
THE UNIVERSITY *of* EDINBURGH

# Anaemia and its impact on recovery and quality of life in survivors of critical illness

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**Doctor of Medicine**

**University of Edinburgh**

**2011**

## Abstract

Survivors of critical illness experience a significant burden of persisting physical, psychological and cognitive dysfunction during recovery as a result of the interaction between factors relating to the ICU environment, the invasive treatments required and the pre-morbid health of the patient. Little is known about the long term complications of critical illness and the impact they have on recovery. Physical morbidity is common due to generalised muscle atrophy and weakness due to the catabolic state and immobility associated with critical illness. There is a high prevalence of anaemia in critically ill patients due to iatrogenic blood loss and the inflammatory state impairing erythrogenesis but little is known about its persistence and effects on physical recovery. The studies presented in this thesis aimed to evaluate the prevalence of anaemia and physical morbidity in survivors of critical illness and to explore the potential contribution of anaemia to impaired physical function and poor quality of life during recovery.

The TRAC study was a single centre, prospective, observational cohort study aimed to determine the prevalence and pathophysiology of anaemia following critical illness. Indices of erythropoiesis, inflammation and health related quality of life were measured over 6 months and showed that anaemia persists up to 6 months and was associated with evidence of an ongoing inflammatory state and impairment of erythropoiesis. Health related quality of life was also noted to be impaired raising the possibility that anaemia may affect quality of life following critical illness.

The Ps and Qs study was a two centre, prospective observational study aimed to investigate actual and perceived physical function during recovery from critical illness and the associated impact upon health related quality of life. Simple measures of psychological state and organ function were also recorded. The study showed that survivors of critical illness had a normal pre-morbid perceived physical function but a reduced quality of life. Both were significantly worsened by the critical illness and remained impaired up to 6 months. Actual physical function in our heterogeneous population was reduced to levels associated with very severe chronic disease. There was evidence of a significant level of post traumatic stress disorder, persisting anaemia and malnutrition but no other organ dysfunction during recovery.

Further analysis of the Ps and Qs data was performed to investigate potential links between anaemia, physical function and quality of life. Perceived physical function, actual physical function and quality of life were all impaired in the presence of anaemia. Additionally, anaemia was associated with a longer ICU stay and increased age but not with severity of illness or the degree of organ failure developed during ICU stay. The persistence of anaemia was also associated with malnutrition and inflammation.

In conclusion these studies show that physical function and health related quality of life are dramatically affected by critical illness. There is a high prevalence of anaemia in survivors of critical illness, which is associated with ongoing inflammation and impaired erythropoiesis. Importantly, the data also show that quality of life and physical recovery are further impaired in the presence of anaemia.

Further studies are required to evaluate the effects of anaemia on physical recovery from critical illness and investigate the potential benefits of treatments for anaemia on physical rehabilitation.

## Declaration

This thesis is entirely my own composition and has not been submitted for any other degree. The described work was performed by me, except where specifically quoted in the text or listed below.

Patient screening, recruitment and assessment were carried out by a dedicated research team and myself. For the TRAC study I was assisted by research nurses Fiona McArdle and Gordon Mills, and the Ps and Qs study by Gordon Mills and David Hope.

## Acknowledgements

I am immensely grateful to my supervisor, Timothy Walsh, for his patience and belief in me.

I would also like to thank the research team Fiona McArdle, Gordon Mills and David Hope whose persistence with recruitment and follow up showed true determination.

I am grateful to The Chief Scientists Office, Scotland for the project grant supporting the work for the TRAC study.

I am grateful to Orthobiotec UK (A pharmaceutical subsidiary of Johnson and Johnson) for an educational grant to support the work in this thesis.

Words cannot express my gratitude to my wonderful wife Anna, for all the sacrifices she has made, support and confidence she has given me during the long evenings and late nights. It would not have been possible without her!

I would also like to thank my amazing children, Sophie and Tess, for being the best sources of distraction in the world! And finally to my parents, Helen and Desmond, who taught me to never give up.

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## List of Abbreviations

| | |
|---|---|
| ADHERE | Acute decompensated heart failure national registry |
| AMT | Abbreviated mental test |
| ARF | Acute renal failure |
| ATS | American Thoracic Society |
| APACHE II | Acute Physiology and Chronic Health Evaluation (second version) |
| ARDS | Acute respiratory distress syndrome |
| BP | Bodily pain dimension of SF-36 measure |
| CABG | Coronary artery bypass graft |
| $CaO_2$ | Oxygen content of arterial blood |
| CIM | Critical illness myopathy |
| CIN | Critical illness neuropathy |
| CO | Cardiac output |
| CRBSI | Catheter related blood stream infection |
| CRP | C-reactive protein |
| $CvO_2$ | Oxygen content of venous blood |
| $DO_2$ | Oxygen delivery |
| DSM-IV | Diagnostics and Statistics Manual of Mental Disorders version 4 |
| DTS | Davidson Trauma Scale |
| FAI | Frenchay Activities Index |
| $FIO_2$ | Fraction of inspired oxygen |
| GH | General health dimension of SF-36 measure |
| HADS | Hospital Anxiety and Depression Scale |

| | |
|---|---|
| Hb | Haemoglobin |
| Hct | Haematocrit |
| HRQoL | Health related quality of life |
| IBCT | Incorrect blood component transfused |
| ICU | Intensive Care Unit |
| MH | Mental health dimension of SF-36 measure |
| MI | Myocardial infarction |
| MUAC | Mid upper arm circumference |
| NICE | National Institute for Clinical Excellence |
| NECC | North American European Consensus Conference |
| $O_2ER$ | Oxygen extraction ratio |
| PAWP | Pulmonary artery wedge pressure |
| $PaO_2$ | Partial pressure of arterial oxygen |
| PF | Physical function domain of SF-36 measure |
| PTSD | Post Traumatic Stress Disorder |
| rHuEPO | Recombinant human erythropoietin |
| RE | Role emotional dimension of SF-36 questionnaire |
| RIE | Royal Infirmary of Edinburgh |
| RP | Role physical dimension of SF-36 questionnaire |
| $SaO_2$ | Arterial oxygen saturation |
| SD | Standard deviation |
| SF | Social functioning dimension of SF-36 questionnaire |
| SF-36 | Medical outcomes short form 36 question health survey |
| SHOT | Serious hazards of transfusion |

| | |
|---|---|
| SIP | Sickness impact profile |
| SOAP | Sepsis Occurrence in Anaemic Patients study |
| TNF-α | Tumour necrosis factor α |
| TRALI | Transfusion related lung injury |
| TRIM | Transfusion related immunomodulation |
| VAP | Ventilator associated pneumonia |
| vCJD | Variant Creutzfeld Jacob Disease |
| Vi | Vitality dimension of SF-36 measure |
| $VO_2$ | Oxygen consumption |
| WGH | Western General Hospital |
| WHO | World Health Organisation |
| 6MWT | Six minute walk test |

## List of Publications, Presentations and Awards

### Original Research

**Bateman A. P.**, McArdle F., Walsh T. S. Time course of anemia during six months follow up following intensive care discharge and factors associated with impaired recovery of erythropoiesis. *Critical Care Medicine. 2009 Jun;37(6):1906-12*

### Abstracts

**Bateman A. P.,** Walsh T. Early predictors of the persistence of anaemia of critical illness. *Critical Care (Supplement) 2006 P412*

**Bateman A. P**, Mills G, McArdle F, Walsh T. Anaemia at discharge from intensive care is associated with an inappropriate erythropoietin response. *Critical Care (Supplement) 2005, P335.*

**Bateman A. P.**, Mills G, McArdle F, Walsh T. Anaemia which persists during recovery from critical illness is associated with elevations of IL-6 and sTfR levels. *Intensive Care Society Annual Spring Meeting Review 2005.*

**Bateman A. P.,** Walsh T.S. Recovery from the anaemia of critical illness is associated with resolution of the inflammatory state despite a depressed erythropoietin response. *Scottish Medical Journal Jan 2006*

### Oral Presentations

**Bateman A. P.** Recovery from the anaemia of critical illness is associated with resolution of the inflammatory state despite a depressed erythropoietin response. *Scottish Intensive Care Society Winter Meeting 2006*

# Chapter One

# Introduction

## 1.1 What is critical illness?

Critically ill patients have an acute physiological insult of life threatening severity and high short term mortality. Without the timely provision of aggressive physiological support to the failing organs it is almost certain that the patient would die. The primary aim of an intensive care unit is therefore "to prevent unnecessary suffering and premature death by intensive treatment of a reversible illnesses for an appropriate period of time" (Gibney 2001).

The demand for intensive care is increasing with more than 100,000 patients admitted to UK critical care units per year. This is due to increased sophistication in intensive care support, surgical techniques and medical interventions which allow life to be prolonged in circumstances which were not previously possible. There are also increased societal (and to some degree medical) expectations of what can be achieved in critical care from a positive depiction of medical technology in the media. Patients previously considered too sick to benefit from intensive care are being referred for assessment and admitted. Whilst intensive care can lead to improved clinical outcomes (Rivers, Nguyen et al. 2001; Simchen, Sprung et al. 2007) it can also prolong death. Critical care physicians must balance the prudent use of resources and equity of access against the finite capacity for the provision of critical care. As delaying and withholding therapy is associated with a high mortality (Kumar, Roberts et al. 2006; Chalfin, Trzeciak et al. 2007) it is important that intensive care beds are available for those who will benefit the most rather than being used for ultimately futile causes.

Critical care research has understandably focused on short term changes in physiological parameters and survival to ICU and hospital discharge. However it has become increasingly apparent with improved short term mortality from critical illness, with 75% of patients now surviving to be discharged home, many patients experience significant and persistent problems with physical and psychological functioning after discharge. The focus of research is therefore changing to include investigation of the potential causes of long term morbidity and impaired quality of life. It is hoped that not only will this lead to improvement in patient centred outcomes but also help inform the discussion on admission to intensive care so that prolonged treatment in patients who will ultimately not have meaningful survival can be avoided.

## 1.2 The treatment of critical illness and its potential complications

Critical illness is not just the time spent on ICU. It begins with the onset of acute deterioration and ends when the patient's risk of late sequelae, such as ongoing mortality, has returned to the baseline risk of a similar patient who had not incurred the acute critical illness (Angus and Carlet 2003). Several studies have suggested that ICU admission has minimal effect on long term outcome when the effects of hospital admission are controlled for (Keenan, Dodek et al. 2002; Keenan 2003), however in many cases the increased risk of death and morbidity remains and may never return to the levels of the normal population (Niskanen, Kari et al. 1996; Wright, Plenderleith et

al. 2003). The development of critical illness can occur in any individual and result in being admitted to intensive care for a wide variety of reasons.

The ICU population is therefore a complex heterogeneous population with intensive care treatment being a complex, individualised intervention. A complex intervention was defined by the Medical Research Council (MRC) as an intervention comprising a number of separate elements which seem essential to the proper functioning of the intervention even though the 'active ingredient' of the intervention is difficult to specify (MRC 2000). Thus analysing the effect of 'ICU admission' involves delineating the components of critical illness and the interventions provided in intensive care units and determining how they inter-relate to the final patient centred outcome. The burden of critical illness can be described as a continuum beginning with the development of the critical illness and continuing into the long term recovery (Figure 1.1). Using this model it is possible to consider some possible patient and process of care factors which have the potential to influence subsequent long term outcome (Figure 1.2).

Pre-ICU factors would include:

- Underlying illness - malignancy related compared to acute infection
- Reason for ICU admission - respiratory failure compared to trauma
- Pre-ICU management - resuscitation, antibiotic timing
- Access to ICU - bed availability

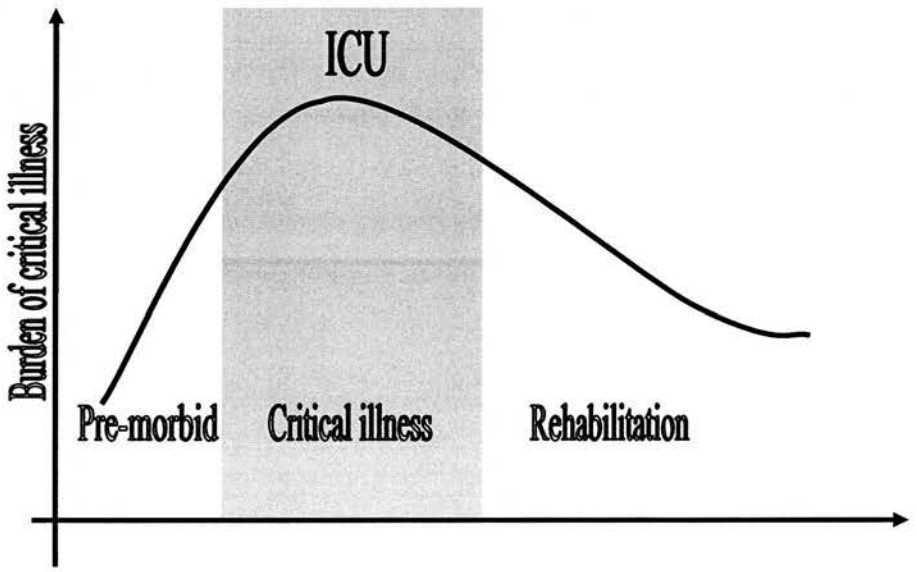



**Figure 1.1The burden of critical illness**

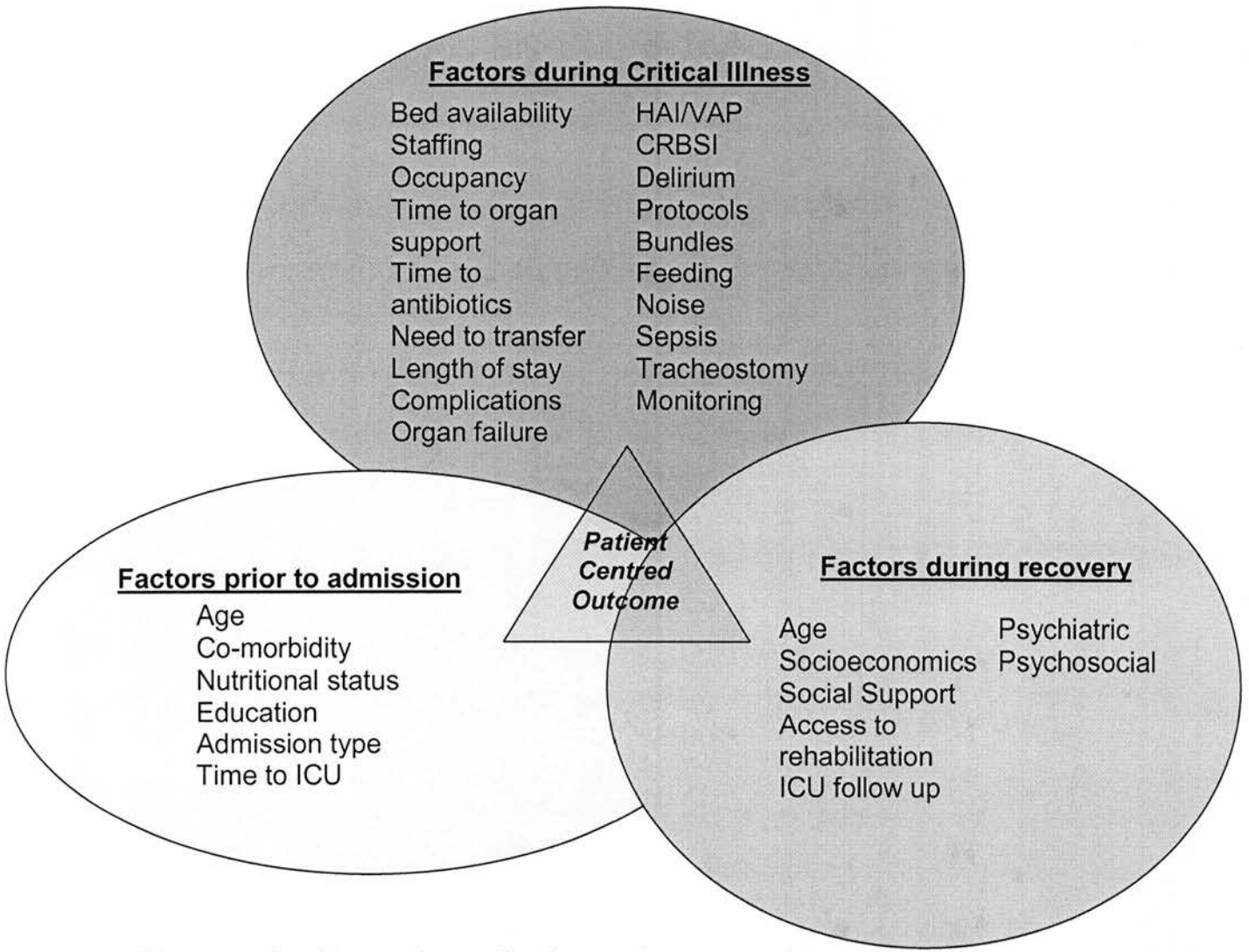



**Figure 1.2 The complex interactions affecting patient centred outcomes following critical illness**

Intra-ICU factors would include:

- Patient course and events – organ dysfunction, sepsis, tracheostomy, ability to wean
- Treatments – monitoring, sedation, feeding, transfusion practice
- Organizational – staffing patterns, protocol use
- Iatrogenesis and environmental – hospital acquired infection, noise pollution

*(adapted from (Angus and Carlet 2003))*

Post ICU factors would include:

- Social status and financial security
- Personal support networks
- Access to rehabilitation services
- Ongoing organ dysfunction e.g. renal failure requiring dialysis, persisting sepsis
- Ongoing morbidity from complications of ICU, e.g. delirium and cognitive impairment, pain, malnutrition

The general perception among patients, families and healthcare professionals that patients undergo a rapid convalescence and recover to their previous life is unfounded. Many patients experience significant and persistent problems with physical, non-physical and social functioning after discharge from critical care (Broomhead and Brett 2002). These problems are frequently unrecognised. The importance of trying to screen for and detect potential patient problems and to prevent the development of complications is now recognised as being of prime importance in ICU practice and

research. The 2002 European Society of Intensive Care 'Round Table' consensus statement (Angus and Carlet 2003)and the National Institute for Clinical Excellence (NICE) guideline 2009 on rehabilitation from critical care (Tan, Brett et al. 2009) have reinforced the need to address post ICU morbidity by delineating those complications that are due to pre morbid patient factors, those due to the underlying illness and those due to intra-ICU events. To this end a brief review of the impact of specific organ failures and common complications of ICU treatment on post ICU mortality and morbidity is detailed below together with a full literature review on anaemia, a common complication of critical illness.

## 1.3 The impact of respiratory failure and the development of Acute Respiratory Distress Syndrome

The heterogeneity of the ICU population and the complications they develop as a consequence of critical illness makes it difficult to describe the population in which the patient centred problems may develop. Acute respiratory failure is the most common organ failure in a general intensive care unit (Walsh 2003). Patients who develop Acute Respiratory Distress Syndrome (ARDS) represent one of the best studied post critical illness populations, as the entity of ARDS has a specific definition and as a population with a single severe organ failure (respiratory failure), it is possible for the population to be characterised. It is also relevant to the whole ICU population as ARDS is common and has the potential to develop in any patient with critical illness. Furthermore, its effects are relatively independent of the precipitating 'critical illness event' and these

effects persist after the initial critical illness has resolved which allows extrapolation of some of the factors affecting the ARDS population into the general ICU population as part of a 'post ICU' syndrome.

Severe respiratory failure has approximately a 14% - 17% (Pettila, Pettila et al. 2002) in hospital and 22% 3 month mortality. It is often followed by failure in other organs and death more commonly occurs because of multi organ failure with isolated irreversible respiratory failure only accounting for 3-10% of deaths in ICU (Flaatten, Gjerde et al. 2003) (Estenssoro, Dubin et al. 2002). When severe respiratory failure is accompanied by other organ failure, the ICU mortality increases to 11% with one other organ failure, and up to 70% with 3 additional organ failures (Flaatten, Gjerde et al. 2003).

The Acute Respiratory Distress Syndrome (ARDS) was originally described in 1967 in 12 patients with acute respiratory distress, cyanosis refractory to oxygen therapy, decreased lung compliance and diffuse infiltrates on the chest radiograph (Ashbaugh, Bigelow et al. 1967). This definition has been reviewed over time and in 1994 a consensus definition which included acute onset, bilateral infiltrates on chest radiograph, pulmonary artery wedge pressure (PAWP) <18mmHg and a $PaO_2$:$FiO_2$ ratio $\leq$ 200. The underlying pathophysiology of diffuse alveolar damage from disruption of the alveolar-capillary barrier resulting in the bidirectional leak of fluid, proteins and inflammatory mediators and the disruption of normal surfactant production and action, is complex and dependent on many host and precipitating insult factors. The syndrome can progress to a form of fibrosing alveolitis in the longer term. Clinical risk factors for developing ARDS include direct factors such as pneumonia, aspiration of gastric contents and lung

contusion, and indirect factors such as non-pulmonary sepsis, massive transfusion, pancreatitis and poly-trauma (Bersten, Edibam et al. 2002). The incidence of ARDS is between 28-59 per 100,000 people and is thought to be increasing, possibly due to ICU factors such as aggressive fluid administration (Bersten, Edibam et al. 2002; Rubenfeld and Herridge 2007). Controversially, the mortality from ARDS is difficult to define. A recent review suggests that mortality has not improved since the North American European Consensus Conference (NECC) statement in 1994, remaining around 40% (Phua, Badia et al. 2009). Other studies suggest that a mortality rate of 30% is more likely (Wheeler and Bernard 2007). This is despite changes in intra-ICU practice aimed at reducing not only the development of ARDS but also the complications associated with it.

In the longer term survivors of ARDS have significant long term physical and neuropsychological consequences which are attributable to ARDS itself not just critical illness (Davidson, Caldwell et al. 1999). Survivors of ARDS have persistent functional disability at 1 year and even in the longer term following discharge from ICU. The pulmonary function of these patients has generally returned to normal by 6 months (Rubenfeld and Herridge 2007). The major sequelae are related to neuromuscular, cognitive and psychological dysfunction. They lose up to 20% of their baseline body weight and describe muscle weakness and fatigue as the main reasons for their functional limitation (Herridge 2002). The objective measures of physical limitation such as distance walked were all reduced even at 12 months (Herridge, Cheung et al. 2003). As well as loss of muscle mass the development of critical illness neuropathy,

entrapment neuropathies and heterotopic ossification appear to contribute to the physical morbidity.

The psychological impact in survivors of ARDS is large. At discharge from hospital 100% of patients show signs of cognitive impairment with 30% still having significant deficits at 1 year (Hopkins, Weaver et al. 1999). The prevalence of clinically significant depressive symptoms was described as 17-43% at ICU discharge with a 21-35% prevalence of psychiatrist diagnosed post traumatic stress disorder (PTSD) which falls to 25% prevalence at 5 years post ICU discharge. These symptoms all had a negative effect on the patient's quality of life (Schelling, Stoll et al. 1998) (Davydow, Desai et al. 2008) and ability to return to work (Rothenhausler, Ehrentraut et al. 2001).

In summary the long term impact of respiratory failure is complex and multifactorial. It is principally related to extrapulmonary factors. As short term survival from respiratory failure is improving it is likely that we will see increasing numbers of patients with the long term effects of severe respiratory failure.

## 1.4 The impact of sepsis

Sepsis is the leading cause of death in critically ill patients with mortality ranging from 28% to 80% depending upon severity, number of subsequent organ failures, age and co-morbidities of the study population (Angus, Linde-Zwirble et al. 2001). There is a persistent increased risk of dying in survivors of sepsis compared to other critical illness survivors, for up to 5 years (Quartin, Schein et al. 1997; Keenan 2003). Survivors of

sepsis have residual organ dysfunction which causes symptoms of dyspnoea, fatigue and impaired function and a reduced quality of life which is similar to that of other survivors of critical illness (Granja, Dias et al. 2004; Yende and Angus 2007).

## 1.5 The impact of neuromuscular failure

Survivors of critical illness have a significant burden of neuromuscular related morbidity (Young 1995). The neurological complications of critical illness involve the central and peripheral nervous system and so the specific effects of neurocognitive impairment, neuromuscular impairment, delirium and traumatic brain injury are discussed below.

### 1.5.1 Neurocognitive impairment

The preservation of neurocognitive function is highly prized among the general population and in survivors of critical illness. 89% of Americans would not wish to survive if they had severe irreversible neurological damage (Fried, Bradley et al. 2002). Neurological dysfunction is common during critical illness (Jones, Griffiths et al. 2006) and is associated with increased mortality (Vincent, Moreno et al. 1996; Russell, Singer et al. 2000). Studies assessing long term neurological outcomes in the critically ill found that the prevalence of long term neurocognitive dysfunction ranges from 25% to 78% (Hopkins and Jackson 2006). The defects described include impairments in memory, attention, executive function and psychiatric disturbance. There is not a uniform cause of post ICU neurological impairment. It is not associated with factors associated with the severity of illness such as APACHE scores, duration of ICU stay, ventilation and

duration of sedatives. Potential causes which may interact to produce the dysfunction include hypoxaemia, use of sedatives and analgesics, hypotension, delirium and metabolic derangement reflecting the two most biologically plausible mechanisms of neurotransmitter abnormalities (dopamine excess secondary to anticholinergic side effects of common medications) and occult diffuse brain injury. Patient factors such as pre-morbid neuro-psychiatric dysfunction and genetic factors are also important (Milbrandt and Angus 2005). Surprisingly, age alone is not associated with neurocognitive dysfunction in its own right, but many of studies excluded patients with pre-existing neurocognitive dysfunction. Of potential relevance, the prevalence of pre-existing dysfunction in elderly ICU patients has been estimated at 35% (Pisani, Redlich et al. 2003).

Cognitive impairments are rarely recognised or evaluated in survivors of critical illness (Jackson, Hart et al. 2003), but have potentially huge impact upon individuals. In patients with ARDS and neurocognitive defects roughly a third returned to work or study, a third were on new disability support as they were unable to return to work and a third were not working or had retired (Hopkins, Weaver et al. 2005). This has huge socio-economic implications for health and social care provision.

