.000	-0.006 0 854	-0 071 0 040	0.028 0.424	-0 070 0 044	-0.126 0.000	1.000				
bdwtlik	-0.139 0 000	0.028 0.427	0.061 0.281	0.005 0 885	0 046 0.182	-0 052 0.135	0.098 0.005	0 040 0.251	-0 024 0.490	-0.034 0 326	0.093 0.007	-0.099 0 004	-0.040 0.247	-0.174 0 000	-0.230 **0.000**	-0.254 **0.000**	-0 071 0.042	1.000			
wtls6	0.005 0.878	0 039 0.257	0 068 0.227	-0.143 0.000	-0 114 0.001	-0 151 0.000	0.012 0.731	0.095 0.006	-0.002 0.946	-0 133 0.000	-0 017 0.615	-0.034 0.327	0.057 0.100	-0.100 0.004	-0.065 0 063	-0.041 0.236	-0 094 0.007	0.332 **0.000**	1.000		
bmir	-0.166 0.000	0.009 0 802	0.027 0.629	0 074 0.032	0.075 0.030	0 070 0.043	0.158 0.000	0.019 0.590	-0.035 0.313	-0 011 0.742	0 082 0.018	-0.064 0.065	-0.022 0.525	-0.172 0.000	-0.226 **0.000**	-0.280 **0.000**	-0 053 0.127	0.737 **0.000**	0 230 **0.000**	1 000	
mac	-0.209 **0.000**	-0 017 0.616	0 098 0.081	-0.014 0 692	0.058 0.098	-0.010 0 782	0.055 0.110	0.070 0 044	-0.050 0.152	-0 066 0.056	0.128 0.000	-0 065 0.059	-0.045 0.195	-0.155 0.000	-0 200 **0.000**	-0.243 **0.000**	-0.120 0.001	0.756 **0.000**	0 287 **0.000**	0.730 **0.000**	1.000
totalsco	0 286 **0.000**	-0.053 0.129	0 030 0.596	-0.002 0.958	-0.082 0 018	-0.033 0.344	0.157 0.000	0.053 0.124	0.037 0.286	-0.143 0.000	0.006 0.859	0.060 0.086	-0 159 0 000	-0 220 **0.000**	-0.129 0.000	-0 052 0 133	-0 250 **0.000**	0 003 0.927	0 035 0.316	0.013 0 717	0.016 0.639

9.5.1 Correlations between variables measuring similar domains

The various measures of body weight were correlated. For body weight Lickert and MAC the correlation coefficient was 0.756, for bodyweight Lickert and BMI it was 0.7368, and for BMI and MAC it was 0.7302. BMI, MAC and bodyweight Lickert were all correlated with weight loss in the previous 6 months, with correlation coefficients of 0.2298, 0.2873, and 0.3320 respectively.

The various measures of functional capacity were correlated. For ADLs and functional score the correlation coefficient was 0.5658. Functional capacity and ADLs were correlated with the patient's self rated quality of life (correlation coefficients 0.4911 and 0.3771 respectively).

9.5.2 Correlations with age

Age was correlated with acute physiology score (correlation coefficient 0.2856). This may be mediated in part by creatinine and urea and also by declining physiological reserve with increasing age. Atrial fibrillation was correlated with age (correlation coefficient -0.2219).

9.5.3 Correlations with intubation

Patients with increasing numbers of impaired activities of daily living and patients with lower functional capacity were less likely to be intubated. This had been noted in the distribution of risk factors between the groups for all treatment versus those not for intubation. Patients using long term oxygen therapy were also less likely to be intubated (correlation 0.1987). Patients with higher acute physiology score were more likely to be intubated. This is not surprising since it is the most severely ill patients who will be intubated.

9.5.4 Correlations with long term oxygen therapy

Patients with lower FEV_1 were more likely to be using long term oxygen therapy (LTOT). LTOT was also correlated with worsening functional capacity.

9.5.5 Miscellaneous correlations

Acute chest x-ray changes are associated with increased acute physiology scores. This is likely to be because causes of acute chest x-ray changes such as pneumonia also cause increased acute physiology scores.

Diagnosis is associated with FEV_1 and this will be because COPD is coded as 1 and COPD/asthma mix is coded as 3. As patient's FEV_1 increases clinicians' certainty that a patient has pure COPD is likely to decrease.

There is a correlation between being on long term oxygen therapy and repeated admissions. This may identify a group who are frailer in whom a minor exacerbation leads to admission.

There is also a correlation between the presence of oedema and congestive cardiac failure, and higher levels of the body weight Lickert, BMI and mid-arm circumference.

9.6 Predictors of 180 day outcome

9.6.1 Characteristics in period of stability pre-exacerbation and 180 day outcome

Table 9.6.1 tabulates the characteristics that describe the patients in the period of stability pre-exacerbation and shows their relationships with 180 day outcome. Considering the odds ratios in the 651 patients without treatment limitation, age and functional capacity show a significant consistent relationship with mortality, with the 95% CI not including 1, and the effect of sex comes close. Better prior quality of life is also related to better outcomes.

There is a suggestion of a relationship between increasing activities of daily living (ADL) and mortality, and between comorbidity and mortality, but the numbers with more than 1 impairment of ADL or comorbidity are small. The low numbers of patients with ADL impairment and comorbidity are likely to reflect selection. In the total group the median (IQR) number of ADLs was 0 (0.0-1.0) whereas in SUPPORT which recruited all COPD patients admitted to 5 US hospitals the median (IQR) number of ADLs was 1.0 (0.0-2.0)[12]. This is an important observation and is consistent with the findings of the Heart of England Critical Care Network study that suggested that UK

clinicians might be nihilistic about the survival prospects of COPD patients[8]. The weak univariate relationship between increasing ADLs and comorbidities will partly be explained by low numbers but also may well be explained by selection in that only the otherwise fitter patients with increased ADL and comorbidity are likely to be recruited to CAOS.

9.6.2 Characteristics in the 24 hours before critical care and outcome

Table 9.6.2 tabulates the characteristics in the 24 hours before ICU admission and outcome. The factors with significant relationships with outcome in the patients for all treatment were diagnosis, length of stay prior to critical care, presence or absence of atrial fibrillation and whether or not the patient was actually intubated.

9.6.3 Body weight variables and 180 day mortality

Table 9.6.3 shows the relationship between body weight variables and 180 day mortality. There is a consistent trend between decreasing weight and mortality. This relationship is also apparent when mid-arm circumference is used as a surrogate for body mass index.

Table 9.6.1 Characteristics in stable pre-exacerbation and 180 day outcome

	All patients n=832				*Patients for all treatment n=651*				*Patients not for intubation n=181*			
Variable	*number dead/n*	*(%)*	*OR*	*(95%CI)*	*number dead/n*	*(%)*	*OR*	*(95%CI)*	*number dead/n*	*(%)*	*OR*	*(95%CI)*
Age												
45-64	91/337	(27.0%)	1		69/285	(24.2%)	1		22/52	(42.3%)	1	
65-74	108/284	(38.0%)	1.66	(1.18-2.33)	82/227	(36.1%)	1.77	(1.20-2.60)	26/57	(45.6%)	1.14	(0.54-2.44)
>75	116/211	(55.0%)	3.18	(2.07-4.88)	70/139	(50.4%)	3.18	(2.10-4.88)	46/72	(63.9%)	2.41	(1.16-5.00)
Sex												
Female	150/435	(34.5%)	1		104/340	(30.6%)	1		46/95	(48.4%)	1	
Male	165/397	(41.6%)	1.35	(1.02-1.79)	117/311	(37.6%)	1.37	(0.99-1.89)	48/86	(55.8%)	1.35	(0.75-2.42)
Functional score												
Fully mobile	54/207	(26.1%)	1		48/189	(25.4%)	1		6/18	(33.3%)	1	
Out of house	113/308	(37.7%)	1.64	(1.11-2.42)	92/267	(34.5%)	1.54	(1.02-2.34)	21/41	(51.2%)	2.1	(0.66-6.67)
Housebound	124/280	(44.3%)	2.25	(1.53-3.33)	70/176	(39.8%)	1.94	(1.24-3.03)	54/104	(51.9%)	2.16	(0.75-6.19)
Bed/chair bound	24/37	(64.9%)	5.23	(2.49-11.00)	11/19	(57.9%)	4.04	(1.53-10.6)	13/18	(72.2%)	5.2	(1.25-21.57)
Prior quality of life	*n=823*				*n=644*				*n=179*			
Very poor	27/60	(45.0%)	1		15/41	(36.6%)	1		12/19	(63.2%)	1	
Poor	100/247	(40.5%)	0.83	(0.47-1.46)	68/178	(38.2%)	1.07	(0.53-2.17)	32/69	(46.4%)	0.50	(0.18-1.44)
Fair	141/357	(39.5%)	0.80	(0.47-1.38)	99/286	(34.6%)	0.92	(0.46-1.81)	42/71	(59.2%)	0.84	(0.30-2.40)
Very good	35/138	(25.4%)	0.42	(0.22-0.78)	28/122	(23.0%)	0.52	(0.24-1.11)	7/16	(43.8%)	0.45	(0.12-1.76)
Excellent	5/21	(23.8%)	0.38	(0.12-1.18)	5/17	(29.4%)	0.72	(0.21-2.45)	4/4	(100%)	†	
Activities of daily living												
0	189/549	(34.3%)	1		158/477	(33.1%)	1		31/72	(43.1%)	1	
1	45/109	(41.3%)	1.34	(0.88-2.04)	24/71	(33.8%)	1.03	(0.61-1.75)	21/38	(55.3%)	1.63	(0.74-3.61)
2	23/67	(34.3%)	1.00	(0.58-1.70)	14/44	(31.8%)	0.94	(0.49-1.82)	9/23	(39.1%)	0.85	(0.32-2.21)
≥3	58/107	(54.2%)	2.25	(1.48-3.43)	25/59	(42.4%)	1.48	(0.86-2.57)	33/48	(68.8%)	2.91	(1.35-6.27)
Comorbidity												
0	135/397	(34.0%)	1		97/321	(30.2%)	1		38/76	(50%)	1	
1	106/260	(40.8%)	1.34	(0.97-1.85)	77/199	(38.7%)	1.46	(1.00-2.11)	29/61	(47.5%)	0.91	(0.46-1.78)
2	50/120	(41.7%)	1.39	(0.91-2.11)	35/93	(37.6%)	1.39	(0.86-2.26)	15/27	(55.6%)	1.25	(0.52-3.02)
≥3	24/55	(43.6%)	1.50	(0.85-2.66)	12/38	(31.6%)	1.07	(0.52-2.20)	12	(70.6%)	2.4	(0.77-7.48)
Long term oxygen												
No	255/694	(36.7%)	1		191/582	(32.8%)	1		64/112	(57.1%)	1	
Yes	60	(43.5%)	1.32	(0.91-1.92)	30/69	(43.5%)	1.57	(0.95-2.61)	30/69	(43.5%)	0.58	(0.31-1.06)
Previous intubation												
No	284/735	(38.6%)	1		201/575	(35.0%)	1		83/160	(51.9%)	1	
Yes	31/97	(32.0%)	0.75	(0.47-1.17)	20/76	(26.3%)	0.66	(0.39-1.14)	11/21	(52.4%)	1.02	(0.41-2.54)
Admitted in past 6 months	204/532	(38.4%)	1		153/434	(35.3%)	1		51/98	(52.0%)	1	
No												
Yes	111/300	(37.0%)	0.94	(0.70-1.26)	68/217	(31.3%)	0.84	(0.59-1.19)	43/83	(51.8%)	0.99	(0.55-1.78)

† Since 4 out of 4 died OR cannot be calculated.

Table 9.6.2 Characteristics in the 24 hours before critical care & 180 day outcome

	All patients n=832		*Patients for all Treatment n=651*		*Patients not for intubation N=181*	
Variable	*number dead/n (%)*	*OR (95%CI)*	*number dead/n (%)*	*OR (95%CI)*	*number dead/n (%)*	*OR (95%CI)*
Diagnosis						
Asthma	9/80 (11.3%)	1	9/78 (11.5%)	1	2/2 (100%)	†
COPD/ Asthma mix	37/117 (31.6%)	3.65 (1.65-8.08)	33/104 (31.7%)	3.56 (1.59-8.00)	4/13 (69.2%)	1
COPD	269/635 (42.4%)	5.80 (2.85-11.81)	179/469 (38.2%)	4.73 (2.31-9.71)	90/166 (54.2%)	2.66 (0.79-9.00)
Length of stay pre-critical care (Odds/day)		1.04 (1.01-1.07)		1.03 (1.00-1.06)		1.12 (1.00-1.26)
Atrial fibrillation						
No	257/729 (35.3%)	1	187/587 (31.9%)	1	70/142 (49.3%)	1
Yes	58/103 (56.3%)	2.37 (1.56-3.60)	34/64 (53.1%)	2.42 (1.44-4.08)	24/39 (61.5%)	1.65 (0.80-3.40)
Chest X-ray						
No acute changes	97/316 (30.7%)	1	71/253 (28.1%)	1	26/63 (41.3%)	1
Acute Changes	217/514 (42.2%)	1.65 (1.23-2.20)	149/396 (37.6%)	1.64 (1.20-2.30)	68/118 (57.6%)	1.58 (0.86-2.88)
Missing	2		2		0	
Congestive cardiac failure as cause						
No	243/645 (37.7%)	1	172/520 (33.2%)	1	72/125 (57.1%)	1
Yes	70/185 (37.8%)	1.0 (0.71-1.40)	48/130 (36.9%)	1.18 (0.79-1.76)	22/55 (40.0%)	0.50 (0.26-0.95)
Missing	2		1		1	
Ankle oedema						
No	232/615 (37.7%)	1	167/493 (33.7%)	1	65/121 (53.7%)	1
Yes	83/216 (38.4%)	1.03 (0.75-1.42)	54/156 (34.6%)	1.04 (0.71-1.52)	29/60 (48.3%)	0.81 (0.43-1.50)
Missing	2		2		0	
Intubated						
No	128/382 (33.5%)	1	34/201 (16.9%)	1	94/181 (51.9%)	
Yes	187/450 (41.6%)	1.41 (1.06-1.87)	187/450 (41.6%)	3.49 (2.31-5.28)	NA	NA

† There were only 2 asthmatics in the not for intubation group and both died so odds ratio is presented for COPD /asthma mix versus COPD

Table 9.6.3 Body weight variables and 180 day mortality

Variable	*All patients n=832*		*Patients for all Treatment n=651*		*Patients not for intubation N=181*	
	Number dead/n (%)	*OR (95%CI)*	*number dead/n (%)*	*OR (95%CI)*	*number dead/n (%)*	*OR (95%CI)*
Body weight Lickert						
Very overweight	29/102 (28.4%)	1	21/78 (26.9%)	1	8/24 (33.3%)	1
Mildly overweight	68/215 (31.6%)	1.16 (0.69-1.95)	56/185 (30.3%)	1.18 (0.65-2.13)	12/30 (40.0%)	1.33 (0.62-4.10)
Normal weight	103/279 (36.9%)	1.47 (0.90-2.41)	73/218 (33.5%)	1.37 (0.77-2.43)	30/61 (49.2%)	1.94 (0.72-5.19)
Mildly underweight	75/172 (43.6%)	1.95 (1.15-3.29)	46/131 (35.1%)	1.47 (0.79-2.72)	29/41 (70.7%)	4.83 (1.64-14.28)
Very underweight	40/64 (62.5%)	4.19 (2.16-8.15)	25/39 (64.1%)	4.85 (2.13-11.05)	15/25 (60.0%)	3.0 (0.93-9.63)
Weight loss in previous 6 months						
No	210/585 (35.9%)	1	156/471 (33.1%)	1	54/114 (47.4%)	1
Yes	96/234 (41.0%)	1.24 (0.91-1.69)	57/168 (33.9%)	1.04 (0.71-1.51)	39/66 (59.1%)	1.60 (0.87-2.96)
Mid-arm circumference						
>30cm	97/329 (29.5%)	1	78/271 (28.8%)	1	19/58 (32.8%)	1
25-29.9cm	98/279 (35.1%)	1.29 (0.92-1.82)	72/228 (31.6%)	1.14 (0.78-1.68)	26/51 (51.0%)	2.13 (0.98-4.64)
20-24.9cm	83/172 (48.3%)	2.23 (1.52-3.27)	46/115 (40.0%)	1.65 (1.05-2.60)	37/57 (64.9%)	3.80 (1.75-8.22)
<20cm	19/30 (63.3%)	4.13 (1.89-9.01)	13/21 (61.9%)	4.02 (1.60-10.08)	6/9 (66.7%)	4.10 (0.92-18.22)
Body Mass Index Per 1kg/m^2 increase		0.96 (0.94-0.98)		0.97 (0.94-0.99)		0.96 (0.93-1.0)

9.7 Summary and implications for outcome model development

9.7.1 Selection bias

A number of centres commented that the unit had a tacit policy of not admitting patients on home oxygen. Patients designated for 'no intubation' were more likely to be on home oxygen [no intubation 38.1% vs. 10.6% for intubation, chi-square 77.5 p<0.001]. It was decided that home oxygen should not be used as an outcome predictor since any patients getting into ICU on home oxygen were likely to have been highly selected as having an unusually good prognosis in other respects and so not representative of the population as a whole.

In addition considering Table 9.2 and using post hoc subgroup analysis to compare the characteristics of patients by intubation designation illustrates that patients designated for 'no intubation' tended to be older [(70.3 vs. 66.1 T-test p<0.001)], to have a lower FEV_1 [(0.7 vs. 1.1 T-test p<0.001)], to have a lower functional score, [out of house or better (no intubation 32.0%, for intubation 70.0%) vs. housebound or worse (no intubation 68.0 % vs. for intubation 30.0%) chi-square 84.2 p<0.001)], to have a poorer prior quality of life, [fair or better (no intubation 50.8% vs. for intubation 66.0%) poor or very poor (no intubation 49.2% vs. for intubation 44.0%) chi-square 13.76 p<0.001], to have more impairments of activities of daily living, [no intubation median (IQR) ADL impairments 1.0 (0.0-3.0) for intubation ADL impairments 0.0 (0.0- 1.0) p<0.001 Mann-Whitney)], and to have had more admissions in the last 6-months, [no intubation median (IQR) 0.0 (0.0-1.0) for intubation 0.0 (0.0-1.0) p=0.0013 Mann-Whitney], though the difference in comorbidities and previous intubation did not reach statistical significance. Though these analyses are post-hoc, subgroup analyses suggest that there is a consistent pattern that indicates that patients designated as not for intubation have been selected using characteristics that suggest that they are older and frailer. In section 9.7.6.iv below the proportion of patients in the worst functional groups is compared with a historical cohort assembled in one centre where all COPD patients admitted to hospital were included irrespective of whether they had been selected for ICU or not.

The historical 'total cohort' study contained a greater proportion of patients who were housebound or worse than the CAOS study.

9.7.2 Proxy responses

Responses describing prior quality of life, activities of daily living and functional score only came directly from the patient in 43%, 42.5% and 38.6% of subjects respectively. Though activities of daily living and function are readily observed and therefore likely to be relatively accurately reported by proxies, patient rated quality of life is subjective and proxy reports may be unreliable.

9.7.3 Complicated variables

The estimation of BMI was difficult, both because of difficulties in weighing and measuring patients, and because many clinicians thought in imperial measures. Thus calculating the BMI involved estimates, conversion to metric measures and then a final calculation.

9.7.4 Missing data

Data was missing in more than 5% of patients for only FEV_1 (missing in 61.8%) and non-ventilated respiratory rate (missing in 5.6%). Though lung function is an important measure of the severity of COPD other studies have also found that it tends not to be available in the acute setting. Even in the SUPPORT study[12] that had full time dedicated data collectors, FEV_1 data was only obtained in 22% of the model development set.

9.7.5 Variables measured with error

Despite measures of oxygenation having a robust association with outcome in patients with respiratory failure (section 3.4.11.2), liaison with the units made it clear that there was uncertainty about the inspired oxygen concentration (FiO_2) delivered to patients when the PaO_2 was measured. Since the PaO_2 can only be interpreted in the light of an accurate FiO_2, oxygenation was not used in the modeling process.

9.7.6 Selected comparisons with other COPD outcome studies

i Age

In the studies identified in the systematic review the mean age ranged from 57 to 69 years and the median from 64 to 70 years. In the UK CMP study the median (IQR) age was 67.5 (60.4-73.5)[27]. In CAOS the age was similar.

ii Sex

Most data sources suggest that men slightly out number women in ICU admissions with COPD. Men made up 51.8% (1869 of 3611) (95% CI 50.1- 53.4%) and women 48.2% (95% CI 46.6-49.9%) of patients with COPD admitted to critical care units in the CMP study that analysed admissions between 1995 and 2001[27]. Though the 95% confidence intervals include the possibility of the predominance of women being accounted for by the play of chance it is interesting to note that whilst age-adjusted mortality rates for men with COPD have fallen over the last 20 years (from 1070 to 634 per million) mortality rates have increased in women from 230 to 323 per million[140]. The predominance of women with COPD admitted to ICU was also observed amongst the eligible patients not recruited to CAOS identified via the CMP patients of which 51% of were women (section 5.3.4). It may be that the predominance of women observed in CAOS reflects demographic changes in the numbers of women with COPD being admitted to ICU.

iii FEV_1

The CAOS result is very similar to the results seen in SUPPORT median (IQR) 0.8 (0.58- 1.20). The similarity to SUPPORT is reassuring in that the SUPPORT study was a total cohort study including both critical care and ward patients.

iv Functional score

Since it is intended that the CAOS model should be used in patients who have not yet reached critical care it would be useful to understand the distribution of functional score in all hospitalised admissions with COPD. An early pilot study in preparation for the

CAOS study applied the functional score to 242 consecutive admissions to hospital with COPD irrespective of the area of care[141]. In this study carried out in one centre, less than 10% of COPD admissions were admitted to a critical care area. Table 9.7.6.iv shows the distribution of functional score between unselected and selected groups of patients and it can be seen that that whereas in the early pilot amongst unselected patients 49% (95% CI 43-56) were housebound or worse, amongst all the CAOS patients only 38% (95% CI 35-42) were housebound or worse.

Table 9.7.6.iv Functional score in patients with COPD.

Functional score	*Hospitalised patients from early pilot n=242*	*All CAOS patients n=832*	*CAOS patients without treatment limitation n=651*	*CAOS patients who would not be intubated n=181*
	% (95%CI)	% (95%CI)	% (95%CI)	% (95%CI)
Fully mobile	12% (8.2-16.8)	24.9%(22.0-28.0)	29.0% (25.6-32.7)	9.9% (6.0-15.3)
Out of house	38.8% (32.7-45.3)	37.0% (33.7-40.0)	41.0%(37.2-44.9)	22.7% (16.8-29.4)
Housebound	42.3% (35.9-48.6)	33.7% (30.4-37.0)	27.0% (23.7-30.6)	57.5% (49.9-64.8)
Bed/chair bound	6.6% (3.8-10.5)	4.5% (3.2-6.1)	2.9% (1.8-4.5)	9.9%(6.0-15.3)

v Activities of daily living

A comparison of the distributions of activities of daily living (ADLs) in this study and in SUPPORT[12] also suggests that important selection is occurring in CAOS. In SUPPORT all patients admitted to 5 US hospitals with COPD and Type II respiratory failure were recruited and the median (IQR) number of ADLs was 1.0 (0-2). In contrast in the 651 patients in CAOS without treatment limitation the median (IQR) number of ADLs was 0.0 (0-1).

9.8 Conclusions

Overall data completeness was good and the variables collected were broadly similar to those collected in other studies that examined COPD outcomes. Comparison of patients for all treatment with those who were not for intubation suggests that the patients

selected for all treatment were on the whole fitter and comparison with a single historical cohort suggests that those patients selected for ICU are likely to be fitter than the total group of hospitalised patients from which they have been drawn. This selection has important implications for the how the model should be used in clinical practice and is discussed in more detail in chapter 12.

Chapter 10 Development of the CAOS survival prediction model

10.1 Introduction

The various stages involved in developing a prognostic model were summarised in Figure 2.1:

1. State clinical aim for model
2. Prepare a list of potential risk factors for mortality based on clinical knowledge in relation to stated aim
3. Select a suitable sample of patients
4. Select an appropriate statistical modelling technique
5. Adopt a systematic strategy to handle missing values for risk factors
6. Adopt a systematic strategy to select a final set of risk factors
7. Fit the model and estimate coefficients
8. Convert regression coefficients to risk scores for mortality
9. Model validation

To allow the model-building process to be presented as a cohesive whole, each of the first 4 stages will be reviewed briefly in the first substantive section of this chapter. This is followed by sections devoted to stages 5 and 6. Stages 7, 8 and 9 are addressed in Chapter 11.