### 1.5.2 Neuromuscular impairment

Physical impairments following critical illness such as heterotopic ossification, entrapment neuropathy, critical illness neuropathy (CIN) and myopathy (CIM) also impair function and quality of life. CIN and CIM can have particularly profound effects

on patients. The absence of a motor response is often interpreted as a grave prognostic sign leading to undue pessimism and limitation of treatment in many patients. It increases the requirement for invasive ventilation (Garnacho-Montero, Amaya-Villar et al. 2005) and doubles the length of time of weaning (De Jonghe, Bastuji-Garin et al. 2004). The mortality of patients who develop CIN or CIM is increased, ICU mortality was 48% compared to 19% (in those without CIN/CIM) in one study (Leijten, Harinck-de Weerd et al. 1995). In the longer term CIN was often associated with persistent disability whilst myopathy tended to be associated with a rapid and complete recovery. Long term data is lacking but 70% of patients have been described as making good functional recovery (spontaneous breathing and independent walking) and 30% remaining severely disabled (Latronico 2003). The disabilities described were mainly profound muscle weakness and dyspnoea secondary to respiratory muscle weakness (Fletcher, Kennedy et al. 2003).

Risk factors for the development of neuromuscular weakness include the severity of illness, specific pharmacological agents especially neuromuscular blocking agents, poor glycaemic control and a persistent inflammatory state. Neuromuscular blocking agents and aminoglycosides alter neuromuscular transmission causing pharmacological muscle denervation, and their use should be restricted to cases where the risks of these agents is outweighed by the potential benefits (Murray, Cowen et al. 2002). Other drugs such as propofol and corticosteroids may cause damage in response to the priming effect of critical illness especially when there is a marked systemic inflammatory response. Propofol may cause the 'propofol infusion syndrome' characterised by severe metabolic

acidosis, rhabdomyolysis and neuromuscular weakness due to the uncoupling of oxidative phosphorylation and direct muscle damage. Corticosteroids have long been recognised as a cause of muscle damage but it has only been recently that their use has been demonstrated as an independent risk factor for critical illness neuropathy and myopathy (De Jonghe, Sharshar et al. 2002). Poor glycaemic control and severe electrolyte abnormailites are also considered risk factors for developing neuromuscular weakness (Hermans, Wilmer et al. 2007).

Prevention and treatment of these complications through changes in sedation, glycaemic control, the use of neuromuscular blocking agents and steroids is being investigated, with the focus of improved ICU care being to reduce the incidence of these complications.

### 1.5.3 Delirium

Delirium is an acute central nervous dysfunction resulting from a number of common insults experienced by the critically ill. It occurs in 60-80% of patients in ICU and is often not recognised and is considered one of the six leading causes of preventable injury in the elderly (Rothschild, Bates et al. 2000). The development of delirium in ICU is associated with significant morbidity (delirium is an independent predictor of nursing home placement and subsequent development of dementia) and higher mortality (Ely, Shintani et al. 2004). It persists in 11% of patients at hospital discharge. Strategies aimed at reducing the development of delirium such as choice of sedative drug (Pandharipande, Pun et al. 2007; Riker, Shehabi et al. 2009), combined with strategies aimed at reducing the impact of the development of delirium such as the daily interruption of sedation and

a multidisciplinary approach to the detection and subsequent treatment of delirium (Kress, Pohlman et al. 2000; Lat, McMillian et al. 2009) are having marked effects on this outcome. As such the Society of Critical Care Medicine has now recommended delirium assessment as a standard of care in intensive care units.

### 1.5.4 Head Injury

Differentiation between pre-morbid neurocognitive deficits, the impact of trauma and the effects of critical illness in this population is difficult. Traumatic brain injury tends to produce focal rather than diffuse changes in the brain leading to characteristic patterns of dysfunction distinct from critical illness. Frontal and temporal lobes are most commonly affected leading to impaired memory, attention and executive function (van 2005). The more severe the brain injury the more severe the subsequent impairment (Demery, Pedraza et al. 2002). It tends to recover over time particularly in cases of mild to moderate injury (Belanger, Curtiss et al. 2005). Thus traumatic brain injury and critical illness is associated with poor outcome, but head injury patients represent a distinct group of survivors from critical illness alone as it is the head injury itself which has the overwhelming impact on subsequent recovery. There is undoubtedly overlap between the two groups and much can be learned from each group to help improve the other. Certainly head injury outcomes are improved by the provision of specialist critical care (Suarez 2006).

## 1.6 Impact of Post Traumatic Stress Disorder and psychological dysfunction

Critical illness and its treatments expose patients to extreme physiological and psychological stressors such as pain, severe dyspnoea and administration of exogenous catecholamines and sedatives, whilst the patient is in a state of altered consciousness, helplessness and with an impaired ability to communicate. Post Traumatic Stress Disorder (PTSD) is a complex disorder with high rates of psychiatric co-morbidity (including the development of harmful coping strategies such as alcohol and drug addiction) which occurs in 5-64% of the ICU population (Kessler 2000; Griffiths, Fortune et al. 2007). The prevalence of clinically significant symptoms is 22% and actually clinically diagnosed PTSD 19% (Cuthbertson, Hull et al. 2004). Risk factors for developing PTSD included degree of exposure to benzodiazepines, physical restraint, duration of mechanical ventilation and non daily interruption of sedation (Davydow, Desai et al. 2008), although the risk is not always related to the severity of illness. The development of PTSD in survivors of critical illness significantly impairs quality of life (Girard, Shintani et al. 2007; Sukantarat and Williamson 2007).

Clinically significant depression is present in 28% of patients after ICU admission (Davydow, Gifford et al. 2009) and is associated with an impaired quality of life. The development of depression is not associated with ICU related factors but is strongly influenced by psychological and physical impairments to recovery. It appears that the initial elation at having survived is replaced by frustration and anger during the

protracted recovery process. Severe anxiety symptoms producing avoidant behaviour are seen in 50-70% of patients and are more common, and more persistent, in those who have impaired recollection of ICU stay (Scragg, Jones et al. 2001).. Sexual dysfunction is common and has been reported in 25% of patients. Reasons for dysfunction included lack of desire, impotence, dyspnoea, surgical disfigurement and fear of precipitating a 'relapse' (Griffiths, Waldmann et al. 2007).

## 1.7 Impact of liver failure

The prognosis of patients who are admitted to ICU with decompensated liver failure who are not suitable for liver transplantation is poor. The hospital mortality of these patients depends upon the associated other organ failures: 68% if associated with respiratory failure, 88% with sepsis and 94% for any other organ failure or a creatinine of more than 120 μmol/l (Mackle, Swann et al. 2006). Most patients will die within the first month after ICU discharge (Gildea, Cook et al. 2004). However in those who do survive the subsequent quality of life is related to the effects of their liver failure which tends to overwhelm the ICU related effects. Generally quality of life is poor (Roth, Lynn et al. 2000) and a significant proportion of the few patients who survived to 1 year described significant pain, which is uncommon in chronic liver failure. These patients also described a wish to die rather than to continue to suffer pain and fluctuating conscious level. The principal problems described are related to the development of encephalopathy, recurrent infections, weakness, malnutrition and redevelopment of ascites and itch.

## 1.8 Impact of renal failure

Acute renal failure (ARF) in the context of critical illness is associated with a high mortality and this mortality is in excess of that which is found in patients with pre-existing established dialysis dependent renal failure admitted to ICU (Clermont, Acker et al. 2002). Risk factors for the development of ARF included previous ischaemic heart disease, stroke, pulmonary disease, diabetes, cancer, connective tissue disease and alcoholism. 64% of patients who develop ARF have died by 1 year following ICU discharge. However in survivors renal recovery occurs in 78% (Bagshaw, Laupland et al. 2005) and the majority of patients who did not recover adequate renal function had significant pre-existing renal impairment. There is no investigation of the long term effects on quality of life in patients who have established renal failure following critical illness. In the chronic renal failure literature it seems likely that the symptom burden imposed by the complications of renal failure such as anaemia, the burden of dialysis and the necessary lifestyle modifications to achieve good dialysis, are likely to conceal the effects of critical illness. In chronic renal failure 61% of patients on developing the requirement for dialysis could not perform their normal activities, 50% of patients described severe difficulties with mobility and pain and 14% had problems with self care (Bagshaw, Laupland et al. 2005). Treatments such as erythropoietin (Obrador and Pereira 2002) are having a significant impact on quality of life and such improvements may provide insight into what areas critical care interventions could focus upon to try and achieve similar results.

## 1.9 Impact of cardiac dysfunction

Myocardial dysfunction such as biventricular dilatation and reduced ejection fraction is associated with acute sepsis and septic shock. This dysfunction persists despite resuscitation and the development of the hyperdynamic phase of septic shock and is not due to myocardial hypoperfusion but rather cytokine mediated effects on myocardial contractility (Court, Kumar et al. 2002). There are no studies examining the long term effects of isolated cardiac failure secondary to critical illness in the absence of infarction (Broomhead and Brett 2002). Animal models suggest that cardiac function returned to normal within a few days of recovery from a septic episode. Postural hypotension, most likely due to residual autonomic neuropathy decreases mobility and independence due to associated 'dizziness' (Griffiths 1999).

Heart failure in its own right is a progressive chronic disease with substantial morbidity and mortality. In hospital mortality is 5% and 33% of patients will die within their first hospitalisation with acute heart failure and 50% will require rehospitalisation within 6 months of the original admission (Aghababian 2002; Jong, Vowinckel et al. 2002). With such severe disease burden the effects of critical illness are to some degree masked by the effects of heart failure but, undoubtedly in trying to optimise therapy in one disease process there are improvements in the other. There is an extensive literature describing the actual morbidity and impairments to quality of life in heart failure (Jeon, Kraus et al.). Generally, in cases of severe heart failure dyspnoea, fatigue, loss of appetite and

psychological reactions to an individual's potential mortality appear to be the most prominent symptoms.

## 1.10 The impact on care givers

75% of patients who survived at least 2 months following ICU require significant caregiver support. Only 33% of the caregivers were working and 30% had reduced or given up work in order to care for the patient (Im, Belle et al. 2004). 33% of care givers had symptoms consistent with clinical depression. In the SUPPORT trial 20% of patients reported a family member who had given up work, 30% lost the major source of income and had lost the majority of the family savings (1995). Depression, lifestyle disruption and employment reduction in caregivers is independent of pre-morbid health (Van Pelt, Milbrandt et al. 2007).

## 1.11 The burden of critical illness

There is a significant physiological and psychological burden imposed upon survivors of critical illness and their families and carers. Identifying the common and important problems experienced by these patients will hopefully enable patient centred rehabilitation strategies to improve the speed and the quality of that recovery. Anaemia is a common complication of critical illness with a multitude of biologically plausible mechanisms by which it could impact upon recovery from critical illness.

## 1.12 The anaemia of critical illness

The cells of the blood are produced from self renewing progenitor stem cells in the bone marrow that subsequently develop into recognisable precursor cells and then mature functional cells in the circulation. Erythropoiesis occurs under the influence of erythropoietin, a glycoprotein hormone secreted by the kidneys with a half life of approximately 5 hours, in response to hypoxia. The hormone acts on the red marrow to cause increased output of erythrocytes until the rise of haemoglobin concentration restores normal delivery of oxygen to the tissues. Other growth factors and cytokines modulate the effects of erythropoietin depending upon the clinical state under which the stimulus for erythropoiesis develops.

Certain dietary constituents such as iron, vitamin $B_{12}$, folic acid, vitamin $B_6$ and amino acids are required for the normal development of the cells and the appropriate production of haemoglobin. A normal western diet provides approximately 15mg per day of iron of which 1 mg is actually absorbed and utilised. 2 micrograms per day of Vitamin $B_{12}$ and 3 mg per kilogram per day of folate are also required for normal haemoglobin production.

### 1.12.1 Definition of anaemia

The symptoms and signs of anaemia are characterized by a decreased oxygen carrying capacity of the blood which in turn is determined by the mass of circulating red blood cells. Red cell mass is not easily measured and the clinical definition of anaemia is based

on the haemoglobin (Hb) concentration or haematocrit (Hct) of whole blood. The World Health Organisation (WHO) definition of anaemia is an Hb concentration below the normal range of a population. For a typical 'western' population the WHO have therefore defined anaemia as a haemoglobin concentration of <130 g/L in males and 120 g/L n females (Organisation 1968). The anaemia of critical illness is defined as the development of haemoglobin concentrations below the normal range in response to an illness of acute onset and is of such severity that advanced physiological support for the failing organ or organs is required.

### 1.12.2 Physiological response to anaemia

#### *1.12.2.1 Oxygen content*

Oxygen is principally carried in the blood bound to haemoglobin (98.5% or ~19.7ml/100ml blood) with only a small amount dissolved in the blood (0.3ml/100ml blood). The oxygen content of arterial blood ($CaO_2$) is described using the equation:

$$CaO_2\,(ml/100ml) = 1.34\,(ml\ O_2/g\ of\ Hb) \times Hb\ (g/dl) \times SaO_2 + (0.23 \times PaO_2\ (KPa))$$

This relationship states that each gram of haemoglobin will bind 1.34 mL $O_2$ when it is fully saturated with oxygen which equates to 19.7ml/100ml for a haemoglobin concentration of 15 g/dL whereas only 0.3 ml/100ml is dissolved in the blood. This relative strength of haemoglobin compared to partial pressure of oxygen in arterial blood ($PaO_2$) in determining the oxygen content of the blood is such that a 50% reduction in haemoglobin concentration is fully expressed as a 50% reduction of $CaO_2$. However a

50% reduction in $PaO_2$ only results in a 20% decrease in $CaO_2$. Haemoglobin concentration therefore has a large impact on arterial oxygenation compared to hypoxaemia.

#### *1.12.2.2 Oxygen delivery*

Oxygen delivery ($DO_2$) is the product of cardiac output (CO) and oxygen content ($CaO_2$):

$$DO_2 = CO \times CaO_2 \text{ mL min}^{-1}$$

Inadequate oxygen delivery can therefore occur from decreased cardiac output, or decreased oxygen content (decreased haemoglobin concentration or arterial oxygen saturation), or increased oxygen consumption.

#### *1.12.2.3 Oxygen extraction*

At rest the normal healthy person consumes approximately 250 ml of oxygen per minute The oxygen consumption ($VO_2$) is a function of the cardiac output and the difference between the arterial and venous blood:

$$VO_2 = CO \times (CaO_2 - CvO_2)$$

Oxygen extraction ratio $O_2ER$ is the ratio of $O_2$ uptake to $O_2$ delivery:

$$O_2ER = VO_2 / DO_2$$

The normal $O_2ER$ is 0.2 to 0.3 indicating that only 20-30% of the oxygen delivered to the capillaries is taken up by the tissues. The oxygen transport system tries to maintain an adequate provision of oxygen to the tissues, depending upon their requirements, and must also be able to respond to changes in conditions where the oxygen demand of a given tissue or even the body as a whole can vary widely. The relationship between oxygen delivery and oxygen uptake is often described as the $DO_2.VO_2$ curve (Figure 1.3). As oxygen delivery decreases below normal the oxygen extraction increases proportionally and the oxygen uptake remains constant. When extraction is maximal (usually 50 to 60% depending on tissue) further decreases in oxygen delivery are accompanied by proportional decreases in oxygen uptake. Oxygen uptake is therefore 'supply dependent' and energy production is limited by the supply of oxygen.

As illustrated above the body responds to the development of anaemia by increasing cardiac output and an increase in oxygen extraction. The increased cardiac output appears to be due to a reduced blood viscosity decreasing resistance to flow and facilitating left ventricular emptying. This results in increased stroke volume and cardiac output. This compensatory mechanism operates only when the anaemia is severe as increasing cardiac output produces increased oxygen consumption in the myocardium at a time when delivery may be precarious and extraction is already maximal. The second compensatory mechanism is to match oxygen delivery to oxygen demand such that blood flow is redistributed to areas of high demand.

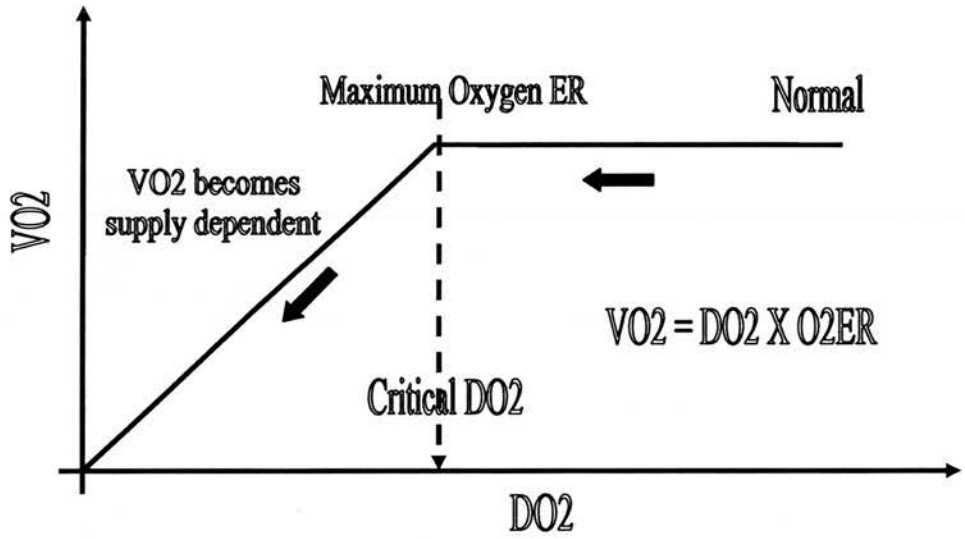



**Figure 1.3 Diagram describing the normal relationship between oxygen delivery ($DO_2$) and oxygen uptake ($VO_2$)**

$O_2ER$ = oxygen extraction ratio

*Adapted from Marino, P. L. The ICU Book (Marino 1997)*

#### *1.12.2.4 The concept of a critical haemoglobin concentration*

The haemoglobin concentration at which the critical oxygen delivery occurs can be considered to represent a critical haemoglobin concentration. It is dependent upon the metabolic activity of the body as a whole or on certain critical organs or tissues whose oxygen requirements are high. The lower limit of tolerance to acute isovolaemic anaemia has not been fully established.

In animal studies a critical haemoglobin level has been demonstrated to be approximately 40 g/L (Wilkerson, Rosen et al. 1988; Rasanen 1992; Van der Linden, Schmartz et al. 1998). In human studies isovolaemic haemodilution to a haemoglobin concentration of 50 g/L produced an increase in cardiac output and reduction in oxygen delivery, although there was no major change in $VO_2$ or plasma lactate reflecting inadequate total body oxygenation. There was some evidence of organ specific hypoxia with asymptomatic ECG changes noted in some subjects at haemoglobin concentrations of 50-70 g/L (Weiskopf, Viele et al. 1998; Leung, Weiskopf et al. 2000). Another study found evidence of cognitive dysfunction at haemoglobin concentrations of less than 60 g/L (Weiskopf, Kramer et al. 2000). Clinical experience with Jehovah's Witnesses suggest that mortality is only increased at haemoglobin concentrations less than 50 g/L (Viele and Weiskopf 1994).

The adequacy of any haemoglobin concentration in a given clinical situation depends on whether a sufficient amount of oxygen is carried to meet the metabolic requirements. In

patients with critical illness oxygen demands are high and the potential for anaemia to impact adversely upon oxygen delivery is significant.

Thus the critical haemoglobin concentration is defined as the haemoglobin concentration below which oxygen consumption is supply dependent assuming normovolaemia. It represents the point where cardiac output and oxygen extraction are maximal and thus a reduction in the oxygen carrying capacity in the blood (a drop in Hb) will cause tissue hypoxia. It is not a fixed value and varies between organs and the metabolic state of the patient.

#### *1.12.2.5 Detecting inadequate oxygen delivery*

As blood transfusion has risks the optimal situation in clinical practice would be where a transfusion could be individually titrated to the patient's oxygen delivery requirements at any given time. It is difficult to detect tissue hypoxia clinically until it is severe. There are no specific clinical signs and whole body oxygen requirements are not representative of individual organ hypoxia. Assessment of the adequacy of oxygen delivery relies on the detection of anaerobic metabolism such as lactic acidosis, but whole blood lactate concentration is not specific for tissue hypoxia.

#### *1.12.2.6 Transfusion thresholds*

In response to the lack of an ideal monitor 'inherited' transfusion thresholds, based on haemoglobin concentration of 10 g/dL historically from the 10/30 rule of Adams and Lundy (haemoglobin more than 10 g/dL and haematocrit more than 30%) based on

clinical observation (Adams 1942) and since the TRICC study (Hebert, Wells et al. 1999) a restrictive threshold of 7 g/dL, have evolved which result in transfusions occurring in response to a haemoglobin concentration rather than on the adequacy of oxygen delivery. Though these thresholds represent a distillation of clinical experience and have erred on the side of optimising the oxygen carrying capacity of the blood there is a lack of evidence to support them. As more is known about the potential risks of blood and of the efficacy of transfused blood in actually improving oxygen carriage these thresholds need to be reviewed.

### 1.12.3 Prevalence of anaemia of critical illness

Estimates of the prevalence of critical illness anaemia varies due to differences in ICU case mix, illness severity and transfusion practice internationally, nationally and even within the same hospital's ICUs.

#### *1.12.3.1 Pre-existing anaemia*

In a cohort study of 3534 patients admitted to European ICUs (the ABC study) the mean haemoglobin concentration at ICU admission was 11.3 g/dL with 30% of patients having a haemoglobin concentration of less than 10 g/dL at admission. Only 13% of patients had a recent history of anaemia and those with severe anaemia had no history of acute blood loss or anaemia (Vincent, Baron et al. 2002). The CRIT study in the United States again found a mean admission haemoglobin concentration of 11 g/dL (Corwin, Gettinger et al. 2004). A cohort study of 1023 sequential admissions to 10 separate Scottish ICUs found that the median haemoglobin was 10.5 g/dL with 25% of patients

had a haemoglobin concentration less than 9 g/dL. This suggests that 20-30% of patients have moderate to severe anaemia with only 10-15% having documented pre-existing anaemia.

#### *1.12.3.2 Anaemia during ICU admission*

In non-bleeding patients haemoglobin concentrations decrease by approximately 0.5 g/dL per day (Chohan, McArdle et al. 2003; Nguyen, Bota et al. 2003). The most rapid decline in haemoglobin concentration occurs within the first 3-4 days of critical illness. Following this phase the rate of decline decreases and a plateau is reached, due to an empiric transfusion threshold being chosen, and as a consequence when this threshold is breached, the anaemia is treated with blood transfusion 'artificially' maintaining the haemoglobin concentration. As such the haemoglobin concentration at which this plateau occurs is strongly influenced by transfusion practice. The TRICC trial (Hebert, Wells et al. 1999) compared liberal (Hb maintained between 100 to 120 g/L) and restrictive (Hb maintained between 70 to 90 g/L) transfusion strategies in non-actively bleeding patients. The primary outcome, 30 day all cause mortality was 18.7% in the restrictive group and 23.3% in the liberal group. Cardiac complications were also more common in the liberal group. Other trials in orthopaedic (Carson, Duff et al. 1998), vascular (Bush, Pevec et al. 1997) and coronary artery bypass graft (CABG) patients (Bracey, Radovancevic et al. 1999) have also found no difference on morbidity or mortality by the adoption of a restrictive transfusion practice. Thus in addressing the long standing practice in which the development of anaemia is perceived as harmful

these studies suggest that there is no harm and in fact there is benefit I the adoption of a restrictive transfusion practice.

Since the TRICC study showed that there was no harm and probable benefit in the adoption of a restrictive transfusion strategy (Hebert, Wells et al. 1999) there has been an adoption of more consistent practice (Chohan, McArdle et al. 2003). Typical pre-transfusion haemoglobin values in ICU are between 78 to 85 g/L.

Audit of transfusion practice of a UK ICU showed that in patients who stayed more than 24 hours, 55% developed an haemoglobin of less than 90 g/L and that this anaemia occurred early (Chohan, McArdle et al. 2003). At ICU discharge 90% of patients were anaemic for gender reference range and 50% had severe anaemia with a haemoglobin of less than 100 g/L (Walsh, Saleh et al. 2006).

#### *1.12.3.3 Anaemia after ICU discharge*

Few patients are transfused after ICU discharge despite anaemia being common at discharge. Patients describe fatigue, breathlessness and other morbidity associated with anaemia during their hospital stay but few receive transfusions. The transfusions usually occur at haemoglobin concentrations of 8-9 g/dL (Vincent, Baron et al. 2002; Corwin, Gettinger et al. 2004). As a consequence it has been shown that 77.4% of all ICU survivors are anaemic when discharged from hospital and 32.5% have a haemoglobin concentration less than 10 g/dL (Walsh, Saleh et al. 2006).

### 1.12.4 Aetiology of anaemia of critical illness

Anaemia can result from blood loss, decreased red cell production, increased red cell destruction or a functional anaemia in response to changes in plasma volume.

#### *1.12.4.1 Blood loss*

Blood loss can occur due to diagnostic sampling, bleeding episodes or practical complications of ICU interventions. The average volume of blood sampled in a critically ill patients is 41mls per day (Vincent, Baron et al. 2002) and diagnostic blood loss contributes on average to 1 to 2 units of blood loss during their hospital stay (Smoller and Kruskall 1986).

Significant overt bleeding (>300 mls) has been shown to occur in 21% patients (Garrioch, Fletcher et al. 2002). Gastrointestinal bleeding is relatively uncommon in critically ill patients and its contribution to the development of anaemia although significant has probably been overstated, especially with increased use of stress ulcer prophylaxis and increased early enteral feeding. The development of acute renal failure is strongly associated with the development of anaemia (Corwin, Parsonnet et al. 1995) and may be due to iatrogenic losses occurring when haemodialysis or haemofiltration circuits fail unexpectedly. Audits of transfusion practice have found that 45-80% of red cell transfusions do not occur in the context of acute bleeding (French, Bellomo et al. 2002; Rao, Boralessa et al. 2002). Other mechanisms must therefore contribute to its development.

#### *1.12.4.2 Decreased red cell production*

Critically ill patients have been shown to have an inappropriately low reticulocyte count in response to anaemia (von Ahsen, Muller et al. 1999; van Iperen, Gaillard et al. 2000) suggesting suppression of the normal bone marrow response. The term 'acute anaemia of chronic disease' (Corwin 2001) was coined to describe the anaemia which appears to develop in the critically ill, as it has many similarities with the anaemia of chronic disease. It is a normocytic normochromic anaemia associated with a reduced reticulocyte response, disturbances in iron homeostasis and is potentially driven by a persisting inflammatory state.

Inflammatory cytokines such as tumour necrosis factor α (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6) have been shown to directly inhibit erythrogenesis (Jongen-Lavrencic, Peeters et al. 1995) and are frequently elevated in patients with sepsis (Blackwell and Christman 1996). The administration of recombinant human erythropoietin (rHuEPO) in high doses can stimulate the bone marrow of critically ill patients (Corwin, Gettinger et al. 1999; van Iperen, Gaillard et al. 2000). Critically ill patients have inappropriately low erythropoietin concentrations for the degree of anaemia (Krafte-Jacobs, Levetown et al. 1994; Rogiers, Zhang et al. 1997; von Ahsen, Muller et al. 1999; van Iperen, Gaillard et al. 2000). This is thought to result from cytokine mediated inhibition of the erythropoietin gene (Wojchowski and He 1993; Jelkmann 1998). Inflammation may also impair iron availability for erythropoiesis. Iron is an acute phase protein and serum ferritin is increased and serum transferrin decreased as part of the acute phase response. ICU patients typically have a low serum iron, total

iron binding capacity but serum ferritin is elevated or normal (Biesma, Van de Wiel et al. 1995; Rodriguez, Corwin et al. 2001) in a primitive immune response attempting to deprive invading pathogens of iron. This response may impair iron availability for subsequent erythropoiesis.

#### *1.12.4.3 Increased red cell destruction*

There is no direct evidence that critical illness reduces red cell life span. However decreased red blood cell survival could occur in critical illness in response to complement activation and increased red cell destruction, though no evidence of haemolysis has been found (von Ahsen, Muller et al. 1999). Several studies have reported reduced red cell deformability in patients with sepsis (Card, Mohandas et al. 1983) which may be associated with reduced viability.

#### *1.12.4.4 Functional anaemia*

Critical illness is often associated with intravascular hypovolaemia requiring fluid resuscitation. The administration of non-haemoglobin containing fluids will cause haemodilution and the altered plasma volume affects measured haemoglobin or haematocrit values which could be interpreted as anaemia or may cause a functional anaemia even in the presence of normal red cell mass.

The development of the anaemia of critical illness is therefore multi-factorial but the main determinants are whole blood loss with phlebotomy as a major cause and a blunted erythropoietic response.

### 1.12.5 The risks of blood transfusion

Blood transfusion has many risks associated with it, from direct iatrogenic complications such as receiving the wrong blood group or contaminated blood (such as hepatitis C) to organ dysfunction, immunosuppresion and decreased survival.

#### *1.12.5.1 Risks of infection*

The risks of contracting HIV or hepatitis C is approximately 1 in 2 million units transfused. Hepatitis B is estimated to be transmitted from 1 to 200 per million units transfused. The risks of death from sepsis related to blood contaminated by bacteria is approximately 1 per million units transfused and in endemic areas parasitic diseases such as malaria can pose a significant risk (Bihl, Castelli et al. 2007). 1 direct death from bacterial infection in transfused blood occurred in the UK in 2008. There are also several suspected cases of transmission of variant Creutzfeld Jacob Disease (vCJD) through blood transfusion (Allain, Stramer et al. 2009). This led to the universal leucodepletion of blood components in the UK as a precaution against this happening again.

#### *1.12.5.2 Adverse reactions to transfusion*

Allergic reactions to transfusions vary from the febrile non-haemolytic transfusion reaction which is clinically benign to anaphylaxis. The acute haemolytic reaction results from haemolysis of donor cells by host antibodies and is usually related to ABO incompatibility and the wrong blood being given to the patient. It has the potential to cause renal failure. Anaphylaxis occurs in approximately 1 in 20,000 transfusions and requires prompt life saving treatment .World wide fatal ABO mismatch reactions occur

roughly 1 per million units transfused. In the UK the Serious Hazards of Transfusions (SHOT) report for 2008 showed that for the 2.5 million transfusions occurring in the UK the incorrect blood component transfusion (IBCT) rate was 16.8 per 100.000. No fatalities occurred but there were 4 episodes of sugnficant morbidity. There were 9 deaths in total attributed to transfusion reactions. Other risks such as fluid overload, hypothermia and the development of coagulopathy also occur.

Idiosyncratic immune reactions such as Transfusion Related Lung Injury (TRALI) and other organ dysfunction such as transfusion related immunomodulation (TRIM) leading to increased vulnerability to infection and malignancy also occur. TRALI has a similar presentation to acute respiratory distress syndrome and as a consequence is likely to be under-diagnosed in the critically ill. There is considerable overlap in pathogenesis in the two conditions and it may well be that TRALI contributes to the development of ARDS (Kleinman, Caulfield et al. 2004).

#### *1.12.5.3 Risks of transfusion in the critically ill*

Blood transfusion is a common occurrence in the critically ill with 40-50% of all patients admitted to ICU receiving at least one allogeneic transfusion (Koch, Li et al. 2006). The indications for these transfusions are often obscure and they are often used to treat anaemia rather than as a specific intervention (Koch, Li et al. 2006). The ABC study in Europe and CRIT study in the United States reported that blood transfusion was associated with increased mortality in ICU patients. A recent European study SOAP study used the same approach as the ABC study but found different results. Initially it

was found that there was a direct relationship between the number of blood transfusions and mortality rate. However the patients who received transfusion were found to be older, more likely to have sepsis, cirrhosis or haematological malignancy and have a greater severity of illness on admission to ICU. After controlling for these factors it was found that blood transfusion was not associated with a worse mortality rate.

The differences between the earlier two studies and the Sepsis Occurrence in Anaemic Patients (SOAP) study highlights an important event that occurred during the CRIT and ABC studies, namely that there was a shift from the general use of non-leucodepleted blood to leucodepleted blood as the standard blood product during the late 1990's and early 2000. It was proposed that residual leucocytes in packed red cells could induce immunological effects and potentiate inflammatory response. During the ABC study 46% centres used leucodepleted blood with 19% never using this product to 76% of centres in the SOAP study routinely using leucodepleted blood. A recent meta-analysis investigating the efficacy of leucodepleted blood in reducing adverse events only showed an improvement for reducing post operative infections (Fergusson, Khanna et al. 2004).

Blood transfusion has also been associated with an increase in nosocomial infections (Taylor, O'Brien et al. 2006) and ARDS (Zilberberg, Carter et al. 2007). Ideally there would be clear clinical indications for blood transfusion which facilitate appropriate transfusion to patients who would benefit but avoid transfusion when the balance of risks of acute anaemia and transfusion are less clear cut.

#### *1.12.5.4 Risks of transfusion in patients with ischaemic heart disease*

The resting oxygen extraction of the myocardium is near maximal. The increase in cardiac output in response to anaemia increases myocardial oxygen consumption and this must therefore be met by increased coronary blood flow through vasodilatation. Coronary artery disease restricts coronary blood flow and therefore oxygen delivery. The risk of myocardial ischaemia in anaemic critically ill patients with ischaemic heart disease is therefore significant and effects of specific transfusion thresholds have potentially profound consequences.

In patients at high risk for, or with established ischaemic heart disease there have been several studies showing a relationship between myocardial ischaemia, adverse cardiac events and anaemia (Nelson, Fleisher et al. 1993; Carson, Duff et al. 1996; Hogue, Goodnough et al. 1998). A retrospective analysis of the TRICC study data showed a trend towards better outcome in patients with ischaemic heart disease and had a Hb > 100 g/L. However a recent study has shown that in anaemic patients who present to hospital with a suspected acute coronary syndrome (ACS) blood transfusion increased the risk of developing an acute myocardial infarction or death (Singla, Zahid et al. 2007; Willis and Voeltz 2009).

### 1.12.6 The risks of anaemia

Anaemia reduces the oxygen carrying capacity of the blood. It has been associated with increased morbidity and mortality in myocardial infarction (Lipsic, van der Horst et al. 2005), heart failure (O'Meara, Clayton et al. 2006) and per-operatively. As discussed

above a critical haemoglobin concentration is defined as the haemoglobin concentration below which oxygen consumption is supply dependent assuming normovolemia is maintained. The risks of anaemia itself remain difficult to determine as erythropoiesis is affected by many factors which could also be associated with poor clinical outcomes and significant co-morbidities. When some of these factors are controlled for, conclusions can be drawn that although the development of anaemia is undoubtedly be associated with poor clinical outcome the subsequent treatment of that anaemia may be more harmful than the anaemia itself.

### 1.12.7 Efficacy of blood transfusion as a treatment for anaemia

There is considerable literature on the effects of transfusion on oxygen kinetics but clarity is lacking due to varying methodology, different cohorts studied and contradictory findings. A review identified 14 studies examining the effects of transfusion on oxygen delivery and oxygen consumption (Hebert 2000). The studies only had patients with moderate anaemia (Hb range 8.3-11.0 g/dL). Transfusion consistently increased $DO_2$ but oxygen consumption only increased in 5 of the studies and these studies calculated oxygen consumption from pulmonary artery catheter measurements which can introduce error in to the measurements to such a degree that direct measures of oxygen consumption have been recommended for future studies. Determining the significance of anaemia requires any transfusion to be considered as a risk factor. Ischaemic complications of anaemia such as MI, neurological or renal injury were not decreased by transfusion even when co-morbidities were controlled for (Murphy, Reeves et al. 2007). This lack of benefit may reflect that haemoglobin levels

rarely limit $DO_2$ in clinical practice and the possible negative effects relate to increased blood viscosity, pro-inflammatory effects and the reduced efficacy of the blood itself. The decreased efficacy is due to the development of storage lesions and even potentially decrease actual oxygen delivery to tissues due to decreased deformability of red cells, sludging and capillary occlusion (Spiess 2007). A recent paper has shown that the use of old blood (more than 2 weeks old) caused a statistically significant increase in ventilator days, renal failure, sepsis and in-hospital mortality (Koch, Li et al. 2008). In the critically ill transfusion has been shown to produce only a modest and transient rise in haemoglobin concentration further questioning the efficacy of transfusion as a treatment for anaemia (McArdle 2001). The assumption that blood transfusion is an effective therapy is now questionable.

### 1.12.8 The risks of erythropoietin

Increased erythropoiesis will result in increased haemoglobin and potentially reduce the need for blood transfusions. Erythropoiesis-stimulating agents (ESAs) are drugs which aim to elevate or maintain red blood cell levels and decrease the need for transfusions. The most common drugs are epoetin alfa and darbepoetin alfa. Treatment of anaemia with these agents can improve patient's quality of life, especially in renal failure (Obrador and Pereira 2002) and cancer (Sabbatini 2000). Concerns over the size of the early studies and the measures of quality of life used, has caused the magnitude of these benefits to be questioned. Subsequent conflicting results from subsequent randomized controlled trials investigating ESAs means that the use of these promising agents has been reviewed. The CHOIR (Correction of Hemoglobin and Outcomes in Renal

Insufficiency) (Singh, Szczech et al. 2006) showed that in trying to produce a normal haemoglobin level rather than aiming for a modest increase in haemoglobin showed no improvement in QOL and increased the risk cardiovascular problems. Other trials such as the Normal hematocrit study (Besarab, Bolton et al. 1998) and TREAT study (Pfeffer, Burdmann et al. 2009) have not shown any significant improvement in quality of life but did show an increase in nonfatal myocardial infarction, nonfatal stoke and death (Unger, Thompson et al.).

Peri-operative studies of the administration of rHuEPO have shown reduced time to recover to baseline haemoglobin (Levine, Rosen et al. 1989; Mercuriali, Zanella et al. 1993). Critically ill patients also respond to rHuEPO and this has been shown to reduce the number of red cells transfused (Corwin, Gettinger et al. 1999). However recent studies have failed to reproduce this reduction in transfusion rates and have shown a trend towards an increased risk of adverse thrombotic events in patients treated with rHuEPO (Corwin, Gettinger et al. 2007).

The results of these studies mean that, at present, we have no obvious alternative treatment to anaemia during critical illness other than blood transfusion.

## 1.13 The impact of the 'anaemia of critical illness'

Anaemia is a common, preventable and potentially treatable complication of critical illness. It is caused by blood loss and impaired erythropoiesis. Most transfusions during critical illness are to treat anaemia rather than acute bleeding and, although there has been a great improvement in transfusion practice, many transfusions are probably

unnecessary. Red cell transfusion has risks both in short term morbidity and mortality. Less is known about the long term consequences of anaemia. Chapter 2 of this thesis examines the time course of anaemia following critical illness and the impact on quality of life.

## 1.14 Quality of life following critical illness

The ideal outcome following critical illness is for the patient to return to their pre-existing state or that expected of a person of the same age and medical condition (Black, Jenkinson et al. 2001). Outcomes research, particularly in critical illness, is complex due the heterogeneity of patients, disease processes and clinical practice within intensive care units. There is a need for the assessment of outcomes which reflect patients' long term health and well being. However a plethora of measures have been used which have often been developed in non-critical illness patient populations. In the following sections the most common outcome measures will be reviewed with particular emphasis on the measures used in the subsequent research chapters of the thesis. Discussion of measure selection for the studies will be included in the appropriate chapter. The information that outcome measures provide must be valid, reliable and responsive.

### 1.14.1 Terminology of social science and outcomes research

The following sections represent a distillation of information of social science terminology from two principal sources: Hayes *et al* 2000 (Hayes, Black et al. 2000) and Black *et al* 2001 (Black, Jenkinson et al. 2001).

#### *1.14.1.1 Validity*

A valid assessment is one that measures what it claims to measure. It requires comparison with some standardized criteria. This is not always easy as there are few 'gold standards' against which comparison can be made but there are standard criteria for validity which can be used.

Face validity refers to whether items on a questionnaire make sense, are easily understood and are appropriate to the phenomenon being measured. It is produced by having 'experts' review the contents of the test to see if the items seem appropriate. This method has inherent subjectivity.

Content validity refers to the extent to which a measure represents all aspects of a given social concept. It is important that items appropriate to the phenomenon under investigation are chosen and if they are weighted in some way, that the weighting reflect the perceived level of difficulty or health problem.

Construct validity reflects the ability of an instrument to measure an abstract concept or construct. It is important in the absence of a gold standard so that theories of the whole attribute of interest are formed and then the extent to which the measure under investigation provides results that are consistent with the original theories are assessed. Criterion validity reflects how well a measure provides results which are consistent with a gold standard.

#### 1.14.1.2 Reliability

Reliability is generally understood to be the extent to which a measure is stable or consistent and produces similar results when administered repeatedly, i.e. the proportion of true variation in scores derived from a particular measure. The total variation in any given score consists of true variation (the variation of interest) and error variation (which includes random error and systematic error). Reliability is generally measured using Cronbach's alpha statistic, a coefficient between 0 and 1. It is used to rate the internal consistency or correlation of the items in a test. A good test is one that assesses different aspects of the trait being studied. If a test has a strong internal consistency it should show only moderate correlation among items. If the correlations are too low then it is possible that different traits are being measured. If the correlation is too high then it is likely that some of the items are measuring the same thing and are redundant.
Test-retest reliability is measured by administering the questionnaire on two occasions separated by a few days. Ideally they should produce almost identical results.
Confounding variables are one aspect of the reliability of a test. Confounding variables are a possible patient factor which is omitted from the measure used but which is actually causing the effects seen. Reliable quality of life measures should not vary according to extraneous factors such as income, gender and ethnicity.

#### 1.14.1.3 Responsiveness

Responsiveness reflects the ability of a test to detect clinically important changes over time.

#### *1.14.1.4 Bias*

Intensive care survival studies generally report on sample sizes of less than 20% of the enrollable population (Hayes, Black et al. 2000) and further loss to follow up of 30% of the recruited population (Hopkins and Jackson 2006). Bias, in various forms, is therefore a fundamental problem in ICU follow up studies. Bias is also a potential problem in quality of life assessments as these assessments predominantly focus on the ability to function whilst in some patients this may not be the most important aspect of their quality of life. This bias may impair the validity of a given assessment as the designers of the assessment may have pre-conceived ideas of what is important to a given patient population. It is therefore appropriate for such quality of life tools to use a wide spectrum of health care practitioners and patients themselves in the designing of measures to ensure that they are valid. Unfortunately this is not often the case. Because of the great potential for bias within the ICU survivor population and in quality of life studies, the degree of extrapolation of results from ICU follow up studies using quality of life measure to the entire survivor of critical illness population must be done with caution.

The types of bias common in ICU studies are discussed below.

##### 1.14.1.4.1 Selection bias

Selection bias occurs when one or more groups of people are over or under-represented in a study population. With the high drop out rate in many ICU follow up studies the population at 6 months may not represent the original study population. This may be

referred to as 'drop out bias', and is thought to be a problem at drop out rates of more than 15% of the original group.

#### 1.14.1.4.2 Participant bias

Participant bias occurs when patients behave in a fashion such that their responses are systematically higher or lower than normal. Survivors of critical illness often have a 'desire to please' and therefore under-report problems especially in the early phases of recovery. This may skew results at this time.

#### 1.14.1.4.3 Observer bias

Observer bias occurs when investigators behave in some way such that the data collected is systematically higher or lower than it actually is.

Measurement bias occurs when some aspect of the measure skews the response in a particular direction.

The methods by which we tried to reduce bias and account for its effects are discussed in section 5.2.1.

### *1.14.1.5 Survival*

Survival is an incomplete endpoint for the recovery of critical illness. ICU patients are not representative of the general population. They have considerable co-morbidity and pre-existing physical limitation. This makes survival data difficult to compare. Most ICU follow up studies compare the study group to matched general population samples

as they are readily available. Ideally ICU patients should be compared with age and gender matched hospital patients with the same disease but not requiring ICU care. In general ICU patients show a high initial mortality which diminishes with time. The survival curves paralleled with the general population between 2-4 years following ICU discharge. The risk factors for decreased survival are age, severity of illness and diagnostic category (Ridley and Plenderleith 1994; Niskanen, Kari et al. 1996; Wright, Plenderleith et al. 2003).

#### *1.14.1.6 Non-mortality outcomes*

Non-mortality outcomes can be broadly classified as measures of:

- Physical impairment and disability
- Physical function status
- Mental function
- Neuropsychological function
- Recovery
- Health related quality of life

#### *1.14.1.7 Impairment*

Impairment refers to objective measures of anatomical, physiological or biochemical status rather than the subjective problems that patient's report. Measures of impairment have largely focused on the respiratory system. Respiratory volumes, gas flow loops, diffusion capacity and imaging of the respiratory tract have all been studied mainly due

to the high level of research into patients who develop ARDS. Pulmonary function tests generally have returned to normal by 6 months and diffusion capacity by 1 year. Only 6% of patients de-saturate during exercise at 1 year.

#### *1.14.1.8 Quality of life*

Quality of life is a descriptive term that refers to people's emotional, social and physical well being, and their ability to function in the ordinary tasks of living. Quality of life is measured using specially designed questionnaires which measure a person's ability to function in the ordinary tasks of living. It is to some degree distinct from utility measures which measure quality adjusted life years. Quality of life measures attempt to directly assess the impact of a disease or treatment on a person's ability to function not the value that they place upon a particular health state which is assessed by utility measures.

A great strength of quality of life measures is that they provide information for planning multi-disciplinary care packages with those responsible for different aspects of the patient's care such as physiotherapists, dieticians, occupational therapists, social workers and the primary carers themselves.

However it should not be assumed that generic measures of quality of life comprehensively measure quality of life status or the effects of an intervention in specific populations. This is due to the domains used to classify quality of life having differing importance to different individuals and as many measures are developed by health care professionals looking at a specific condition and then subsequently used different populations from that in which they were originally intended. This represents a

systematic difficulty in the use of quality of life measures in a heterogeneous population such as survivors of critical illness. It is therefore appropriate to try and use generic, widely used and well validated tools for assessment. It may also be appropriate to try and avoid measures which generate a single score to represent the diverse and complex factors which determine quality of life.

In a consensus conference on surviving critical illness two measures of quality of life were recommended for use in the critically ill: the medical outcomes short form 36 question health survey (SF-36) and the EuroQol-5D (EQ-5D) (Angus and Carlet 2003). The SF-36 is a quality of life measure and the EQ-5D has health utility aspects.

#### *1.14.1.8.1 SF-36*

The medical outcomes short form 36 question health survey (SF-36) is a widely used, generic, patient-report measure created to assess health related quality of life (HRQoL) in the general population. It was developed as part of the Medical Outcomes Study, a two year study of patients with chronic conditions (Ware and Sherbourne 1992). It is the most commonly used generic instrument for measuring quality of life (de Haan 2002). It is simple to administer either by the patient or via the telephone and takes approximately ten minutes to complete. In areas outside of critical care it has good reliability with Cronbach's alpha ($\alpha$) coefficient generally exceeding 0.8 for all scales except social functioning. It has been shown to be responsive to change again especially in the physical function domains, has good test-retest reliability ($\alpha = 0.81$) (Brazier, Harper et al. 1992) and shows sensitivity to change over time (Garratt, Ruta et al. 1994; Beaton, Hogg-Johnson et al. 1997). Its validity is supported by comparison to similar domains of

condition specific measures. It has been shown to be appropriate for critically ill patients (Chrispin, Scotton et al. 1997; Ridley, Chrispin et al. 1997; Weinert, Gross et al. 1997; Cuthbertson, Scott et al. 2005) and as a proxy measure from next of kin (Rogers, Ridley et al. 1997).

The SF-36 questionnaire comprises eight dimensions: physical functioning (PF) 10 items; social functioning (SF) 2 items; role limitations due to physical problems (RP) 4 items; role limitations due to emotional problems (RE); general mental health (MH) 5 items; energy / vitality (Vi) 4 items; bodily pain (BP) 2 items; general health perceptions (GH) 5 items. Item scores for each dimension are summated and transformed using a scoring algorithm into a scale ranging from 0% (worst health) to 100% (best health). The SF-36 may have ceiling effects. A ceiling effect occurs when test items aren't challenging enough for a group of individuals and hence the score will not increase for a subset of people who have improved because they have already reached the highest score possible.

#### *1.14.1.8.2 EQ-5D*

EQ-5D is a standardised instrument for measuring health outcome. It is applicable to a wide range of health conditions and treatments and provides a simple descriptive profile and a single index value for health status. It can be completed either as a postal questionnaire or by face to face interview in clinics or other settings and takes 5-10 minutes to complete. It has been recommended by national bodies such as the National Institute for Clinical Evidence (NICE) for the use in clinical and economic evaluation of

health care. There is a wide body of normative data both for the general population and specific illness groups.

The EQ-5D consists of five dimensions: mobility, self care, usual activities, pain / disorder and anxiety / depression, with three response options: nil, moderate and severe and respondents are also asked to indicate their present health state using a visual analogue scale.

The responsiveness of EQ-5D in critically ill patients was assessed and found to detect a significant increase in mobility, significant decreases in self care and usual activities and no significant change in pain and discomfort, anxiety and depression or the visual analogue scale (Vainiola, Pettila et al.). Age, severity of illness, ICU length of stay and diagnostic category have been shown to be related to reduced EQ-5D and EQ-VAS scores (Badia, Diaz-Prieto et al. 2001; Dowdy, Eid et al. 2005). However when pre-morbid factors (co-morbidity, smoking status, education and social status) are accounted for the ICU variables may not be as strongly associated with EQ-5D (Badia, Diaz-Prieto et al. 2001). It can be used retrospectively to determine health related quality of life prior to ICU admission (Badia, Diaz-Prieto et al. 2001).

#### *1.14.1.9 Other measures of health related quality of life*

Sickness Impact Profile (SIP) is a measure of the impact and disability on daily life, and has been validated in various patient populations including ICU patients (Frick, Uehlinger et al. 2002). It is a multidimensional cumulative health index consisting of a

list of 136 questions, divided into 12 categories of daily living. These categories can then be aggregated into 'physical', 'psycho-social', and 'independence' categories. The questionnaire can be self administered or taken with the help of an interviewer. Patients are asked to indicate those items that describe a dysfunction that they experience at this time. Scores of 0-5 are found in a healthy population and 5-15 corresponds to moderate disability and a score of more than 15 reflects significant impairment of quality of life. The original form has been found to be reliable, valid and sensitive to change (Black, Jenkinson et al. 2001; Frick, Uehlinger et al. 2002).

Nottingham Health Profile is a measure of perceived distress. It was designed to assess severe ill health and may be prone to ceiling effects. It has two parts. Part one measures perceived or subjective functional status by answering 38 questions associated with 6 dimensions. Each dimension has the potential score 0-100 where 0 indicates good health and 100 indicates poor health. Part 2 focuses upon the quality of life. This second part is no longer recommended by the developers. NHP focuses on the severe extremes of ill health and may be highly skewed thus minor improvements are likely to be missed. The validity and criterion validity has been established in critical care patients. The reliability and responsiveness of the NHP has not been established in critical care. The test-retest coefficients have been described from 0.77 to 0.85 for part 1 and found to be very poor for part 2 leading to the recommendation for its withdrawal (Hunt 1997).

#### 1.14.1.10 Functional status

Impairment may not always affect a person's health or functional status by giving rise to symptoms or limitations in their ability to function. Low haemoglobin may be associated with breathlessness and an inability to walk to the shops. However diminished function (such as the need to use a car to get to the shops) may not be reported if quality of life is not affected (Hayes, Black et al. 2000).

##### *1.14.1.10.1 Frenchay Activities Index*

The Frenchay Activities Index (FAI) (Holbrook and Skilbeck 1983) is a measure of instrumental activities of daily living. It was developed for use in patients recovering from stroke. The FAI assesses range of activities associated with everyday life and provides a broad measurement of actual activity rather than focusing on issues related to self care alone (Wade, Legh-Smith et al. 1985). The FAI compromises 15 activities, each of which is scored on a 4 point scale to yield a score from 0 (inactive) to 45 (active) and the scoring is based upon the frequency with which the activities is carried out. It takes approximately 5 minutes to administer and this can be done either as an interview or mailed questionnaire and can be used with proxy respondents. It correlates with the SF-36 score physical functioning subscale. It has been validated in a normal UK population, has good construct validity in middle aged and elderly respondents and good test retest reliability (Turnbull, Kersten et al. 2000). Men generally score lower on the subscale relating to domestic chores but this is often related to marital status.