10.2 Stages 1 to 4.

10.2.1 Clinical aim of the model and choice of outcome variable

The aim of the model is to provide clinicians, who are assessing a patient with an exacerbation of obstructive airways disease, with an estimate of the patient's survival to 180-days if they are treated with all appropriate therapy (section 1.2). An important issue in decisions of this kind is whether survival is associated with such poor quality of life that the patient would rather have died. One way of addressing this would have been to develop a model that predicted survival with acceptable quality of life[124]. However the CAOS study had missing quality of life data in 20% of the surviving

subjects. Developing the model on only the 80% of the subjects would have reduced power and could have introduced bias.

Fortunately 96% of 180-day survivors who did return the questionnaire stated that under circumstances similar to their original ICU admission they would want such treatment again. There was no evidence that this percentage was any different in prompt, delayed and very delayed respondents (section 7.5, Table7.5). Carrying out a sensitivity analysis in which it was assumed that all the non-respondents would *not* choose critical care again, it was nevertheless found that 77.2% of all patients would want ICU again (section 7.7). It was therefore decided to focus on survival, with the implicit assumption that almost all surviving patients found their quality of life worthwhile.

10.2.2 Potential risk factors

The risk factors associated with outcome identified in the systematic review are given in Tables 3.5.1, 3.5.2 and 3.5.3. The distributions of these risk factors in the study population are given in the Tables in chapters 8 and 9. In order for a risk factor to be used in model building, the data had to be available before critical care admission occurred. The only exception to this was the use of the patients' intubation status.

10.2.3 A suitable sample of patients

The 651 patients selected for model development were

- aged 45 years or older; and
- in hospital with an exacerbation of obstructive lung disease; and
- classified clinically as COPD, asthma or a mixture of COPD and asthma; and
- admitted to a critical care area; and
- considered suitable for any treatment including intubation by the clinicians supervising the patients' care.

10.2.4 An appropriate statistical modelling technique

The outcome was the binary outcome of survival/non-survival at 180 days and therefore logistic regression was used to develop the model.

10.3 Handling missing values for risk factors according to a systematic strategy

10.3.1 The imputation strategy

The rationale behind the approach to missing values is outlined in section 2.6. Variables with more than 5% of the data missing were dropped from the modelling process because imputational strategies become speculative beyond this level and because variables that are frequently missing are likely to be unavailable at the bed side. Data that were missing in less than 5% of patients were imputed using either the total population mean or median, or using the mean or median for the closest category in a correlated variable for which data were not missing

10.3.2 Variables dropped because of too much missing data

Two variables, FEV_1 (61.8% missing) and non-intubated respiratory rate (5.6% missing), were eliminated. Respiratory rate is often not measured outside ICU because there is no machine to measure it. In addition it had been decided that a composite acute physiology score would be developed using data from the Case Mix Programme database, and in this database non-intubated respiratory rate is often unavailable because many patients in ICU are intubated.

10.3.3 Imputation for characteristics in the period of stability pre-critical care.

i Prior quality of life

Nine patients (1.1%) had missing data. Functional score and prior quality of life were strongly correlated ($r = 0.49$ $p<0.0001$), and 9 patients with data missing on prior quality of life had data on functional score. Table 10.3.3 shows the most common prior quality of life category for each functional score category, and this mapping was used for imputation in the numbers of cases also shown in the table.

Table 10.3.3 Prior quality of life imputation strategy

Functional score category	*Number of patients with missing data on prior quality of life*	*Commonest prior quality of life category*
Fully mobile	4	Very good
Gets out of house to do basic necessities	4	Fair
Out of house rarely	1	Poor
Bed or chair bound	0	Poor

ii Activities of daily living

There were four patients (0.5%) with missing data, in one patient for all domains, in one patient for four domains, and in two patients for one domain. The commonest state, "no impairment", was imputed for all missing data.

iii Previous admissions in the past 6 months

One patient had missing data and the commonest state, "no admissions" was imputed.

10.3.4 Imputation for characteristics in the 24 hours prior to critical care

i Chest X-ray appearance

Eleven patients (1.3%) had missing data. The most common chest X-ray appearance, "acute changes", was imputed.

ii Congestive cardiac failure as a cause

Two patients (0.2%) had missing data. The commonest state, "congestive cardiac failure absent" was imputed.

iii Ankle oedema

Two patients (0.2%) had missing data. The commonest state, "ankle oedema absent", was imputed.

10.3.5 Imputation for data relating to body weight

i Weight loss in the previous six months

Weight loss data were missing in 13 patients (1.6%). The commonest state, "no weight loss", was imputed.

ii Mid-arm circumference (MAC)

MAC had one of the highest frequencies of missing data: 22 (2.6%). It seems likely that these values were not missing at random; 18 of the 22 people with missing MAC (81.2%) died within 180 days. To use the mean MAC for patients who died would be to introduce bias given that the main outcome of interest is 180-day survival. However MAC is closely correlated with the Lickert score for body weight ($r = 0.756$, $p<0.0001$) and all the patients with missing MACs had data on Lickert score. MAC values were imputed using the mean MAC for the subject's Lickert score.

Table 10.3.5ii Lickert rating and corresponding MAC measurement

Lickert rating	*N dying before 180 days with missing data*	*N surviving 180 days with missing data*	*MAC measurement mean (SD) cm*
Very underweight	3		21.2 (2.6)
Mildly underweight	2	2	24.3 (3.4)
Normal weight	6	1	27.7 (3.3)
Mildly overweight	6	1	31.5 (3.7)
Very overweight	1		35.8 (4.7)

iii Body mass-index

Nine patients in total (1%) had height and/or weight data missing (5 weight, 3 height and one both), making calculation of BMI impossible. However all had Lickert estimates of weight. Figure 10.3.5 below shows that there was a relationship between BMI and Lickert weight estimates, and missing BMIs were imputed using the median BMI of their Lickert weight group.

Figure 10.3.5 **Body mass index according to estimated weight using Lickert scale**

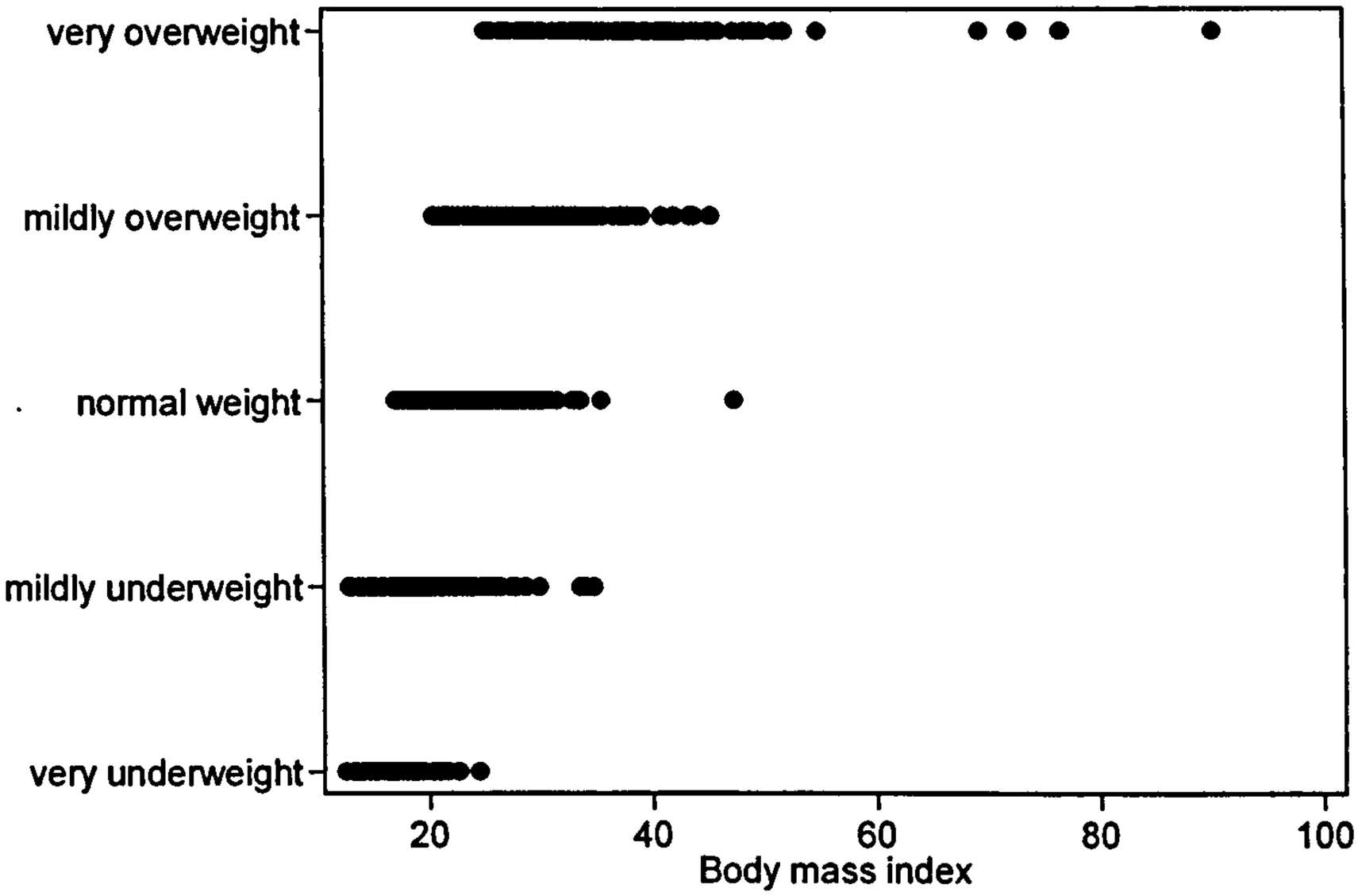


Table 10.3.5.iii **Lickert score for weight and estimated BMI**

Lickert weight	*BMI Kg/m²* *Mean (SD)* *Median (IQR)*
Very underweight	16.8 (3.9) 17.0 (15.1-18.6)
Mildly underweight	20.5 (4.0) 20.2 (18.1-22.6)
Normal weight	24.2 (3.7) 24.2 (21.9-25.9)
Mildly overweight	28.4 (5.8) 28.4 (25.8-30.9)
Very overweight	38.2 (10.9) 36.8 (32.3-41.8)

10.3.6 Imputation for acute physiological variables

The ten physiological variables with less than 5% missing data are summarised in the table below, which also shows the mean values for all patients with data, which were used for imputation.

Table 10.3.6 Imputation for acute physiological variables

Acute physiology variable	*Number (%) missing*	*Imputed value*
FiO_2	3 (0.4%)	48.1%
Systolic Blood pressure	2 (0.2%)	131mmHg
Diastolic Blood pressure	3 (0.4%)	69mmHg
Central Temperature	5 (0.6%)	37.0 ^{0}C
Heart rate	1 (0.1%)	118 bpm
Potassium	2 (0.2%)	4.5mmol/L
Albumin	3 (0.4%)	34.5g/L
Bilirubin	15 (1.8%)	11.5 mmol/L
Glucose	14 (1.7%)	9.2mmol/L
Glasgow coma scale	3 (0.4%)	12.0

10.4 A systematic strategy to select a final set of risk factors

10.4.1 Introduction

Five physiological variables were dropped during the development of the COPD specific acute physiology score (CAPS), i.e. potassium, temperature, $PaCO_2$, glucose, and bilirubin (table 8.5.1). The CAPS was developed using a data driven strategy in a model building set of 5513 patients, and then tested in the other 3014 patients. The nine physiological variables retained in the CAPS were: heart rate, white blood count,

sodium, pH, creatinine, albumin, systolic blood pressure, diastolic blood pressure and urea.

A number of strategies were used to reduce the remaining potential risk factors to a smaller number for use in the final model. This was necessary since with 220 deaths in the model development data, a maximum of around 20 variable levels could be modelled. Also the model was intended for use by busy clinicians at the bedside so that model parsimony was an important consideration. Data driven variable selection processes were to be avoided, and the criteria for dropping or retaining variables were as set out in chapter 2.

- Practicality and simplicity
- Accuracy of measurement
- Lack of subjectivity
- Low correlation with other variables
- Unlikely to introduce selection bias
- Less than 5% missing data

10.4.2 Practicality and simplicity

Information provided by units about the practical aspects of data collection was outlined in Chapter 9.

There were practical problems with body mass index because weight and height often had to be estimated rather than measured, and the estimates tended to be in imperial units, which would require conversion for use in the model.

There were some practical problems with the data on Activities of Daily Living (ADLS). Clinicians found the scale unfamiliar and if it were to be used as part of the CAOS score a description of the ADL scale would need to be provided leading to difficulties in producing a score that fitted on a single side of paper. The Charlson Co-morbidity score was also unfamiliar to clinicians and posed similar problems. However it was decided not to drop these two variables at this stage but to continue

model development so as to understand the implications for discrimination and calibration of dropping them or retaining them at a later stage.

10.4.3 Variables dropped because of concerns over accuracy in measurement

Any data collected inaccurately would tend to reduce the apparent effects of the variable concerned if the errors are random, and might lead to biased results if the errors are systematic.

The variables in Table 10.4.3 below were dropped because of concerns about accuracy of measurement.

Table 10.4.3 Variables dropped because of concerns over accuracy in measurement

Variable	*Reasons for dropping*
PaO_2/FiO_2 ratio	Units commented that it was often difficult to be sure of the delivered FiO_2 outside critical care.
Congestive cardiac failure as a cause	It was found difficult to differentiate between patients with congestive cardiac failure and Cor pulmonale, and the two conditions have very different prognoses.

10.4.4 Variables dropped because of subjectivity

The CAOS model was developed because clinicians' subjective estimates of outcome were highly variable, and every effort was made to ensure that the CAOS model was as objective as possible. The widespread use of estimates of weight and/or height as a basis for BMI has already been referred to. Because of the combination of subjectivity in these estimates and practical problems in conversion of imperial to metric units, it was decided to drop BMI.

The assessment of prior quality of life was subjective, not least because 57% of the data were provided by proxies. It was decided to drop this variable.

Body weight Lickert is subjective and dropping it was considered as it was felt that an objective measure of body weight would be superior. However it was retained for

modelling because it correlated well with mid-arm circumference (MAC) and could provide a substitute for missing MAC data.

10.4.5 Variables dropped because of correlation

The various measures of body weight were not surprisingly highly correlated. BMI was dropped on subjectivity and practicality grounds, but the correlation coefficient for MAC and Lickert bodyweight assessments was 0.756. There were a priori grounds for choosing MAC in the model because though body weight Lickert is easier to obtain, it is subjective and the MAC is better at identifying the thin patients at highest risk (MAC<20cm); all these patients are lumped together in the lowest category of the body weight Lickert scale. It was decided to check this once the remainder of the variable selection process was complete, by examining the ROC and Hosmer-Lemeshow statistics for logistic regression models with 180-day survival as the dependent variable and MAC or body-weight Lickert among the independent variables.

The Glasgow Coma Scale was correlated with intubation and many other factors that are associated with intubation such as pH. (Impaired conscious level is often used as a reason to intubate.). Also the GCS is a scale that involves collecting data on several variables and therefore adds complexity. For these reasons it was decided to drop it.

10.4.6 Variables dropped because of possible selection bias.

The problem of selection bias is discussed in section 2.5.4 and section 9.7.1. Long term oxygen therapy (LTOT) was a risk factor that seemed to be mentioned frequently as a reason not to intubate and selection on the basis of LTOT use seemed to be sufficiently widespread that the patients on LTOT admitted to CAOS might be highly selected. For this reason LTOT was dropped from model development. It might be argued that functional capacity also showed selection, but there was not the same explicit consensus about the level below which patients should or should not be admitted as for LTOT.

10.4.7 Summary of variable selection prior to modelling with outcome

Table 10.4.7 below shows the variables that were dropped before any modelling with outcome was undertaken. This left 16 variables that were taken forward to the next stage.

Table 10.4.7 Summary of variable selection prior to modelling with outcome

Variable	*Reason*
Body mass index	Complicated and unreliable
PaO_2/FiO_2	Unreliable
Congestive cardiac failure	Concerns over accuracy
FEV_1	Missing data
Respiratory rate	Missing data and often unavailable in CMP
Prior quality of life	Subjective
Glasgow coma scale	Correlated with intubation
Long term oxygen therapy	Selection bias
$PaCO_2$	Dropped by physiology score process
Glucose	Dropped by physiology score process

10.4.8 Variables dropped following backward stepwise selection using $p < 0.2$

Using backward stepwise selection can introduce bias because relatively subtle differences in the distribution of risk factors in a population may cause them to be selected for inclusion in the model in one data set and rejected in another[21]. Also important risk factors that are relatively rare (atrial fibrillation might be such a factor in the CAOS dataset) may be dropped because of a borderline significance value that reflects its rarity in the population rather than its importance as a predictor. For this reason Harrell advocates defining risk factors in advance and then producing a full model that contains all those risk factors. If risk factor selection is to be based on a data driven strategy Harrell suggests that the significance level should be very conservative

and advocates only deleting predictors if their total chi-square is < 2 x d.f. (degrees of freedom)[21].

Because this study involved collecting data on a number of risk factors for which there was only weak prior evidence of association with outcome, it was decided to use a very conservative data driven strategy to test whether these variables should be retained in the model. These were variables where an association with outcome might have been noted in one study (ankle oedema[142], previous intubation[43]) or associations that were part of the folklore but without much evidence, such as recent weight loss and recent hospital admissions. The model subjected to backward stepwise reduction also contained variables that had a good base in the evidence and were likely to be correlated, such as functional score and activities of daily living, and it was decided a priori that these would be retained at this stage of model development even if dropped by the stepwise selection process.

Backward stepwise selection was carried out using the 651 patients without treatment limitation. The variables in the model subjected to backward stepwise selection were:

- Length of stay pre critical care
- Ankle oedema
- Age groups
- Sex
- COPD acute physiology score
- Activities of daily living
- Functional score
- Mid-arm circumference
- Atrial fibrillation
- Intubation
- CXR appearance
- Admissions in past 6 months
- Weight loss in previous 6 months
- Diagnosis
- Comorbidities

- Previous intubation

Backward elimination identified a further five variables that might be dropped (Table 10.4.8). Four of these were accepted as suitable for dropping at this point since the evidence that they might be important in the systematic review was relatively weak. However chest X-ray appearance was kept in the model at this stage because the majority of clinicians put great emphasis on this in their decision-making.

Table 10.4.8 Variables dropped after backwards selection.

Candidate variable	*Variables with >0.2*	*Values dropped*	*Rationale for exclusion*
Chest X-ray aetiology	X		Chest X-ray appearances are established in the folklore as important and clinicians frequently mention them in decision making processes[6] so they were kept in the model until the next round.
Ankle oedema	X	X	It is likely that ankle oedema patients include both patients with a good prognosis i.e. those with congestive cardiac failure as the cause and those with cor pulmonale. In addition ankle oedema had only been identified as associated with outcome in a single study that included all COPD hospital admissions and not just those admitted to critical care[142].
Previous intubation	X	X	Dropped on grounds of parsimony since there is no real effect on outcome and only identified in one study as important. Likely to be a marker of survivor bias.
Previous admissions in past 6m	X	X	Dropped on grounds of parsimony since no real effect on outcome and included in the study to investigate a part of the folklore rather than because of previous high quality study evidence. Also possibly affected by levels of health care provision.
Weight loss in past 6m	X	X	Dropped on grounds of parsimony since no real effect on outcome and included in the study to investigate a part of the folklore rather than because of previous high quality study evidence.

10.4.9 Mid-arm circumference (MAC) or bodyweight Lickert?

Comparisons of ROC area and likelihood ratio statistic were made for models with mid-arm circumference (MAC) and with bodyweight Lickert. The models had very similar discriminative ability in terms of ROC area (MAC: 0.7809; Lickert: 0.7801). In terms of the likelihood ratio Chi- square, both variables were significant contributors to the model (MAC: $p = 0.021$, Lickert: $p = 0.013$). However the advantage of the MAC is that it separates out the thinnest patients who are at highest risk into two categories whereas the Lickert scale amalgamates these patients into a single category. It was for

this reason that it was decided to use the MAC in the final model. In addition given two scales that measure a similar domain the least subjective should be chosen as long as this does not have too great a price in terms of ease of use. The MAC is easy and quick to use and for this reason this was chosen for the final model.

10.4.10 Further simplification: reducing the number of new scores required

After the backward stepwise selection there were 12 risk factors left in the model. In section 10.4.2 the possibility of dropping the Charlson comorbidity index and activities of daily living was raised on grounds that they involved additional scales that are not in common clinical practice. At that stage it was decided to keep them in so that the impact of dropping them from a simpler model could be assessed in terms of the trade off between parsimony and model performance. In addition comorbidity is very difficult to measure using simple scales and the Charlson comorbidity scale was likely to be considered inadequate by clinicians. For example simply scoring the presence of prior myocardial infarction misses important factors such as the ECHO findings that document residual left ventricular function in myocardial infarction survivors. Elixhauser has argued that counting comorbidities is an inadequate way to take them into account and that each comorbidity should be weighted depending on the primary condition[95]. Currently studies have not reported a weighting scheme for comorbidities that coexist with COPD patients, and of course the more specific weighting that would be required would be for patients with COPD who are intubated.

The effect on the model of dropping these variables was assessed using the area under the receiver operating characteristic curve (ROC) to estimate effects on discrimination and the Hosmer-Lemeshow Chi-square statistic to estimate the effects on calibration. This process is summarised in Table 10.4.10 and outlines the impact of dropping the complex ADL and Charlson scores and also the effect of dropping the chest X-ray classification that had been forced into the model up till this point. Dropping the ADL score reduced the ROC from 0.781 to 0.776. The Hosmer-Lemeshow Chi-square statistic, was 3.76 ($p = 0.333$) and the Log-ratio chi-square, a measure of whether the variable makes a significant difference to the fit of the model, was 3.4 ($p = 0.333$).

Dropping the Charlson index reduced the ROC from 0.781 to 0.771. The Hosmer-Lemeshow Chi-square statistic, was 2.4 (p = 0.966) and the Log-ratio chi-square was 3.37 (p = 0.338).

Table 10.4.10 ROC and HL statistics as variables are removed from the reduced model

Independent variables in model (n = 651)	Variable	ROC area	HL	LR test	Decision
los agegrp sex APS ADL funsc MAC AF intubation CXR diagnosis comoborbidity		0.7809	HL Chi-sq 5.9 P=0.655		
	Length of stay	0.7660	HL Chi-sq 5.9 P=0.656	LR Chi-sq = 4.74 P=0 0295	Length of stay is significantly associated with 180-day outcome so retain in final model
	Age group	0.774	HL Chi-sq 8.5 P=0.38	LR Chi-sq= 9.08 P=0.028	Age is significantly associated with 180-day outcome so retain in final model
	Sex	0.7765	HL Chi-sq 6.8 P=0.55	LR Chi-sq =3.35 P=0.067	Sex has a borderline significant association with 180-day outcome once other factors adjusted for
	Acute physiology score	0.765	HL Chi-sq 3.2 P=0.92	LR Chi-sq =12.5 P=0.0004	APS is significantly associated with 180-day outcome so retain in final model
	ADLs	0.776¥	HL Chi-sq 3.76 P=0.878	LR Chi-sq =4 P=0.333	ADL is not significantly associated with 180-day outcome.
	Functional score	0.772	HL Chi-sq 7.04 P=0 532	LR Chi-sq =8.47 P=0.0372	Functional score is significantly associated with 180-day outcome so retain in final model
	Mid-arm	0.7685†	HL Chi-sq 9.29 P=0.318	LR Chi-sq =10.45 P=0 0151	MAC is significantly associated with 180-day outcome so retain in final model
	Af	0.778	HL Chi-sq 7.9 P=0.443	LR Chi –sq 2.49 P=0.1149	AF not significantly associated with 180-day outcome when other factors taken into account, but retained in backward stepwise regression and easy to measure so retain
	Intubation status	0.7491	HL Chi-sq 10.8 P=0 21	LR Chi –sq 34.9 P=0 0000	Intubation significantly associated with 180-day outcome
	X-ray	0.7803	HL Chi-sq 5.7 P=0.67	LR Chi-sq 0.05 P=0.83	Chest X-ray appearances are not associated with 180-day outcome
	Diagnostic group	0.773	HL Chi-sq 4.7 P=0.78	LR Chi-sq =9.68 P=0.0079	Diagnosis significantly associated with 180-day outcome
	Comorb-idity	0.7706	HL Chi-sq 2.4 P=0.966	LR Chi-sq =3.37 P=0.338	Co-morbidity not significantly associated with outcome- though ROC falls

¥The ROC hardly changes i.e. 0.78 to 0.776 a marker that ADLs are not improving discrimination.

† The ROC falls from 0.78 to 0.76 when MAC is removed showing the importance of MAC

Note using the Hosmer-Lemeshow chi-squared goodness of fit statistic on 10 degrees of freedom, values over 18.30 indicate a significant lack of fit at the 5% significance level. Hence removing ADL, CXR appearance and AF makes little difference to the ROC AUC or the LH statistic, but taking out age groups though making little difference to the ROC makes a big difference to the LH statistic.