#### *1.14.1.10.2 Six minute walk test*

Timed walk tests were originally developed as non-laboratory estimates of physical fitness in healthy subjects that correlate with maximal oxygen uptake. These tests have also been shown to have some similarity with the activities of daily living. The six minute walk test (6MWT) (Butland, Pang et al. 1982; Guyatt, Sullivan et al. 1985) is a functional walking test in which the distance that a patient can walk within six minutes and is administered according to the American Thoracic Society (ATS) protocol (2003). It has excellent test-retest reliability (Liu, Drutz et al. 2008) and correlates with other physiological measures (Eng, Dawson et al. 2004) and can detect change well. It is sensitive to clinical signs of disease as shortest distances observed were observed in the patients with greatest co-morbidity (Enright 2003). It may also reflect prognosis (Bittner, Weiner et al. 1993) and quality of life (Guyatt, Townsend et al. 1991).

#### *1.14.1.10.3 Hand grip dynamometry*

Hand grip strength has been found to be a consistent predictor of clinically important outcomes such as survival and postoperative complications in many different populations (Bohannon 2008). Low grip strength is associated with a greater likelihood of functional disability in many studies (Shibata, Haga et al. 1992; Sarkisian, Liu et al. 2001) especially in pneumonia (Bohannon, Maljanian et al. 2004; Vecchiarino, Bohannon et al. 2004). It has also been found to be a good indicator of nutritional status (Davies, Jones et al. 1984).

#### *1.14.1.10.4 Other measures of functional status*

Karnofsky Performance Index was developed as a measure of overall health status in lung cancer patients with scores ranging from 0 (dead) to 100 (normal) (Karnofsky, Graef et al. 1948). It is not designed for the measurement of quality of life but rather assesses physical function according to clinician's opinion rather than the patient. It correlates well with the physical component of the SF-36 score.

New York Heart Association (NYHA) functional grades are a functional and therapeutic classification for the description of physical activity for patients with cardiac disease (Association 1964). It ranges from grade I, no limitations, to grade IV any physical activity results in discomfort with symptoms of cardiac insufficiency even present at rest. It correlates poorly with exercise testing suggesting high inter-observer variability. It is an expert panel measure, principally for patients with heart failure, and there has been little assessment of its validity, reliability and responsiveness in critical care patients.

The Barthel Index was developed to compare physical functional status before and after an intervention and indicate potential nursing requirements (Mahoney and Barthel 1965). It is only suitable for institutionalized patients. The score elicits a score from 0 (wholly dependent) to 100 (wholly independent).

#### *1.14.1.11 Neuropsychological measures and mental function*

Most tests have been developed for use in patients recovering from head injury. There is little evidence for there use in other groups. The Hospital Anxiety and Depression Scale (HADS) is a self assessment scale to measure mood disorders of anxiety and depression in non-psychiatric patients. It compromises 14 items that are divided into two subscales for which each patient rates the item on a four point scale. It does not include somatic symptoms of depression. It is brief and easy to administer. It has been shown to be a valid tool for use in the critically ill (Rowan 1992).

##### *1.14.1.11.1 Davidson Trauma Scale*

Davidson Trauma Scale (DTS) (Davidson, Book et al. 1997) is a self rating scale which assesses 17 symptoms that correspond to DSM-IV and each is rated for both frequency and severity on 5 point scales using a past-week time frame. It has been shown to be reliable (α coefficient 0.97-0.99) for the frequency, severity and total scales and the test-retest correlation was also shown to be good. The scale is sensitive (0.69) and specific (0.95) accurately identifying patients who meet the diagnostic criteria for PTSD with a DTS of more than 40. The DTS when compared to other scales appears to detect clinically important change in response to treatment (Norris 2004).

### 1.14.2 Summary of outcome measures in critical care used in this thesis

In assessing outcomes in critical illness it is difficult to find recommendations on which measures should be used. It has been proposed that an agreed list of measures should be developed which studies should endeavour to use in their research. This would allow

comparisons between studies to be made more easily. In the research chapters of this thesis the most common measure of quality of life (SF-36) has been used. In assessing physical function we have used the six-minute walk test as our gold standard and compared it to other actual and perceived measures of physical function, principally the FAI. FAI has not been used in the critical illness population previously but was chosen because of its ability to reflect a broad spectrum of physical function and its good correlation with the SF-36 measure.

## 1.15 Aims of thesis

Patients who survive critical illness have an excess mortality compared to age / gender matched general populations for many years after the original illness (Wright, Plenderleith et al. 2003) with 20-25% of patients dying within the following 12 months. The cumulative burden of mortality and morbidity among survivors is largely unknown. Many survivors suffer from a range of disabilities that comprise a "post intensive care syndrome". Morbidity ranges from physical disability to psychological problems. The research of this thesis aimed to address one of the common complications of critical illness, anaemia (The TRAC Study, Chapter 2), and to determine the impact of critical illness on physical function and quality of life (Ps and Qs Study, Chapter 3). A third chapter (Chapter 4) explores the possible links between anaemia, physical function and quality of life by sub-group analysis of the Ps and Qs cohort.

# Chapter Two

# The TRAC Study

## The Resolution of Anaemia following Critical illness

## 2.1 Introduction

Anaemia is a common complication of critical illness (Corwin, Gettinger et al. 2004). Once present it frequently persists until intensive care unit discharge (ICU) unless modified by blood transfusion or less well established transfusion practices such as erythropoietin administration. The Transfusion requirements in Critical Care (TRICC) study (Hebert, Wells et al. 1999) established that a restrictive transfusion policy was at least as effective as a liberal transfusion strategy (as detailed in section 1.12.3.2) and has resulted in a more consistent use of restrictive transfusion practice with typical median pre-transfusion haemoglobin values between 78-85 g/L (Chohan, McArdle et al. 2003). When a restrictive transfusion policy is employed the prevalence of anaemia is as high as 80% (Walsh, Lee et al. 2006). Recent studies have shown that anaemia is still frequently present at hospital discharge (Walsh, Saleh et al. 2006) and has normochromic normocytic characteristics similar to that of the anaemia of chronic disease. Other epidemiological studies followed patients for up to 28-30 days following ICU admission, but did not report anaemia outcomes specifically for the post ICU recovery period (Vincent, Baron et al. 2002; Corwin, Gettinger et al. 2004). It is not known how long anaemia persists among ICU survivors or what factors influence its rate of recovery.

Many patients suffer reduced quality of life after hospital discharge, often associated with symptoms typical of anaemia such as fatigue and breathlessness (Herridge 2002; Herridge, Cheung et al. 2003). Whilst these symptoms may have a multi-factorial

aetiology in other settings such as chronic renal failure (Obrador and Pereira 2002), cancer (Caro, Salas et al. 2001) and cardiovascular disease (Horwich, Fonarow et al. 2002; Silverberg, Wexler et al. 2002) anaemia is specifically associated with a poor quality of life and treatment of the anaemia improves symptoms (Ross, Fahrbach et al. 2003). These observations are consistent with hypothesis that anaemia contributes to morbidity following critical illness.

Our primary aim was to determine the time period between ICU discharge and resolution of anaemia in a cohort of patients discharged with significant anaemia (haemoglobin <100 g/L). Our secondary aims were to investigate what factors contribute to the persistence of anaemia and to measure quality of life in patients discharged from intensive care with anaemia.

## 2.2 Methods

### 2.2.1 Design and setting

We performed a prospective cohort study following patients over a 6 month period following ICU discharge. The study received local ethics approval and informed consent was obtained from the patients. Patients were recruited from the 18-bedded medico-surgical ICU of the Royal Infirmary of Edinburgh, a university hospital receiving acute admissions for all specialities except neurosurgery, colorectal surgery and urology.

### 2.2.2 Recruitment

We planned to recruit all eligible patients over a 6 month period. As an exploratory study no formal power calculation was made. We intended to recruit 40 patients which we believed would give adequate data to define the common patterns of anaemia that occur. Based on our own data, 62% of patients are discharged from the study ICU with significant anaemia (haemoglobin less than 100 g/L) and admission rates were expected to be approximately 700 patients per year. With a 25% ICU mortality we therefore anticipated 300 patients to be discharged with significant anaemia per year. Allowing for patients not meeting inclusion criteria and assuming a 50% agreement of approached patients to actually take part in the study we predicted a recruitment rate of 100 patients per year. We estimated it would take 20 weeks to recruit the 40 patients.

Our inclusion criteria were: patients requiring > 24 hours of advanced physiological support (invasive ventilation alone or non-invasive ventilation plus at least one other organ failure); haemoglobin concentration <100 g/L at ICU discharge; age >16 years. Exclusion criteria were: pre-existing haematological disorder; treatment with immunosuppressant or cyto-toxic drugs; acute or chronic renal failure requiring renal replacement therapy at time of discharge; patients residing out-with reasonable geographical follow up; patients discharged for palliative care or not expected to survive to hospital discharge, and patients unable to give informed consent.

### 2.2.3 Patient characteristics

We recorded demographic data, clinical diagnosis, Acute Physiology and Chronic Health Evaluation score (APACHE II) (Knaus, Draper et al. 1985) score and worst Sequential Organ Failure Assessment (SOFA) (Vincent, de Mendonca et al. 1998) score during ICU stay, haemoglobin concentration on admission to ICU and ICU length of stay. We recorded the number of blood transfusions received whilst in ICU. At follow-up we recorded whether patients had received further blood transfusions, iron, vitamin $B_{12}$ or folate supplements during the study period.

### 2.2.4 Study protocol

Patients were followed up at 1, 3, 6, 9, 13 and 26 weeks post ICU discharge either in hospital or their homes. We measured haemoglobin (Hb) concentration (g/L), mean cell haemoglobin (MCH, pg), mean corpuscular haemoglobin (MCHC, g/dL), mean red cell volume (MCV, fL) and serum creatinine (Creat, μmol/L) at all visits. We used locally defined reference ranges for haemoglobin to define anaemia (male <130 g/L; female <115 g/L). We obtained advice from an expert group prior to the study and established a range of measures to assess:

1. Iron status: ferritin, percentage hypochromic red cells (%HYPO), reticulocyte haemoglobin (RH, pg)
2. Erythropoiesis; serum erythropoietin concentration (EPO, mIU/ml), soluble Transferrin receptor concentration (sTfR, nmol/L), reticulocyte count (Retics, number $x10^9$/l)

3. Inflammation; C-reactive protein (CRP, mg/dL) and serum Interleukin-6 concentration (IL-6, pg/ml)

We defined the following abnormalities *a priori*:

Absolute iron deficiency was defined as a plasma ferritin concentration of <12 μg/L or <100 μg/L in the presence of elevated inflammatory markers as ferritin is an acute phase protein and is elevated in the presence of inflammation. Patients with ferritin >100 μg/L were defined as having no evidence of iron deficiency irrespective of inflammatory markers (Cavill 1999).

Functional iron deficiency (impaired incorporation of iron during erythropoiesis despite adequate body iron stores) was defined as the presence of >5% hypochromic red cells (%HYPO) and / or reticulocyte haemoglobin (RH) of <28 pg (Thomas and Thomas 2002).

Vitamin $B_{12}$, plasma folate and red cell folate deficiency were defined as values below the local laboratory reference ranges, (<150 ng/L, <2.0 μg/L, <95 μg/L respectively). Inappropriate erythropoietin response to anaemia was defined as a circulating erythropoietin concentration that was lower than published normal values relating haemoglobin with plasma erythropoietin concentration (Kendall 2001; Elliot, Virankabutra et al. 2003). Specifically, we defined an abnormal erythropoietin concentration as <40 mIU/ml and <20 mIU/ml for the haemoglobin concentrations of <100 g/L and 120 g/L respectively.

Persistent inflammation was defined as detectable (>10 pg/ml) circulating interleukin-6 (IL-6) and / or C-reactive protein (CRP) >5 mg/dL (Abel, Spannbrucker et al. 1996). IL-6 was chosen as a marker of inflammation as unlike other pro-inflammatory cytokines it remains elevated in the presence of persistent inflammation and its repeated measurement is a good indicator of activation of the cytokine cascade in various conditions (Martin, Boisson et al. 1997; Oda, Hirasawa et al. 2005).

Evidence of new erythropoiesis (a measure of bone marrow responsiveness) was defined as a reticulocyte count above the normal range (>55 x $10^9$) (Hirose, Yamane et al. 2005) and / or an increase in soluble transferring receptors (sTfR) concentrations above normal values using a locally determined control distribution.

Assessment of renal function was made by serial calculation of the estimated glomerular filtration rate (eGFR) from the plasma creatinine concentration at all visits (Burden and Tomson 2005).The schedule for blood sampling is detailed in Table 2.1.

Quality of life was assessed using the Medical Outcomes Survey 36-Item short form health survey (SF-36) (Ware J E 1992) at 3 and 6 months and compared to published normal populations (Jenkinson, Layte et al. 1997; Keller, Ware et al. 1998) and data from a Scottish unselected ICU survivor cohort study (Cuthbertson, Scott et al. 2005).

**Table 2.1 Blood sampling schedule for TRAC study**

| Time (+/-Days) | Baseline 1-7d | 3 weeks +/- 5d | 6 weeks +/- 5d | 9 weeks +/- 5d | 13 weeks+/-5d | 26 weeks+/-5d |
|---|---|---|---|---|---|---|
| Test | | | | | | |
| Full Blood count | X | X | X | X | X | X |
| Reticulocyte count | X | X | X | X | X | X |
| Reticulocyte Hb Concentration (CHR) | X | X | | X | X | X |
| Serum Erythropoietin Concentration (EPO) | X | X | | X | X | X |
| Serum Soluble Transferrin Receptor (sTfR) | X | X | | X | X | X |
| Plasma Ferritin Concentration | X | | | | X | X |
| Plasma Red Cell Folate Concentration | X | | | | X | X |
| Plasma Vitamin $B_{12}$ and Folate levels | X | | | | X | X |
| Serum Interleukin 6 Concentration | X | X | X | X | X | X |
| Serum C-reactive protein | X | X | X | X | X | X |
| Plasma Creatinine | X | X | X | X | X | X |
| Plasma Albumin | X | X | X | X | X | X |

Samples were taken within 7 days of discharge from ICU and then at the specific visits as detailed above. X indicates samples taken

### 2.2.5 Analytical Methods

Analyses of the standard haematological and biochemical parameters were carried out in the local hospital laboratory using the Sysmex KX21 Counter for haematogical parameters and Sysmex Corporation analyser for biochemical parameters. %HYPO, RH analyses were carried out within 3 hours of sampling at specialized hospital centres. Specialized analyses of percentage hypochromic red cells and reticulocyte haemoglobin were analysed by the Haematology Laboratory, Wishaw General Hospital, Scotland, UK. Specialized analyses of reticulocyte count, mean cell haemoglobin concentration and mean cell haemoglobin were analysed by the Haematology Laboratory, Monklands General Hospital, Scotland, UK.

Samples for serum assays were spun within 2 hours and stored at -80°C. Serum erythropoietin concentrations were measured by enzyme linked immunosorbant assay (ELISA) at Simbec Research Ltd, Methyr Tydfil, UK. Serum IL-6 and sTfR concentrations were measured using ELISA kits (Quantikine R&D Systems, Minneapolis, USA).

In addition to the above quantitative measures the expert panel met to review all the data from all the patients after the study completion. A consensus 'expert opinion' was reached regarding the main factors contributing to the pathogenesis of anaemia following ICU discharge and the factors accounting for the lack of recovery among patients.

### 2.2.6 Data Analysis

#### *2.2.6.1 Time to resolution of anaemia*

Haemoglobin values against time were plotted and the proportion of anaemic patients at each time point was calculated. The lower limits for gender specific population reference ranges were used as the cut off values. To assess the rate of recovery from anaemia we calculated rates of increase in haemoglobin between visits. An increase of 10 g/L per week is frequently quoted as a healthy response to blood loss. We also included a lower cut off at 5 g/L to assess for a reduced rather than an absent response often seen in acute illness.

#### *2.2.6.2 Responders and Non-Responders*

We explored differences between patients who recover more quickly from anaemia after ICU discharge, 'responders' with those who remained anaemic or recovered slowly, 'non-responders'). Responders were defined as the patients who had returned to sex specific reference range by 13 weeks following ICU discharge and Non-responders as those patients whose haemoglobin concentration remained below sex specific reference range at 13 weeks. To explore factors associated with poor recovery we compared variables at week 3. Week 3 was chosen as it was expected that the greatest divergence between the two groups would be apparent early in those who would recover.

#### *2.2.6.3 Statistical Methods*

The data is presented with the median value 1$^{st}$ and 3$^{rd}$ quartiles and range for the measured parameters. For the Responder / Non-Responder groups we used the Mann-

Whitney test for continuous data and Fisher's Exact test to compare proportions. Microsoft Excel and GraphPad Prism were used for analysis and graphical figures.

## 2.3 Results

### 2.3.1 Study recruitment

We recruited 30 patients (77% recruitment rate for eligible patients, Figure 2.1). Six patients (20%) died during the study follow up and 5 patients (17%) were lost to follow up.

### 2.3.2 Baseline characteristics

Demographic and clinical characteristics for the study cohort are shown in Table 2.2. The timing and causes of death during the study period are shown. No patients had a known associated malignancy independent of their reason for ICU admission which could have contributed to the persistence of their anaemia.

No patients received blood transfusions during the study follow up period and none were prescribed iron, folate or vitamin $B_{12}$ supplements. No patients received exogenous erythropoietin during the study.

**Figure 2.1 Recruitment to TRAC study**

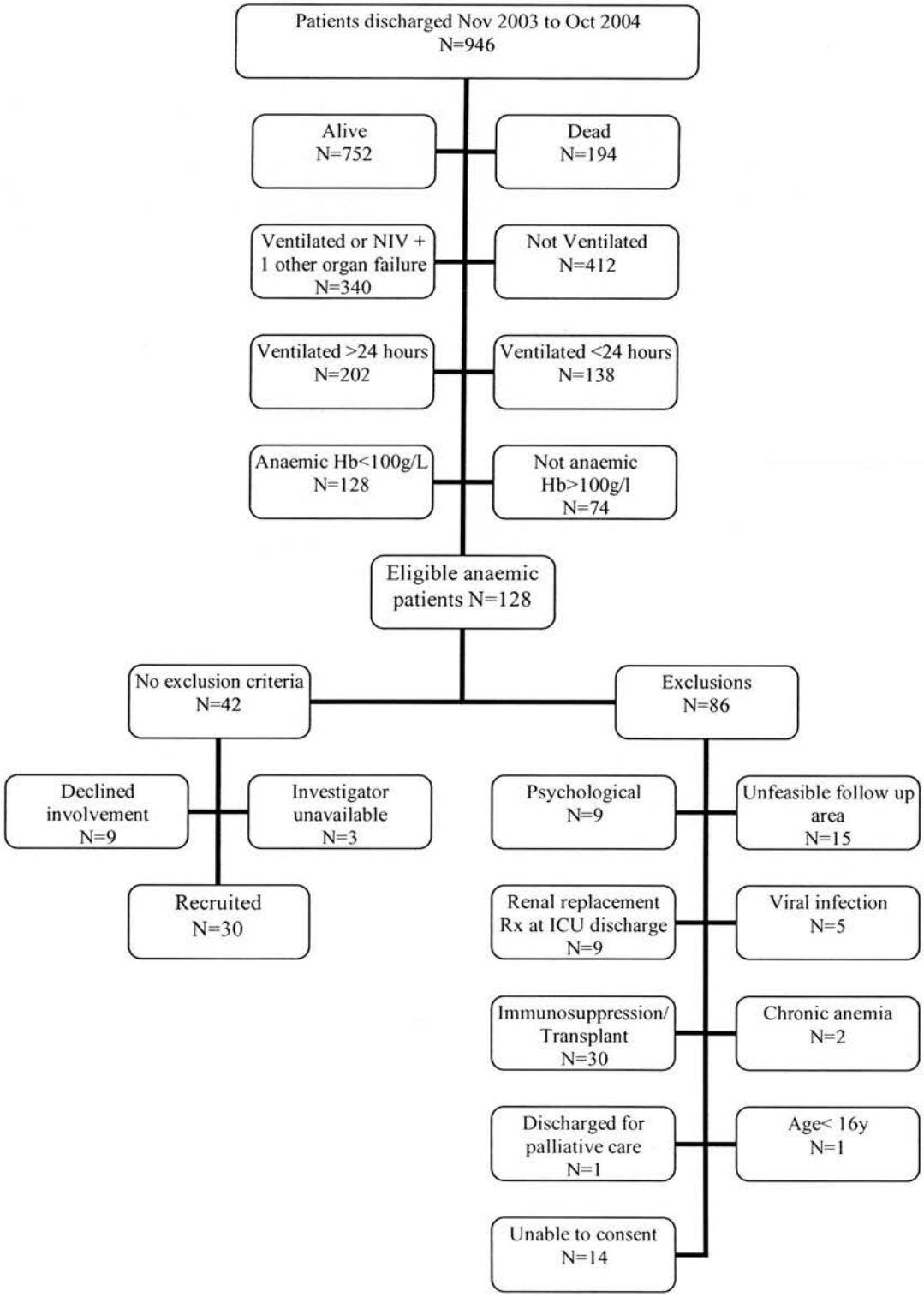


**Table 2.2 Demographics, baseline characteristics and study mortality**

| Demographic | Number. Median (1st & 3rd Quartiles; Range) |
|---|---|
| Gender (♂/♀) | 20/10 |
| Age (years) | 66.5 (55, 77; 35-83) |
| APACHE II at admission | 21 (16, 24; 7-38) |
| Worst SOFA score during ICU stay | 9.5 (7.2, 14.0; 5-18) |
| ICU length of stay (days) | 12 (9, 23; 2-46) |
| Haemoglobin at ICU admission (g/L) | 96 (80, 104; 65-164) |
| eGFR at study entry (ml/min/1.73m$^2$) | 84.9 (53, 102; 13-154) |
| **Primary Diagnosis** | **Number** |
| Respiratory | |
| Infective Exacerbation of COPD | 7 |
| Pneumonia | 3 |
| Cardiac | |
| Cardiac failure | 3 |
| Post cardiac arrest | 1 |
| GI | |
| Perforated Viscus | 4 |
| Alcoholic liver disease | 2 |
| Variceal haemorrhage | 1 |
| Acute pancreatitis | 1 |
| Vascular | |
| Ruptured abdominal aortic aneurysm | 2 |
| Unexpected complication of surgery | |
| Excess bleeding (thyroidectomy) | 1 |
| Protracted surgery (elective abdominal aortic aneurysm repair) | 1 |
| Intraoperative cardiac ischaemia | 1 |
| Endocrine | |
| Diabetic Ketoacidosis | 1 |
| Other Sepsis | |
| Liver abscess | 1 |
| No organism identified | 1 |
| **Deaths** | |
| Characteristics, Time in study | Cause of death |
| Male 85y, 1 week | Cardiac failure |
| Male 83y, 1week | Respiratory failure |
| Female 49y, 3 weeks | Decompensated liver failure |
| Male 81y, 9 weeks | Respiratory failure |
| Female 62y, 9 weeks | Infective exacerbation COPD |
| Female 79y, 9 weeks | Pulmonary embolism |

Two of the female patients were pre-menopausal. One patient had normal menses and was no longer anaemic by the third week of follow up. The other patient did not return to normal menses until 3 months following ICU discharge; her haemoglobin returned to normal range by 6 months.

There was no association between age, ICU length of stay, severity of illness at ICU admission (APACHE II), or during ICU stay (SOFA max), or the number of transfusions received in ICU and time to recover from anaemia in those patients whom completed the study.

### 2.3.3 Time course of anaemia after ICU discharge

Haemoglobin concentrations during the study period are shown in Figure 2.2. Among the patients remaining in the study, 63% (12/19) were anaemic at 13 weeks and 53 % (10/19) were anaemic at 26 weeks. 32% (6/19) and 16% (3/19) of the patients had a haemoglobin concentration <110 g/L at 13 and 26 weeks respectively. Among the patients whose anaemia recovered during the study period the median time to entering the gender specific normal reference range was 11 weeks ($1^{st}$ and $3^{rd}$ quartiles 9 and 26; range 1 to 26 weeks). Using rates of increase in haemoglobin concentration between visits, from weeks 1 to 3 only 30% (n=7) patients demonstrated a haemoglobin increase of ≥10 g/L per week and 60% (n=13) an increase ≥5 g/L per week. Amongst those patients still anaemic at 6 weeks post-ICU discharge, none demonstrated an increase ≥5 g/L per week over the study period (Table 2.3).

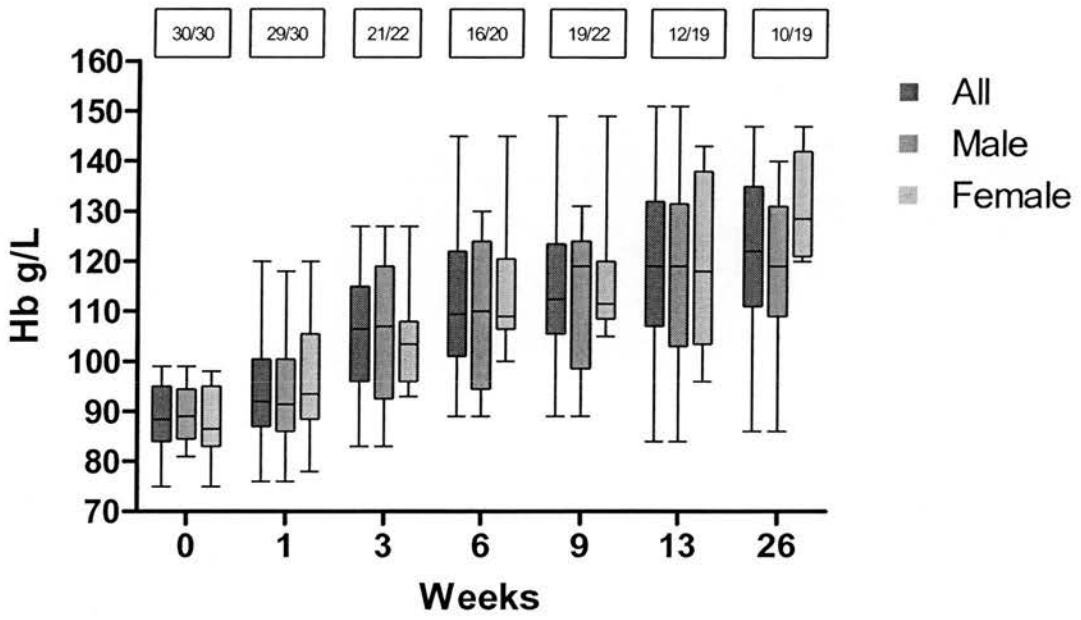



**Figure 2.2 Changes in haemoglobin concentration during course of study**

The proportion of patients still anaemic are shown in boxes above each time point.

**Table 2.3 Rate of change of haemoglobin for all patients in TRAC study**

| | Week 1 | Week 3 | Week 6 | Week 9 | Week 13 | Week 26 |
|---|---|---|---|---|---|---|
| Number of patients with Hb <gender specific ref range | 29/30 | 21/22 | 16/20 | 19/22 | 12/19 | 10/19 |
| Proportion (number) of anaemic patients whose Hb did not increase by an average 10g/L per week since last visit | 71 (20) | 71 (15) | 100 (16) | 84 (16) | 100 (12) | 100 (10) |
| Number of anaemic patients whose Hb did not increase by an average 5g/L per week since last visit | 54 (15) | 38 (8) | 81 (13) | 74 (14) | 83 (10) | 100 (10) |

### 2.3.4 Aetiology of anaemia

Baseline haemoglobin levels (median ($1^{st}$, $3^{rd}$ quartile)) for patients at recruitment (week 0) were 88.5 g/L (84.0, 95.0). Subsequent values and additional haematological parameters are summarised in Table 2.4.

#### *2.3.4.1 Absolute iron deficiency*

Ferritin concentrations were >12 µg/L in all patients throughout the study. Some anaemic patients with detectable circulating inflammatory markers had ferritin values 12-100 µg/L, particularly at later time points, but this was unusual. The data suggested that absolute iron deficiency was rare, but may have been present in a small number of patients during the later stages of recovery. This suggestion comes from extrapolation of the data regarding ferritin concentrations at later time points. A rapid decline in ferritin concentration was seen although never to a concentration less than 12 µg/L. With the observed rate of decline seen in some patients it was possible they may, in due course, have developed absolute iron deficiency.

#### *2.3.4.2 Functional iron deficiency*

The HR was >28 pg throughout the study in virtually all cases. Some patients had >5% hypochromic red cells early in the study, but this was not seen later in the study. Among patients with >5% hypochromic red cells the mean cell haemoglobin concentration (MCHC) was normal. These data suggest that detection of functional iron deficiency was test specific. If present, based on percent hypochromic red cells it was only present in the early post-ICU period.

**Table 2.4 Haematological parameters, CRP and IL-6 concentrations at all time points during study**

| Parameter (NR) | Week 1 | Week 3 | Week 6 | Week 9 | Week 13 | Week 26 |
|---|---|---|---|---|---|---|
| **Haemoglobin g/L** | 92 (87, 100) | 106 (96, 115) | 109 (101, 122) | 112 (105, 123) | 119 (107, 132) | 122 (111, 135) |
| **Ferritin µg/L (NR <12 or <100 if CRP>5)** | 367 (146, 769) | - | - | - | 130 (44, 386) | 76 (24, 179) |
| **CHR pg (NR 28-35)** | 32.1 (30.4, 33.9) | 32.0 (30.5, 33.5) | - | 30.8 (29.2, 32.6) | 30.4 (28.9, 31.8) | 31.9 (26.3, 32.9) |
| **%HYPO (NR<5%)** | 4.05 (2.05, 6.95) | 2.90 (0.75, 6.10) | - | 2.05 (0.70, 5.10) | 1.40 (0.70, 3.20) | 0.70 (0.15, 1.50) |
| **STfR nmol/L (NR <51)** | 38.4 (19.7, 45.7) | 30.3 (22.8, 50.9) | 37.1 (24.0, 47.8) | 38.2 (27.9, 46.6) | 36.5 (22.3, 48.5) | 42.4 (22.7, 49.1) |
| **EPO mIU/ml (NR>40 if Hb<100)** | 18.1 (8.8, 25.9) | 14.0 (9.7, 21.6) | - | 17.9 (11.4, 23.7) | 11.3 (8.6, 20.2) | 12.8 (9.9, 21.9) |
| **IL6 pg/ml (NR<10)** | 49.1 (30.9, 99.1) | 29.3 (12.7, 58.8) | 14.8 (9.4, 36.9) | 18.2 (8.9, 39.5) | 12.3 (7.8, 27.1) | 10.9 (8.6, 17.5) |
| **CRP mg/dL (NR <5)** | 51.0 (21.0, 108.0) | 16.5 (5.0, 60.0) | 10.0 (5.0, 23.5) | 15.0 (5.0, 61.5) | 9.0 (5.0, 21.0) | 5.0 (5.0, 11.5) |
| **Vit B12 ng/L (NR 170-730)** | 610 (429, 1279) | - | - | - | 353 (296, 494) | 326 (265, 410) |
| **Serum Folate µg/L (NR 2.0-13.5)** | 5.70 (3.70, 7.45) | - | - | - | 7.85 (3.70, 8.85) | 6.50 (3.80, 9.80) |
| **Red cell folate µg/L (NR 95-570)** | 254 (198, 391) | - | - | - | 283 (147, 322) | 237 (164, 398) |
| **Reticulocytes ($\times 10^{9}$) (NR <55)** | 99.9 (72.8, 140.7) | 72.6 (54.9, 91.0) | - | 63.4 (45.8, 91.3) | 62.4 (46.7, 92.5) | 67.0 (51.9, 96.9) |

Median ($1^{st}$, $3^{rd}$ quartile). NR = normal range. CHR = Concentration Hemoglobin in Reticulocytes, %HYPO = percentage hypochromic red cells, STfR = Soluble transferrin receptor, EPO = erythropoietin, IL6 = Interleukin-6, CRP = C-reactive protein

#### 2.3.4.3 Evidence of vitamin $B_{12}$ or folate deficiency

Only one patient had a vitamin $B_{12}$ level marginally below the reference range (value 165 ng/L) at week 26. One patient had a folate level marginally below the reference range (value 1.8 μg /L) at week 13, which recovered without treatment by week 26. For all other cases and time points there was no biochemical evidence of vitamin $B_{12}$ or folate deficiency. The data showed that vitamin $B_{12}$ and folate deficiency rarely contribute to anaemia after intensive care.

#### 2.3.4.4 Persistent inflammation

IL-6 and CRP concentrations were elevated in most patients at ICU discharge and persisted in many patients at the early evaluation time points .There was a highly variable pattern during long-term follow up, but some patients continued to have elevated circulating concentrations of inflammatory markers at 3 and 6 months after ICU discharge (Figure 2.3).

#### 2.3.4.5 Inappropriate erythropoietin response

We found that inappropriately low erythropoietin concentrations were highly prevalent throughout the study, and were present in all patients who remained anaemic during the later stages (Figure 2.4). These data showed that the healthy erythropoietin response to anaemia was either blunted or absent.

**Figure 2.3 Inflammation parameters – CRP and IL-6**

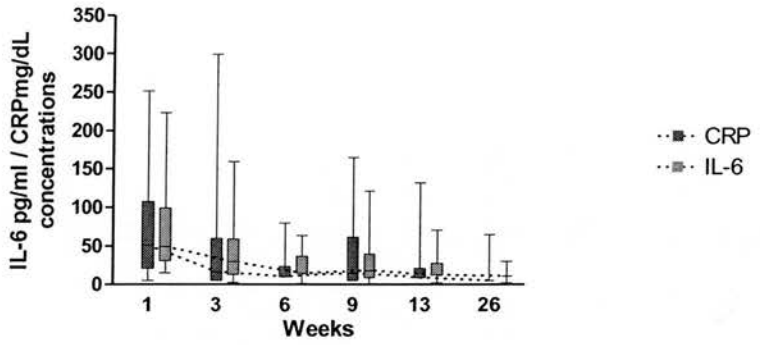



**Figure 2.4 Erythropoietic parameters - Erythropoietin and reticulocyte count**

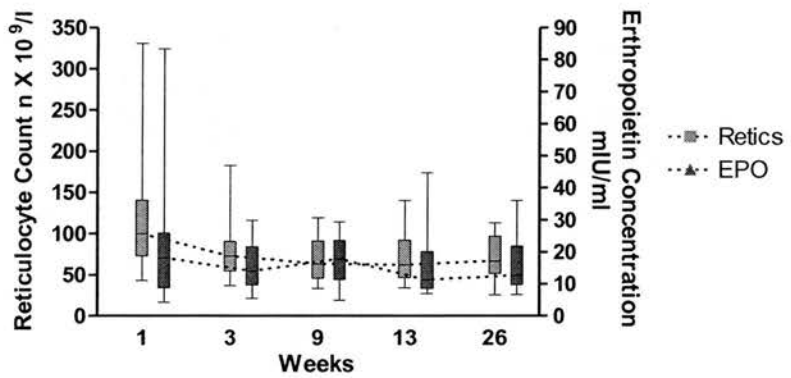



**Figure 2.5 Indices of new erythropoiesis and iron status**

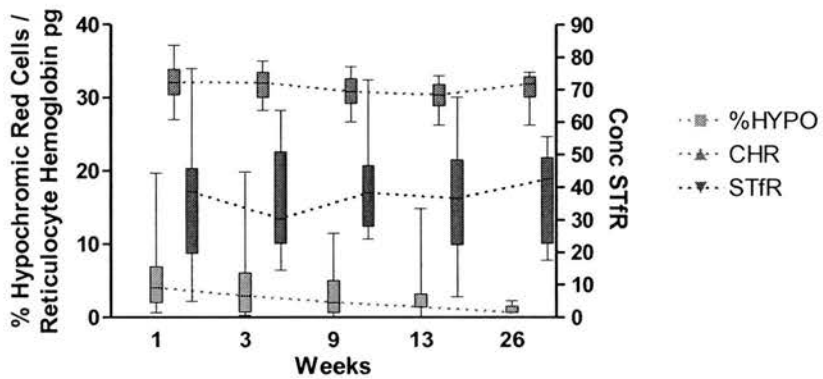


**Figure 2.3 Inflammation parameters – CRP and IL-6**

Box and whisker plots showing median, inter-quartile range and range for measured serum IL-6 (light grey) and CRP (dark grey) concentrations. Normal concentrations (non inflammatory states) less than 12 pg/ml and 5mg/dL respectively.

**Figure 2.4 Erythropoietic parameters - Erythropoietin and reticulocyte count**

Box and whisker plots showing median, inter-quartile range and range for measured plasma reticulocytes (retics, left axis) and serum erythropoietin concentration (EPO, right axis). Evidence of new erythropoiesis was defined as a reticulocyte count $>55x10^9/l$. Evidence of an erythropoietin response to anaemia was dependent upon the degree of anaemia (Specifically we defined an abnormal erythropoietin concentration as <40 mIU/ml and <20 mIU/ml for haemoglobin concentrations of <100 g/L and <120 g/L respectively).

**Figure 2.5 Indices of new erythropoiesis and iron status**

Distribution of hypochromic red cells (%HYPO, light grey), reticulocyte haemoglobin (CHR, mid grey) and soluble transferrin receptor concentrations (STfR, dark grey). Box and whisker plots showing median, inter-quartile range and range for percentage of hypochromic red cells in plasma (left axis), amount of reticulocyte haemoglobin (left axis) and concentration of soluble transferrin receptor in serum (right axis).

#### *2.3.4.6 Evidence of new erythropoiesis*

A minority of patients (approximately 20%) had elevated sTfR concentrations during the study period, but these levels were only modestly increased compared to controls and did not appear to relate to the degree of anaemia. There was a range in patterns of reticulocyte response (Figure 2.5). Patients who remained anaemic at later time points tended to demonstrate a lack of reticulocyte response to anaemia. Together, the data showed a hypo-active bone marrow given the degree of anaemia.

### 2.3.5 Quality of Life

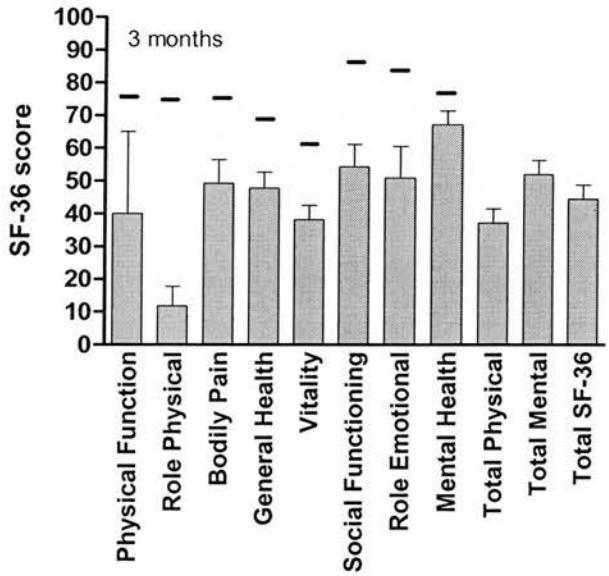
Results from the SF-36 assessments at 3 and 6 months are shown in Figure 2.6 and Table 2.5 together with comparative data from the UK normal population matched for the median study group age (Ware J E 1992; Jenkinson, Layte et al. 1997). Data from a Scottish study of quality of life after ICU discharge are also shown for comparison (Cuthbertson, Scott et al. 2005). This study group had a similar mean age to our study group. Our patients had low quality of life scores across all domains but particularly for the role physical.

### 2.3.6 Comparison of responders and non-responders at week 3 after ICU discharge

#### *2.3.6.1 Baseline Characteristics*

There were no statistically significant differences in baseline characteristics between the groups (Table 2.6).

**Figure 2.6 SF-36 scores at 3 and 6 months**
Solid bar indicates UK normal population values



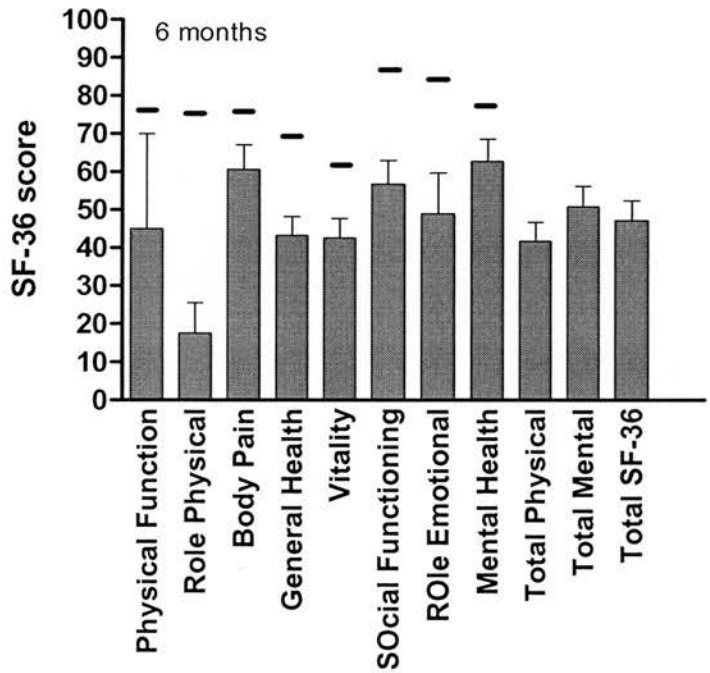



**Table 2.5 SF-36 scores for entire cohort with values for UK normal population and UK non-selective ICU population**

| | Physical Function | Role Physical | Bodily pain | General Health | Vitality | Social Function | Role Emotion | Mental Health |
|---|---|---|---|---|---|---|---|---|
| UK Normal population | 76.2 (22.3) | 75.9 (37.5) | 76.9 (24.0) | 68.1 (21.9) | 61.8 (21.2) | 86.2 (22.7) | 84.8 (30.6) | 76.4 (18.4) |
| **3 months post-ICU discharge** | | | | | | | | |
| UK ICU Non-selected cohort | 59.4 (24.1) | 47.4 (32.8) | 63.4 (30.2) | 58.0 (23.7) | 48.4 (22.9) | 63.7 (35.7) | 79.3 (28.1) | 75.5 (20.1) |
| Study group | 40.2 (27.3) | 11.9 (26.9) | 49.3 (32.5) | 47.8 (22.5) | 38.1 (20.5) | 54.2 (31.2) | 50.8 (44.2) | 67.2 (18.9) |
| **6 months post-ICU discharge** | | | | | | | | |
| UK ICU Non-selected cohort | 61.7 (28.7) | 53.1 (34.1) | 66.0 (31.7) | 58.7 (25.4) | 51.9 (24.3) | 69.2 (32.9) | 81.3 (28.0) | 76.8 (19.7) |
| Study group | 44.6 (30.4) | 17.6 (32.8) | 60.6 (26.5) | 43.3 (20.2) | 42.6 (21.4) | 56.6 (25.8) | 49.0 (44.3) | 62.8 (24.1) |

Mean (standard deviation) shown

It is notable that the responder group were generally younger, 57 years (54-63), median ($1^{st}$ and $3^{rd}$ quartiles) compared to 69 years (64-75) and had a shorter ICU stay 11.0 (4-12) days compared to 14.5 (9-17). The number of transfusions received during ICU stay failed to reach significance. The Non-responder group received more blood during there ICU stay, 2 (0 – 8), median ($1^{st}$ and $3^{rd}$ quartiles) for Responders versus 7 (4 – 16) units for Non-responders. There were no clinically or statistically important differences in measures of absolute or relative iron deficiency, vitamin $B_{12}$ status, red cell folate, or serum folate between responders and non-responders either at 3 weeks after ICU discharge or at any time point over the study period (data not shown).

#### *2.3.6.2 Parameters at week 3*

A comparison of patient parameters at the 3 week time point is shown in Table 2.6. Patients whose anaemia did not recover by week 13 had significantly higher CRP concentrations (p=0.013) and a trend to a greater proportion of patients having abnormally high IL-6 concentrations (p=0.06) at week 3 after ICU discharge. These patients had lower reticulocyte counts (p=0.014) consistent with persisting marrow hypo-responsiveness in the post-ICU period.

There was no difference in circulating erythropoietin concentrations between the groups as both groups had inappropriately low erythropoietin concentrations 3 weeks after ICU discharge. Examining trends over time, the non-responder group tended to have higher indices of inflammation and lower indices of erythropoiesis over the course of the study. Graphs showing these trends are shown in Figures 2.7 and 2.8. Data for sTfR is not

**Table 2.6 Comparison of Haemoglobin 'Responders' and 'Non-Responders' at 3 months post ICU**

| Parameter | Responder Group (N = 7) | Non-Responder Group (N = 12) | P-Value |
|---|---|---|---|
| **Baseline characteristics** | | | |
| Age (years) | 57.2 (54.0 – 63.0) | 69.9 (64.5 – 75.5) | 0.075 |
| ICU stay (days) | 11.0 (4.0 – 12.0) | 14.5 (9.0 – 17.0) | 0.150 |
| APACHE II (admission) | 23.0 (16.0 – 28.0) | 20.5 (14.5 – 25.0) | 0.554 |
| SOFA max (not neuro) | 8.0 (6.0 – 12.0) | 10.5 (7.5 – 14.5) | 0.472 |
| ICU Transfusions (units) | 2.0 (0.0 – 8.0) | 7.0 (4.0 – 16.0) | 0.188 |
| eGFR proportion with abnormal eGFR (<60ml/min/1.73m$^2$) | 2/7 (28.5%) | 5/12 (41.6%) | 0.654 |
| **Parameters** | | | |
| Haemoglobin (g/L) | 115 (110.0 – 120.5) | 105 (100.5 – 115.0) | 0.208 |
| Erythropoietin concentration (mIU/mL) | 14 (10.2 – 19.25) | 13.2 (10.7 – 14.2) | 0.690 |
| Number (proportion) with inappropriately low erythropoietin levels | 5/7 (71%) | 8/11 (72%) | 1.000 |
| CRP (mg/dL) | 5 (5 – 11) | 60 (27.8 – 124.5) | **0.013 *** |
| Number (proportion) with elevated CRP | 2/7 (28%) | 8/8 (100%) | **0.007*** |
| IL-6 (pg/mL) | 11.99 (8.01 – 14.44) | 32.48 (18.03 – 49.62) | 0.197 |
| Number (proportion) with elevated IL-6 | 1/7 (14%) | 6/9 (66%) | 0.060 |
| Reticulocytes (× 10$^9$) | 62.1 (53.2 – 98.0) | 43.6 (33.8 – 54.8) | **0.014*** |
| Number (proportion) with reticulocytes <55 x10$^9$ | 2/7 (29%) | 9/11 (81%) | **0.049*** |
| Ferritin µg/L 3 months | 90.0 (15.0 – 130.0) | 365.5 (45.5 – 512.5) | **0.0312*** |
| Vitamin $B_{12}$ ng/L 3 months | 348 (297 – 541) | 359 (285 – 589) | 0.7577 |
| Folate µg/L 3 months | 9.4 (6.2 – 17.1) | 5.8 (2.6 – 8.1) | 0.0549 |

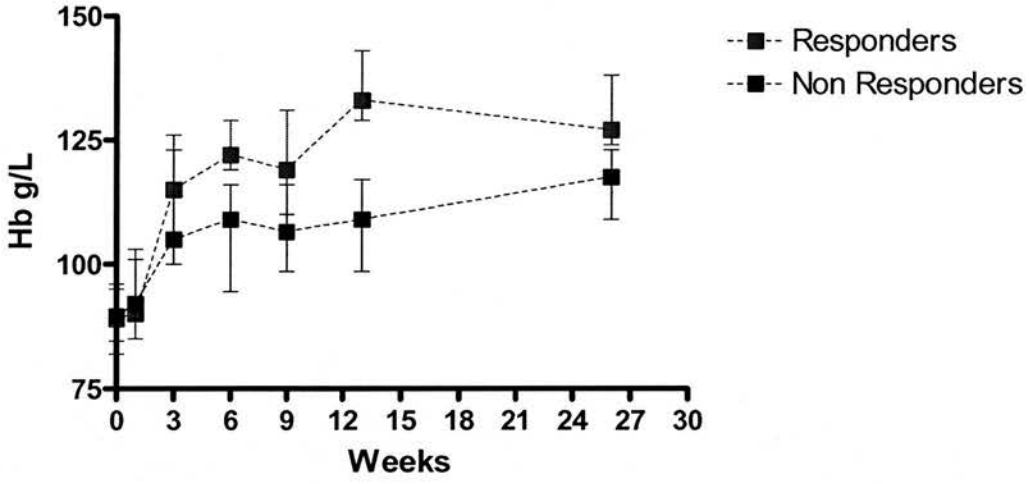
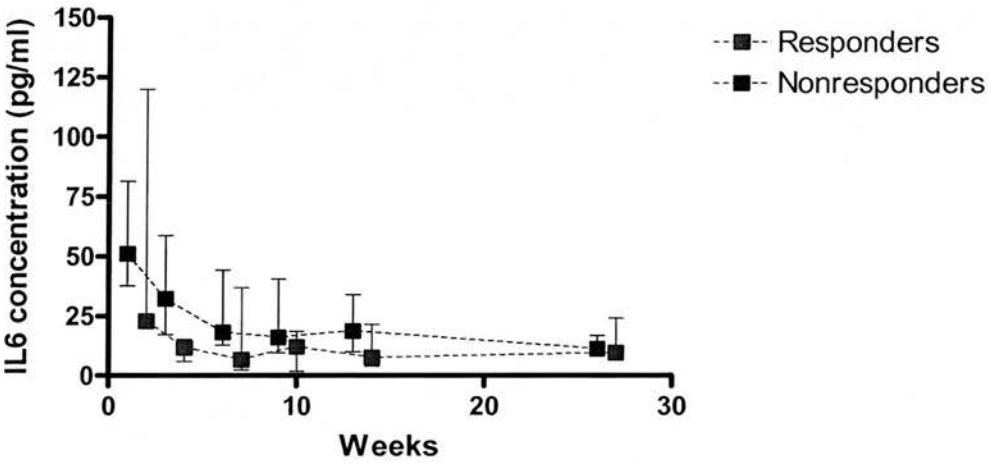


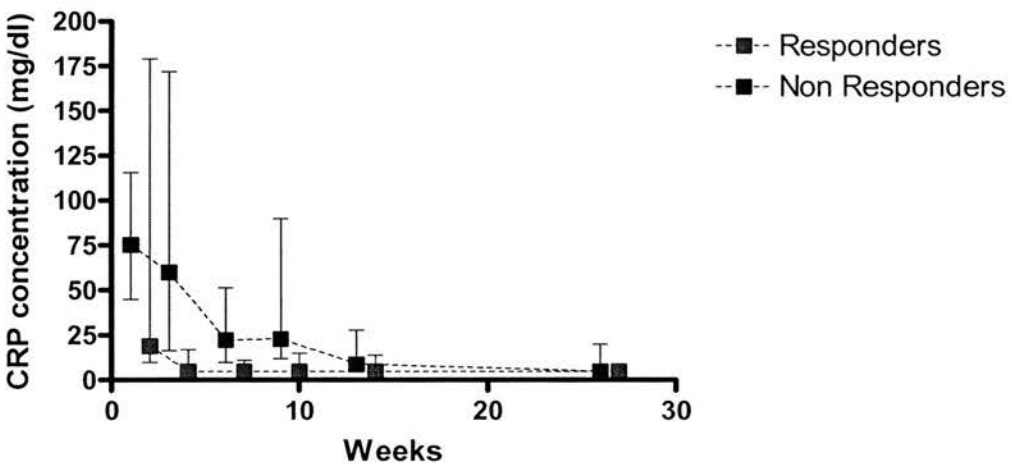

**Figure 2.7 Haemoglobin concentrations of responder and non-responder groups**

Median and interquartile range shown

**Figure 2.8 Changes in inflammatory markers between responder and non-responder groups**

IL-6 and CRP values shown as median and inter-quartile range



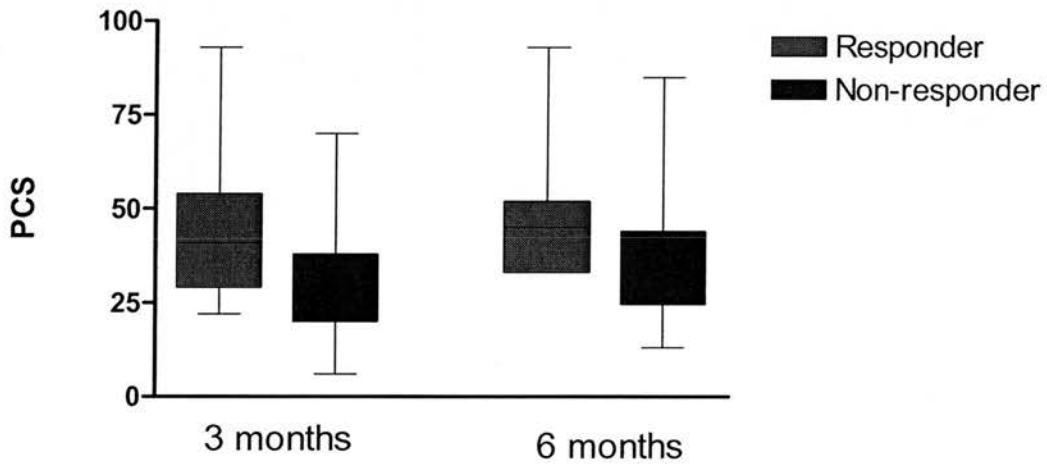



shown due to the very small numbers of patients in each group with data available. There was no statistically significant difference in quality of life of these two groups but it is again worth noting that the responder groups did score higher in the role physical at 3 and 6 months (Figure 2.9 and Table 2.7).