Despite the limitations of this method (i.e. that the result may not be stable in samples of patients with different distributions of risk factors) it does provide some reassurance that dropping these factors is not likely to affect the performance of the model.

10.4.11 Testing of chest X-ray appearance in a final parsimonious model

Given the importance attached to chest X-ray appearance in the folklore, backward stepwise variable selection with a p value of 0.2 was repeated in the final parsimonious model i.e. the model from which activities of daily living and the Charlson co-morbidity score had been dropped. Once again chest X-ray appearance was dropped and no further attempt was made to force this variable into the model.

10.5 Final model

Dropping activities of daily living, comorbidities and chest X-ray leaves a final model which is a good compromise between parsimony and predictive performance and includes 10 variables with 15 levels (where a variable with k categories contributes k-1 levels). This allows fitting in a data set with almost 15 events per variable level. The variables (with numbers of categories) included are age group (3), diagnosis (3), sex (2), functional score (4), atrial fibrillation (2), grouped mid-arm circumference (4) and intubation status (2). The continuous variables are COPD acute physiology score and length of stay prior to critical care. It is assumed that the effects of the continuous variables are linear. The Lowess Smoother Plot Figure 9.2.3 suggested that a linear relationship between length of stay and outcome was reasonable. The linear relationship between acute physiology score and outcome was assumed since the acute physiology score was constructed from the predicted log odds of mortality (i.e. a linear predictor) in the CMP data.

Chapter 11 Model testing and development

11.1 Introduction

In this chapter the variables selected in chapter 10 are used to construct a parsimonious prognostic model using the 651 patients without treatment limitations. This model, with 10 variables and 15 parameters, is described. A prognostic scoring system is then derived by approximation to the exact model coefficients, and the performance of this is tested.

11.2 The final parsimonious model

Table 11.2.1 shows the univariate and multivariate risk ratios for the variables in the final model.

11.3 Final parsimonious model in patients with and without treatment limitation

It was decided to produce the model for patients without treatment limitation (section 2.5.4). Using a model based on the final variables (but prior to bootstrapping) the model performed better in the patients without treatment limitation (n=651) than in the total group that included patients in whom treatment limitation decisions were made (n=832). In the total cohort of 832 patients the ROC for the parsimonious model was 0.7565 (Figure 11.3.1), compared to the value of 0.7750 in the 651 patients without treatment limitation (Figure 11.3.2). This is what would be expected given that prognostic models should take account of important treatments.

Table 11.2.1 Odds ratios for 180-day mortality for risk factors in final model

Variable/level	*Number (% of 651)*	*Number died (% of group)*	*Univariate odds ratio*	*Multivariate odds ratio†*
Length of stay			1.03 (1.00-1.06)	1.03 (1.00-1.05)
Age 45-64	285 (43.8%)	69 (24.2%)	1	1
Age 65-74	227 (34.9%)	82 (36.1%)	1.80 (1.23-2.64)	1.30 (0.84-2.00)
Age ≥75	139 (21.4%)	70 (50.4%)	2.24 (2.10-4.98)	2.07 (1.25 -3.44)
Female	340 (52.2%)	104(30.6%)	1	1
Male	311 (47.8%)	117 (37.6%)	1.35 (0.97-1.87)	1.43 (0.98-2.08)
Acute physiology score			1.03 (1.00-1.06)	1.03 (1.01-1.05)
MAC* ≥ 30 cm	277 (42.5%)	82 (29.6%)	1	1
MAC>25cm <30 cm	234 (35.9%)	77 (32.9%)	1.2 (0.8-1.7)	1.23 (0.80-1.88)
MAC >20 <25cm	119 (18.3%)	48 (40.3%)	1.6 (1.0-2.5)	1.73 (1.04-2.90)
MAC ≤ 20 cm	21 (3.2%)	13 (61.9%)	3.9 (1.5-9.7)	4.52 (1.55-13.14)
Not intubated	201(30.9%)	34 (16.9%)	1	1
Intubated	450(69.1%)	186 (41.3%)	3.5 (2.3-5.2)	3.88 (2.43-6.21)
"Pure" Asthma	78(12.0%)	8 (10.3%)	1	1
COPD & Asthma	104 (16.0%)	33 (33.8%)	4.07 (1.76-9.42)	2.73 (1.10-6.78)
"Pure" COPD	469 (72.0%)	179 (38.2%)	5.40 (2.54-11.49)	3.52 (1.54-8.04)
Fully mobile	189 (29.0%)	47 (24.9%)	1	1
Restricted	267 (41.0%)	92 (34.5%)	1.6 (1.04-2.4)	1.63 (1.02-2.60)
Housebound	176 (27.0%)	70 (39.8%)	2.0 (1.3-3.1)	1.90 (1.13-3.18)
Bed/Chair bound	19 (2.9%)	11 (57.9%)	4.2 (1.6-10.9)	3.80 (1.31-11.01)
Atrial fibrillation absent	587 (90.2%)	186 (31.7%)	1	1
AF present	64 (9.8%)	34 (53.1%)	2.4 (1.5-4.1)	1.63 (0.89-2.97)

† Using the final CAOS model i.e. containing the variables in this table.

** MAC = mid-arm circumference*

Figure 11.3.1 ROC curve for final model in the total cohort of 832

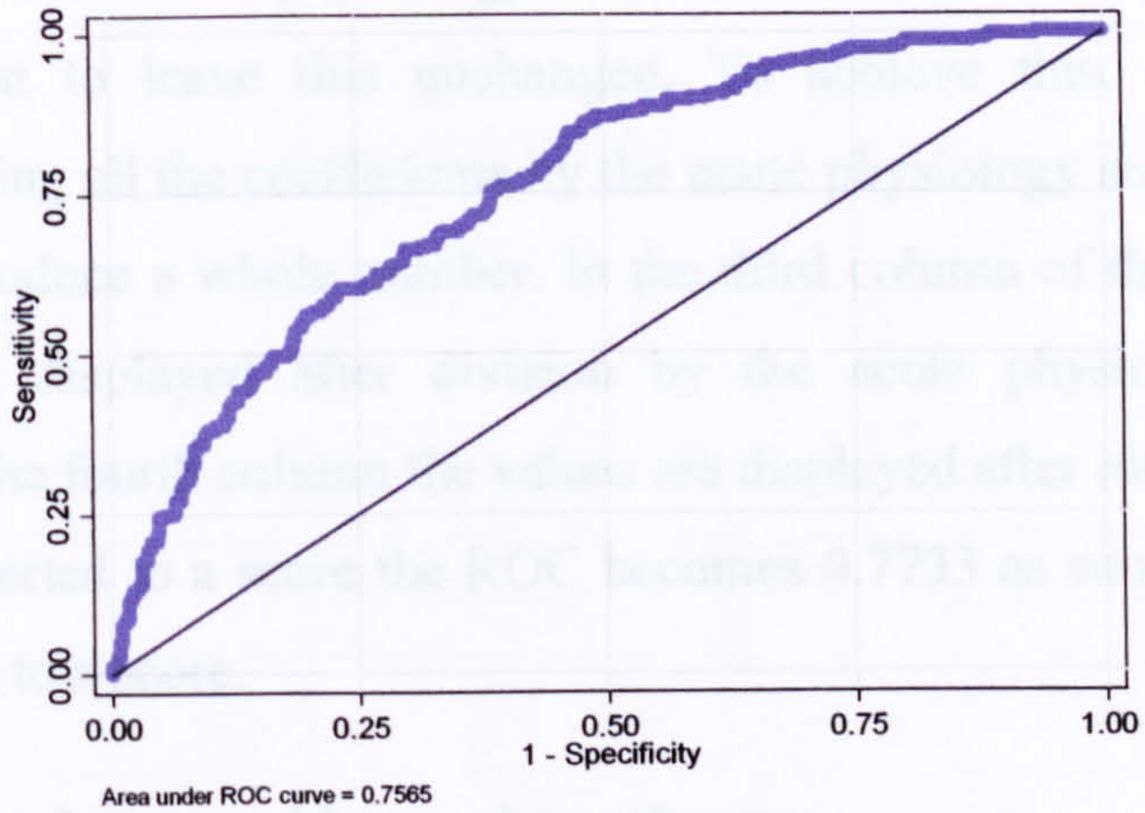
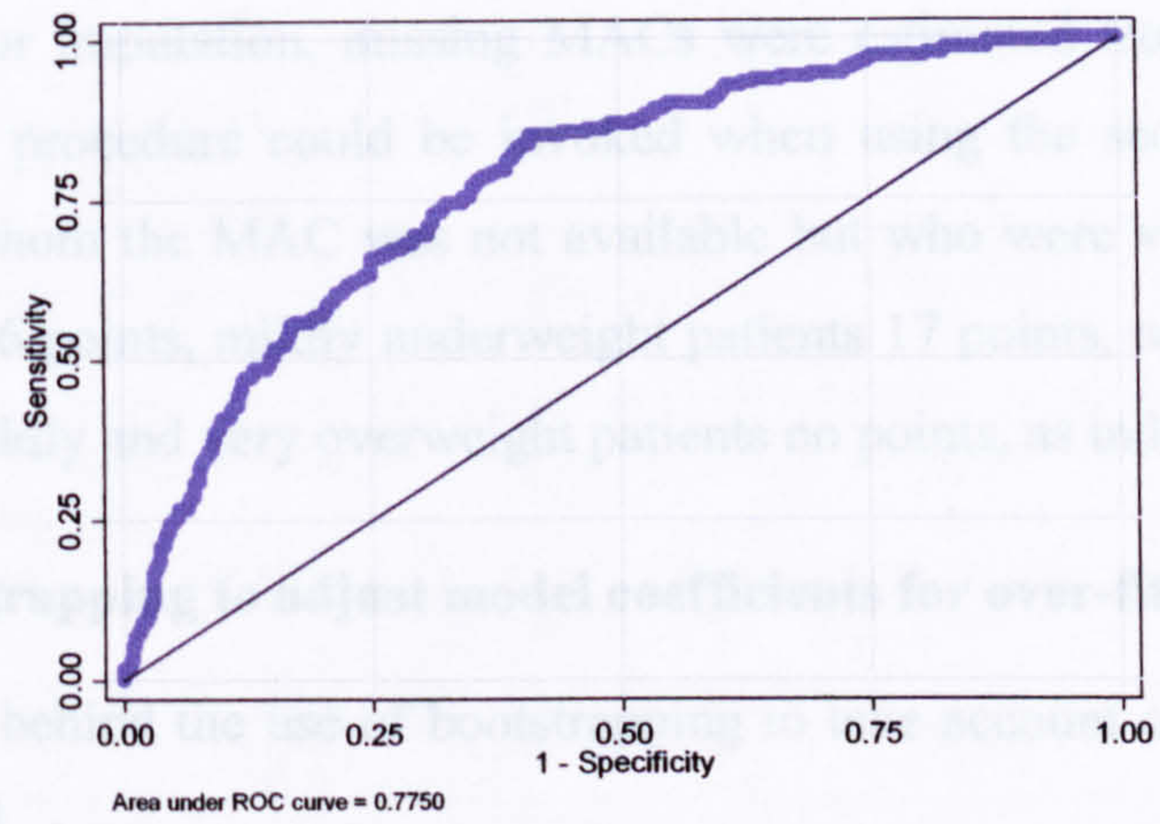


Figure 11.3.2 ROC curve for final model in 651 patients without limitation



11.4 Construction of risk scores

11.4.1 Converting individual risk factor coefficients to integers

To facilitate the use of the prognostic model in clinical practice the coefficients for the risk factors in the model were converted to integers. The resulting total score can then be easily calculated and used with a "look-up graph" displaying the risk of 180-day mortality for each score.

The coefficients in the original model are given in the second column of Table 11.4.1. The COPD specific acute physiology score took a value that ran from 0 to 100 and it was convenient to leave this unchanged. To achieve this, conversion to integers involved dividing all the coefficients by the acute physiology score coefficient and then rounding to produce a whole number. In the third column of the table the value of the coefficients is displayed after division by the acute physiology score coefficient (0.03278). In the fourth column the values are displayed after rounding. Once the model has been converted to a score the ROC becomes 0.7733 as compared to 0.7750 before the conversion to a score.

11.5 Missing data on mid-arm circumference

The mid-arm circumference (MAC) was missing in 22 (2.6%) of the 832 patients in the CAOS study and in 16 patients (2.5%) in the model building population. According to the strategy for imputation, missing MACs were estimated from bodyweight Likerts, and the same procedure could be invoked when using the score in clinical practice. Patients for whom the MAC was not available but who were very underweight would be allocated 46 points, mildly underweight patients 17 points, normal weight patients 6 points, and mildly and very overweight patients no points, as indicated in Table 11.4.1.

11.6 Bootstrapping to adjust model coefficients for over-fitting

The rationale behind the use of bootstrapping to take account of overfitting is outlined in section 2.11.

For the purposes of this analysis, the CAOS model was formulated as:

$$\text{predicted log odds} = \text{alpha} + \text{beta} \times \text{CAOS score}$$

The initial process of fitting the model in the sample of 651 produced the following equation

$$\text{predicted log odds} = -4.873 + 0.03218 \times \text{score}$$

Table 11.4.1 Converting individual risk factor coefficients to integers

Predictor	*Coefficient in original model*	*Raw value after division by 0.03278*	*Final score after rounding*
Length of stay	0.02773	0.846	1
Age 45-64	0	0	0
Age 65-74	0.2490	7.59	8
Age ≥75	0.7167	21.866	22
Female	0	0	0
Male	0.3747	11.43	11
Acute physiology score	0.032778	1	1
Mid-arm circumference ≥ 30 cm	0	0	0
Mid-arm circumference >25cm <30 cm or normal weight	0.1898	5.790	6
Mid-arm circumference >20 <25cm or mildly underweight	0.5422	16.542	17
Mid-arm circumference ≤ 20 cm or very underweight	1.4901	45.46	45
Not intubated	0	0	0
Intubated	1.35715	41.40	41
"Pure" Asthma	0	0	0
Mixture COPD & Asthma	0.8601	26.24	26
"Pure" COPD	1.1159	34.046	34
Fully mobile	0	0	0
Restricted	0.4600	14.035	14
Housebound	0.6209	18.94	19
Bed/Chair bound	1.3149	40.11	40
Atrial fibrillation	0.4899	14.94	15

The 651 subjects in the CAOS study can be considered as a sample from a larger population of people with COPD and/or asthma admitted to high dependency care and without treatment limitations. This equation provides the best predictions of mortality for this sample, but would in general perform less well on other samples from the same population. To adjust the CAOS equation to perform better on other samples, similar equations were derived for each of 500 bootstrap samples from the CAOS data, each bootstrap sample generating a slightly different intercept and coefficient. The process that modifies the original equation takes the form below.

Fit the original model (logodds = alpha + beta score) in the original dataset

We are now looking for "shrunk" estimates for alpha and beta to account for any overfitting. We take N bootstrap samples
For i = 1 to N
Fit the original model in bootstrap sample i, and calculate the predicted log odds from this model (logodds_i)
Fit the model (logodds = gamma0_i + gamma1_i logodds_i) in the original data
Store the estimates gamma0_i and gamma1_i
For the N bootstrap samples
Calculate gamma0 and gamma1 as the mean of gamma0_i and gamma1_i over the N samples
The shrunk estimates for alpha and beta are:

alpha_new = gamma0 + gamma1 alpha
beta_new = gamma1 beta

11.7 The discriminatory performance of the CAOS model in new populations

The second bootstrapping procedure is a form of internal validation of the model that provides an estimate of the discriminatory performance of the CAOS model in future patient populations. The assumption of this estimate is that though future populations may differ in their mix of patients, all the types of patients included in future populations would have been included in the original population. In other words the estimate of future performance assumes that the original population resembles future populations, and that temporal change will not produce important new combinations and characteristics in changes in the future patient populations but will merely affect the proportions of patients of different types. As a simplification if we are assuming that the

original population contained three types of patients ABC each comprising 33.3% of the original population, subsequent populations will still contain patients of the type ABC but in different proportions rather than patients of type ABD for example, where patient D is a patient type that was not represented in the original population at all.

The procedure involves fitting a model using the final parsimonious set of variables (i.e. length of stay, sex, acute physiology score, mid-arm circumference, diagnosis functional score, atrial fibrillation and intubation status) for each of a series of 500 bootstrap samples (which differ from the original 651 patients of the original model development set by random deletion and replacement of varying numbers of the original sample).

Model-fitting for each bootstrap sample produces a set of coefficients. The model using these coefficients is tested on its bootstrap sample and the area under the ROC curve is measured (ROC boot). The model is then tested on the original 651 patients and the area under the ROC curve is measured again (ROC original). This procedure is repeated for each of the 500 bootstrap samples and the average values of mean (ROC boot) and mean (ROC original) are calculated. There is no ideal number of samples for a bootstrap, but bootstrapping is a time (and computer) consuming process. Five hundred samples were chosen because once so many samples have been used little additional precision is obtained by using further samples and this is enough for it to be reasonable to expect that any optimism in the ROC estimate was 'small'. The difference between ROC boot and ROC original is a measure of the 'optimism' of the original model. The discriminatory performance of the original model in future populations is calculated by subtracting this measure of optimism from the ROC of the original model run in the original population.

In this case the estimate of optimism in the area under the ROC curve was 0.0190 (95% CI -0.0217 to 0.05685).

The original area under the ROC curve for the model developed as a score was 0.7733. Though moving from the original model with unrounded coefficients changed the ROC of the model from 0.7750 to 0.7733 the process of revising the coefficients by bootstrapping did not alter the discrimination of the model but merely altered the

calibration so the area under the ROC curve after the coefficients were revised by bootstrapping was also 0.7733. The estimate of the discrimination of the model in future samples is given by subtracting the measure of over optimism from the area under the ROC curve calculated using the final model in the original population:

Area under the ROC curve for the final model in the original population

= 0.7733

Estimate of over optimism in area under ROC curve

= 0.0190 (95% CI 0.0217 to 0.0569)

Estimate of discrimination in future samples

= 0.7543 (95% CI 0.7950 - 0.7164)

11.8 Development of look-up graph

The CAOS score can now be directly calculated as an integer score and this runs from 0 to around 300, though there is no absolute maximum since each additional day in hospital prior to critical care entry adds a further unit to the score. The CAOS total score corresponds to a probability of 180-day mortality. The two can be plotted against each other and the 95% confidence intervals can be estimated from the standard error of the linear predictor from the logistic regression model. The predicted mortality is plotted against the CAOS score in a look-up graph in Figure 11.8.

11.9 95% confidence intervals for group predictions

The 95% confidence intervals are for the group of patients with a given predicted mortality. If we wanted to represent the 95% confidence intervals around the CAOS prediction for an individual patient they would be much wider[15]. However the approach to decision making based on group probabilities is the usual one because it has a straightforward interpretation, i.e. “if I had 100 patients like you I would expect 70 to survive and 30 to die. What would you like to do?” They look relatively narrow on the graph but that is partly because of the log odds scale. As expected, in the areas where there are fewest patients i.e. at the highest and lowest scores, the 95% confidence intervals are wider. Figure 11.9

Figure 11.8 **Graph showing probability of 180-day survival according to CAOS score**

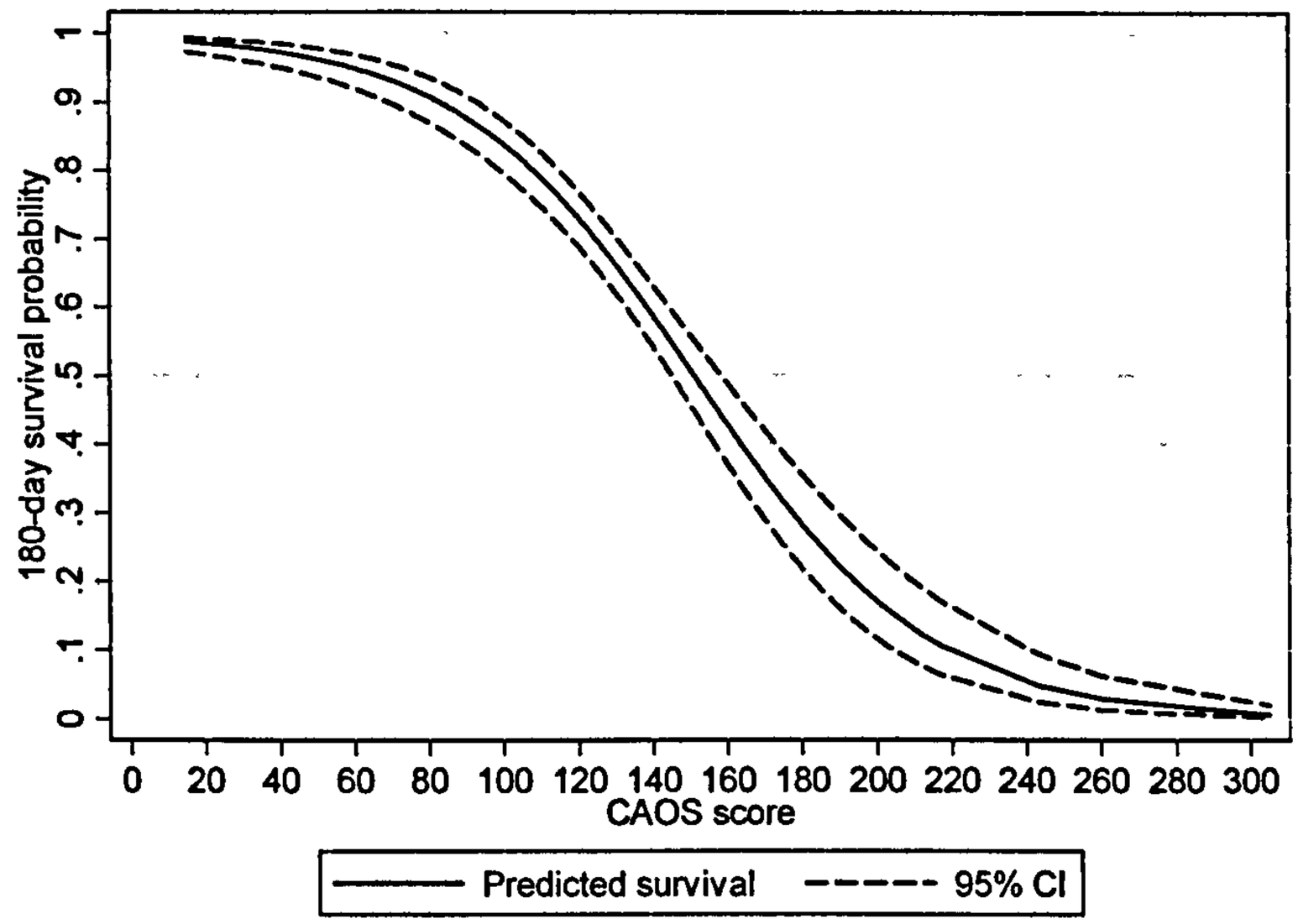
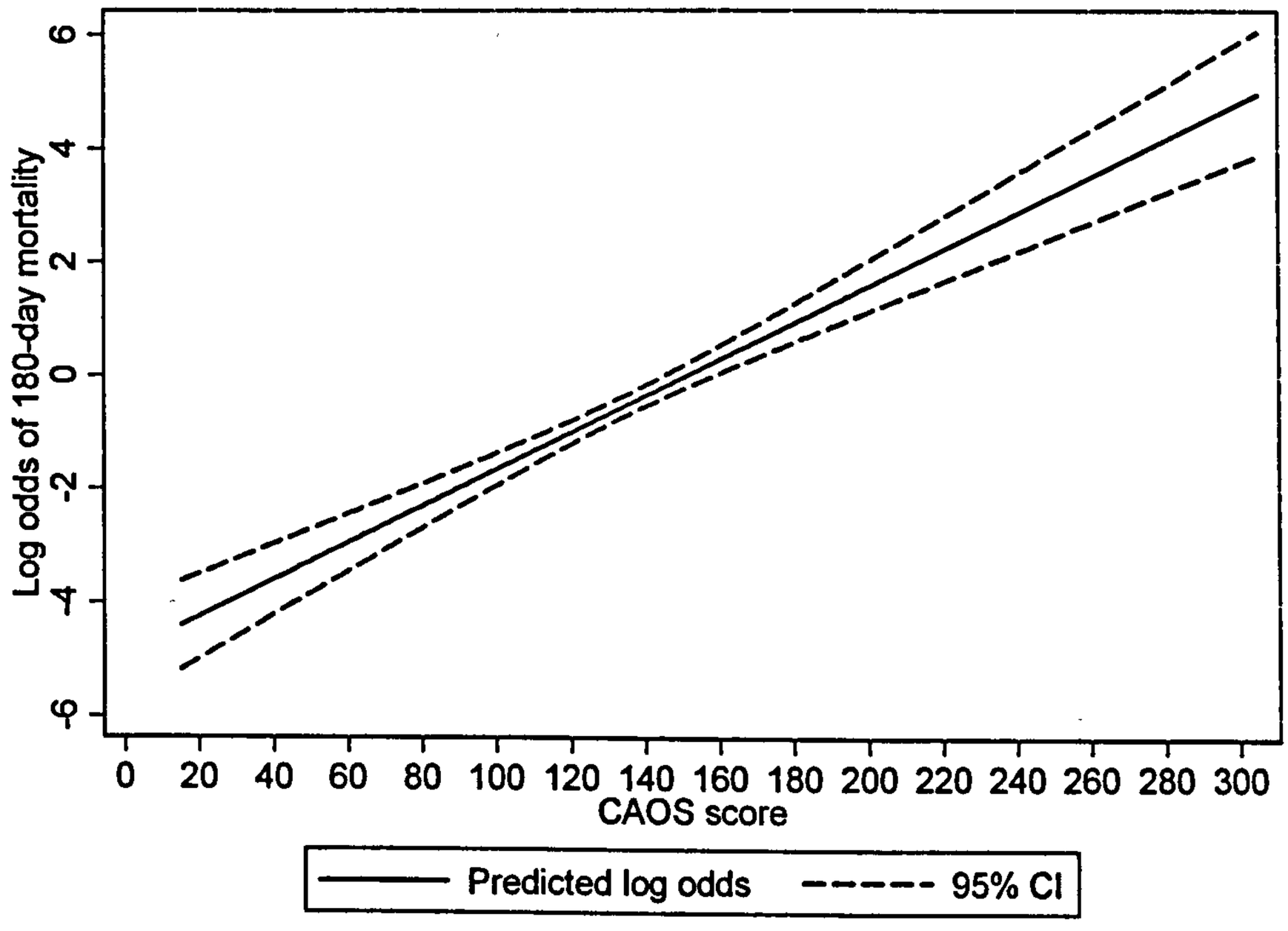


Figure 11.9 **95% confidence intervals around the CAOS model predictions**



11.10 Calibration curves

Calibration curves are a useful ways of describing the predictive performance of prognostic models. Patients are grouped in a number of equally sized groups and the mean predicted probability of 180-day survival for each group is plotted against the observed of 180-day survival. Calibration curves can also be plotted to show the proportion predicted to die versus the proportion actually dying. In Figure 11.10.1 a calibration curve is plotted for 10 equal sized groups comparing observed and expected survival rates. It can be seen that there is some variability in the predictions simply due to the relatively small size of the groups, and in Figure 11.10.2 the plot is repeated with four larger groups.