### 2.3.7 Renal Function

As part of the inclusion criteria for the study, no patient was enrolled if they required renal replacement therapy at time of ICU discharge. No patients required further renal therapy during follow up. We measured the patient's serum creatinine at every visit and calculated the eGFR accordingly. Of all 30 patients recruited, 9 had eGFR <60 ml/min/1.73m$^2$ (range 13 to 59) at discharge from ICU. Of these 5 patients were classified as 'non-responders' and 3 did not return to an eGFR of greater than 60 ml/min/1.73m$^2$ during the study period. Analysing the group of patients which completed the study there was no statistical association between the presence of eGFR less than 60 ml/min/1.73m$^2$ at ICU discharge and recovery from anaemia.

**Figure 2.9 SF-36 physical (PCS) and mental (MCS) component summary scores for responder and non-responder groups at 3 and 6 months**



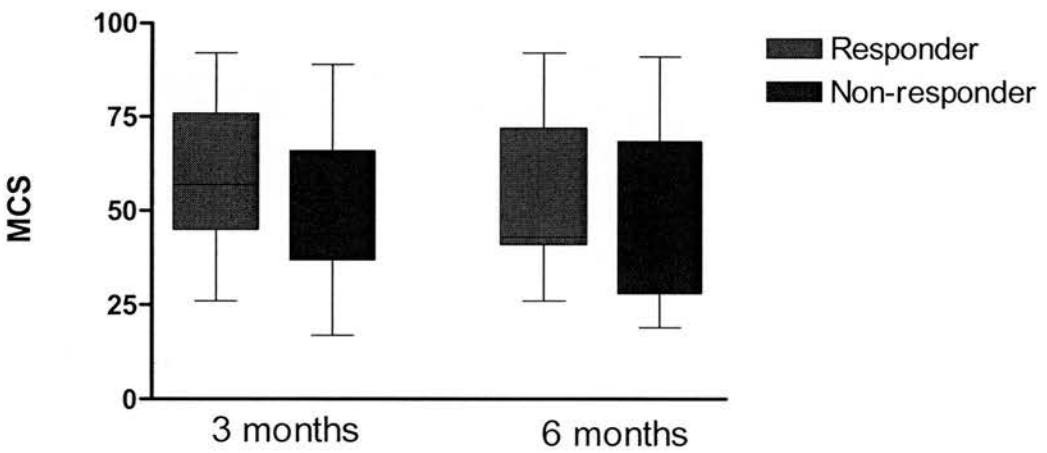



**Table 2.7 Quality of life measures in responder and non-responder groups**

| Parameter | Responder Group | Non-Responder Group | P-Value |
|---|---|---|---|
| **Quality of Life Parameters** | | | |
| **3 month data** | | | |
| Physical Function | 41 (29-54) | 34 (20-38) | 0.128 |
| Mental function | 57 (45-76) | 43 (37-66) | 0.398 |
| Total SF-36 Score | 53 (39-80) | 36 (30-51.5) | 0.0832 |
| **6 month data** | | | |
| Physical Function | 45 (33-52) | 32 (24-44) | 0.108 |
| Mental function | 43 (41-72) | 48 (28-65) | 0.812 |
| Total SF-36 Score | 41 (40-64) | 40.5 (26-58) | 0.410 |

Median and interquartile range shown

## 2.4 Discussion

This was the first study examining the time course and pathophysiology of anaemia during long term follow up after critical illness. The results of this prospective cohort study indicated that anaemia recovered at rates expected for healthy individuals in only 30% of cases. In the majority of patients recovery was slow or absent such that 63% and 53% of all patients were still anaemic at 3 and 6 months respectively, and 32% and 16% respectively had haemoglobin values less than 110 g/L.

### 2.4.1 Critique of study methodology

Our cohort was an unselected mixed general ICU population with a high illness severity and varied case-mix. Patient numbers were relatively small as the protocol required frequent follow-up either in hospital or at the patients' home and multiple blood analyses. This may have deterred a proportion of eligible patients. As a result there was a possibility of type II error, so we limited analysis to descriptive methods, with the exception of the exploratory comparison of patients whose anaemia recovered at 13 weeks versus those with persisting anaemia. We achieved high rates of follow-up and sampling, which decreased the chance of bias. The investigations used to describe the aetiology of anaemia and the definitions of different contributory factors were pre-defined by an independent expert panel of haematologists. Some important subgroups were excluded, notably patients with persisting acute renal failure or pre-ICU chronic renal failure. These patients have an independent reason for erythropoietin deficiency and impaired erythropoiesis, and also tend to have greater ongoing blood loss from

sampling and dialysis circuits (Lipkin, Kendall et al. 1990). Although treatment decisions were not dictated by the study, no patients received any blood transfusions, iron, folate or erythropoietin therapy or other treatments that might have confounded our findings.

### 2.4.2 Meaning of our findings

Our data strongly suggest that recovery was limited primarily by a hypo-reactive bone marrow. This may have been in part a result of inappropriately low circulating erythropoietin levels, although this was a feature of both responders and non-responders early in the study follow up. It is well documented that circulating erythropoietin concentrations are lower than expected in anaemic patients during ICU stay (Elliot, Virankabutra et al. 2003) and our data indicate that this persists into the recovery period. The hypo-reactive bone marrow that characterized the non-responding patients is typical of an anaemia of chronic inflammatory disease in which pro-inflammatory mediators inhibit erythrogenesis (Baer, Dessypris et al. 1990; Wolfe and Michaud 2006). Circulating IL-6 and CRP concentrations were higher in the non-responder group during this early period of recovery, which supports the conjecture that persistent anaemia after critical illness is associated with a chronic inflammatory state. During follow up, 65% and 60% of patients still had detectable circulating IL-6 concentrations, at 3 and 6 months respectively after ICU discharge, and 48% and 31% had elevated CRP concentrations. This is a possible explanation for the "inappropriate" erythropoietin response and impaired erythropoiesis. Inflammatory mediators are known to inhibit erythropoietin production and the marrow response to circulating erythropoietin (Corwin

and Eckardt 2005; Ferrucci, Guralnik et al. 2005). Serum from ICU patients, particularly those with sepsis, directly inhibits erythroid precursors, and can induce apoptosis of red cell precursors (Lang, Lang et al. 2003; Lang, Lang et al. 2005).

There was little evidence of iron, folate or $B_{12}$ deficiency at any point in the study. In a small number of patients ferritin concentrations fell late in follow up period, particularly in patients whose anaemia recovered, often in association with normalisation of inflammatory markers. This could indicate either resolving inflammation, as ferritin is an acute phase protein, or a decrease in iron stores resulting from active erythrogenesis. None of these patients developed evidence of absolute iron deficiency during the study period using our pre-defined criteria. The interpretation of the indices of functional iron deficiency was difficult and contradictory between methods of assessment. Overall there was little evidence for significant functional iron deficiency. The high percent of hypochromic red cells observed in some patients early after ICU discharge was consistent with previously reported findings during ICU stay (Rogiers, Zhang et al. 1997; Bellamy and Gedney 1998; Patteril, vey-Quinn et al. 2001). Although this could indicate impaired incorporation of iron into red cells another explanation could relate to red cell shape changes that occur during sepsis and inflammation (Herridge, Cheung et al. 2003; Piagnerelli, Boudjeltia et al. 2003) which are not accounted for in the automated red cell analysis. It is also possible that functional iron deficiency only becomes apparent when the marrow is stimulated with exogenous erythropoietin.

#### *2.4.2.1 Interplay between cytokine activation and recovery from critical illness*

Cytokine changes during critical illness have been studied extensively. Cytokines are produced in response to a variety of tissue insults and contribute to tissue dysfunction (Oberholzer, Oberholzer et al. 2000). Studies have consistently shown that pro-inflammatory cytokines are higher in non-survivors than in survivors of critical illness (Dimopoulou, Orfanos et al. 2008) and that IL-6 either alone, or in combination with severity of illness scoring, is of use in predicting outcome (Wunder, Eichelbronner et al. 2004). Little is known, however, about cytokine changes during the recovery period. In patients with community acquired pneumonia whom required admission to hospital, the presence of an elevated IL-6 concentration at subsequent discharge from hospital was associated with an increased risk of death over the subsequent 3 months, even though only 13% of these patients had abnormal vital signs at discharge (Yende, D'Angelo et al. 2008). This suggests that many patients have a persisting inflammatory response even though the clinical signs have resolved (Halm and Teirstein 2002). The persistence of low grade inflammation and immunosuppression may play an important role in complications after hospitalization after community acquired pneumonia such as cardiovascular death, renal failure and repeat infections (Ridker, Rifai et al. 2000; Mortensen, Coley et al. 2002; Shlipak, Fried et al. 2003) and it may therefore be that the cytokine profiles during recovery influence different mechanisms or cause specific mortality. Our data suggest that the bone marrow is another body system so affected. This underscores the need to examine the cellular response and cytokine influences on the recovery of the haematopoietic and immune system after critical illness.

#### 2.4.2.2 *Immunomodulation of erythrogenesis*

Inflammatory cytokines such as IL-6 can inhibit iron absorption and metabolism through the regulation of hepcidin (Nemeth and Ganz 2006; Nemeth 2008). Thus the persistence of inflammation would continue to prevent resolution of anaemia. Looking at the time course of IL-6 with anaemia in the responder and non responder groups there is a trend showing that the resolution of inflammation is temporally related to the subsequent resolution of anaemia.

#### 2.4.2.3 *Antibiotics and the bone marrow*

It is also possible that the medications, especially antibiotics such as the oxylazones, which critically ill patients are often exposed to during their ICU and hospital stay, could directly inhibit erythropoiesis. If there is ongoing infection it is possible that the exposure of such patients may be greater to such drugs inhibiting the bone marrow and that this may also contribute to the anaemia seen. We did not specifically examine the use of antibiotics in ICU or during the recovery period but anecdotally we did not have any patients on protracted courses of oxylazones during recovery period. Due to the very broad case mix contributing to a study group we felt that it is unlikely that this effect on its own would have significantly contributed to different responses to anaemia.

#### 2.4.2.4 *Inflammation and renal function*

The erythropoietin response must be considered in the context of the renal function of the patients as the development of chronic kidney disease would affect the response to anaemia. Despite none of our study group requiring renal replacement therapy at ICU

discharge 30% had an eGFR consistent with chronic kidney disease. This must be interpreted with some caution as eGFR has not been validated for use in acute renal failure (which may be resolving by the time of ICU discharge), or oedematous states, muscle wasting states and malnourishment, which many patients are suffering from at the time of discharge. None of our patients went on to require renal replacement strategies during the study period and only 16% (3/19) of patients who completed follow up had an eGFR<60, though 2 of these patients did remain anaemic at 6 months. There is also a prevalence of reduced eGFR measured within the general population without a specific diagnosis or awareness of having chronic kidney disease. This prevalence can be as much as 30% in those aged over 75 years (Cirillo, Laurenzi et al. 2006) and therefore a level of abnormal eGFR is likely to be present in our study population. Elliot *et al* demonstrated that EPO levels were the same for critically ill patients with and without acute renal failure and this persisted into the chronic phase of critical illness (Elliot, Virankabutra et al. 2003). Thus although the development of chronic kidney disease during recovery from critical illness will affect the recovery from anaemia it would have been difficult to exclude patients from the study on the basis of their eGFR at ICU discharge alone. There was no statistical difference in eGFR at discharge between groups who recovered from anaemia compared to those that did not.

#### *2.4.2.5 The clinical importance of anaemia during recovery from critical illness*

The clinical importance of anaemia during recovery from critical illness is unknown. It is well documented that patients suffer fatigue and breathlessness following critical

illness even without demonstrable lung pathology (Herridge, Cheung et al. 2003). It is possible that anaemia contributes to these symptoms. Our patients had low quality of life scores at 3 and 6 months after ICU discharge in all domains, but especially in the role physical. The observed scores were lower than reported in a non-selected population of patients surveyed after intensive care discharge in a similar (Scottish) population (Cuthbertson, Scott et al. 2005). These data suggest an association between anaemia at intensive care discharge and poor long term quality of life. Our data suggest that anaemia is potentially important during recovery from critical illness, and supports the hypothesis that treating anaemia could potentially improve some of the symptoms suffered by patients.

A study in long term ICU patients showed that treatment with erythropoietin had modest effects on haemoglobin concentration and blood transfusions and no effect on recovery rates (Silver, Corwin et al. 2006). Recent data suggest that erythropoietin treatment alone during ICU care is not effective for reducing red cell transfusion (Corwin, Gettinger et al. 2007) and in fact may actually be detrimental due to increased complications, especially venous thrombosis. Our data suggest that an abnormal erythropoietin response and significant anaemia persists for at least 6 months after ICU discharge in many patients, particularly those with persisting inflammation. It is likely that red cell transfusions either alone or in combination with erythropoietin are required to achieve haemoglobin concentrations approaching reference values in the post-intensive care period. Few studies have evaluated the importance of treating anaemia during this period, and specifically whether interventions with blood transfusions or

erythropoietin during recovery improve patient quality of life, as has been reported for anaemia associated with other chronic diseases (Horwich, Fonarow et al. 2002; Obrador and Pereira 2002; Silverberg, Wexler et al. 2004). Current recommendations are based on the findings of the TRICC trial in which restrictive and liberal strategies were only compared during ICU care. This practice may not be appropriate to the extended recovery period.

## 2.5 Conclusions

We have shown that anaemia persists for at least 6 months following intensive care discharge in many patients with no history of pre-illness anaemia. The erythropoietin response to anaemia is blunted during this period and bone marrow is hypo reactive in many patients, especially those with persistent systemic inflammation. Patients discharged with anaemia from intensive care have a reduced quality of life compared to other ICU groups. A greater focus upon the treatment of the anaemia of critical illness in the recovery phase rather than the acute phase could be a mechanism by which the potentially detrimental effects of such interventions could be avoided.

# Chapter Three

## The Ps and Qs Study

## Physical function and Quality of life following critical illness

## 3.1 Introduction

Critical care medicine represents the provision of advanced, aggressive and expensive medical support to individuals with an illness of life threatening severity and high short term mortality. Critical care research has, until recently, understandably focused on short term physiological parameters and short term clinical outcome measures such as survival to ICU and hospital discharge. With improved short term survival from critical illness, research is now focusing on the long term impact upon the individual and their families. Surviving critical illness is just the beginning and recovery from critical illness is protracted and associated with significant morbidity. Health Related Quality of Life (HRQL) is the term used to refer to the subjective experience of the effect of health and treatment on a patient's satisfaction with life.

But what is health? The WHO provides a standard language and framework for the description of health and health related states in the International Classification of Functioning, Disability and Health (ICF) (Organisation 2002). Everyone experiences a decrement in their health at some point but the impact of this change in health status will be different for each individual depending upon many factors including previous health, previous family experience, expectations of health, and environmental and socio-economic factors. As a consequence the ICF aims to place the effects of a change in health in context by recording the impact on an individuals function rather than in respect to the severity of the cause of the disability itself.

Pre-existing disease will therefore modulate the impact of critical illness on an individual. It was noted in the TRAC study (Chapter 2) that patients with a significant

pre-morbid illness burden and subjectively a greater degree of overall illness burden during recovery from critical illness often reported a greater quality of life than those who were healthier both before and after the critical illness. We therefore proposed that the change in health Rather than the actual level of disability was the most important determinant of quality of life following critical illness.

### 3.1.1 Health Related Quality of Life following critical illness

There are many methods of determining HRQL (Black, Jenkinson et al. 2001). The two measures recommended by the 2002 consensus conference on surviving critical illness, the SF-36 and EQ-5D have only been used in 2% of ICU studies. Studies have shown conflicting results.

### 3.1.2 Pre-morbid HRQL

Cuthbertson *et al* showed that pre-morbid quality of life in critically ill patients was impaired compared to the normal population (Cuthbertson, Scott et al. 2005). It was also significantly reduced in the physical components at three months following ICU discharge and gradually returned to the pre-morbid values, but remained less than the general population, at 1 year. Mental components of quality of life were not impaired at any time point. Wehler *et al* found that preadmission HRQL was severely impaired in intensive care patients due to a significant level of chronic co-morbidity prior to the acute event and that this co-morbidity contributed to the reported reduced HRQL in the recovery period (Wehler, Geise et al. 2003). These studies show that HRQL in the survivors of critical illness was impaired prior to the illness requiring ICU admission.

Angus *et al* demonstrated that in an apparently previously fit cohort of patients who developed ARDS as part of their critical illness, significant impairment of quality of life was evident and these patients remained at an increased risk of death during the extended recovery period after ICU discharge (Angus, Musthafa et al. 2001). They assessed the physical function and recalled pre-morbid quality of life and found that it was essentially the same as that of a non-critically ill population. Many of the symptoms during recovery were associated with pulmonary impairment. It was therefore suggested that it was physiological impairments developed as a consequence of critical illness (in this case specifically pulmonary problems) that were contributing to the reduced quality of life.

It seems logical that if a significant burden of pre-illness ill health is present in patients who go on to have a critical illness this will contribute to the quality of life after recovery. As previously 'fit' patients go on to have a similar magnitude of impairment to quality of life (as measured by HRQL scores) it remains unclear how much pre-morbid health contributes to post critical illness quality of life. It may therefore be that the *change* in quality of life is a more meaningful measure of the impact of critical illness on quality of life.

### 3.1.3 Complications of critical illness and HRQL

Garcia Lizana *et al* showed that it was mental elements rather than physical disability which showed the greatest impairment following critical illness compared to pre-morbid state (Garcia Lizana, Peres Bota et al. 2003). However 25 % of their patients had reduced mobility and autonomy, with 8% described as being severely incapacitated

suggesting that there was a significant burden of physical disability present. Davidson *et al*, (Davidson, Caldwell et al. 1999) found that the HRQL in patients with ARDS compared to a matched cohort of patients who did not develop ARDS, was significantly reduced and suggested this reduction was caused exclusively by the development of ARDS and its sequelae. This exemplifies the concept that it is the complications of critical illness rather than the initial critical event which contribute to the long term outcomes of patients. There is some debate however, about what contributes to reduced quality and quantity of life in patients who survive critical illness. Herridge *et al* demonstrated that in ARDS survivors most pulmonary physiological impairments, as measured by pulmonary function tests, had returned to normal by 6 months (Herridge, Cheung et al. 2003). Although many of the symptoms described by the patients were attributable to pulmonary problems the objective pulmonary physiological burden was modest. It was therefore proposed that significant symptoms of impairment were due to common extra-pulmonary complications of critical illness, especially neuro-muscular impairment. These complications have been discussed in detail in Section 1.3.

### 3.1.4 Time course of HRQL following critical illness

In a study assessing quality of life in patients discharged from a general ICU with principally medical, cardiovascular and pulmonary problems, Graf *et al* observed no improvement in the mental health dimensions of SF-36 score over time whereas the physical health summary scale consistently improved over the 9 months of the study (Graf, Koch et al. 2003). They concluded that quality of life after intensive care was a dynamic process. Hofhuis *et al* showed that in critically ill patients, pre-morbid HRQL

was worse than for the general population, and that critical illness was associated with a decline in HRQL which took 6 months to return to pre-morbid levels. Furthermore, early measures of post ICU HRQL were better in those patients who survived to 6 months than those who did not (Hofhuis, Spronk et al. 2008). In various sub groups such as those with sepsis (Hofhuis, Spronk et al. 2008) HRQL was again shown to be impaired. From our own work in the TRAC study (Section 2.3.5) we noted a significant impairment of quality of life in anaemic patients following critical illness. It was observed during the follow up that the patients who had co-morbidities prior to critical illness often had a better reported quality of life during the recovery period than 'fitter' individuals suggesting that it is the change in function rather than the absolute level of function which impacts upon the individual. It was also observed that there was a temporal relationship in the reporting of quality of life and physical function. The TRAC study patients reported at 3 months that they had impaired physical function but a good quality of life whereas at 6 months when there had been some improvement in physical function they reported their quality of life as worse. We believe that this reflects a change in expectations of health following critical illness.

### 3.1.5 Investigating health related quality of life

The link between critical illness and post ICU disability is therefore challenging to evaluate. It is multi-factorial in nature and relates to intrinsic patient factors but also to events in ICU practice and subsequent periods of rehabilitation. The questions posed by current literature are whether patients with significant co-morbidity and therefore reduced quality of life prior to the development of critical illness account for the

majority of the reduced quality of life found in patients who survive critical illness, and whether it is physical or psychological morbidity which has the greatest impact on post ICU health. These questions have led us to investigate the relationship between changes in quality of life after intensive care, together with measurement of functional ability and patient's perception of health. We also sought to determine what common complications of critical illness may be contributing to the persistence of adverse physical function and quality of life.

## 3.2 Hypothesis and Objectives

### 3.2.1 Hypothesis

We hypothesised that health related quality of life following critical illness was impaired due to impaired physical function.

### 3.2.2 Objectives

We aimed to examine the relationship between pre-morbid physical function and quality of life and the same measures during recovery from critical illness to determine whether the change in perceived functional ability had a greater impact on physical quality of life recovery than could be accounted for by the actual limitation of function encountered by these patients. We also aimed to determine the prevalence of common physiological abnormalities encountered during recovery from critical illness and to examine their impact on physical function and quality of life.

Our research questions were:

- What is the impact of critical illness on perceived physical function?
- What is the impact of critical illness on physical components of quality of life?
- What is the actual physical function in a general cohort of survivors of critical illness?
- What is the time course of recovery of quality of life, perceived and actual physical function following critical illness?
- Does the change in perceived and actual physical function affect the physical components of, and overall quality of life, in survivors of critical illness?
- Does the magnitude of change in perceived physical function reflect the magnitude of impairment in physical quality of life?
- Does the magnitude of change in perceived physical function reflect the degree of actual physical impairment?
- What is the relationship between anaemia, inflammation, nutritional status, renal function and serum albumin and impaired physical recovery from critical illness?
- What is the prevalence of significant psychological morbidity (post traumatic stress disorder) in our study cohort and does the presence of significant psychological illness affect physical components of, and overall, quality of life?

Our primary outcome measures were:

- Change in SF-36 score from recalled assessments of pre-morbid quality of life compared to follow up at 3 and 6 months post ICU discharge.

- Change in FAI score from recalled assessments of pre-morbid perceived physical function compared to follow up at 3 and 6 months post ICU discharge.
- Distance walked in metres as part of a formal 6 minute walk test at 3 and 6 months following ICU discharge.

Our secondary outcome measures were:

- Haemoglobin concentration at 3 and 6 month follow up.
- Assessment of nutritional status at ICU discharge and 3 and 6 month follow up - body weight, serum albumin, anthropometry (mid arm circumference, mid calf circumference).
- Assessment of hepatic and renal function with serial measurements of serum bilirubin and creatinine concentrations at 3 and 6 months following ICU discharge.
- Assessment of other possible contributory symptoms – fatigue, pain and lack of appetite - using visual analogue scales.
- Secondary assessment of physical function with hand grip dynamometry.
- Secondary assessment of quality of life using the EURO-QOL thermometer visual analogue scale.
- Assessment for symptoms of post traumatic stress disorder using Davidson's Trauma Score (DTS).

## 3.3 Materials

### 3.3.1 Selection of outcome measures

#### *3.3.1.1 Measures of quality of life*

##### *3.3.1.1.1 SF-36*

SF-36 is discussed in Section 1.14.1.8.1. Many of the studies characterizing health related quality of life in the survivors of critical illness have methodological problems (Heyland, Guyatt et al. 1998). The use of SF-36 in patients recovering from critical illness is supported in many studies (Chrispin, Scotton et al. 1997; Chaboyer and Elliott 2000; Hayes, Black et al. 2000) and it has been extensively validated in other patient populations. It was recommended for use in assessing patient centred outcomes by the 2002 Consensus conference (Angus and Carlet 2003). In critically ill patients the test has been found to take longer to administer, 20 minutes compared to 10 minutes usually, however this is still thought to be acceptable to patients and carers. The internal consistency in the critically ill population was found to be good with Cronbach's $\alpha$ coefficient exceeding 0.85. Its validity has also been described as good (Chrispin, Scotton et al. 1997).

##### *3.3.1.1.2 The EuroQol VAS thermometer*

The EuroQol thermometer is a component of the EuroQol 5-D questionnaire, a generic instrument designed to measures health outcome (1990). The thermometer represents a visual analogue scale to record perceptions of the patient's current overall perceived health. It is can be seen as a supportive assessment due to the more reflex nature of the

response to visual analogue scales, to see how the patient was feeling on the day of the assessment as this may affect their responses to the more formal assessments of quality of life.

#### 3.3.1.2 Measures of physical function

##### 3.3.1.2.1 The Frenchay Activities Index (FAI)

The Frenchay Activities Index (Holbrook and Skilbeck 1983) is discussed in Section 1.14.1.10.1. Physical function represents an important patient centred outcome following critical illness. The Frenchay Activities Index (FAI) was developed to measure social activities in stoke patients. The index aims to reflect higher order activities of daily living (ADL) and was developed due to the limited scope of conventional measures of ADL which had generally focused on abilities of self care. It has not been assessed or validated in critical care populations but has had extensive use in elderly and young physically disabled populations due to its broader scale incorporating complex functional status, social and life-style activities more relevant to the post critical illness population. It has been validated in the normal population (Turnbull, Kersten et al. 2000). The use of proxy recall of these measurements has been investigated. A proxy is generally considered to be a person, usually a family member, who is in physical contact with the patient at least three times per week and performs at least two care-giving tasks on those occasions. The proxy scores in many studies correlate well with the patient's scores but there are often marked differences in specific areas. The best agreement was for objective items of preparing meals, washing-up, washing clothes, shopping and driving. The poorest agreement was for participation in hobbies, social outings and

heavy housework (Tooth, McKenna et al. 2003; Tooth, McKenna et al. 2003). The recalled use of FAI by the patient has also been assessed and found to correlate well with the proxy assessment of their physical function prior to illness such as stroke and there is some anecdotal evidence that this method may be extrapolated to critical illness (Wyller, Sveen et al. 1996).

The FAI was chosen because it does not require training to administer, it takes only five minutes to complete (which was felt to be an important factor in patients who were coming for a battery of assessments) and it can be used as an interview or mailed questionnaire with excellent correlation between the methods (r=0.94) (Carter, Mant et al. 1997) which would allow data to be collected even if the patient was not able to attend follow up clinics. It has been proven (in patients with stroke) to be appropriate for recalled use so that pre-morbid functional status can be assessed and subsequent change recorded (Holbrook and Skilbeck 1983). The use of proxy respondents has been well validated (Segal and Schall 1994). The measure has also been shown to have excellent correlation with the physical component summary score of SF-36 and adequate correlation with the EQ-5D. It has also been found to have adequate correlation with measures of actual physical function such as the timed up and go test.

#### *3.3.1.2.2 The Six Minute Walk Test*

The six minute walk test (6MWT) represents an objective rather than subjective evaluation of functional capacity and is discussed in Section 1.14.1.10.2. It was chosen as it was developed to evaluate exercise tolerance in patients with respiratory disease

(the most frequent diagnosis in survivors of critical illness), is easy to administer and better tolerated than other measures such as the 12 minute walk test and is more reflective of performance in activities of daily living than other walking tests (Solway, Brooks et al. 2001). The 6MWT is unique in its ability to evaluate, in a non-laboratory setting, cardiovascular and respiratory exercise performance. It also shows similarity with the activities of daily life (Grotz, Hohensee et al. 1997; Enright 2003). It does not assess balance, quality of movement, use of assistive devices and amount of physical assistance needed (Barak and Duncan 2006). The distance walked is potentially influenced by some common neuromuscular complications of critical illness such as muscle weakness, balance problems and neuropathies. The 6MWT was therefore chosen over other measures such as the shuttle test as it is regarded to be safer, easier to administer, better tolerated and reflects normal activity.

#### *3.3.1.2.3 Hand grip dynamometry*

Hand grip dynamometry is discussed in Section 1.14.1.9.3. Survivors of critical illness are a diverse patient group with many different factors contributing to their functional limitation during recovery. Hand grip strength has been found to be a consistent predictor of clinically important outcomes such as survival and postoperative complications in many different populations (Bohannon 2008). For our study cohort we felt that low grip strength, which is associated with a greater likelihood of functional disability in many studies (Shibata, Haga et al. 1992; Sarkisian, Liu et al. 2001), especially in pneumonia the commonest admission diagnosis for our study cohort (Bohannon, Maljanian et al. 2004; Vecchiarino, Bohannon et al. 2004), would be a

valuable measure in the assessment of physical function. It has also been found to be a good indicator of nutritional status (Davies, Jones et al. 1984).

#### *3.3.1.3 Measures of post traumatic stress disorder*

Psychological symptoms have been shown to occur commonly in critically ill patients and have significant impact on QOL and actual morbidity following critical illness. Cuthbertson *et al* found a high incidence of symptoms consistent with Post Traumatic Stress Disorder (PTSD) 3 months after ICU discharge and a significant need for further psychological support services post critical illness (Cuthbertson, Hull et al. 2004). Jackson *et al* investigated the prevalence and types of neuropsychological impairment among general medical ICU patients (Jackson, Hart et al. 2007). They found that impairment was common and occurred with a greater than anticipated frequency when compared with relevant normative data. These studies also established a role for the Davidson Trauma Score (DTS) in recovering ICU patients whereas previously it had only been used in specific groups such as burns, neurological injury and cardiac surgery. The DTS has been used widely in the initial assessment of patients who have undergone a range of physically or psychologically traumatic events that could be related to the development of PTSD. The DTS measures all 17 primary PTSD symptoms relating to the 3 main symptom areas, Intrusion, Avoidance and Hyper-arousal, with specific criteria for both frequency and intensity rated on a five point scale. Two threshold scores are used to convert the continuous scores into dichotomous categories for the analyses of the data. A score of 40 or greater is associated with high specificity for the DSM-IV diagnosis of PTSD. A score of 27 - 39 identified individuals with a high levels of PTSD

psychopathology but who have equivocal diagnostic criteria for PTSD. We aimed to quantify the risk factors for symptoms related to the diagnosis of PTSD using a measure validated in a variety of trauma populations in a general cohort of critically ill patients at 3 and 6 months post ICU discharge using the DTS.

#### 3.3.1.4 Organotopic Measures

In addition to assessments of physical function and quality of life we performed simple tests to look for evidence for organotopic sequelae in the long-term recovery after critical illness which may contribute to impaired quality of life.

##### *3.3.1.4.1 Anaemia*

Anaemia is an important and common complication after critical illness. 80-90% of survivors of critical illness are anaemic at ICU discharge (Walsh, Saleh et al. 2006) and 75% of patients are still anaemic when discharged home (Saleh 2006). There is clear evidence for an association between anaemia, physical function and HRQL in patients with chronic renal failure (Obrador and Pereira 2002), cancer (Caro, Salas et al. 2001) (Cella 2002)and chronic inflammatory disease (Peeters, Jongen-Lavrencic et al. 1996) and heart failure (Silverberg, Wexler et al. 2002). Treating this anaemia has been shown to improve quality of life. Haemoglobin concentration was therefore measured at ICU discharge and at 3 and 6 months.

#### *3.3.1.4.2 Nutrition*

Up to 40% of hospital patients in the UK are underweight (Elia and Stratton 2000). In ICU patients there is extensive muscle catabolism despite aggressive nutrition because of inflammation and the stress response to critical illness. This process is exaggerated by immobility and critical illness neuropathy. Previous work conducted in our population has found that patients typically lost 20% of body mass during ICU admission and many had not regained pre-illness weight 12 months after discharge. In patients recovering from ARDS it was noted that marked reductions in aerobic capacity, physical function and HRQL was attributable to muscle cachexia rather than residual pulmonary disease (Herridge, Cheung et al. 2003).

Grip strength has been shown to be an indicator of nutritional status (Webb, Newman et al. 1989; Wang, Sea et al. 2005) and potentially a more appropriate marker than weight loss and albumin in patients with serious post operative complications, a patient group with many characteristics similar to the survivors of critical illness (Klidjian, Foster et al. 1980). Hand grip strength is also a marker of 'frailty' providing a measure of the multiple problems and their potential impact upon an individual and is a consistent predictor of important outcomes. It is has been found to be a robust measure of the complex problems found in patients requiring rehabilitation reflecting the overall impact of illness better than comparable laboratory and clinical measures of outcome. It was therefore felt that it would be a worthwhile test in our battery of assessments. In addition to this measure the standard nutritional measures of weight, albumin and mid upper arm circumference (MUAC) were included.

#### *3.3.1.4.3 Markers of inflammation*

In the previous study described in Chapter 2 we found that there was a persistence of the inflammatory state well into the recovery phase from critical illness. This persistence of inflammation has been associated with anaemia, neuromuscular dysfunction, impaired nutrition and impaired recovery from critical illness (Ho, Lee et al. 2008). We felt that other markers of inflammation such as interleukins had a response time that was potentially too short for the limited follow up clinics available to measure markers of inflammation. C-reactive protein (CRP) rises within hours of an inflammatory stimulus but remains elevated in the chronic inflammatory state and is used for monitoring the progress of chronic inflammatory conditions such as rheumatoid arthritis. It was therefore considered the most appropriate test for assessing inflammation during follow up.

#### *3.3.1.4.4 Renal and hepatic function*

Simple laboratory measures of renal and hepatic function were measured to determine if there was significant organ failure in the cohort which may be contributing to impaired quality of life.

## 3.4. Methods

### 3.4.1 Study design and size

The study was an observational study. We aimed to recruit a prospective cohort of 140 to 200 patients discharged from the recruiting centres. We calculated that a total of 200

evaluated patients would produce estimates of the prevalence of important complications following critical illness at 3 months post ICU discharge and have a standard error of 3.5% or less. From previous studies we assumed 80% recruitment and 15% incomplete follow up at 3 months. We estimated we would be able to recruit and assess 200 patients over 12-13 months and that this would result in at least 100 patients completing 6 month follow up.

#### *3.4.1.1 Study Population*

Patients were recruited from the Intensive Care Units of the Royal Infirmary of Edinburgh (RIE) and Western General Hospital (WGH), Edinburgh. The RIE represents an 18 bedded general ICU of a university hospital. It accepts patients undergoing liver, kidney and pancreas transplant. These patients were excluded from the study as they had a chronic pre-morbid condition due to the underlying need for a transplant which would not reflect a general population. The WGH represents an 8 bedded general ICU of a university hospital with a significant caseload from the neurosurgical services located on this site. All patients admitted with a primary head injury diagnosis were excluded due to established evidence that this will be the primary determinant of their outcome following ICU stay.

#### *3.4.1.2 Recruitment*

All patients who required ≥48 hours of ICU (Level 3) care and were discharged alive from the ICUs were considered. These inclusion criteria were chosen because patients

requiring 48 hours of level 3 care comprise about 50% of ICU admissions, but utilise >80% of ICU bed days and develop most complications.

The exclusion criteria were:

1. Patient transferred directly from ICU to another hospital.
2. Patient discharged for terminal care.
3. Follow up not feasible for geographical reasons (outwith Lothian, >1 hour travel from Edinburgh).
4. Primary neurological diagnosis requiring ICU admission (e.g. head injury; in this population residual neurological handicap is the major problem).
5. Patients undergoing organ transplantation.

Screening for eligibility was performed on a daily basis by the study investigators. We accounted for all eligible patients in the study log.

#### *3.4.1.3 Consent and ethical issues at recruitment*

Incapacity for adults is defined in the Adults with Incapacity (Scotland) Act 2000 section 1(6) as: being ' incapable of (a) acting; or (b) making decisions; or (c) communicating decisions; or (d) understanding decisions; or (e) retaining the memory of decisions ... by reason of mental disorder or of inability to communicate because of physical disability'.

Capacity is defined as the ability to comprehend and retain information material to the decision to consent (in this case to take part in the research study). For this observational study the ethical considerations related to the intrusion into patients and relatives time during difficult life events related to the critical illness. It was felt that a patient could

potentially benefit from inclusion in the study as the detection of significant medical problems would be reported back to the patient's GP by the research team.

Approaching the relatives during the patient's critical illness was conducted with tact and discretion but as the majority of our patients remained incapacitated during their ICU stay it was necessary to obtain assent from the relatives for the patient to be considered for the study. The relatives and subsequently the patients themselves were provided with a study information sheet and given an opportunity to discuss the study with the research team and an independent advisor.

As soon as the patient was discharged from level 3 care and competent, informed consent was sought from the individual themselves before continuing in the study. Ability to give informed consent was determined by an abbreviated mental test (AMT) (Hodkinson 1972) score of more than 7. The AMT is one of the commonest used screening tests for cognitive impairment as it only takes two minutes to complete. It is a ten question test with a score of less than seven indicating cognitive impairment and has been verified in a variety of clinical and research areas (Jitapunkul, Pillay et al. 1991) and is recommend as a screening tool for cognitive impairment in all elderly patients admitted to hospital. The research group also acted in the patient's best interest during the study and when there was concern that the patient did not fully understand the nature of consent even with an appropriate AMT score, enrolment was deferred and the patient retested at a later date. Patients who did not regain capacity to give informed consent continued in the study unless the patient's relatives expressed a wish for them not to participate further. The study received approval from the regional ethics committee (ethics number 04/MRE00/59).

Figure 3.1 summarises the timing of assent and consent and the subsequent assessments.

#### *3.4.1.4 Assessing baseline characteristics*

##### *3.4.1.4.1 Baseline assessment at time of discharge from ICU*

At discharge from ICU patient consent (or proxy consent if the patient did not have capacity) was sought to continue in the study. Ability to give informed consent was determined by an AMT score of more than 7. Patients who did not regain capacity to give informed consent continued in the study unless the patient's relatives expressed a wish for them not to participate further. After consent we recorded the following baseline data for the recruited patient: age; sex; pre-illness chronic co-morbidity using the Charlson Co-morbidity Index (Charlson, Pompei et al. 1987; Needham, Scales et al. 2005). We performed a case-note review of ICU records and recorded the following measures from ICU stay: admission diagnostic category (namely surgical, medical or trauma), APACHE II score (a measure of illness severity during the first 24 hours of ICU care), worst organ failure developing during ICU stay for each of respiratory, cardiovascular, renal, coagulation, and liver systems using the Sequential Organ Failure Assessment (SOFAmax), a validated daily measure of organ severity graded 0 to 4 and ICU length of stay.

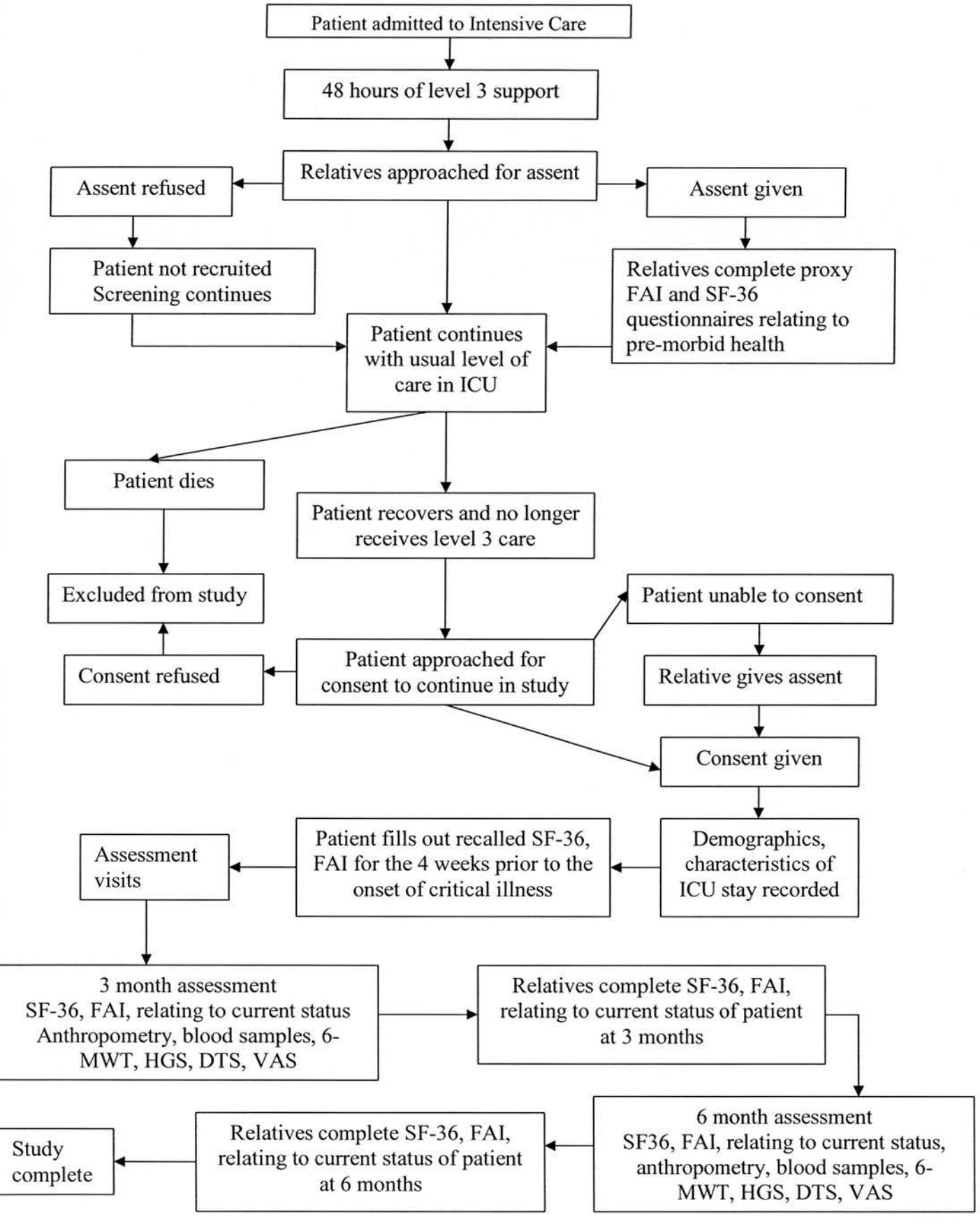



**Figure 3.1 Recruitment and follow up**

Patients were recruited into the study and underwent assessment according to study protocol.
FAI = Frenchay Activity Index; SF-36 = Short form quality of life questionnaire; 6-MWT = 6 minute walk test; HGS = hand grip strength; DTS = Davidson's Trauma Scale; VAS = visual analogue scores

**Table 3.1 Timing of assessments**

| Measure | ICU discharge | 3 month follow up | 6 month follow up |
|---|---|---|---|
| ***Quality of life measure*** | | | |
| SF-36 | Recalled for pre-morbid state | X | X |
| EQ-5D VAS | Recalled for pre-morbid state | X | X |
| Perceived physical function | | | |
| FAI | Recalled for pre-morbid state | X | X |
| ***Actual physical function*** | | | |
| 6 minute walk test (m) | | X | X |
| Hand grip strength (Kg) | | X | X |
| ***Organotopic measure*** | | | |
| Haemoglobin concentration (g/dL) | Last measure recorded whilst in ICU | X | X |
| Creatinine (µmol/L) | Last measure recorded whilst in ICU | X | X |
| Bilirubin (µmol/L) | Last measure recorded whilst in ICU | X | X |
| Albumin (g/L) | Last measure recorded whilst in ICU | X | X |
| ***Anthropometry*** | | | |
| BMI ($Kg/m^2$) | | X | X |
| MUAC (cm) | | | X |
| ***Visual analogue scales and Psychometric assessments*** | | | |
| VAS for pain, fatigue, appetite | | X | X |
| Davidson's Trauma Scale | | X | X |

X indicates that measure was assessed at this time point.
SF-36 = medical outcomes questionnaire; FAI = Frenchay Activity Index; EQ-5D VAS = EuroQol health status thermometer; BMI = body mass index; MUAC = mid upper arm circumference; VAS = visual analogue scale

#### 3.4.1.5 *Initial assessment and follow-up visits*

Figure 3.1 and Table 3.1 summarise the timing and nature of tests at follow up visits. Initial assessments were conducted in hospital following discharge from intensive care and before discharge from hospital. The patient was asked to complete SF-36 and FAI relating to the 4 weeks before the critical illness. The final haemoglobin concentration, serum creatinine, albumin and bilirubin before ICU discharge were also recorded. Follow up visits were conducted at the Clinical Research Facility of the Royal Infirmary of Edinburgh or in the patients' home if this was preferred. To minimise loss to follow up, an appointment was given for follow up prior to discharge from hospital and a further letter sent 1 month prior to the clinic date as a reminder. One week prior to attendance patients were contacted by post to confirm travel arrangements. During these visits the patients underwent a structured visit protocol involving completion of the questionnaires relating to functional activity, quality of life and post traumatic stress disorder, venepuncture and clinical assessment for the simple organotopic measures and subsequently measures of actual physical function with the 6MWT and hand grip dynamometry performed. The protocols for the individual components of the visit are documented below.

##### 3.4.1.5.1 *Recalled assessments for pre-morbid condition and contemporaneous FAI, SF-36 and EQ-5D VAS at 3 and 6 months following hospital discharge*

The assessment was carried out by trained investigators. The patient was first assessed with the AMT and a score of less than 8 caused the test to be deferred until the cause of

the deterioration has been recovered from. Following an appropriate AMT the test was administered in a structured and reproducible way and repeated at 3 and 6 months following hospital discharge. The FAI questionnaire is included in Appendix 1. The EQ-5D VAS, standard scales for pain and fatigue were also completed.

#### *3.4.1.5.2 Patient assessment for the 6MWT*

The American Thoracic Society has issued guidelines for the 6MWT (2003) and these were adhered to during the study. A self powered non-adjustable treadmill was used. Standardized phrases whilst using the test were also used as investigator encouragement can alter the result by up to 30%. This technique has been used in previous ICU studies (Cooper, Ferguson et al. 1999; Herridge, Cheung et al. 2003). The distance walked in 6 minutes was recorded. In patients who were unable to attempt the 6MWT due to symptom severity were classified as 0m distance walked.

#### *3.4.1.5.3 Patient assessment of hand grip strength*

Hand grip strength was measured using a Takei Digital TAK005 hand grip dynamometer in the non-dominant hand 3 times with the best result recorded.

#### *3.4.1.5.4 Patient assessment for PTSD*

Following an appropriate AMT the DTS questionnaire was administered by trained investigators at discharge and the 3 and 6 month follow up visits. The questionnaire is included in Appendix 2.

#### *3.4.1.5.5 Organotopic measures*

Baseline values to assess renal (creatinine), markers of inflammation (CRP) and haematological function (haemoglobin) were determined by review of the last blood results available on the patient prior to discharge from level 3 care. This endpoint was chosen as there was a potential for great variability in time to hospital discharge which could act as a confounding variable should baseline samples be drawn then. Blood sampling was repeated at the three and six month follow up visits. Nutritional status was determined through measurement of body mass index (BMI), mid arm circumference (MUAC) and measurement of hand grip strength.

#### *3.4.1.5.6 Visual Analogue Scores*

The patients were given copies of the EuroQOL 5D thermometer (Appendix 3) and visual analogue charts for appetite (0 = poor appetite, 10 = good appetite), pain (0 = no pain, 10 = severe pain) and fatigue (0= no fatigue 10 = severe fatigue) and asked to mark their current status on the chart.

## 3.5 Analysis

Analysis of the data was as follows:

### 3.5.1 Characteristics of study cohort

Baseline characteristics and characteristics of ICU stay were recorded. All variables were tested for normality. Descriptive statistics include median and inter-quartile range and range unless otherwise stated. Student's t-test was used to compare means of

normally distributed data. Non-parametric rank test (Mann-Whitney U test) was used in non-normally distributed data.

#### *3.5.1.1 Comparison of patients who survived and those who died during follow up*

Details of patients who died during the follow up period were recorded. Patients who were lost to follow up were considered to be still alive. Differences in demographics, characteristics of ICU stay and study parameters at ICU discharge between survivors and non-survivors at recruitment were analysed with Student's t test or Mann-Whitney test as appropriate.

For tests of statistical difference of a variable between time points only complete data sets were included. We acknowledged that this may produce bias within the results and that the data should be interpreted with caution.

### 3.5.2 Quality of life and perceived physical function for study cohort

SF-36 scores and FAI for entire cohort were described at each time point (recalled scores for pre-morbid assessment assessed at ICU discharge and at 3 and 6 months). Change in SF-36 and FAI scores over time for the entire cohort's data sets were also analysed and the effect size of this change calculated. The effect size between these time points were calculated according to Kazis (Kazis, Anderson et al. 1989) using the mean change of a variable divided by its baseline standard deviation (SD). An effect size of $\geq 0.2$, $\geq 0.5$ and $\geq 0.8$ respectively were considered to be small, medium and large (Cohen 1988).

To analyse changes between time-points only complete data sets were analysed. One way ANOVA for repeated measures was used with Bonferroni's post test analysis was used to determine the significance for each time point.

### 3.5.3 Actual physical function

#### *3.5.3.1 6 minute walk test data*

Many patients attending clinics or being visited in their home refused to attempt the test. The reasons for refusal were not always clear. For this reason patients who gave a definitive reason for not attempting the test because they felt their symptoms precluded this were scored as 0 metres walked. Other responses were excluded from the analysis. 6MWT results were recorded and tested for statistical difference between 3 and 6 months with the Mann-Whitney U-test.

#### *3.5.3.2 Hand grip strength*

The raw HGS data was transformed into percentage of normal for age and gender to allow comparison of the group as a whole (Klidjian, Foster et al. 1980; Goode 1985). The data was tested for statistics difference with Student's t-tests.

### 3.5.4 Assessment for post traumatic stress disorder

DTS sores were recorded for the entire cohort attending follow up clinics and the proportion of patients meeting threshold criteria and actual criteria for PTSD recorded.

### 3.5.5 Prevalence of anaemia

For the entire cohort we analysed the prevalence of anaemia at ICU discharge and at each time point for those remaining in the study. The change of haemoglobin over time was analysed for those who had haemoglobin measures at all three time points. We hypothesised that anaemia would contribute significantly to post ICU recovery and therefore determined *a priori* to analyze the cohort according to groups dependent upon haemoglobin concentration. These analyses are included in Chapter 4 of the thesis.

### 3.5.6 Organotopic measures

#### *3.5.6.1 Renal function*

The serum creatinine concentrations were converted to eGFRs according to (Levey, Greene et al. 1993; Burden and Tomson 2005). Median, inter-quartile range and range for entire cohort were recorded. Change in creatinine and eGFR between time points was assessed with Student's t-test.