Figure 11.10.1 Calibration curve for 10 equal sized groups.

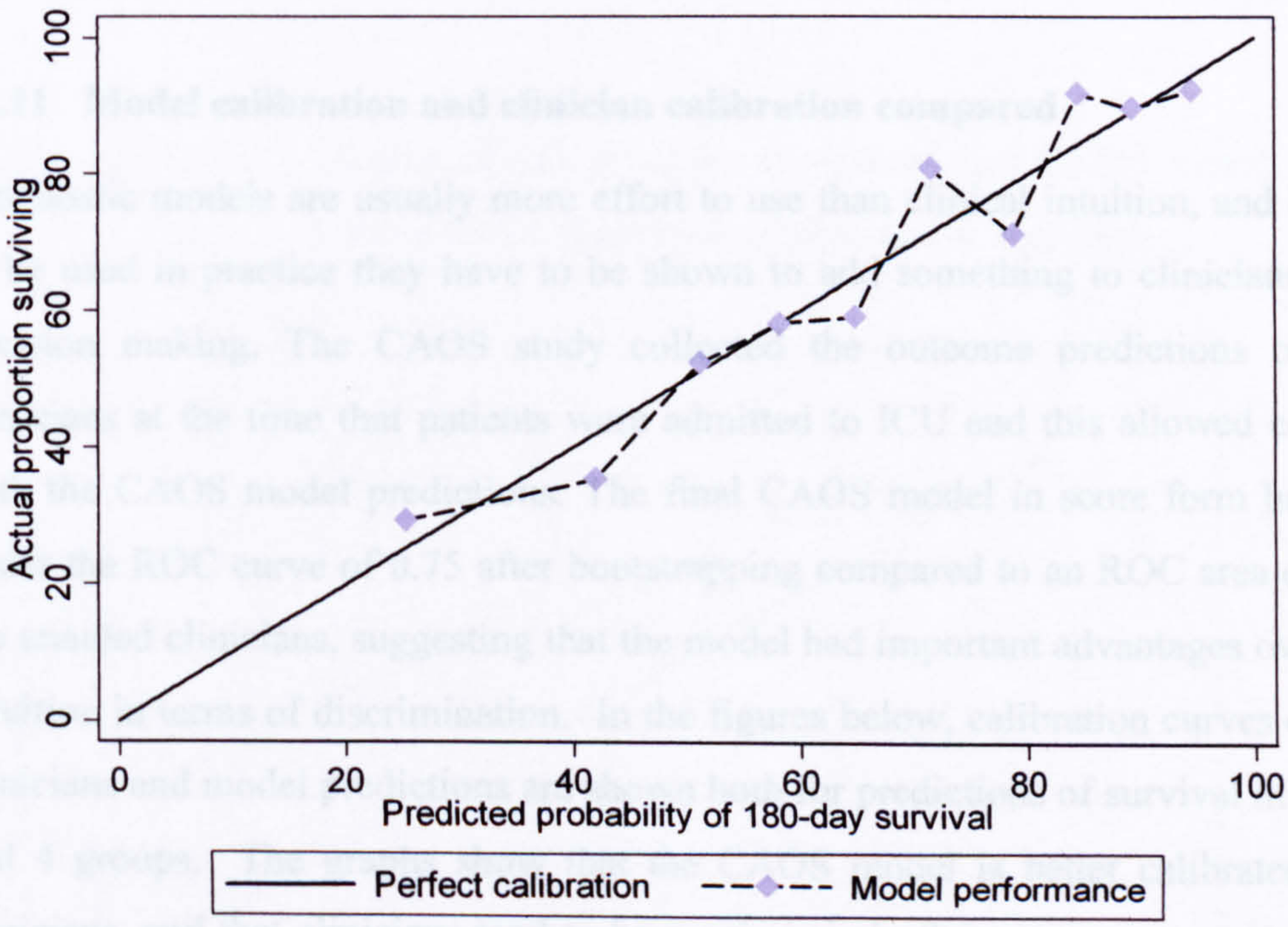
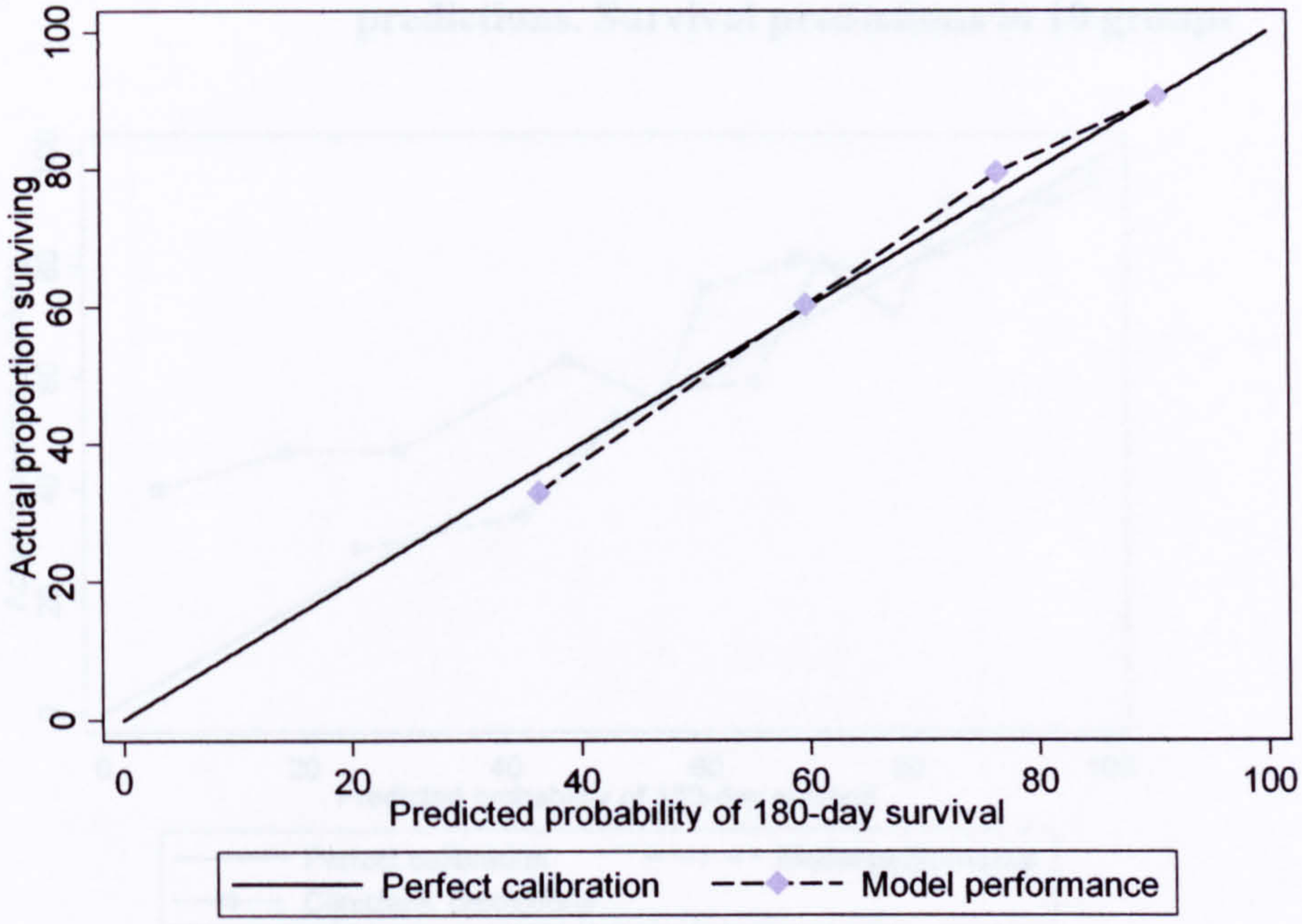


Figure 11.10.2 **Calibration curve for 4 equal sized groups**



11.11 Model calibration and clinician calibration compared

Prognostic models are usually more effort to use than clinical intuition, and if they are to be used in practice they have to be shown to add something to clinicians' unaided decision making. The CAOS study collected the outcome predictions of unaided clinicians at the time that patients were admitted to ICU and this allowed comparison with the CAOS model predictions. The final CAOS model in score form had an area under the ROC curve of 0.75 after bootstrapping compared to an ROC area of 0.71 for the unaided clinicians, suggesting that the model had important advantages over clinical intuition in terms of discrimination. In the figures below, calibration curves comparing clinicians and model predictions are shown both for predictions of survival in 10 groups and 4 groups. The graphs show that the CAOS model is better calibrated than the clinicians, and that clinicians tend to be pessimistic in the more severe patients. These findings are consistent with the findings of the Heart of England Critical Care Network study which suggested that clinicians were pessimistic compared to the SUPPORT model[8]. It is interesting to note the similarity between the calibration curve produced in the CAOS study and the calibration curve produced in the SUPPORT study.

Figure 11.11.1 **Calibration curves for clinicians' and CAOS model predictions. Survival predictions in 10 groups**

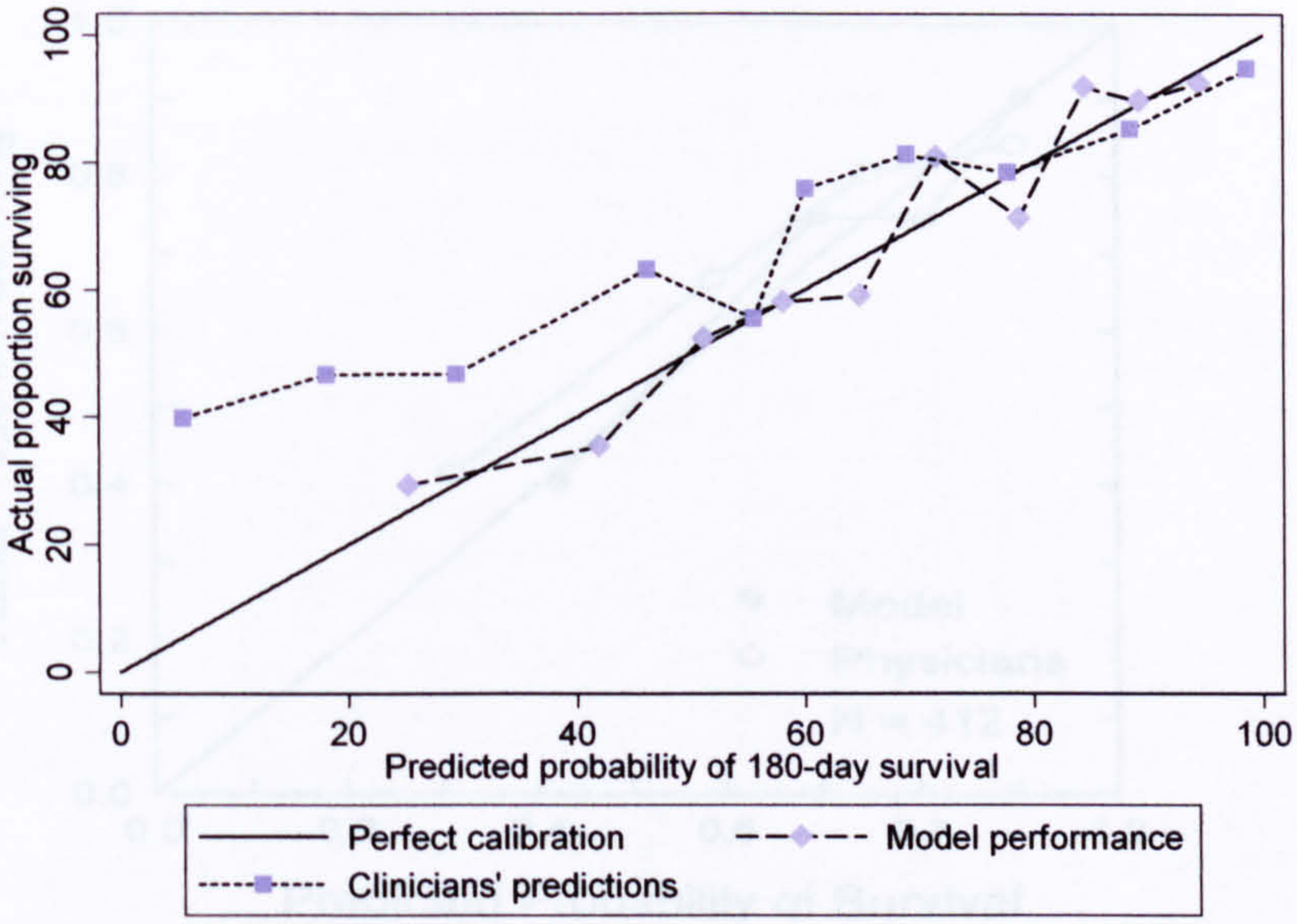


Figure 11.11.2 **Calibration curves for clinicians' and CAOS model predictions. Survival predictions in 4 groups**

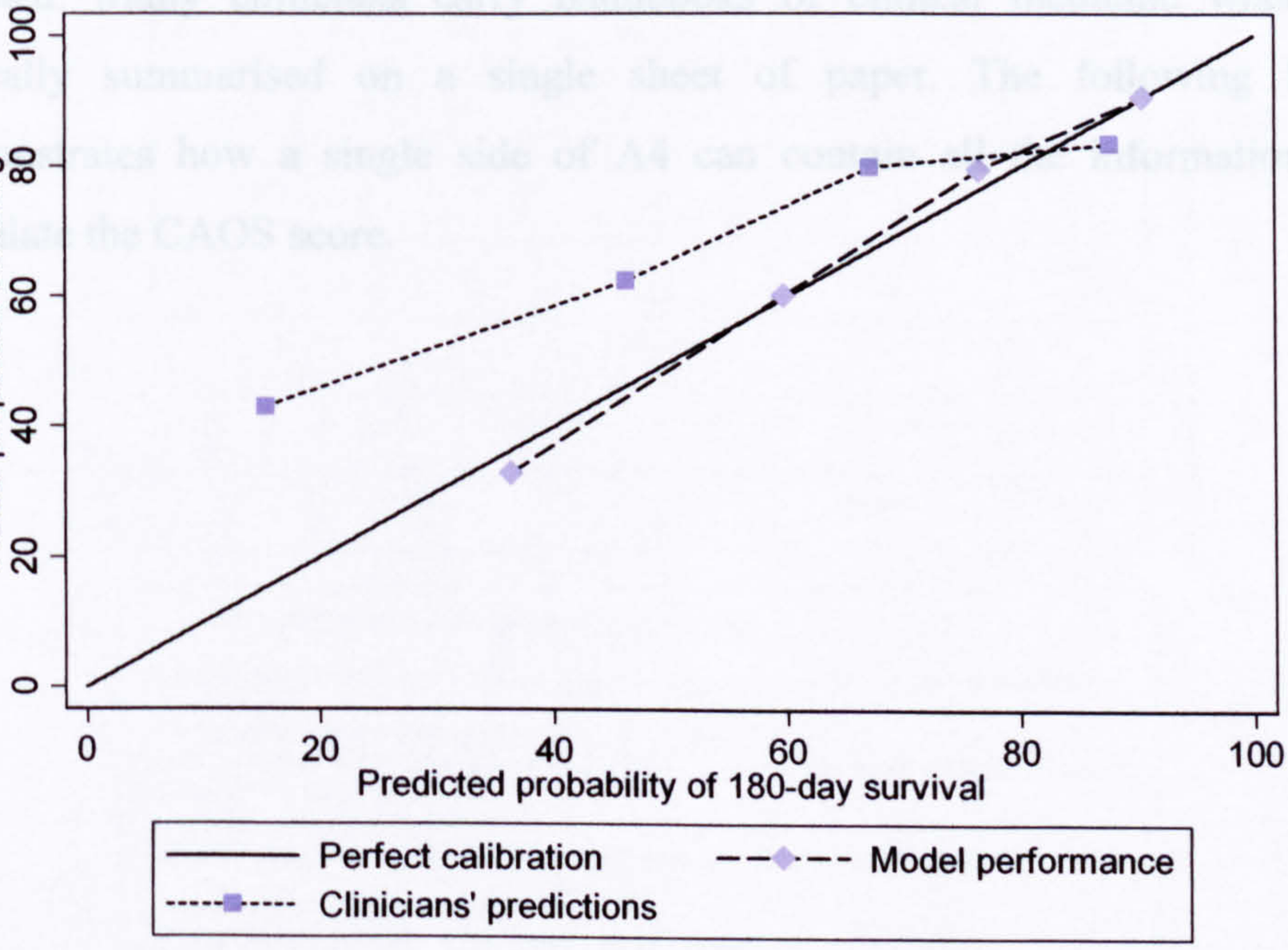
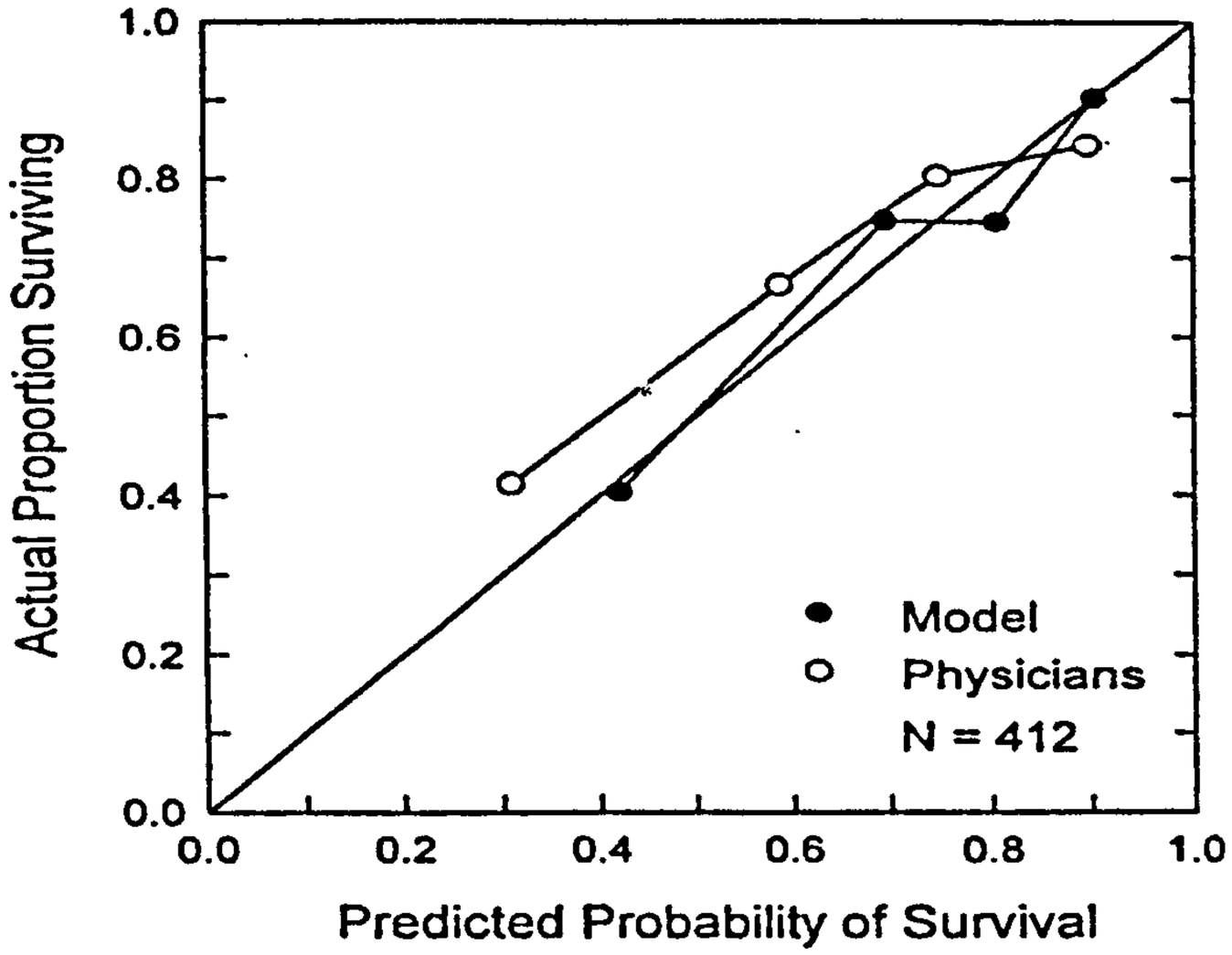


Figure 11.11.3 **Calibration curve for clinicians and the SUPPORT model predictions. From the SUPPORT study.**



11.12 Calculating the CAOS score

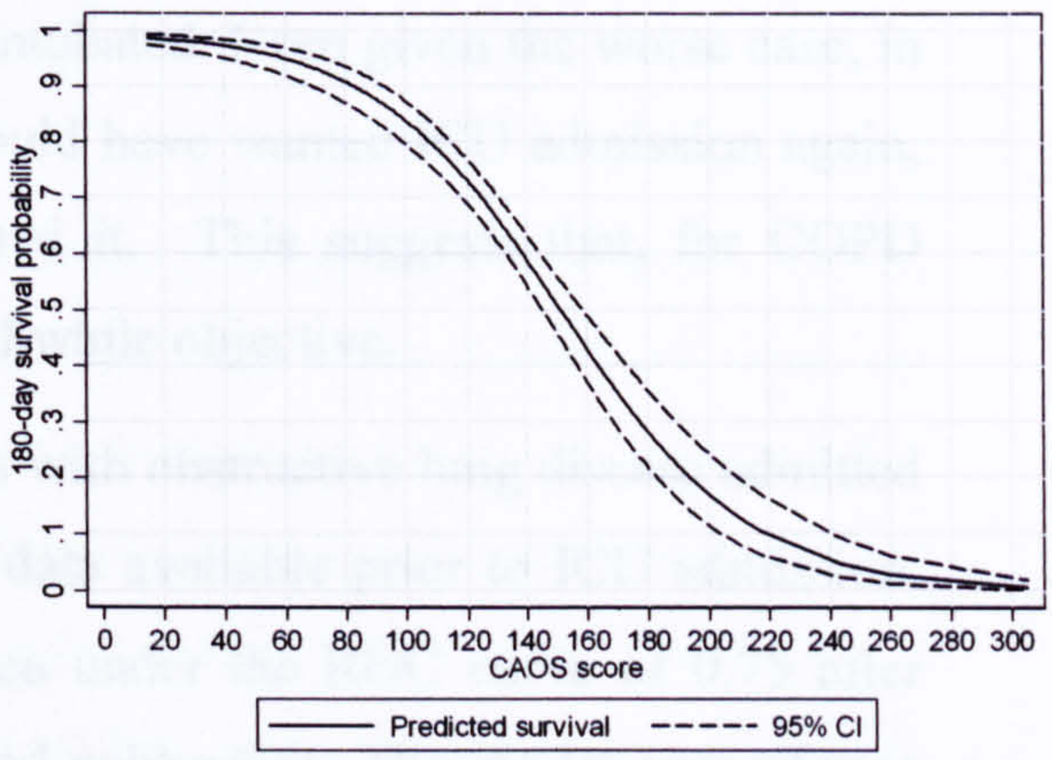
Using scores in clinical practice needs to be as simple as possible if they are to be adopted. Many clinicians carry handbooks of clinical medicine where topics are typically summarised on a single sheet of paper. The following Figure 11.12 demonstrates how a single side of A4 can contain all the information required to calculate the CAOS score.

Figure 11.12 Calculating the CAOS score

A Assess the patient and determine: 1) Length of stay. 2) Age. 3) Sex. 4) Acute physiology score. 5) Mid-arm circumference 6) Predominant cause of airway obstruction. 7) Functional capacity in period of stability prior to this exacerbation. 8) Heart rhythm
B Calculate the points the patient earns in each of the eight categories using the table below.
C Calculate the total points the patient has scored.
D Look up the predicted 180-day mortality corresponding to the total score using the predicted mortality graph below.

Predictor		score
Length of stay	Score 1 point per day in hospital	
	45-64 years	0
	65-74 years	8
	≥ 75 years	22
Sex	Female	0
	Male	11
Acute physiology score	Use total from algorithm below	
Mid-arm circumference MAC (cm)	≥ 30cm	0
	>25 <30cm	6
	>20 <25cm	17
	< 20 cm	45
Predominant cause of airways disease	"pure" COPD	34
	Mixed COPD & Asthma	26
	"Pure" asthma	0
Functional capacity	Fully mobile and living without assistance	0
	Able to live alone and get out of house to do basic necessities but severely limited exercise tolerance	14
	Cannot get out of house or gets out of the house rarely, able to perform self-care but unable to do heavy chores such as house cleaning, cannot live alone, may be institutionalised	19
	Bed or chair bound	40
Atrial fibrillation	AF present	15
Intubated		41

Predicted mortality graph



Heart rate	bpm *score*	< 80 *3*	80 – 109 *0*	110 – 129 *2*	130 – 149 *3*	150 – 169 *5*	≥ 170 *7*
MAP	mmHg *score*	< 40 *19*	40 – 49 *12*	50 – 59 *9*	60 – 69 *6*	70 – 89 *3*	90 – 99 *0*	≥ 100 *4*
pH	pH *score*	< 7.00 *9*	7.00 – 7.09 *6*	7.10 – 7.19 *3*	7.20 – 7.24 *1*	≥ 7.25 *0*	
Sodium	mmol/l *score*	< 130 *6*	130 – 134 *2*	135 – 144 *0*	≥ 145 *2*		
Urea	mmol/l *score*	< 2.5 *0*	2.5 – 6.7 *8*	6.8 – 11.9 *16*	12.0 – 17.9 *22*	≥ 18.0 *24*	
Creatinine	µmol/l *score*	< 150 *0*	150 – 199 *5*	≥ 200 *8*			
Albumin	g/l *score*	< 15 *20*	15 – 19.9 *14*	20 – 24.9 *8*	25 – 29.9 *6*	30 – 34.9 *4*	≥ 35 *0*
WBC	$\times 10^9$/l *score*	< 4 *7*	4 – 14.9 *0*	15 – 19.9 *1*	20 – 24.9 *4*	≥ 25 *7*	

Acute Physiology Score

1) Use the most extreme value from the last 24 hours.
2) Read off the score for each of the eight variables in the acute physiology score to produce a score between 0 and 100.
3) Add the points from the acute physiology score to the other components of the total score.

MAP: Mean Arterial Pressure; WBC: White Blood Count
Mean arterial blood pressure = (diastolic + diastolic + systolic)/3 e.g. 120/80 = 80 + 80+120/3 = 280/3= 93

Measuring mid-arm circumference (MAC)

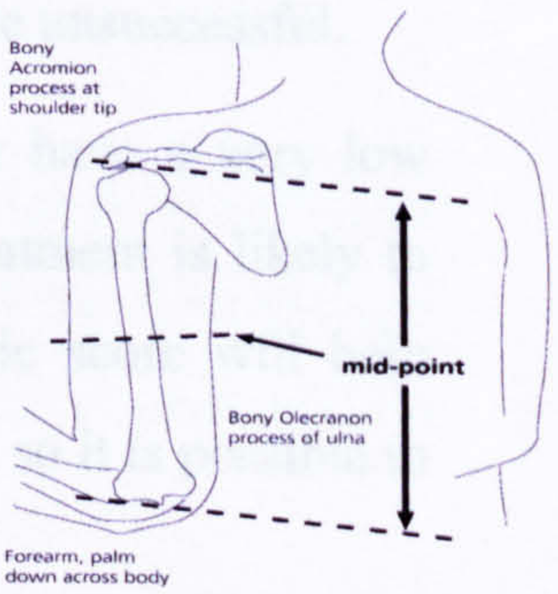
Use the non-dominant arm. For most people who are right handed this will be the left arm.

Finding the mid-point of the upper arm
Bend the arm to 90^O with the palm facing downwards in order to locate the landmarks.
Locate the tip of the shoulder.
Locate the bony tip of the elbow.
Mark the mid-point between the tip of the shoulder and the bony tip of the elbow.

Measuring the mid-arm circumference.
Having marked the mid-point, straighten the arm again.
Measure the circumference of the arm at the mid-point you have just marked.

Look up the score that corresponds to the MAC in cm

Identifying the mid-point of the upper arm



Chapter 12 Conclusions and implications

12.1 Statement of principal findings

Of 832 patients admitted to this study, 518 (62.3%) survived to 180 days and 420 (81%) provided answers to the follow-up health status questionnaire. Four hundred responders (95.2%) would want admission to the ICU again under similar circumstances, as would 204 out of 212 patients (96.2%) who had been intubated. Even given the worse case, in which none of the non-responding survivors would have wanted ICU admission again, over 75% of ICU survivors would have wanted it. This suggests that, for COPD patients, survival to 180 days after ICU is a worthwhile objective.

A model to predict 180 day survival for patients with obstructive lung disease admitted to ICU has been successfully developed using data available prior to ICU admission. The model has fair discrimination, with an area under the ROC curve of 0.75 after bootstrapping to adjust for 'optimism' and good calibration. The model outperforms clinicians in terms of discrimination (ROC area 0.71) and also in terms of calibration, the clinicians having a tendency to pessimism.

12.2 Using the score in clinical practice

The question is how to manage a patient with obstructive lung disease and respiratory failure who has not yet been admitted to ICU, and has deteriorated to the point at which intubation is at least a possibility. Intubation requires admission to intensive care. The issue then is, if their condition does turn out to be severe enough for intubation, whether their prognosis with intubation is good enough to make the intubation worthwhile.

The question of prognosis after intubation also arises when patients are started on non-invasive ventilation. The British Thoracic Society Guidelines recommend that at this point a decision should be made about whether to intubate if NIV were unsuccessful.

Some patients with obstructive lung disease and respiratory failure have a very low probability of survival, whether intubated or not. Escalation of treatment is likely to merely prolong the process of dying. Using the CAOS prognostic score will help identify these patients. The score includes a weighting for intubation, so it is possible to

get some estimate of the probability of survival either with NIV alone or with intubation. It should be noted that the "intubation variable" adds enormously to the score and identifies a group with a much worse prognosis. This is likely to be because intubation is an indicator for a group of prognostic factors not actually measured elsewhere in the score.

12.3 Strengths of the study

12.3.1 Representativeness

The study has collected prospective data from 95 units in England, Wales and Northern Ireland. Of these, 92 units were ICUs in the Case Mix Programme (CMP) and made up 51.7% of the 172 units in the CMP at the time the study was carried out (section 5.1.1 above). Using data from the CMP it was possible to compare the characteristics of 90 of these units with those of 80 units not involved in the study. It was found (Table 5.1.2) that in terms of hospital type, ICU type, numbers of ICU beds, % of admissions eligible for this study and mean COPD acute physiology score, there were no material differences between the units that participated and those that did not.

Data from the CMP also allowed comparison of the characteristics of 684 eligible patients in the participating units during the recruitment period who were included in the study (36.5%) and the 1189 that were not. (This number is less than 852 because it does not include those patients admitted to RHDUs [108] and because for some periods of CAOS data collection the CMP database was not yet cleaned and available for analysis.) They were similar in terms of ICU mortality, acute physiology score (APS), age, sex and day of admission. It seems reasonable to conclude that the patients recruited are representative of the type of patients admitted to UK ICUs with exacerbations of obstructive lung disease.

12.3.2 Rigorous model building

Study size is particularly important in this context because of the need to have sufficient power to develop a model with the number of predictors indicated by the literature review. With complete 180 day follow-up and data available prior to ICU admission on

651 patients without treatment limitation, this is the largest UK cohort and prognostic modelling study for COPD. The only other study to look at factors associated with survival after intubation in UK COPD patients was a retrospective study of only 42 patients[64]. Use of the CMP data set to develop a COPD specific acute physiology score avoided the problems of inadequate power that would nonetheless have occurred in weighting physiological variables.

Chapters 3 and 9 outline the approach to model building, which sought to avoid data-driven variable selection as far as possible. Bootstrapping enabled the model coefficients to be adjusted for overfitting, which should improve the performance of the prognostic model in other data.

12.3.3 An understanding of the quality of survival

A good response rate to the follow-up questionnaire interpreted in the light of sensitivity analysis provides the assurance that though patients who survive to 180 days will have many symptoms of obstructive lung disease, at least 75% of them, and probably nearer 95%, would want to be admitted to intensive care again under similar circumstances.

12.3.4 Feasibility of use

Informal feedback during the data collection helped to identify risk factors that it was practical to collect reliably. As a result the CAOS score is simple and quick to use in clinical practice. All the data required for the model should be readily available. The scoring sheet, that includes both the weights attached to patient characteristics and the look-up graph, easily fits on a single sheet of A4 that could be incorporated into a junior doctor's hand book or a hospital guideline (Figure 11.12). Calculating a CAOS score and reading off the survival probability can be accomplished in less than 5 minutes.

12.4 Weaknesses of the study

12.4.1 Selection bias

To make the study feasible, all the patients recruited to CAOS had to have been selected for admission to ICU. However the prognostic score is intended for use with patients who are being considered for escalation of treatment prior to the process of selection either for admission to ICU or admission to an area where NIV can be used. As such the score is intended for use amongst patients not yet selected for ICU yet the data collected in CAOS suggests that only a proportion of these patients will be selected for unlimited treatment (section 9.7.1). A careful exploration of the likely extent of selection bias and its potential implications is crucial in understanding the limitations of the CAOS model in these patients who have not yet entered ICU in order to understand its limitations in clinical practice.

12.4.2 The implications of selection

A crude representation of the population of hospitalised COPD patients with respiratory failure might involve a continuum running from those with an excellent prognosis if admitted to ICU and intubated as required, to those who have entered a phase of terminal respiratory failure in whom intubation might be considered most likely merely to prolong the process of dying (Figure 12.4.2). If clinicians taking part in the study consistently admitted only patients with an excellent chance of survival with ICU, only patients in the left hand portion of the continuum in Figure 12.4.2 will have been recruited to the study. A model developed only in the left hand portion of the population used to make predictions about those patients in the right hand portion (the sickest patients) would be likely to be over-optimistic.

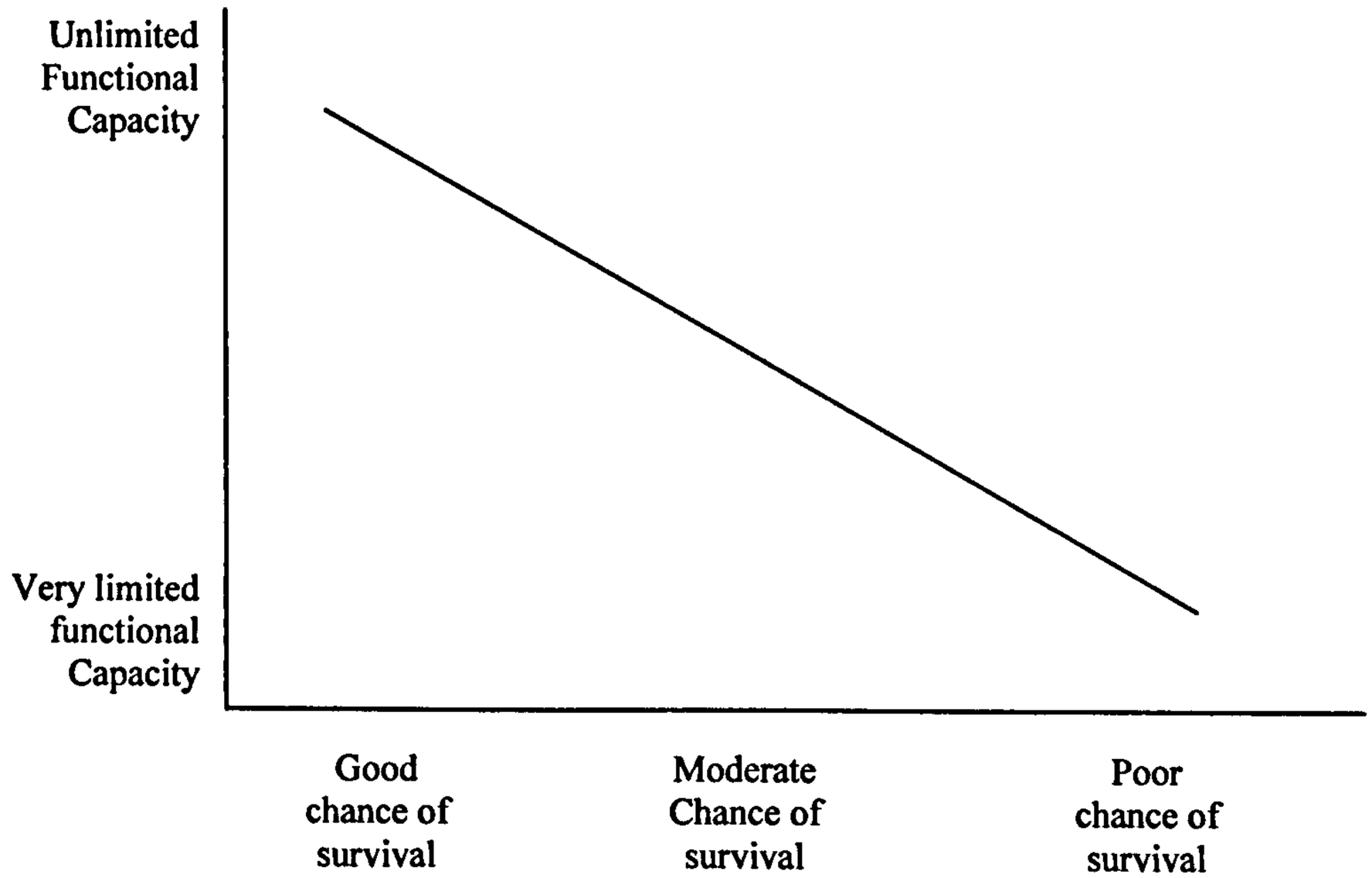
However the degree of consistency in selection will have an impact on the consequences for risk factors identified in the model development process. Suppose there were data on only 2 risk factors, age and sex, with women on average having poorer outcomes. Doctors might consistently only admit women who had the same prognosis at given a age as men, i.e. they might be more selective of women than men.

Then sex would not emerge as a factor in the model. Applying the model in the wider population would lead to optimistic estimates for women.

Another scenario helps to illustrate the complexity of selection. Suppose that half the doctors take sex into account and half do not. On average the women in the study will be healthier than the wider population, although not as healthy as the men in the study. Sex will appear in the model as a factor, but the weighting will be underestimated.

Suppose anyone over 85 has a survival rate below the threshold at which clinicians switch from admitting to not admitting Most doctors will not admit them, but as long as those that do admit them pick over 85s who are not unusually healthy, the model will give advanced age the correct weighting.

Figure 12.4.1 COPD patients considered for ICU admission



12.4.3 Evidence for selection in the CAOS sample

Some light can be thrown on the types of patient likely to have been 'selected out' of the CAOS study by considering the factors associated with treatment limitation for

patients who were included. Also there are some data from other studies about the characteristics of the broader population of patients with exacerbated COPD, and these can be compared with data on the CAOS subjects (section 9.7.1, 9.7.6.iv and 9.7.6.v above). These comparisons suggest that selection did occur with a tendency for older, frailer patients to be less likely to be admitted to ICU and thus to enter CAOS. This finding is consistent with the suggestion in the Heart of England Critical Care Network Study that in the UK a historic lack of ICU beds has lead clinicians to form a nihilistic view of the prognosis of COPD patients to minimise the cognitive dissonance that would otherwise arise if patients were felt to have a good chance of survival with ICU, yet no ICU beds were available. However with hundreds of judges making decisions in 95 centres selection is unlikely to be consistent.

12.4.4 Baseline risk in the model

The baseline risk for the CAOS ICU patients will be lower than for the wider population of COPD patients if there are important prognostic factors that are not included in the model, and which are under-represented in the ICU population. The initial selection of variables in the model was based on the scientific literature and SUPPORT, the best of these studies, was a total cohort study that developed a risk adjustment model on all patients admitted to hospital irrespective of whether they were admitted to ICU. It is noteworthy that the distribution of ADLs in the SUPPORT study was higher than in CAOS suggesting that patients with greater numbers of ADL impairments tended to be selected out of the CAOS study.

However there is good reason to believe that there is a good deal of variation in ICU selection processes. In the wider medical literature it is reported that even when there are reasonably clear criteria about the appropriateness of treatments, some patients who according to accepted criteria should not receive a treatment do receive it and some who should receive the treatment do not. In Hemmingway's study of coronary artery bypass graft surgery (CABG) in patients investigated by angiography, 23% of 992 patients who underwent CABG had indications for CABG rated as inappropriate or uncertain[31]. In the case of decisions about which patients with COPD should be intubated, the available

recommendations are vague ('The decision on which patients with exacerbations of COPD who will benefit from intubation is difficult and involves balancing health status with an estimate of expectation of survival'[4]), and the majority of studies that might inform predictions of outcome are of poor quality with highly variable estimates of survival (Figure 3.3.1). In the Heart of England Critical Care Network study of clinicians who had made a median of ten (IQR 6.0-20.0) intubation decisions in the previous 12 months[8], different decisions were made for COPD patients with identical characteristics and identical preferences, in the face of identical availability of resources. The Heart of England clinicians also varied widely in their opinions about the hospital survival rate at which they would move from admitting to not admitting a patient with COPD to ICU; some clinicians suggested that they would intubate patients even if they thought they had a 90% probability of hospital mortality.

One of the strategies in CAOS for limiting the effects of selection bias was to recruit from a large number of ICUs so that it was likely that any single unit would recruit only a small proportion of the total patients and any individual clinician even smaller. Variation in overall unit clinical thresholds, in individual decision-maker thresholds, and in the consistency in the operation of these thresholds would be expected to result in all the patient *types* that some clinicians somewhere would consider admitting having been recruited to CAOS. With 95 units contributing patients it seemed likely that this inconsistency in gatekeeping strategies would mean that the recruited patients would be spread along most of the continuum of severity (Figure 12.2.1), even if their distribution along this continuum was not representative of the wider population of people with exacerbation of COPD. On this basis it can be argued that the model is unlikely to have omitted important prognostic factors entirely.

Thus with at least 95 judges all making independent decisions, it seems likely that selection will have been inconsistently applied; high risk groups will be under-represented but not totally unrepresented, and the main prognostic factors should have been captured by the model. One outstanding question is whether any of the factors that were rejected because they were difficult to measure might otherwise have had material prognostic value.

12.4.5 Risk weightings for predictors in CAOS and SUPPORT compared

Though it might be hoped that comparison of the weightings given to risk factors that are common to the CAOS model and to the best total cohort study in the literature (SUPPORT), might give a rough indication of whether CAOS is correctly weighting risk factors, such comparisons are bedevilled by problems of selection. In SUPPORT the patient population were less sick with only 51% requiring ICU admission compared to 100% in CAOS. Table 12.4.5 below illustrates that the point estimate of risk in CAOS per 10 year increase in age is higher than in SUPPORT though the 95% confidence intervals overlap. This is consistent with the patients in CAOS being sicker. It is interesting that the point estimate of the risk with increasing age is actually lower in the patients not for intubation presumably because younger patients selected not for intubation are biologically older than their chronological age.

This comparison highlights that the model will only be accurate in a population with identical inclusion criteria.

Table 12.4.5 Age related mortality risk in CAOS and SUPPORT

	SUPPORT* 1016	CAOS 832	CAOS 'for intubation' 651 patients	CAOS 'no intubation' 181 patients
Age (per 10 years)	1.30 (1.14-1.47)	1.68 (1.44-1.97)	1.67 (1.39-2.01)	1.43 (1.03-1.98)

* SUPPORT presented risk as a Hazard ratio, in CAOS the risk is odds of death at 180-days

12.4.6 Lead time bias

Lead time bias can be important in risk scoring, and the CAOS score does not allow weighting for acute physiology measured after a period of NIV during which the patient continues to deteriorate. This means that the score may be over optimistic in patients

who deteriorate despite many hours of NIV. Consequently though the use of the intubation variable gives some idea of what the patients' prognosis would be if they were to be intubated. The limitations of the observational design of the study mean that unmeasured selection processes may have influenced the use of intubation for patients treated with NIV who deteriorate after ICU admission. The acute physiology measured prior to ICU will be likely to be different to the patients' acute physiology after a period of unsuccessful NIV. For this reason survival probabilities after intubation are likely to be relatively robust for those patients intubated at the time of ICU admission. Probabilities of survival that estimate the likely survival of a patient admitted to ICU for NIV who subsequently requires intubation should be considered extrapolations that go beyond the data collection methodology of CAOS and should be treated as highly speculative. It is most likely that estimates of survival if intubated, for patients who are not intubated immediately (i.e. if patients deteriorate despite treatment in ICU) will be optimistic since the model does not take account of deterioration despite treatment which as mentioned above is a form of lead time bias that typically has an important influence on risk adjustment models.

12.4.7 The role of non-invasive ventilation

As discussed in section 3.4.17 systematic reviews have suggested that non-invasive ventilation (NIV) is the optimal first line treatment for patients with Type II respiratory failure due to exacerbations of COPD [3 119 120], though there are some limitations to the generalisability of these results because patients who required immediate intubation were excluded prior to randomisation.

At the time CAOS was carried out, some units did not have NIV available or had NIV available intermittently, and so some patients would have been intubated who might have been successfully managed with NIV.

As discussed in section 12.2 the application of the CAOS model to patients who have deteriorated despite hours or days of NIV might be prone to error because the prognostic significance of the acute physiology score is likely to be different for patients who have had hours of treatment with NIV compared to those who are largely

untreated. The CAOS dataset did not provide for a distinction between acute physiology measured before, during or after NIV, and users of the CAOS model should bear in mind that if the acute physiology used to compute the CAOS model probability follows many hours of failed NIV the predictions may well be overoptimistic.

12.5 CAOS in practice

12.5.1 Implications of selection bias for the use of the CAOS model

Perfect prediction of outcomes is not possible, and a judgement about the appropriate role of the CAOS model in decision making cannot be made without a careful consideration of the alternatives. A decision-maker attempting to decide whether a patient with COPD will benefit from intubation has only four alternatives, to use clinical intuition alone, to use CAOS alone, to use CAOS alongside clinical intuition or to conclude that since all predictions are uncertain the appropriate response in the face of uncertainty is to institute life supporting therapy in all cases and then reassess. It should be remembered that clinicians' predictions arise from an intuitive model developed from their experience, and their interpretation of the evidence base. The evidence from studies of human decision-making makes it clear that human decisions are not free from bias (section 1.5) and in Table 12.5.1 below the biases affecting both the CAOS prognostic model and an individual clinicians' intuitive prognostic model are compared.

This suggests that though predictions derived from the CAOS model will have limitations, the major competing probabilities that come from a single clinician's intuition are likely to be even more influenced by selection and other biases. The results of both CAOS and SUPPORT[12] demonstrate that when clinicians and the model make predictions for the same patients the prediction models show better discrimination and calibration. It is likely therefore that, for the type of patients used to develop the CAOS model, the best prognostic estimates are likely to be obtained when the CAOS model is used alongside clinical judgement. This assertion is consistent with the findings of the SUPPORT study, where the most accurate predictions occurred when clinical judgement and the SUPPORT model were used together[12].

However there is strong evidence that selection has played an important role in the patients included in CAOS, and this must be borne in mind when applying the model. For example, comparison with SUPPORT suggests that patients with ADL impairments were unlikely to reach ICU in the UK (section 8.5.1) and this highlights the fact that the CAOS has model has been developed on patients selected to be less frail than the total population of COPD patients admitted to hospital. Users of the CAOS model should be aware of the limitation that selection has imposed on the model, and recognise that patients who would tend to be rejected by many ICUs will not have contributed to the CAOS model and that the model is likely to be overoptimistic if applied to such patients. These will tend to be the patients with multiple comorbidities, impaired ADLs and/or on LTOT.

12.6 Future research

It will be clear that though the study had the advantages of recruitment across many units only 53% of all units took part and only 40% of eligible patients were recruited. This has the potential to introduce bias. Only around 40% of the patients eligible for CAOS were recruited and section 5.3.1 to 5.3.6 shows that there were no systematic differences in the ICU mortality, acute physiology score, age, sex, day or hour of admission between patients eligible for CAOS and those actually recruited and it seems most likely that patients were missed at random. There were a limited number of data collectors in each unit who would typically work shifts and it was found that when these unit "champions" were away patients tended to be missed. Nevertheless since the model has only been developed in a subset of all the units in the UK and in a subset of the patients admitted to those units, selection bias in the patients recruited to CAOS cannot be excluded. In addition as section 12.4.1 above makes clear it is inevitable that selection has occurred in that patients admitted to CAOS had to be selected to enter ICU. The fact that CAOS model was produced on a subset of all UK COPD ICU admissions and that selection was involved in making the decision about which patients actually entered ICU means that external validation of the model is particularly important. External validation will need an adequate sample size (In order for the validation to be meaningful Harrell suggests the sample needs to contain around 100 events[33], in England, this would be likely to require 95 units collecting data for 9 months, or 48 units collecting data for 18 months) and until advances such as the electronic patient record allow automatic data collection such a study will be a major undertaking. This makes it clear that the next step is for a validation study to be carried out in which the raw data collected in CAOS is collected in a new sample. This will allow validation of the original score to be carried out and also offers the potential to allow the score to be recalibrated if behaviour is changing.

Table 12.5.1 Implications of bias: clinical intuition and CAOS compared

Bias	*CAOS*	*Impact*	*Clinical intuition*	*Impact*
Selection bias	651 "decisions" by > 95 individual decision makers with evidence of only moderate discrimination (ROC 0.71) with studies suggesting that clinicians stated admission thresholds can vary from admitting patients with predicted hospital mortality of 90% to predicted mortality of 45%[8].	Patients from much of the continuum of severity might be expected to be selected so that final model will have been influenced by characteristics across the spectrum. Adjusting calibration by bootstrap estimates of alpha & beta will increase contribution of relatively rarer characteristics in final model.	Typical ICU admits 400 patients per year of which 2.5% are COPD patients; so that in an average year a hospital might intubate around 10 COPD patients & an individual many less. Even if a clinician admitted and remembered all 10 of these patients in 5 years only 50 patients would be sampled using one clinician's selection process.	Any individual will have "learnt" from a narrower range of patients than the model and will have been operating only their own selection criteria and so their intuition will be likely to be informed by a more selected sample than CAOS.
Availability bias in identifying predictors	Predictors in CAOS identified by systematic review of literature and independently weighted in model	Model can take fair account of independent contribution of multiple cues	The cues selected will be the ones remembered possibly from a non-systematic recollection of the literature and the weight given to individual cues may be biased by patients who are memorable because they did particularly well or badly.	A limited number of cues are likely to be used with weights that have not been systematically developed.
Incomplete follow-up	180 day follow-up was complete	Outcome predictions use all information.	180 day follow-up for all patients unlikely to be complete	Feedback on association between predictions and outcome unlikely to be complete leading to poor calibration.

The outcomes in the group could then be assessed without the problems of selection and if outcomes were deemed satisfactory the exercise might be repeated extending the inclusion criteria to a sicker group.

12.6.2 Strategies to deal with the effect of treatment

Many patients will be considered for intubation after a period of unsuccessful NIV (section 12.4.2). The CAOS study did not collect data on the duration of NIV prior to intubation, nor was it possible to determine whether the acute physiology was measured before or after a period of NIV. Not collecting this data was a pragmatic decision in order to keep data collection simple and quick; the data collectors were all volunteers who collected the CAOS data in addition to their normal duties. If sufficient resources could be obtained, future studies might also be designed to take greater account of the effects of NIV on the acute physiology used in the model by carefully documenting the duration of any NIV delivered before or during the measurement of the CAOS acute physiology score.

12.6.3 Evaluation of the CAOS score in clinical practice

Evaluation of the CAOS score in clinical practice is not straightforward. Harrell suggests that a data set with at least 100 events would be required (section 2.8.1 above). Given that 95 units recruiting patients for around 18 months yielded 221 deaths, an adequately powered evaluation study will be a major undertaking. This is an important problem in the use of prognostic scores, and improvements in the quality of routine data, perhaps via evolution of the electronic patient record, might eventually make ongoing evaluation of scores a more feasible proposition. In addition changes in practice are likely to affect the performance of scores, especially in terms of calibration, which is another reason why readily available data to carry out evaluation of prognostic scores are so important.

12.6.4 More sophisticated modelling strategies

Given a certain data set there will often be several models that fit the data equally well. In the development of the CAOS model as far as possible it was attempted to use data-

independent methods in variable selection. However more sophisticated approaches to variable selection are now being developed that may make models more generalisable. For example bootstrap methods can be used in variable selection and such an approach might go some way to minimise the impact of the case mix of the model development data set on the variables selected[143 144]. Such sophisticated modelling approaches were not possible within CAOS, but would certainly be worth exploring in the future.

12. 7 Conclusions

CAOS has shown that data readily available prior to ICU admission have the potential to give fairly accurate predictions about the 180 day survival of patients with COPD. Follow-up of patients suggests that despite many symptoms of airways disease the majority of survivors would want to go through ICU again. Clinicians were less well calibrated than the model with a tendency to pessimism. The major drawback of the CAOS model is that it has only been developed on patients selected for ICU. This means that caution should be exercised when using it. Clinicians should be aware that the model has mainly been developed on patients without impairments of daily living and that it will tend to give falsely optimistic predictions of outcome for frailer patients with multiple comorbidities. A sensible strategy would be to suggest that it would be appropriate to use the model alongside clinical judgement to predict outcome for COPD patients assessed outside ICU, with the caveat that selection bias should be borne in mind, and that the model should only be used for patients whom at least a significant proportion of clinicians would consider appropriate for ICU.

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Appendix 1

Sensitive search strategies, studies describing the outcome for COPD patients

Appendix 1

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Sensitive search strategies to identify studies describing the outcome for COPD patients

Ovid Medline sensitive prognosis filter

1) exp Incidence
2) exp Mortality
3) exp Follow-Up Studies
4) mo.fs
5) prognos$.tw
6) course.tw
7) predict.tw
8) or/1-7
9) exp lung diseases, obstructive
10) 8 and 9

Ovid Embase sensitive prognosis filter

Taken from the CASP website

http://www.phru.nhs.uk/casp/filters.htm#findingfilters and accessed 2.3.04

1) incidence/
2) exp mortality/
3) cause of death/
4) fatality/
5) survival rate/
6) follow up/
7) prognos$.tw.
8) predict$.tw.
9) course.tw.
10) or/1-9
11) exp chronic-obstructive-lung-disease
12) 10 and 11

Appendix 2

Letter to CMP units from Dr Kathy Rowan

ICNARC

Intensive Care National Audit & Research Centre

12 November 2001

«DIR_TITLE» «DIR_INIT» «DIR_SURN»
«DIR_PRF»
«UNIT»
«HOSPITAL»
«ADDRESS1»
«ADDRESS2»
«TOWN»
«COUNTY» «POSTCODE»

Dear «DIR_TITLE» «DIR_SURN»

Research and the Case Mix Programme
Through a broad programme of research, ICNARC is seeking to help critical care practitioners by encouraging and supporting collaboration between individuals/units with similar interests. In relation to this, I am pleased to announce a new research project to run in parallel with the Case Mix Programme. The project is a collaboration between units participating in the Case Mix Programme, ICNARC and the Health Services Research Unit, London School of Hygiene & Tropical Medicine. The initial details of this project are outlined below.

COPD and Asthma Outcome Study (CAOS)
The aim of this Study is to investigate the factors that affect the short- and medium-term outcomes of admissions to critical care units with COPD and asthma. These conditions are likely to represent less than five percent of admissions to most units. By collecting a minimal amount of additional data, over and above those collected for the Case Mix Programme, we hope to provide important prognostic information to guide patients, relatives and clinicians. The Study will be co-ordinated by Dr Martin Wildman, Medical Research Council (MRC) Training Fellow in Health Services Research and Specialist Registrar in Respiratory Medicine.

We hope you will want to participate in this new and exciting project. Please register your interest, or not, by completing and faxing the enclosed form to ICNARC. The Study Co-ordinator will then send you more detailed information.

Yours sincerely

Dr Kathy Rowan
Director

Enc

ICNARC

Intensive Care National Audit & Research Centre

Facsimile

To:	Dr Kathy Rowan	From:	«UNIT», «HOSPITAL»
Company:	ICNARC	Date:	21 January 2004
Fax No:	020 7388 3759	Re:	Research and the Case Mix Programme register of interest
Number of pages (including this one):	1		

Please indicate below whether, or not, your unit is interested in collaborating in the new research project to be run in parallel with the Case Mix Programme:

	Yes	**No**
COPD and Asthma Outcome Study (CAOS)	☐	☐

Please supply your contact details to enable the Study Co-ordinator to send further information:

Contact name .....

Contact address .....

.....

.....

.....

.....

fax

Appendix 5

GP correspondence

ICNARC
Intensive Care National Audit & Research Centre

Supported by the
MRC
Medical Research Council

CAOS study

Dr Martin Wildman,
CAOS study Co-ordinator,
CAOS Co-ordinating Centre,
Heartlands Research Institute,
Birmingham Heartlands Hospital,
Birmingham,
B9 5SS
martin.wildman@lshtm.ac.uk
Tel. 0121 424 2644

Dear Dr ,

I am writing to you on behalf of the COPD and Asthma Outcome Study (CAOS) steering group to ask for information about **Date of Birth :** **admitted to** **Hospital on** We wish to determine whether is alive / dead.

We would hope to telephone your surgery and confirm these details with your receptionist in around 14 days time if that meets with your approval.

The aim of the study is to develop an outcome model to predict intensive care, hospital and 180-day survival for patients admitted to intensive care with acute respiratory failure due to chronic obstructive pulmonary disease. We are also including patients over the age of 45 admitted to ICU with asthma. Diagnostic difficulty sometimes means that older patients labelled as asthmatic actually have COPD. There is some evidence that older asthmatics admitted to ICU have similar outcomes to COPD patients and subgroup analysis of the asthmatics will allow us to investigate this.

We are collecting information on patients with acute respiratory failure admitted to Intensive Care units throughout England and Wales with the aim of recruiting around 750 patients during the one-year recruitment period. Patients are then followed-up 180 days after intensive care to establish their vital status and the health related quality of using the well validated EuroQol and AQ20 questionnaires.

The CAOS data has been collected with patient identification data in order to allow the CAOS centre to carry out 180-day follow-up. The non-anonymised data has only been handled by Dr Martin Wildman the Research co-ordinator and the research nurse who are both governed by their respective professional bodies confidentiality procedures. The questionnaire sent out to the patient will only carry the patients study number. Patient identification data is kept separate from patient study data at the study co-ordinating centre and all analyses and publications will only handle fully anonymised data.

We will enclose a consent form for patients receiving questionnaires and obviously patients will be free to not return questionnaires if they do not wish to do so. Patients were also given an information sheet explaining that we would contact them before they were discharged from intensive care.

The study has been considered by the MREC and they are satisfied that patient confidentiality and consent has been dealt with appropriately given the difficulties of obtaining consent from severely ill patients on Intensive Care. A copy of her consent form is enclosed with this letter for your information.

ICNARC

Intensive Care National Audit & Research Centre

Supported by the MRC Medical Research Council

CAOS study

I hope you will feel able to provide the information we require. If you have any questions about the details of the study I can be contacted at the MICCOS co-ordinating centre.

Please note we will follow-up this letter with a phone call in 2 weeks time and if you agree to help all you need do is attach the enclosed slip to the patients notes for your receptionist to release the required information.

Many thanks

Yours sincerely

Dr Martin Wildman
CAOS Study Co-ordinator.

CAOS Co-ordinating Centre • Heartlands Research Institute • Lincoln House • Birmingham Heartlands Hospital • Bordesley Green East • Birmingham B9 5SS
E: martin.wildman@lshtm.ac.uk • T: 0121 424 1631/1634 • F: 0121 424 1634

Appendix 6

CAOS Newsletter

CAOS study

Issue 3 COPD and Asthma Outcome Study February 2003

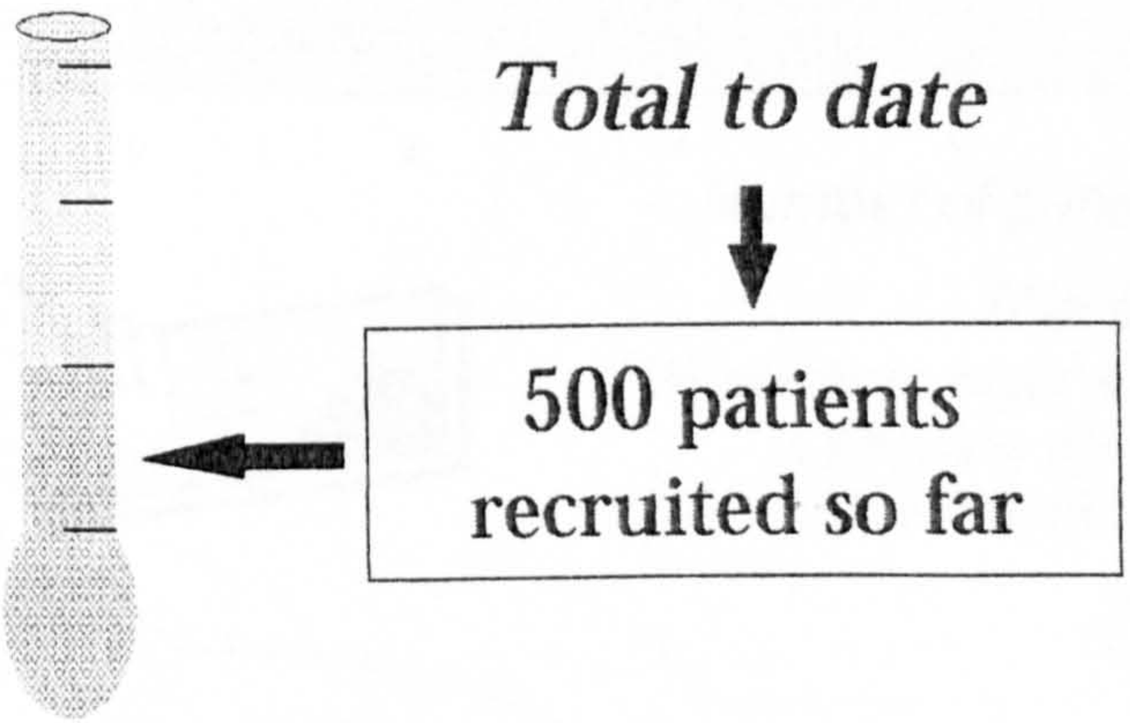
Well done – 500 patients recruited!

Despite relatively mild weather over Christmas, you have kept the data coming. CAOS biscuits go to Royal Preston Hospital who faxed us data on a patient on Christmas Day and to Bedford Hospital who faxed us data on a patient on New Years Day...

Crème de la crème – 100% total CAOS

Congratulations to those units who have not missed any patients. COPD patients are admitted intermittently but most units are succeeding in keeping up with every single patient admitted. Well done!

CAOS – progress so far



Any questions...?

Does it matter if we can't fax the data within 24 hours?

The earlier you send us the data, the quicker we can check it. This means that ambiguities can be sorted out while the patient is still in your unit. However, don't worry if you can't get it to us within 24 hours, send it as soon as you can.

Inside this issue:

Contacting us

For more information, please contact Dr Martin Wildman CAOS Co-ordinator– at martin.wildman@lshtm.ac.uk or on 07702 123764

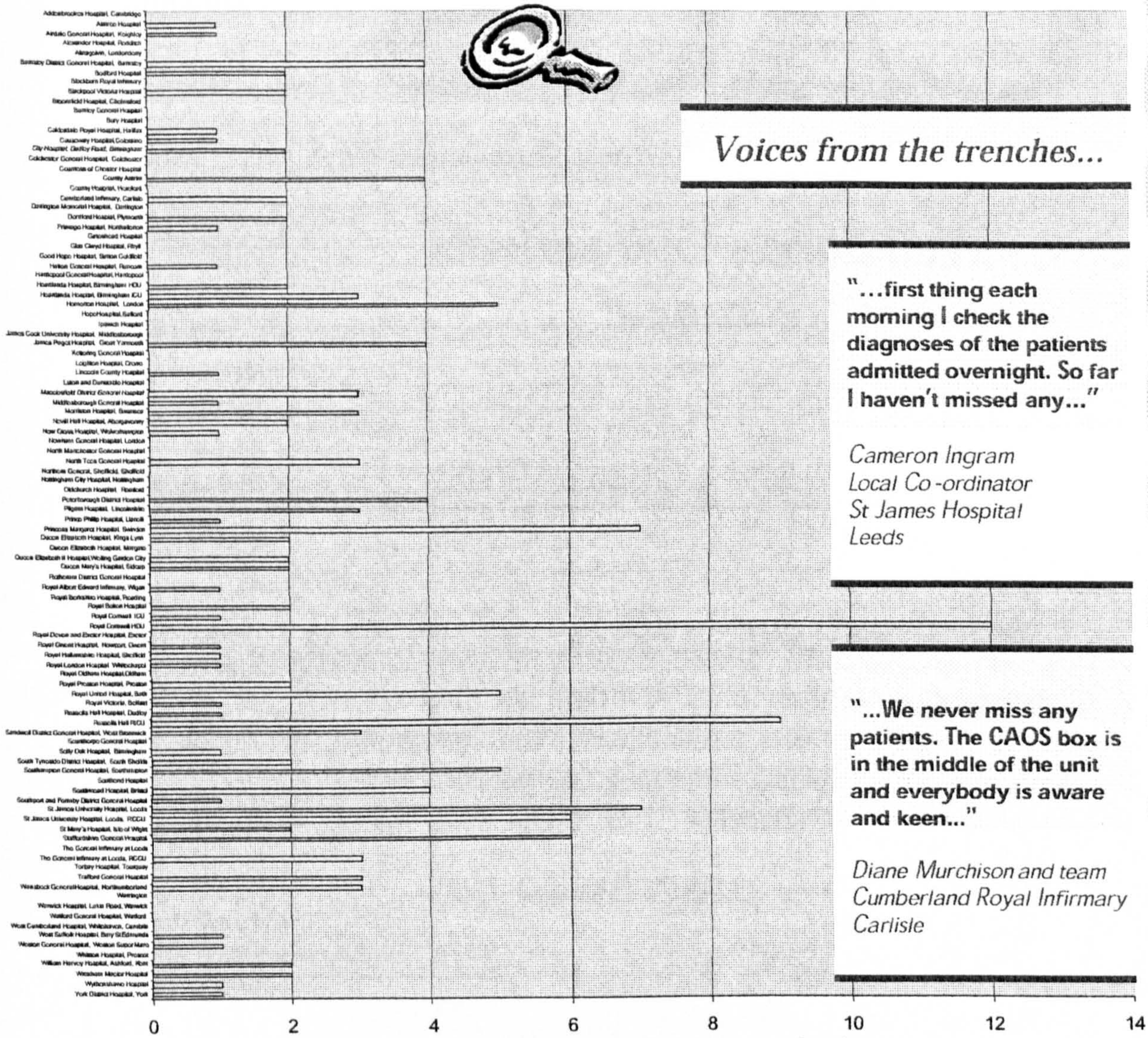
or

Ms Jayne Groves CAOS Research Nurse – at Jayne.Groves@heartsol.wmids.nhs.uk or on 0121 424 2644

Missing patient competition...

Thanks to those of you who have told us how you manage to recruit all eligible patients. Keep your suggestions coming and we will post the winning comments in the "Voices from the trenches" section.

Recruitment by unit–Dec 2002 to mid-Jan 2003



Voices from the trenches...

"...first thing each morning I check the diagnoses of the patients admitted overnight. So far I haven't missed any..."

Cameron Ingram
Local Co-ordinator
St James Hospital
Leeds

"...We never miss any patients. The CAOS box is in the middle of the unit and everybody is aware and keen..."

Diane Murchison and team
Cumberland Royal Infirmary
Carlisle

No need for dreary walls. If you want more CAOS posters, please e-mail us and we will send you a pdf poster file

If in doubt, contact CAOS...

We are always happy to discuss patients with you. If you are unsure as to whether or not to include a patient, please contact us on: 0121 424 1631 or out-of-hours on: 07702 123764.

CAOS prizes...

400th patient -
The team at Trafford Hospital.
500th patient -
The team at Prince Phillip Hospital, Llanelli
Christmas Day fax -
The team at the Royal Preston Hospital.
New Years Day fax -
The team at Bedford Hospital.
Missing patient competition -
Cameron Ingram at St James' Hospital, Leeds.
Diane Murchison and team at Cumberland Royal Infirmary

Appendix 7

CAOS Poster

CAOS study

COPD & Asthma Outcome study

CREATECAOS

Is this patient 45 years or older with COPD or asthma?

If so *please* enrol them into the CAOS study

Creating CAOS: Helping to understand the outcomes of patients admitted to critical care with COPD & asthma

---

No Forms? — ring CAOS 0121 424 1634

Appendix 8

Letter of MREC approval

Our Ref: JR/MT/MREC/01/7/ 53/approval

Dr Martin Wildman
MICCOS Co-ordinating centre
Heartlands Research Institute
Lincoln House
Heartlands hospital
Bordesley Green East
Birmingham, B9 5SS

3 September 2001

Dear Dr Wildman

Research Protocol: Outcome prediction and gatekeeping strategies for chronic obstructive pulmonary disease patients in intensive care

Study Protocol, amended 31st August 2001
Protocol Amendment No. 1 dated 31st August 2001
Letter to GP with enclosure to append GP Patient Notes, version 3 dated 31st August 2001
Patient Information Booklet to be given to Patient at Discharge, version 2 dated 10th August 2001
Patient Information Booklet to accompany Questionnaires at six-month follow-up, version 2 dated 10th August 2001
Application Form, dated 4 July 2001
Letter of Indemnity, dated 3 July 2001
C.V, dated July 2001
Patient Consent Form, dated 26 June 2001
Patient Invitation Letter, undated
Data collection form, undated
Questionnaire, undated

The West Midlands MREC reviewed your application on 25th July 2001 and agreed that there is no objection on ethical grounds to the proposed study. I am, therefore, happy to give you our approval on the understanding that you will follow the conditions of approval set down below. A record of the review undertaken by the MREC is contained in the attached MREC Response Form. The project must be started within three years of the date on which MREC approval is given.

While undertaking the review of your application the MREC noted the research involves the use of an existing database collected for previous research or other purposes with subsequent

patient contact patient. **For this reason you are asked to read carefully the sections concerning LREC involvement and local NHS management set out below as there are specific requirements involved when undertaking such research.**

MREC Conditions of Approval

- No research procedures are undertaken until the appropriate local research ethics committees is informed of the research including the name of the local clinician involved.
- The local clinician must inform his/her NHS organisation of their co-operation in the research project.
- The protocol approved by the MREC is followed and any changes to the protocol are undertaken only after MREC approval.
- If projects are approved before funding is received, the MREC must see, and approve, any major changes made by the funding body. The MREC would expect to see a copy of the final questionnaire before it is used.
- You must promptly inform the MREC of:
  (i) any changes that increase the risk to subjects and/or affect significantly the conduct of the research;
  (ii) any new information that may affect adversely the safety or welfare of the subjects or the conduct of the trial.
- You must complete and return to the MREC the annual review form that will be sent to you once a year, and the final report form when your research is completed.

LREC involvement

When undertaking the review of your project the MREC observed that there is/ limited patient contact by a local clinician who is performing technical procedures or additional data collection as described in the MREC approved protocol/ initial contact by a local clinician for purposes of recruitment. It is felt that these tasks appear well within his/her routine professional competence and adequate facilities for such procedure are available as part of his/her normal professional practice.

For this reason you are asked to only inform the appropriate LREC of the project by sending a copy of this letter and also **giving the name and contact details of the local clinician involved**. If (unusually) the LREC has any reason to doubt that the local clinician is competent to carry out the tasks required, it will inform the clinician and the MREC that gave ethical approval giving full reasons.

You are not required to wait for confirmation from the LREC before starting your research.

Local NHS Management

The local clinician must inform his/her NHS organisation of their co-operation in the research project and the nature of their involvement. Care should be taken to ensure with the NHS organisation that local indemnity arrangements are adequate.

Legal and Regulatory Requirements

It remains your responsibility to ensure in the subsequent collection, storage or use of data or research sample you are not contravening the legal or regulatory requirements of any part of the UK in which the research material is collected, stored or used. If data is transferred outside the UK you should be aware of the requirements of the Data Protection Act 1998.

ICH GCP Compliance

The MRECs are fully compliant with the International Conference on Harmonisation/Good Clinical Practice (ICH GCP) Guidelines for the Conduct of Trials Involving the Participation of Human Subjects as they relate to the responsibilities, composition, function, operations and records of an Independent Ethics Committee/Independent Review Board. To this end it undertakes to adhere as far as is consistent with its Constitution, to the relevant clauses of the ICH Harmonised Tripartite Guideline for Good Clinical Practice, adopted by the Commission of the European Union on 17 January 1997. The Standing Orders and a Statement of Compliance were included on the computer disk containing the guidelines and application form and are available on request or on the Internet at www.corec.org.uk

Yours sincerely

Maureen Thrupp
Administrator, MREC West Midlands

Enclosures *MREC Response Form*
Annual Review Form

Appendix 9

CAOS information sheets

For further information about the trial contact
Dr Martin Wildman, Trial Co-ordinator
Heartlands Research Institute
Birmingham Heartlands Hospital
Bordesley Green East
Birmingham
B9 5SS
martin.wildman@lshtm.ac.uk
0121 424 2644

07702 123764

Multi-centre Intensive care outcome study.

This leaflet contains information to explain that you will be Contacted in 6-months time to see how you are getting on Following your time in intensive care.

Multi-centre study of outcomes after Intensive Care

Invitation to take part in this study

You are being invited to take part in a research study that will involve completing and returning a questionnaire 6-months after you leave intensive care. The study may also involve using information held by the NHS and records maintained by the General Register Office to follow-up your health status and keep in touch with you. There is no need to do anything now because we will write to you again in 6 months. However we wanted to explain a little bit about the study now so that it won't be a surprise when you hear from us later.

Please take time to read the following information carefully and discuss it with others if you wish. You can contact us at the address or phone number on the back of this leaflet if anything isn't clear or if you would like more information.
Thank you for reading this.

What is the purpose of the study?

When patients and doctors are making decisions about admission to intensive care it can be important to know how people will feel once they leave intensive care. This helps patients and doctors to choose the best treatment. We will contact people who were admitted to intensive care and ask them questions about how they feel six months after their first day in intensive care. By asking these questions we will learn about the health of people after intensive care. This will enable us to give patients considering intensive care admission better information about how they would be likely to feel if they were to be admitted to intensive care.

Why have you been chosen?

You have been chosen because of your stay in intensive care. The study team will be helped by Intensive Care Units around the country to identify people admitted to intensive care because of breathing problems. We intend to collect information from around 700 patients in total.

Do you have to take part?

It is up to you to decide whether or not to take part. You are entirely free to choose whether to take part and if you decide not to take part it will certainly not affect the standard of care you receive.

How to opt out

If you do not want to take part in the study please ask a member of the nursing or medical staff to phone the study team using the number on the back of this booklet. If you wish you can phone us yourself. We want to emphasise that you are entirely free to choose whether to take part and if you decide not to take part it will certainly not affect the standard of care you receive.

What will happen if you decide to take part?

If you decide to take part this will involve completing the questionnaire that we send you in 6 months time and returning them in the FREEPOST envelope provided. Your questionnaire answers will be kept confidential and will be used along with the replies from other people in the study to help us understand people's health after intensive care. Once you have returned the questionnaire you will have given us the help we need and we will not need to bother you again. We may use information maintained by the General Register Office to follow up your health status, but this will not involve you in any further questionnaires.

What are the possible benefits of taking part?

It is hoped that the study will help us understand what patients health will be like after intensive care. By helping with the study you will be bringing benefits to other people.

What if you are unhappy about this study?

If you wish to complain, or have any concerns about any aspect of the way that you have been approached or treated in this study, the normal National Health Service complaints mechanism are available to you.

What will happen to the results of the study?

The information from the study will be analysed when the study finishes in May 2003. The results will then be published so that other people working in the health service can learn what has been found. ***No patients taking part in the study will be identified in any report or publication.***

Who is organising and funding the research?

The research is being funded by the Medical Research Council and is being organised by Heartlands Research Institute, the London School of Hygiene and Tropical Health and the Intensive Care National Audit and Research Centre.

The study has been reviewed by an ethics committee

The West Midlands Multi-Centre Research Ethics Committee has reviewed the study.

Contact for further information.

Dr. Martin Wildman Trial Co-ordinator can be contacted at Heartlands Research Institute, Birmingham Heartlands Hospital, Bordesley Green East. B9 5SS. Tel. 07702 123764.

Thank you for your help if you decide to take part.

ICNARC

Intensive Care National Audit & Research Centre

CAOS

Supported by the MRC Medical Research Council

Patient Information about the COPD and Asthma study

Patient name.....
Date of birth.....
Address.....
.....
.....
(or affix patient label)

The above named patient who has been looked after in our critical care unit was given a COPD and asthma outcome study information booklet before leaving critical care.

Signed .....(for critical care unit)
Please print name.....
DATE .....

I have received an information booklet that explains that I will be contacted about 6 months after I leave hospital to see how I am feeling.

Signed .....(Patient)

PLEASE FAX THIS FORM TO THE COPD & ASTHMA OUTCOME STUDY
0121 424 1634 AND THEN FILE IT IN THE PATIENT'S NOTES

For further information about the trial contact
Dr Martin Wildman, Trial Co-ordinator
Heartlands Research Institute
Birmingham Heartlands Hospital
Bordesley Green East
Birmingham
B9 5SS
martin.wildman@lshtm.ac.uk
0121 424 2644

07702 123764

Multi-centre Intensive care outcome study

This leaflet contains information to explain why you have been invited to answer our questionnaires

Supported by the
MRC
Medical Research Council

Multi-centre study of outcomes after Intensive Care

Invitation to take part in this study

You may recall being given a leaflet about this study whilst you were in Intensive Care six months ago. This leaflet explains why we are contacting you and how you can help us. You are being invited to take part in a research study that will involve completing and returning questionnaires. The study may also involve using information held by the NHS and records maintained by the General Register Office to follow-up your health status. Before you decide whether to take part it is important that you understand why the research is being done and what it will involve.

Please take time to read the following information carefully and discuss it with others if you wish. You can contact us at the address or phone number on the back of this leaflet if anything isn't clear or if you would like more information.

Thank you for reading this.

What is the purpose of the study?

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Why have you been chosen?

We have been helped by Intensive Care Units around the country to identify people admitted to intensive care because of breathing problems. The team who were looking after you on intensive care have told us you had been admitted and we are now contacting you 6 months later to see how you are feeling. We intend to collect information from around 700 patients in total.

Do you have to take part?

It is up to you to decide whether or not to take part. You are entirely free to choose whether to take part and if you decide not to take part it will certainly not affect the standard of care you receive.

What will happen if you decide to take part?

If you decide to take part this will involve completing the questionnaire and returning it in the FREEPOST envelope provided. Your questionnaire answers will be kept confidential and will be used along with the replies from other people in the study to help us understand people's health after intensive care. Any information that we analyse will have your name and address removed so that you cannot be recognised from it. Once you have returned the questionnaire you will have given us the help we need and we will not need to bother you again. We may use information held by the NHS and records maintained by the General Register Office to follow your health status but this will not involve you in any further questionnaires.

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Thank you for your help if you decide to take part.

Multi-Centre Intensive Care Outcome Study Coordinating Centre
Heartlands Research Institute,
Birmingham Heartlands Hospital
Bordesley Green East,
Birmingham
B9 5SS
Tel 0121 424 2644
Dr Wildman Trial coordinator 07702 123764

Consent Form

Title of Project: Multi-centre study of outcomes after Intensive Care.
Name of Researcher: Dr Martin Wildman

Please initial box

1) I confirm that I have read and understood the information sheet for the above study. I am aware of the contact phone number to ring if I wish to ask questions and know that I am welcome to use it if I wish. ☐

2) I understand that my participation is voluntary and I am free not to take part without giving any reason, without my medical care or legal rights being affected. ☐

3) I understand that sections of any of my medical notes may be looked at by responsible members of the study team or from regulatory authorities where it is relevant to me taking part in research. I give permission for these individuals to have access to my records. ☐

4) I agree to take part in the study. ☐

5) I agree for information held by the NHS or records used by the General Register Office to be used in order to follow up my health status. ☐

Name of patient _____ Date _____ Signature _____

Please return this copy of the Consent form with the questionnaires in the FREEPOST envelope.

Multi-Centre Intensive Care outcome Study
Heartlands Research Institute,
1st Floor Lincoln House
Heartlands Hospital
Bordesley Green East
B9 5SS
0121 424 2644

Dear ,

Dr lead clinician at Hospital , let me know about your admission to Intensive Care Unit in this year. My name is Dr Martin Wildman and I am the Co-ordinator of the Multi-Centre Intensive outcome Study that is currently being carried out in England and Wales. As well as carrying out this study I work as a Doctor in intensive care and look after patients with chest problems.

I am writing to you because we are trying to understand more about the health of people admitted to intensive care with breathing problems. In the envelope I have sent to you I have included a full explanation of the study and how you can help with it if you wish to do so. I have also explained that taking part is entirely up to you and if you choose not to take part that will not affect your future care in any way.

If you do wish to take part , the information from the questionnaire will have your personal details removed and it will than be analysed with information from other people who have been admitted to intensive care, to help us understand more about how people get on after they have been admitted to intensive care. This will help us talk to patients in the future who might need intensive care to explain what is likely to happen if they are admitted. Dr sent us some details about how ill you were when you entered Intensive Care and these details have been coded at the study centre so that they are anonymous and the data that you send back to us will be joined with this information.

Once you have returned this questionnaire we will not need to contact you again. However if you agree we may use this information held by the NHS or records used by the General Register Office in order to follow up your health status.

If you have any questions about the study you can contact the co-ordinating centre using the contact details at the head of this letter.

With best wishes,

Yours sincerely,

Martin Wildman

Multi-centre Intensive Care outcome study

This booklet contains questions to help us to understand how you feel today

CAOS study
COPD & Asthma Outcome Study

Supported by:
MRC
Medical Research Council

CAOS/ICOC/1/702

There are **4 pages** of questions, including this one.
Please answer the questions on **each** page

Today's date is: d d / m m / y y y y

Please choose one of the descriptions that **best** describes you **today**

Please tick (✓) **ONE** box only

Fully mobile and living without assistance	☐
Able to live on your own and get out of the house to do basic necessities, but severely limited in how far you can walk	☐
Cannot get out of the house unassisted or get out of the house rarely, able to perform self-care but unable to do heavy chores such as house cleaning, cannot live alone without help	☐
Bed or chair bound	☐

	Yes	**No**
Thinking back to your admission to intensive care, under the same circumstances, would you be willing to undergo similar intensive care treatment again.	☐	☐

Thinking back to how you were before you became ill and had to be admitted to intensive care 6 months ago. Please choose the **one** description that best describes how you are now compared to how you were **6 months ago**.

Please tick (✓) **ONE** box only

My health today is **much worse** than it was when I was at home 6 months ago.	☐
My health today is **a little worse** than it was when I was at home 6 months ago.	☐
My health today is **about the same** as it was when I was at home 6 months ago.	☐
My health today is **a little better** than it was when I was at home 6 months ago.	☐
My health today is **much better** than it was when I was at home 6 months ago.	☐

YOUR OWN HEALTH STATE TODAY

By placing a tick (✓) in **one** box in **each** group of questions below, please indicate which statement best describes your own health today

Mobility

- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

Self-care

- I have no problems with self-care ☐
- I have some problems washing and dressing myself ☐
- I am unable to wash and dress myself ☐

Usual activities (e.g. work, study, housework, family or leisure activities)

- I have no problems with performing my usual duties ☐
- I have some problems with performing my usual duties ☐
- I am unable to perform my usual duties ☐

Pain/Discomfort

- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

Anxiety/Depression

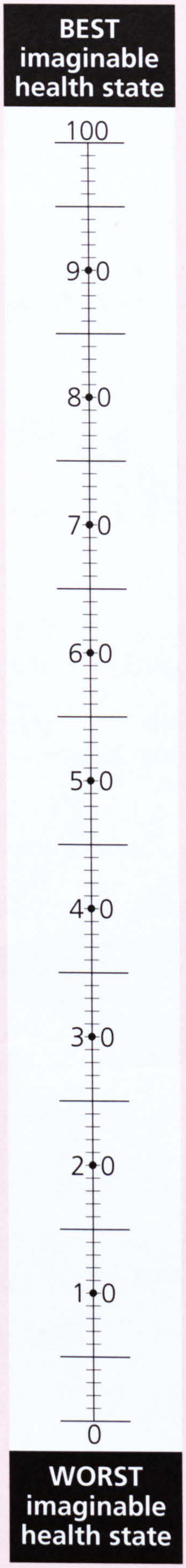
- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

YOUR OWN HEALTH STATE TODAY

To help people say how good or bad a health state is, we have drawn a scale on which the best state you can imagine is marked **100** and the worst is marked at **0**

We would like you to indicate on the scale how good or bad your own health is today, in your opinion. Please do this by drawing a fine line from the box below to which ever point on the scale indicates how good or bad your health state is

Your own health state today



Please tick (✓) **one** box **per** question – If it does not apply to you please tick **Not applicable**)

		Yes	No	Not applicable
1	Do you cough often during the day?	☐	☐	☐
2	Does your chest trouble often make you feel restless?	☐	☐	☐
3	Does gardening make you breathless?	☐	☐	☐
4	Do you worry when going to a friend's house that there might be something there that will upset your chest?	☐	☐	☐
5	Do you get chest problems when you come into contact with strong smells, exhaust fumes, cigarette smoke, perfume etc?	☐	☐	☐
6	Does your partner find your chest trouble upsetting?	☐	☐	☐
7	Do you feel breathless when trying to sleep?	☐	☐	☐
8	Do you worry about the long term effects of the drugs you take for your chest trouble?	☐	☐	☐
9	Does getting emotionally upset make your chest trouble worse?	☐	☐	☐
10	Are there times when you have difficulty getting around the house because of your chest trouble?	☐	☐	☐
11	Does your chest problem make you breathless when you do things at work? (paid employment)	☐	☐	☐
12	Does walking upstairs make you breathless?	☐	☐	☐
13	Do you get breathless doing housework?	☐	☐	☐
14	Does your chest trouble make you go home sooner than others after a night out?	☐	☐	☐
15	Do you suffer from breathlessness when you laugh?	☐	☐	☐
16	Does your chest trouble often make you feel impatient?	☐	☐	☐
17	Do you think the fullness of your life is limited by your chest trouble?	☐	☐	☐
18	Do you feel drained after a cold because of your chest trouble?	☐	☐	☐
19	Do you have a feeling of chest heaviness?	☐	☐	☐
20	Do you worry a lot about your chest trouble?	☐	☐	☐

Thank you very much for your help

You have now answered all the questions

Please put the completed booklet into the FREEPOST envelope and post back to us, there is no need to add a stamp

ICNARC

Intensive Care National Audit & Research Centre

Supported by: MRC Medical Research Council

CAOS study

COPD & Asthma Outcome Study

A study to understand the prognosis of patients, 45 years and older, admitted to critical care unit with respiratory failure due to an exacerbation of COPD or asthma

Please complete a patient data booklet for all non-surgical patients, aged 45 years or older, admitted to your critical care with respiratory failure due to an exacerbation of COPD or asthma as their major reason for admission

CAOS Co-ordinating Centre

Mrs Jayne Groves (Research Nurse): **0121 424 2644**

Dr Martin Wildman (Study Co-ordinator): **0121 424 1631/Mobile: 07702 123764**

Centre fax number: **0121 424 1634**

FAX BACK: 0121 424 1634

Patient No.: 2389

Please fax odd pages between 1 to 13 (light blue pages) within 24 hours of the patient admission to your critical care unit

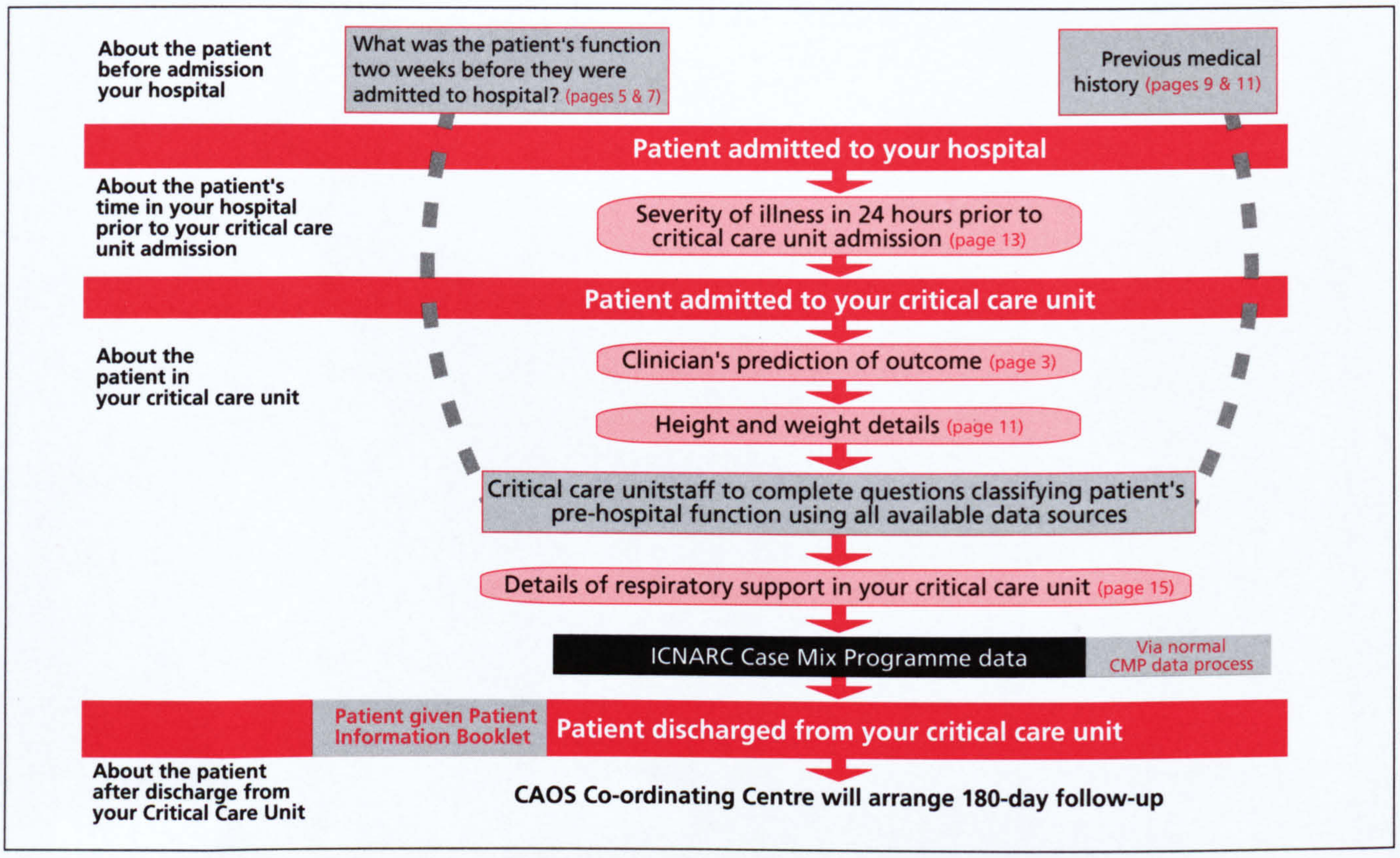
CAOS study

COPD & Asthma Outcome Study

Study overview

1) When a patient aged 45 years or older is admitted to your critical care unit with breathlessness, respiratory failure or change in mental status due to an exacerbation of COPD or asthma as the major reason for admission they must be recruited.
2) If the patient has had surgery in the past ten days they should be excluded.
3) If the patient was transferred from another hospital they should be excluded.
4) Odd pages 1 to 13 (light blue) of the data booklet collect information available at or before admission to your critical care unit . It is important that the first seven odd pages are faxed to the CAOS Co-ordinating Centre (0121 424 1634) within 24 hours of the patient's admission to your critical care. This will enrol the patient in the Study and allow us to validate CAOS data during their critical care stay. **Information for all pages (except page 15, yellow) should be available within the first 24 hours.** Don't worry if you have a few pieces of missing data, we will chase these with you once the pages are faxed to us.
5) After faxing the pages and enrolling the patient, file the CAOS patient data booklet with the patient's notes and the CAOS team will contact you to complete data validation.
6) At discharge from your critical care unit please give the patient a Patient Information Booklet and fax page 15 (yellow) to the CAOS Co-ordinatiung Centre.
7) Six weeks after the patient has been discharged from your critical care we will contact you once more to determine the patient's hospital outcome.
8) At 180 days following admission to your critical care unit, and before sending the 180 day follow-up questionnaire, the CAOS Co-ordinating Centre will contact the patient's GP to ensure the patient is still alive.

Data collection in CAOS



Deciding on the clinical diagnosis of COPD or asthma (Q 1, 2 & 3)

Patients to be included are those who are aged 45 or older, admitted with breathlessness, respiratory failure or a change in mental status due to an exacerbation of COPD or asthma. It may be difficult to be sure to what extent the patient has pure COPD or pure asthma. The criteria below are for guidance, however, in the absense of the previous investigations, we ask that clinicians make a clinical categorisation.

- Patients with COPD will have airway obstruction with an FEV_1 <80% predicted and an FEV/VC ratio <70% which does not change markedly over many months. For the purposes of this study COPD includes emphysema.
- Patients with asthma will have episodic airway obstruction that can be restored towards normal with treatment.
- Patients with a mixture of COPD and asthma may have marked variability in airway obstruction superimposed on fixed irreversible airway narrowing

CAOS study

COPD & Asthma Outcome Study

SPECIAL NOTE

Please fax odd pages **1 to 13**
(light blue)
of this questionnaire to the
CAOS Co-ordinating Centre
Fax: 0121 424 1634
within 24 hours of the patient's
admission to your critical care unit

FAX BACK: 0121 424 1634 Patient No.: 2389

CAOS study

COPD & Asthma Outcome Study

Please complete a patient data booklet for ALL non-surgical patients aged 45 years or older admitted to critical care with respiratory failure due to exacerbation of COPD or asthma as the major reason for admission

Full inclusion and exclusion criteria can be found at the CAOS website **www.caos.lshtm.ac.uk.** For further advice contact 07702 123764 (24hours)

INCLUSION CRITERIA

Please tick (✓) Yes for **ONLY ONE** of the questions 1 to 3

1 Is the clinical diagnosis breathlessness, respiratory failure or change in mental status due to an exacerbation of COPD? **Yes** ☐ **Include**

2 Is the clinical diagnosis breathlessness, respiratory failure or change in mental status due to an exacerbation of asthma? **Yes** ☐ **Include**

3 Is the clinical diagnosis breathlessness, respiratory failure or change in mental status due to an exacerbation of a mixture COPD and asthma? **Yes** ☐ **Include**

EXCLUSION CRITERIA (The patient CANNOT be entered if any of the boxes below are ticked)

4 Is the patient below 45 years of age? **Yes** ☐ **Exclude**

5 Has the patient had surgery in the past 10 days? **Yes** ☐ **Exclude**

6 Has the patient been transferred from another hospital? **Yes** ☐ **Exclude**

DATE AND TIME OF ADMISSION

7 a) Date of admission to your hospital ☐☐/☐☐/☐☐☐☐ (d d / m m / y y y y)

b) Time of admission to your hospital ☐☐:☐☐ (24 hr clock)

8 a) Date of admission to your critical care unit ☐☐/☐☐/☐☐☐☐ (d d / m m / y y y y)

b) Time of admission to your critical care unit ☐☐:☐☐ (24 hr clock)

PATIENT DETAILS

9 Family name: _____
(or attach a label with these details)

Given name: _____ Sex: Male ☐ Female ☐

Address : _____

_____

Postcode: _____ Date of birth: ☐☐/☐☐/☐☐☐☐ (d d / m m / y y y y)

NHS Number: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

GP DETAILS

10 GP Details: name: _____
(or attach a label with these details)

Address: _____

_____

Postcode: _____ Telephone No.: _____

Guidance Notes

[1]Q 11.3
A clinical diagnosis of congestive cardiac failure should be made when it is thought to be contributing to the patient's current illness

[2]Q 12.1-4
The most senior doctor involved in making the decision to admit the patient to your critical care unit should complete this section as early as possible after admission so that predictions reflect the doctor's view at the time the decision to admit was made.

FAX BACK: 0121 424 1634 Patient No.: 2389

CAOS study
COPD & Asthma Outcome Study

ADMITTING DOCTOR(S) TO COMPLETE THIS SECTION AT THE TIME OF ADMISSION TO YOUR CRITICAL CARE UNIT

11.1 Is the patient in atrial fibrillation? Yes ☐ No ☐

11.2 Is there any abnormal shadowing on the **pre-critical care unit** chest x-ray? Yes ☐ No ☐

11.2.1 If abnormal shadowing is present, are there any old x-rays available at the time of admission to aid interpretation of admission chest x-ray? Yes ☐ No ☐ Not applicable ☐

11.2.2 What, in your judgement (at the time of admission to your critical care unit), is responsible for the abnormal chest x-ray shadowing?

Not applicable ☐ infection ☐ heart failure ☐ combined heart failure **and** infection ☐

other ☐ *please specify:* _____

11.3 Does the patient have congestive cardiac failure as a contibutory cause for this deterioration[1]? Yes ☐ No ☐

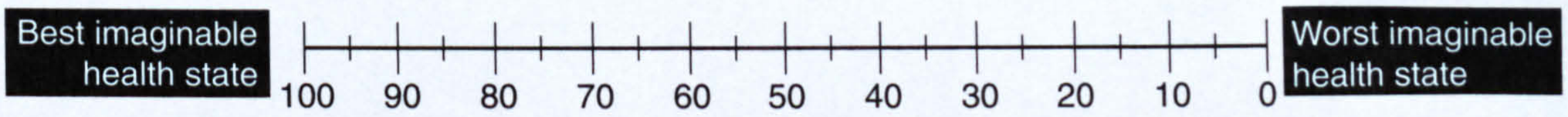
ADMITTING DOCTOR'S OUTCOME PREDICTION AT THE TIME OF ADMISSION TO YOUR CRITICAL CARE UNIT

12.1 What is your probability of this patient surviving to leave your critical care Unit[2]? ☐☐☐%

12.2 What is your probability of this patient surviving to leave your hospital? ☐☐☐%

12.3 What is your probability of this patient surviving for 180 days? ☐☐☐%

12.4 Indicate your prediction of the patient's quality of life at 180 days if the patient survives for:180 days.



Date and time of prediction: Date: ☐☐/☐☐/☐☐☐☐ (d d / m m / y y y y) Time: ☐☐:☐☐ (24 hours)

Speciality of clinician making prediction: _____

Grade of clinician making prediction: _____

Name of clinician making prediction: _____

[1] ABOUT THE PATIENT IN THE PERIOD OF STABILITY TWO WEEKS PRIOR TO ADMISSION TO YOUR HOSPITAL

- This information is designed to indicate what the patient was able to do before they became acutely unwell.
- Some patients may have been unwell for many months and may not report a recent period of stability. For these patients fill in the data sheet to describe the best that the patient has been in the 2 weeks prior to admission to your hospital.

CAOS Study
COPD & Asthma Outcome Study

ABOUT THE PATIENT IN THE PERIOD OF STABILITY TWO WEEKS[1] PRIOR TO ADMISSION TO YOUR HOSPITAL

13 Functional Score

Choose the **ONE** description that best describes the patient in the period of stability **TWO WEEKS** prior to admission to your hospital

Fully mobile and living without assistance ☐

Able to live on their own and get out of the house to do basic necessities but severely limited in exercise ability ☐

Cannot get out of the house unassisted or gets out of the house rarely, able to perform self-care but unable to do heavy chores such as house cleaning, cannot live alone, may be institutionalised ☐

Bed or chair bound ☐

Information source (tick (✓) all that apply) Clinical record ☐ Patient ☐ Other witness ☐

PATIENT'S SELF-RATED QUALITY OF LIFE TWO WEEKS[1] PRIOR TO ADMISSION TO YOUR HOSPITAL

14 How would the patient have rated their quality of life in the period of stability two weeks prior to the admission to your hospital

☐ Excellent ☐ Very good ☐ Fair ☐ Poor ☐ very poor

Information source (tick (✓) all that apply) Clinical record ☐ Patient ☐ Other witness ☐

[1] ABOUT THE PATIENT IN THE PERIOD OF STABILITY TWO WEEKS PRIOR TO ADMISSION TO YOUR HOSPITAL

- This information is designed to indicate what the patient was able to do before they became acutely unwell.
- Some patients may have been unwell for many months and may not report a recent period of stability. For these patients fill in the data sheet to describe the best that the patient has been in the 2 weeks prior to admission to your hospital .

[2]Q15

Activities of Daily Living scale

For each activity choose one description/description pair that best describes the patient's activity in the period of stability prior to admission to your hospital.

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ABOUT THE PATIENT IN THE PERIOD OF STABILITY TWO WEEKS[1] PRIOR TO ADMISSION TO YOUR HOSPITAL

15 Activities of Daily Living scale[2]

Tick (✓) **ONE** box per activity that corresponds to the description(s) that best describes the patient in the period of stability **TWO WEEKS** prior to admission to your hospital.
(The word "assistance" means supervision, direction or personal assistance)

Bathing (Either sponge bath,tub bath, or shower)	Receives no assistance (gets in and out of tub by self if tub is usual means of bathing) **OR** Receives assistance in bathing only one part of the body (such as back or leg)	☐	Receives assistance in bathing more than one part of the body **OR** not bathed	☐
Dressing (Gets clothes from closets and drawers-including underclothes, outer garments and using fasteners and braces if worn)	Gets clothes and gets completely dressed without assistance **OR** Gets clothes and gets dressed without assistance except for assistance in tying shoes.	☐	Receives assistance in getting dressed, or stays partly or completely undressed.	☐
Toileting (Going to the "toilet room" for bowel and urine elimination; cleaning self after elimination, and arranging clothes.)	Goes to "toilet room," cleans self, and arranges clothes without assistance (may use object for support such as cane, or wheelchair and may manage night bedpan or commode, emptying same in morning)	☐	Receives assistance in going to "toilet room" or in cleansing self or in arranging clothes after elimination or in walker, use of night bedpan or commode. **OR** Doesn't go to room termed "toilet" for the elimination process.	☐
Transfer	Moves in and out of bed as well as in and out of chair without assistance (may be using object for support such as cane or walker)	☐	Moves in and out of bed or chair with assistance. **OR** Doesn't get out of bed.	☐
Continence	Controls urination and bowel movement completely by self.	☐	Has occasional "accidents" **OR** Supervision helps keep urine or bowel control; catheter is used, or is incontinent.	☐
Feeding	Feeds self without assistance **OR** Feeds self except for getting assistance in cutting meat or buttering bread.	☐	Receives assistance in feeding or is fed partly or completely by using tubes or intravenous fluids	☐

Information source (tick (✓) all that apply) Clinical record ☐ Patient ☐ Other witness ☐

[1]Evidence to assess co-morbidities

Evidence to assess medical history can be from hospital case notes, doctors' or nurses' case note, GP case notes, information from patient, the patient's relatives, friends or GP.

FAX BACK: 0121 424 1634

Patient No.: 2389

CAOS study
COPD & Asthma Outcome Study

PAST MEDICAL HISTORY

16 About the patient's past medical history

Is there any evidence[1] available to assess past medical history/co-morbidity? **Yes** ☐ **No** ☐

Co-morbidity	Definition	Please tick (✓) one box for **EACH** condition	Present	Absent
Myocardial infarction	History of **medically documented** myocardial infarction		☐	☐
Congestive heart failure	Has the patient **ever been treated** for heart failure?		☐	☐
Peripheral vascular disease	Intermittent claudication, peripheral artery bypass for insufficiency gangrene, acute arterial insufficiency, untreated aneurysm (>6cm)		☐	☐
Cerebrovascular disease (except hemiplegia)	History of transient ischaemic attack (TIA), or Cerebrovascular accident (CVA) with no or minor sequellae		☐	☐
Hemiplegia	Difficulty in moving an arm or leg as a result of a stroke or Cerebrovascular accident		☐	☐
Dementia	Chronic cognitive defect		☐	☐
Chronic pulmonary disease	Symptomatic dyspnoea due to chronic respiratory conditions (including asthma)		☐	☐
Connective tissue disease	SLE, polymyositis, mixed connective tissue disease, polymyalgia rheumatica, moderate to severe rheumatoid arthritis		☐	☐
Peptic ulcer disease	Patients who have required treatment for peptic ulcer disease		☐	☐
Mild liver disease	Cirrhosis **without** portal hypertension, chronic hepatitis		☐	☐
Moderate or severe liver disease	Cirrhosis **with** portal hypertension ± variceal bleeding		☐	☐
Moderate or severe renal disease	Creatinine **greater than** 265 µmol/l or dialysis or transplantation		☐	☐
Diabetes (without complications)	Diabetes treated with insulin or medication, but without complications		☐	☐
Diabetes with end organ damage	Retinopathy or neuropathy or nephropathy		☐	☐
Cancer (non-metastatic)	Any cancer other than haematological cancer or skin cancer, **without metastasis** initially treated in past 5 years. Exclude non-melanomatous skin cancers and in situ cervical cancer		☐	☐
Cancer (metastatic)	Any cancer other than haematological cancer or skin cancer, with metastasis		☐	☐
Leukaemia	Chronic myeloid leukaemia (CML), chronic lymphoid leukaemia (CLL),Acute myeloid leukaemia, (AML),Acute lymphoblastic leukaemia (ALL), polycythemia rubra vera (PV)		☐	☐
Lymphoma, multiple myeloma	Non-Hodgkin's lymphoma (NHL), Hodgkin's, Waldenstroms macroglobulineamia, multiple myeloma		☐	☐
AIDS			☐	☐

[1]Q17

Inhaled steroids are often described by patients or their families as a brown or orange or purple inhaler.

Inhaled steroids include: Beclomethasone, Aerobec, Asmabec, Beclazone, Becodisks, Becotide, Qvar, AeroBec Forte, Becloforte, Ventide, Budesonide, Pulmicort, Symbicort, Flixotide, Seretide.

[2]Q18

This question refers to patients who have been assessed for home oxygen and prescribed an oxygen concentrator. Please do **NOT** tick "yes" for patients who have cylinders at home that they use on an as required basis.

ABOUT THE PATIENT'S WEIGHT AND HEIGHT

[3]Measuring mid-arm circumference

Why are we asking you to measure mid-arm circumference?
There is strong evidence that Body Mass Index (BMI) predicts outcome for COPD patients admitted to critical care units.
Weight can be difficult to measure in very sick patients, so BMI may be difficult to measure reliably.
mid-arm circumference provides a readily obtained surrogate for BMI and can be obtained on all patients.

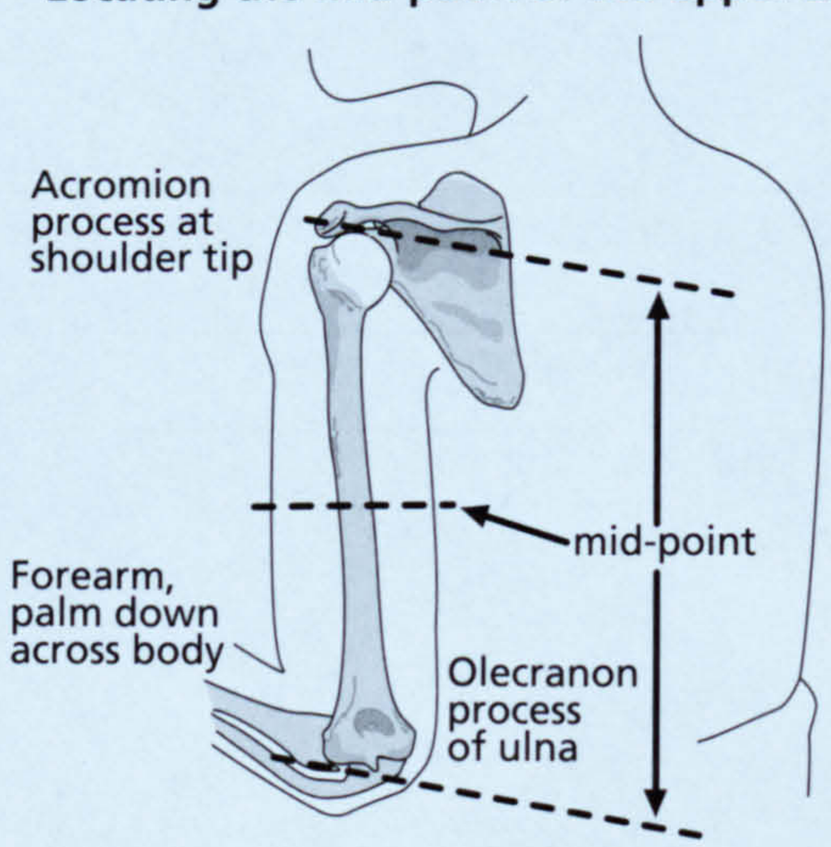
How to measure mid-arm circumference.

(1) Use the non-dominant arm. For most of the population who are right handed this will be the **left arm**.

(2) Finding the mid-point of the upper arm.
   a) Bend the arm to 90^0 with the palm facing downwards in order to locate the landmarks and mark the mid-point of the upper arm.
   b) Locate the tip of the shoulder. *(This is the acromiom process.)*
   c) Locate the bony tip of the elbow. *(This is the olecranon).*
   d) Mark the mid-point between the tip of the shoulder and the bony tip of the elbow.

(3) Measuring the mid-arm circumference
   a) Now straighten the arm again.
   b) Measure the circumference of the arm at the mid-point that you have just marked.

Locating the mid-point of the upper arm



Having located the mid-point, straighten the arm before measuring

CAOS study
COPD & Asthma Outcome Study

PAST MEDICAL HISTORY

(continued)

17 Was the patient taking inhaled steroids prior to admission to your hospital[1]? **Yes** ☐ **No** ☐ **Don't know** ☐

18 Does the patient use home oxygen via a prescribed oxygen concentrator[2]? **Yes** ☐ **No** ☐

19 Has the patient required intubation and ventilation before? **Yes** ☐ **No** ☐ Number of times ☐☐

Information source (tick (✓) all that apply) Clinical record ☐ Patient ☐ Other witness ☐

20 How long ago was the last episode of intubation and ventilation in months? ☐☐☐ months

21 Please record the patient's most recent lung function. FEV_1 ☐.☐☐ and date performed ☐☐/☐☐/☐☐☐☐ (d d m m y y y y)

Not available ☐

22 How many admissions to hospital with breathing problems has the patient had in the past 6 months, excluding the current admission? (Please use old notes, informants,GP) ☐☐ admissions

Information source (tick (✓) all that apply) Clinical record ☐ Patient ☐ Other witness ☐

23 About the patient's smoking history

23.1 Is the patient

a current smoker **Yes** ☐ **No** ☐

an ex-smoker **Yes** ☐ **No** ☐

a 'never' smoker **Yes** ☐ **No** ☐

23.2 For **current** and **ex-smokers** please state:

a) Average number of cigarettes smoked per day over the years as a smoker ☐☐☐ cigarettes per day

b) Approximate total number of years smoked ☐☐ years

ABOUT THE PATIENT'S WEIGHT AND HEIGHT

24 Please tick (✓) the response that best represents the patient's body weight today?

very underweight ☐ mildy underweight ☐ normal weight ☐ mildly overweight ☐ very overweight ☐

25 Has the patient lost any weight in the past six months? **Yes** ☐ **No** ☐

Weight loss ☐☐☐ lbs **or** ☐☐.☐ kg

Information source (tick (✓) all that apply) Clinical record ☐ Patient ☐ Other witness ☐

26 How tall is the patient? either ☐ feet ☐☐ inches **or** ☐☐☐ cms

Please tick (✓): estimated ☐ measured ☐

27 How much does the patient weigh? either ☐☐☐.☐ kg **or** ☐☐ stones ☐☐ lbs

Please tick (✓): estimated ☐ measured ☐

28 What is the patients left mid-arm circumference[3]? ☐☐☐.☐ cms

[1]ABOUT THE PATIENT'S CONDITION FOLLOWING ADMISSION TO YOUR HOSPITAL BUT BEFORE ADMISSION TO YOUR CRITICAL CARE UNIT

1) This page collects physiological and laboratory data to describe the patient's condition immediately before admission to your critical care unit and should document the highest and lowest values from the 24 hours preceding critical care unit admission. For some patients, these will be the data from the clerking carried out in casualty immediately prior to admission to your critical care Unit .
2) Some patients may only have had urea and electrolytes measured in the 24hours prior to admission and in these cases please phone the laboratory to request albumin, glucose, and bilirubin.
3) We recognise that some patients will only have one set of results to choose from, in that case please record them all in the lowest column.
4) Some patients may be transferred directly from casualty to critical care. These patients will have been in hospital much less than 24 hours prior to critical care. For these patients record the data from the tests done after the patient reached hospital but before critical care admission.

[2]Q 29.1

FIO_2 approximations

Conversion table for FIO_2 when measured on nasal cannula or mask

Nasal cannula		**Face Mask**		**Face mask with reservoir bag**		**"Venturi" type face mask e.g. Ventimask**		**Aerosol face mask O_2 15 litres min-1 via nebuliser**	
Litres min-1	FiO_2	Litres min-1	FiO_2	Litres min-1	FiO_2	Set %	FiO_2	Set %	FiO_2
1	0.22	2	0.25	6	0.6	24	0.24	35	0.28
2	0.25	3	0.27	7	0.7	28	0.28	40	0.30
3	0.27	4	0.30	8	0.8	35	0.35	70	0.50
4	0.30	5	0.35	9	0.85	40	0.40	100	0.60
5	0.35	6	0.40	10+	0.9	60	0.60		
		7	0.45						
		8+	0.50						

Table taken from appendix page 169 CMP data collection programme. The CMP manual has references supporting the table findings

[3]Q 29.3 and 29.4

Central/non-central temperature

- Tympanic membrane, nasopharyngeal,oesophageal,rectal, pulmonary artery, bladder are considered as central temperature measurement sites.

[4]Q 29.17

Assessment of Glasgow coma scale

- Use the notes or interview clinical staff involved in the patients' pre-critical care management to asses the patients worst Glasgow coma score prior to critical care admission.

The best eye opening response

Spontaneous	4
To verbal command	3
To pain	2
No response	1

The best motor response

Obeys verbal command	6
Localises pain	5
Flexion withdrawal	4
Flexion-abnormal/decorticate rigidity	3
Extension/decerebrate rigidity	2
No response	1

The best verbal response

Orientated and converses	5
Disorientated and converses	4
Inappropriate words	3
Incomprehensible sounds	2
No response	1

If an admission is **intubated**, use clinical judgement to score verbal response as follows:

Appears orientated	5
Responsive but ability to converse questionable	3
Generally unresponsive	1

[5]Q30

Oedema is considered to be present if gentle pressure with a finger to the leg, around the ankle, produces an indentation that persists when the finger is removed.

FAX BACK: 0121 424 1634 Patient No.: 2389

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Please record the data below that describes the patient's condition after admission to your hospital but before admission to your critical care unit

ABOUT THE PATIENT'S CONDITION IMMEDIATELY PRIOR[1] TO ADMISSION TO YOUR CRITICAL CARE UNIT

29 Did the patient receive non-invasive ventilation elsewhere in your hospital **prior** to admission to your critical care unit? **Yes** ☐ **No** ☐

If all tests have not been done please order the test on the blood taken prior to this critical care unit admission which should already be with the labs.

29.1 Most acidic gases in the 24 hours **prior to critical care** admission[2].

Highest H^+	☐☐.☐
Lowest pH	☐.☐☐
FIO_2 %	☐☐☐[2]
paO_2	☐☐.☐ Kpa **or** ☐☐.☐ mmHg
$PaCO_2$	☐☐.☐ Kpa **or** ☐☐.☐ mmHg
Actual bicarbonate	☐☐.☐ mmol l^{-1}
Base excess (±)	☐* ☐☐.☐ *Please indicate +ve or –ve

29.2 Blood pressure *(record systolic and diastolic from reading with lowest diastolic)*

	Lowest	**Highest**[3]
Systolic	☐☐☐	☐☐☐
Diastolic	☐☐☐	☐☐☐

29.3 Central temperature (°C)[3]	☐☐.☐ °C	☐☐.☐ °C
29.4 Non-central temperature (°C)[3]	☐☐.☐ °C	☐☐.☐ °C
29.5 Heart rates (beats min^{-1})	☐☐☐ beats min^{-1}	☐☐☐ beats min^{-1}
29.6 Non-ventilated respiratory rate (breaths min-1)	☐☐ breaths min-1	☐☐ breaths min-1
29.7 Haematocrit (%)	☐☐.☐ %	☐☐.☐ %
29.8 Haemoglobin (g dl^{-1})	☐☐.☐ g dl^{-1}	☐☐.☐ g dl^{-1}
29.9 White blood cell count (x$10^9 l^{-1}$)	☐☐☐.☐ x$10^9 l^{-1}$	☐☐☐.☐ x$10^9 l^{-1}$
29.10 Serum sodium (mmo l^{-1})	☐☐☐.☐ mmo l^{-1}	☐☐☐.☐ mmo l^{-1}
29.11 Serum potassium (mmol l^{-1})	☐☐.☐ mmol l^{-1}	☐☐.☐ mmol l^{-1}
29.12 Serum creatinine (µmol l^{-1})	☐☐☐☐.☐ µmol l^{-1}	☐☐☐☐.☐ µmol l^{-1}
29.13 Urea (mmol l^{-1})	☐☐.☐ mmol l^{-1}	☐☐.☐ mmol l^{-1}
29.14 Albumin (g l^{-1})	☐☐.☐ g l^{-1}	☐☐.☐ g l^{-1}
29.15 Bilirubin (µmol l^{-1})	☐☐☐.☐ µmol l^{-1}	☐☐☐.☐ µmol l^{-1}
29.16 Glucose (mmol l^{-1})	☐☐.☐ mmol l^{-1}	☐☐.☐ mmol l^{-1}
29.17 Glasgow coma scale[4]	☐☐	☐☐

30 Does the patient have bilateral ankle oedema[5]? **Yes** ☐ **No** ☐

[1]Q31

About non-invasive respiratory support during the stay in your critical care unit

We are only collecting information about non-invasive ventilation used as

EITHER the **sole** means of respiratory support in critical care

OR the respiratory support preceding intubation on the **first** occasion the patient is intubated during the critical care stay

NOTE

We realise some patients will receive non-invasive ventilation **following** extubation.
We are **NOT** collecting information about this.

[2]Q32.2

Did the patient receive a tracheostomy during the stay in your critical care unit?

- Answer yes if the patient received a tracheostomy that was at any time used as the airway.
- Answer no if the patient either only received a mini-tracheostomy for clearing secretions or did not receive any form of tracheostomy.

CAOS study

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SPECIAL NOTE

Please fax **page 15** (yellow)
of this questionnaire to the
CAOS Co-ordinating Centre

Fax: 0121 424 1634

ONLY when the patient **leaves**
your critical care unit

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ABOUT THE PATIENT'S TIME IN YOUR CRITICAL CARE UNIT

This page to be faxed to the CAOS Co-ordinating Centre when the patient is discharged from your critical care unit

31 About non-invasive respiratory support during the stay in your critical care unit[1]

These questions ask about non-invasive ventilation either as the sole means of respiratory support or as the means of respiratory support preceding the initial intubation [1].

31.1 Was the non-invasive ventilation:

a) Bilevel non-invasive ventilation ie a different level of support during inspiration from that delivered during expiration **Yes** ☐ **No** ☐ **Not applicable** ☐

b) CPAP (delivered by face mask) i.e. a constant level of support delivered during both inspiration and the same constant level of support delivered during expiration **Yes** ☐ **No** ☐ **Not applicable** ☐

c) A mixture of Bilevel non-invasive ventilation and CPAP (delivered by face mask) **Yes** ☐ **No** ☐ **Not applicable** ☐

31.2 Did the patient receive non-invasive ventilation in critical care as the sole assisted means of ventilatory support? **Yes** ☐ **No** ☐

31.2.1 For patients receiving non-invasive ventilation as the sole means of ventilatory support would the patient have been intubated if non-invasive ventilation had not been successful ? **Yes** ☐ **No** ☐ **Not applicable** ☐

31.3 Did the patient receive non-invasive ventilation in critical care prior to intubation? **Yes** ☐ **No** ☐

31.4 Did the patient only receive medical treatment (eg intensive nebuliser treatment etc) without either non-invasive ventilatory support or invasive support as the sole means of treatment whilst in the critical care unit? **Yes** ☐ **No** ☐

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32 About intubation

32.1 Was the patient intubated at any time in the critical care stay? **Yes** ☐ **No** ☐

If **Yes**:

a) what date and time was the patient intubated? ☐☐/☐☐/☐☐☐☐ ☐☐:☐☐ (24 hours)
d d m m y y y y

b) how many hours was the patient intubated for during the first intubation of this admission ☐☐☐ hours

32.2 Did the patient receive a tracheostomy during the critical care stay[2]? **Yes** ☐ **No** ☐

If **Yes**: on what date and time was the tracheostomy performed? ☐☐/☐☐/☐☐☐☐ ☐☐:☐☐ (24 hours)
d d m m y y y y

Thank you

Please fax odd pages **1 to 13** (light blue) of this questionnaire to the CAOS Co-ordinating Centre **within 24 hours** of the patient's admission to your critical care unit.

AND

page 15 (yellow) when the patient **leaves** your critical care unit

COAS Co-ordinating Centre Fax: 0121 424 1634