#### *3.5.6.2 Nutritional status*

##### *3.5.6.2.1 Nutrition by hand grip strength*

Hand grip dynamometry after conversion to percentage of normal for age and gender was used to determine which patients may be at risk for protein malnutrition as suggested by a HGS of less than 85% of normal. The proportions of patients with evidence of malnutrition at each time point are described.

#### *3.5.6.2.2 Serum albumin*

Serum albumin concentrations were recorded and analysed for change between each time point with Student's t-test. The proportion of patients at each time point with low albumin (Albumin < 30 g/L) was also recorded.

#### *3.5.6.2.3 Weight and Body Mass Index*

Weight and BMI (using height and weight as recalled by proxy for pre-morbid state) was recorded and analysed for change with Student's t-test.

#### *3.5.6.2.4 Anthropometry*

Change in MUAC was assessed with Student's t-test between each time-point.

### *3.5.6.3 Markers of inflammation*

C-reactive protein measures were analysed for statistical difference at 3 and 6 months using Student's t-test. An elevated CRP was defined as >10mg/L.

## 3.5.7 Associations between physical components of quality of life and perceived and physical function

### *3.5.7.1 Analysis of correlation between quality of life (PCS of SF-36) and perceived physical function (FAI)*

To answer the research question of whether physical quality of life as measured by the SF-36 questionnaire reflects the activities of daily living as measured by FAI we performed correlation analysis between the two scores at all time points we plotted the

PCS scores against corresponding FAI scores and the strength of the association was determined with Pearson's test for correlation for normally distributed data.

#### *3.5.7.2 Analysis of correlation between quality of life (PCS of SF-36) and actual physical function (6MWT)*

To answer the research question of whether physical quality of life as measured by the SF-36 questionnaire reflects the actual physical function we performed correlation analysis between the PCS score and distance walked at 3 and 6 months. We plotted the PCS scores against corresponding 6MWT distance and the strength of the association was determined with Spearman's test for non-Gaussian distributions.

#### *3.5.7.3 Additional exploratory analysis of the relationship between PCS and FAI*

To answer the question of whether a good physical quality of life is more common in patients with good perceived physical function we performed an additional exploratory analysis for the relationship between PCS and FAI. We compared the proportion of patients who had impaired FAI scores of less than 28 for males and 31 for females in patients who had either a normal (PCS≥50) or abnormal PCS score (PCS<50) with Fisher's Exact Test. The values for FAI were chosen as they are less than a median UK gender specific score for population aged 55-64 years which includes the median age range of our cohort.

#### *3.5.7.4 Additional exploratory analysis of the relationship between PCS and 6MWT*

To answer the question of whether a good physical quality of life is more common in patients with good actual physical function we performed an additional exploratory analysis for the relationship between PCS and 6MWT distance. We compared the proportion of patients who had impaired actual physical function of 200m at 3 months and 400m at 6 months (Herridge, Cheung et al. 2003) in patients who had either a normal (PCS>50) or abnormal PCS score (PCS<50) with Fisher's Exact Test. These distances were chosen as they were less than median values for a large cohort of survivors with ARDS at 3 and 6 months and represented the best cohort of ICU survivors who had their actual physical function measured with 6MWT.

#### *3.5.7.5 Analysis of correlation between magnitude of change in PCS score and magnitude of change in perceived physical function (FAI)*

To answer the question whether the change in PCS score reflected the magnitude of change in FAI score we used correlation analysis. We plotted the change in PCS score from pre-morbid to 3 months and from 3 months to 6 months against corresponding change in FAI scores. The strength of the association was determined with Pearson's test for normally distributed data.

#### *3.5.7.6 Analysis of correlation between magnitude of change in PCS score and magnitude of change in actual physical function (6MWT)*

To answer the question whether the change in PCS score reflected the magnitude of change in 6MWT distance we used correlation analysis. We plotted the change in physical component summary score (PCS) from 3 months to 6 months against the corresponding change 6MWT distances. The strength of the association was determined with Spearman's test for non-Gaussian distributions.

#### *3.5.7.7 Additional exploratory analysis of the relationship magnitude of change in perceived physical function (FAI score) and PCS score*

To answer the question of whether a good physical quality of life is more common in patients with a significant improvement in the ability to perform the activities of daily living as measured by the FAI score we performed an additional exploratory analysis for the relationship between PCS score and the change in FAI score. We compared the proportion of patients who had a significant improvement in FAI score of 4 (Harrington, Taylor et al.) in patients with either a normal (PCS$\geq$50) or abnormal PCS score (PCS<50) with Fisher's Exact Test.

#### *3.5.7.8 Additional exploratory analysis of the relationship between the magnitude of change in actual physical function (6MWTdistance) and PCS score*

To answer the question of whether a good physical quality of life is more common in patients with a significant improvement in distance walked as measured by the 6MWT

we performed an additional exploratory analysis for the relationship between PCS score and the change in 6MWT distance. We compared the proportion of patients who had a significant improvement in 6MWT distance of 200m with either a normal (PCS≥50) or abnormal PCS score (PCS<50) with Fisher's Exact Test. As so few patients increased the distance walked by this amount we also analysed the data for 100m to see if any improvement in actual physical function was more common in patients with good PCS scores

#### *3.5.7.9 Analysis of correlation between magnitude of change in FAI score and magnitude of change in and actual physical function (6MWT) and hand grip strength.*

To answer the question of whether change in perceived physical function is reflected in a change in actual physical function we analysed the change in FAI score from 3 months to 6 months against corresponding change in 6MWT distances and hand grip strength. The strength of the association was determined with Pearson's test for correlation for normally distributed data (HGS) and Spearman's test for non-Gaussian distributions (6MWT).

#### *3.5.7.10 Analysis of relationship between common complications of critical illness and physical components of quality of life*

Tests of correlation between PCS score and serum albumin, serum creatinine, serum CRP concentration and percentage change in hand grip strength were performed with Pearson's test.

#### *3.5.7.11 Analysis of relationship between common complications of critical illness and perceived physical function*

Tests of correlation between FAI score and serum albumin, serum creatinine, serum CRP concentration and percentage change in hand grip strength were performed with Pearson's test.

#### *3.5.7.12 Analysis of relationship between common complications of critical illness and actual physical function*

Tests of correlation between 6MWT distance and serum albumin, serum creatinine, serum CRP concentration and percentage change in hand grip strength were performed with Spearman's test.

### *3.5.8 Analysis of affect of post traumatic stress disorder on physical components of quality of life*

The data for PCS and DTS score at 3 and 6 months was analysed for correlation with Spearman's test. The proportion of patients with threshold and diagnostic symptoms (DTS score of more than 26) and diagnostic symptoms alone (DTS score of more than 39) and a PCS score of less than 50 was calculated and analysed with Fisher's Exact Test at each time point.

### 3.5.9 Statistical software

Data was recorded in a Microsoft Access database and data extracted to Microsoft Excel. All statistical analyses were carried out using GraphPad Prism version 4.

## 3.6 Results

### 3.6.1 Recruitment

There were 1399 admissions to the ICU during the study period. We recruited 68 patients to the study and 35 patients remained in the study for the 6 month duration. The recruitment is summarised in Figure 3.2. Table 3.2a and 3.2b summarise the reasons for exclusion and enrolment performance.

#### *3.6.1.1 Loss to follow up*

Reasons for loss to follow are summarised in Figure 3.3. 68 patients were recruited at ICU discharge. At 3 months follow up, 14 (21%) of this cohort did not attend. 12 were lost to follow up and 2 withdrew consent. At 6 months, a further 10 did not attend. Again, the main reason for non-attendance was loss to follow up with 8 patients not responding to contact and 2 withdrew consent.

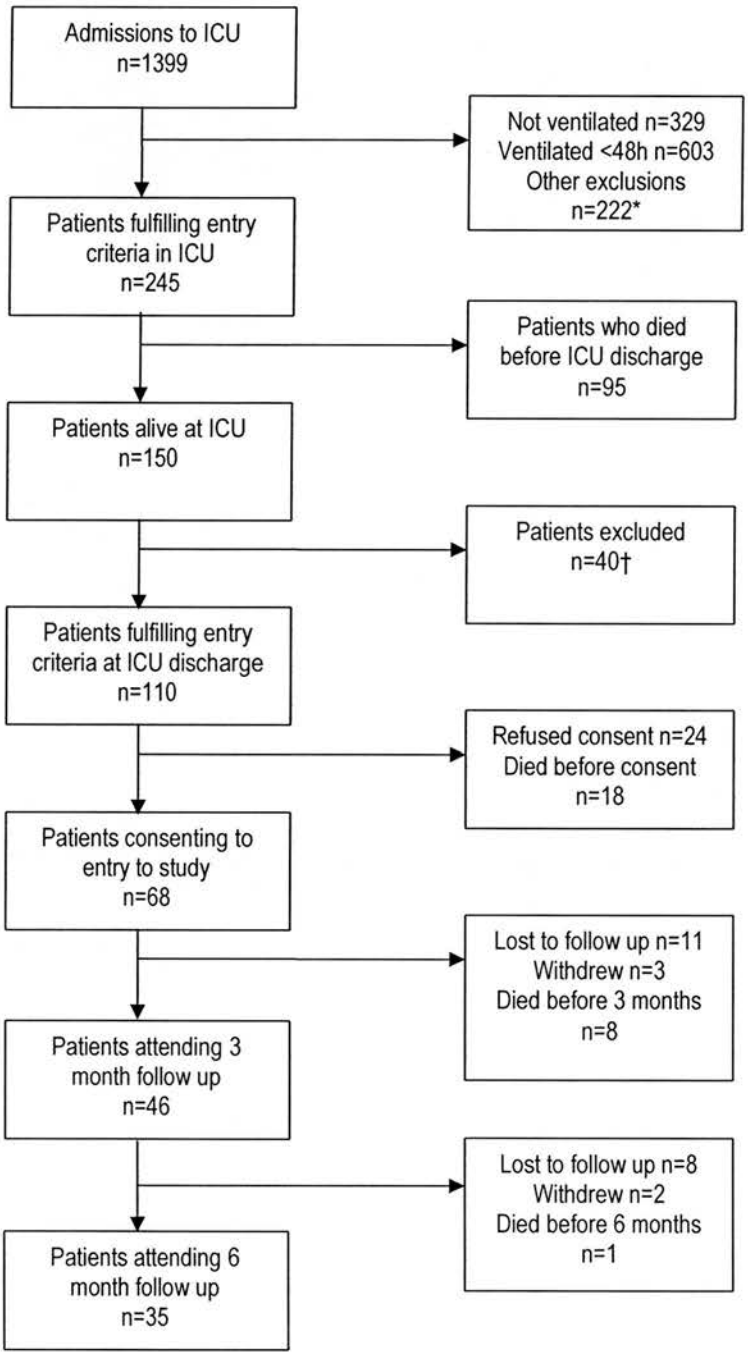
#### *3.6.1.2 Deaths*

8 patients died prior to attending clinic at 3 months. At 6 months one person died prior to attending.

### 3.6.2 Demographic and clinical characteristics of cohort

Demographic, clinical characteristics and characteristics of ICU stay for the study cohort are shown in Table 3.3. There were 51 medical patients (25 male and 26 female) and 17 surgical patients 10 male and 7 female).

**Figure 3.2 Recruitment flow diagram**
Number of patients excluded or discontinuing involvement in study at each stage of study protocol.




* reasons for exclusions can be found in Table 3.2
† reasons for exclusions can be found in Table 3.2

**Table 3.2a Reasons for patient exclusion during study**

| **Reason for exclusion in ICU** | **n (%) Total n=222** |
|---|---|
| Primary diagnosis neurological | 127 (57.2) |
| Geographical | 65 (29.3) |
| Enrolled in other study | 17 (7.7) |
| Transplant | 4 (1.8) |
| Communication issues | 4 (1.8) |
| Age<18 | 3 (1.4) |
| Other | 2 (0.9) |
| **Reason for exclusion following ICU discharge** | **n (%) Total n=40** |
| Transferred other ITU | 17 (42.5) |
| Discharged for palliative care | 14 (35) |
| Communication issues | 4 (10) |
| Transferred other hospital | 3 (7.5) |
| AMT<7 | 2 (5) |

**Table 3.2b Proportion of eligible patients continuing in study**

| **Time point** | **n (%)** |
|---|---|
| ICU discharge | 68/110 (62) |
| 3 months | 46/68 (68) |
| 6 months | 35/68 (51) |

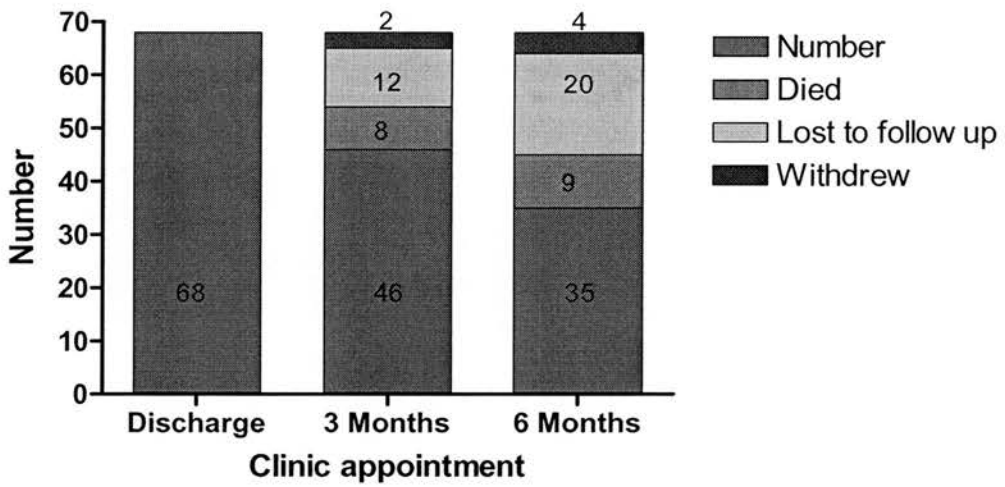



**Figure 3.3 Proportion of patients lost to follow up during study**

Figure detailing the proportion of the 68 patients enrolled in the study at ICU discharge that were lost to follow up at 3 and 6 months.

## Table 3.3 Baseline demographics and admission diagnosis for study population

| Demographic | Data |
|---|---|
| Gender M:F | 35:33 |
| Age (years) | 60.5 (48.8, 70.0; 18-86) |
| APACHE II at admission | 19.0 (15.5, 23.0; 2-36) |
| Worst SOFA max score during ICU stay | 10.5 (7.0, 13.0; 3-18) |
| ICU length of stay (days) | 11.3 (5.5, 21.2; 2.9-67.8) |
| Haemoglobin at ICU admission (g/L) | 93 (85.0, 101.0; 78.0-138.0) |
| Charlson co-morbidity index | 2 |
| **Primary Diagnosis** | **Number of patients** |
| Respiratory | |
| Infective exacerbation of COPD | 1 |
| Pneumonia | 22 |
| Sepsis - lung | 3 |
| Asthma | 1 |
| Other respiratory failure | 5 |
| ARDS | 1 |
| Cardiac | |
| Cardiac failure | 1 |
| Post cardiac arrest | 3 |
| Cardiogenic shock | 1 |
| GI | |
| Perforated viscus | 3 |
| GI tract sepsis | 2 |
| Variceal hemorrhage | 1 |
| Pancreatitis | 4 |
| Bleeding ulcer | 3 |
| Liver failure – paracetamol overdose | 1 |
| Obstruction | 3 |
| Vascular | |
| Ruptured abdominal aortic aneurysm | 2 |
| Trauma | 3 |
| Unexpected complication of surgery | |
| Protracted surgery GI tract | 1 |
| Potential sepsis | 1 |
| Renal | |
| Renal failure – obstructive cause | 1 |
| Endocrine | |
| Diabetic Ketoacidosis | 1 |
| Other Sepsis | |
| No organism identified | 2 |
| Overdose | 1 |

Data expressed as median (1st quartile, 3rd quartile; range); SOFA=Sequential Organ Failure Assessment;COPD = chronic obstructive pulmonary disease; ARDS = Acute Respiratory Distress Syndrome; GI = gastrointestinal

The median age of the population was 60.5. For the 35 males and 33 females the median age, (1st and 3rd quartiles and range) was 54 (46, 66; 18-76) and 62, (55,73; 26-86) respectively. 4 patients required renal replacement therapy during their ICU stay.
The median APACHE II score and median cumulative SOFA score without the neurological component suggest an ICU mortality of more than 40% for our cohort (Vincent, de Mendonca et al. 1998). The median Charlson co-morbidity index was 2 reflecting an expected ICU mortality of 18% and 1 year survival of 86% in those that survived to ICU discharge (Williams, Dobb et al. 2006).

#### *3.6.2.1 Differences in ICU characteristics of survivors and non survivors during follow up*

In those patients who died during follow up 3 were surgical and 6 were medical. None of the patients who died received renal replacement therapy compared with 4 of the patients who did survive to 6 months. Table 3.4 shows the differences in ICU stay and organotopic measures at ICU discharge between survivors and non-survivors. CRP results were only available at 3 and 6 month visits as CRP was not routinely measured in ICU. There was insufficient data to allow comparison of CRP between survivors and non-survivors.

#### *3.6.2.2 Summary of measures for cohort at each time-point*

Table 3.5 summarises the data for the entire cohort at each time-point. The median, inter-quartile range and range for all parameters measured during the study are shown.

**Table 3.4 Comparison of survivors and non-survivors of cohort**

| | Survivors | Non-survivors | p-values |
|---|---|---|---|
| **Age years** | 59.0 (48, 68; 18-86) | 71.5 (58.5, 75; 55-78) | **0.010** |
| **APACHE II score** | 18 (14,22; 2-36) | 20 (18.5, 24.5; 17-26) | 0.135 |
| **ICU length of stay** | 11.5 (7.2,21.8; 2.9-67.8) | 5.2 (3.0, 5.0; 3.0-30.7) | 0.574 |
| **Serum Creatinine** | 61 (50,92; 28-307) | 140 (69, 303; 48-421) | **0.011** |
| **Haemoglobin concentration** | 93.0 (85,104.0; 79-138) | 95.0 (85.5, 100; 78-119) | 0.631 |
| **Albumin** | 25 (21,28; 11-33) | 23 (18.5, 27; 13-28) | 0.251 |
| **Gender M:F** | 29:30 | 6:3 | |

**Table 3.5 Summary table of all data measured during study**

| | Pre-Morbid | 3 months | 6 months |
|---|---|---|---|
| SF-36 PCS | 39.0; 27.0-55.1, 13.5-63.8 | 33.0; 25.9-39.4, 17.9-57.8 | 32.0; 27.1-40.0, 20.1-58.2 |
| SF-36 MCS | 48.5; 35.6-55.9, 9.7-68.2 | 42.8; 34.8-55.7, 14.1-66.0 | 47.0; 35.0-60.1, 14.2-69.0 |
| FAI | 28.0; 21.0-33.0, 9.0-45.0 | 21.0; 13.0-29.0, 0.0-45.0 | 23.0; 15.5-29.0, 3.0-39.0 |
| | **ICU discharge** | **3 months** | **6 months** |
| 6MWT (metres) | | 198; 0-390, 0-669 | 193; 0-476, 0-870 |
| HGS (Newtons) | | 69.0; 56.0-87.5, 24.0-149.0 | 85.0; 60.0-101.0, 32.0-175.0 |
| Hb (g/dL) | 93.0; 85.0-101.0, 78.0-138.0 | 125.0; 114.0-138.0, 79.0-169.0 | 130.0; 120.0-135.0, 95.0-164.0 |
| Creatinine mmol/L | 63.5; 51.0-108.0, 28.0-421.0 | 82.0; 68.0-102.0, 45.0-161.0 | 82.5; 73.5-94.5, 8.0-151.0 |
| Albumin g/L | 25.0; 21.0-28.0, 11.0-33.0 | 40.0; 36.0-42.0, 18.0-46.0 | 41.0; 39.0-42.0, 28.0-47.0 |
| Bilirubin mmol | 6.0; 4-12.5, 2.0-329.0 | 6.0; 4.0-9.5, 3.0-120.0 | 7.0; 6.0-10.0; 4.0-14.0 |
| Weight (Kg) | | 69.5; 58.8-82.6, 45.0-119.6 | 70.5; 63.0-82.0, 47.0-125.0 |
| EQ-5D VAS | | 60; 50-75, 20-100 | 65; 50-80, 10-95 |
| Pain score | | 4; 1-7, 0-10 | 5; 1-7, 0-10 |
| Fatigue score | | 5; 3-7, 0-10 | 5; 3-7, 0-10 |
| Appetite score | | 8; 5-9, 0-10 | 8; 5-10, 0-10 |
| Davidson's Trauma score | | 17.0; 5-41.5, 0.0-136.0 | 7.5; 2.0-34.0, 0.0-130 |

Data shown as median; interquartile range, range.

The descriptive statistics are also shown for clarity with the associated figure for each parameter where appropriate.

### 3.6.3 Quality of life

#### *3.6.3.1 SF-36 scores for entire cohort*

The SF-36 data was found to be normally distributed. Figure 3.4 (median, interquartile range, range) summarises the individual component score data for the study population. Normal data for UK population are included for comparison. The summary component scores for the cohort are shown in Figure 3.5.

#### *3.6.3.2 Change of SF-36 scores with time*

There were 35 patients who had completed SF-36 questionnaires for pre-morbid, 3 and 6 month time points. The mean physical component score was found to change significantly over time ($p<0.018$) with the Bonferroni post test showing the change from pre-morbid quality of life to 3 months was significant ($p<0.05$, mean change 6.1, 95% confidence interval of difference 0.91-11.41). The mental component score did not change significantly, mean change pre-morbid to 3 months of 3.8 (95% confidence interval of difference -1.5 to 9.0) and from 3 to 6 months -4.3 (95% confidence interval of difference-9.5 to 1.0). The effect size for the physical component summary score and mental component summary score was small at all time points in comparing baseline to 3 months (PCS -0.43, MCS -0.3) and 6 months (PCS -0.28, MCS 0.03), and from 3 to 6 months (PCS 0.2, MCS 0.3).

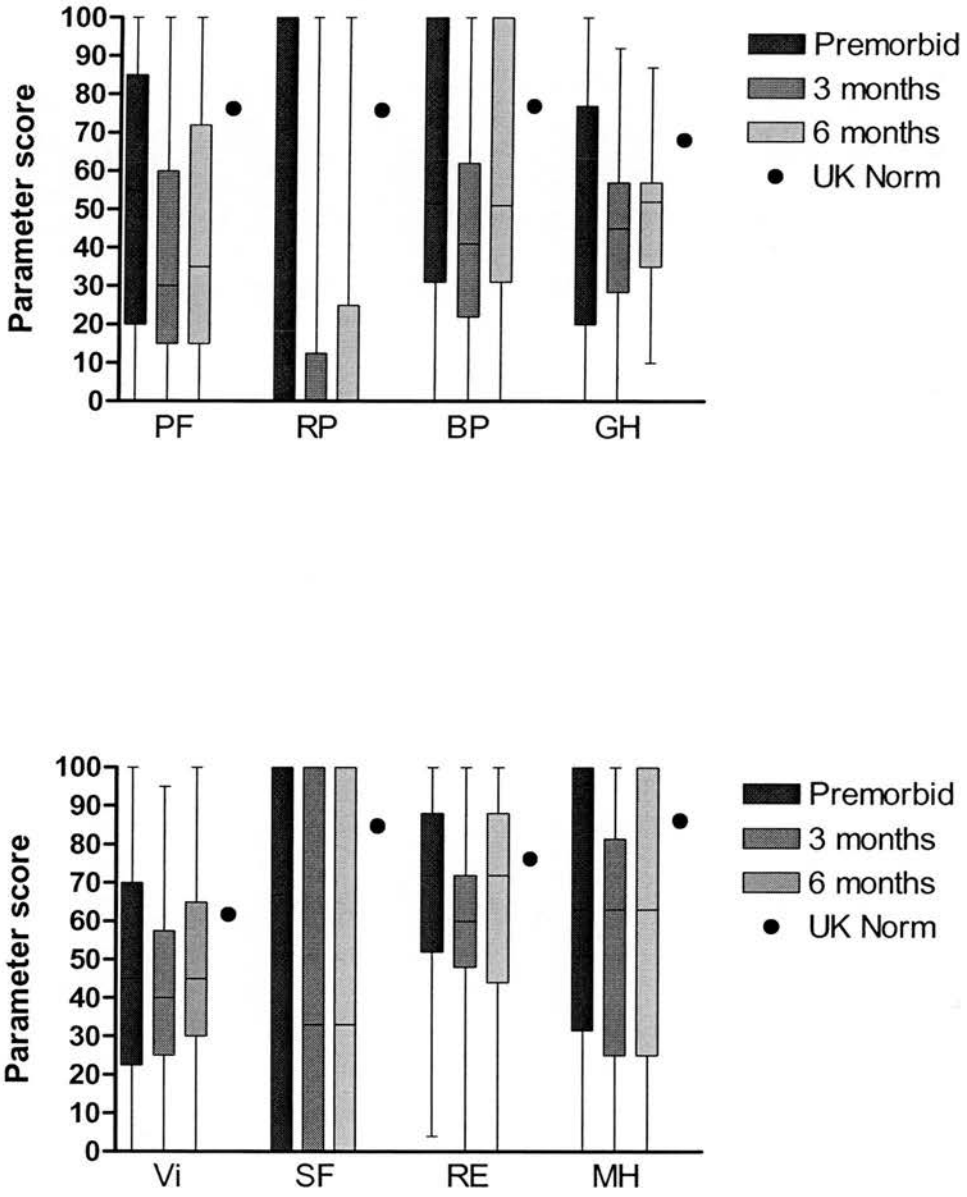



**Figure 3.4 SF-36 individual component scores for cohort**

Top panel shows physical components, bottom panel shows mental components. PF = physical function, RP = role physical, BP = bodily pain, GH = general health, Vi = vitality, SF = social function, RE = role emotional, MH = mental health. UK norm indicates mean value for component of age matched normal UK population.

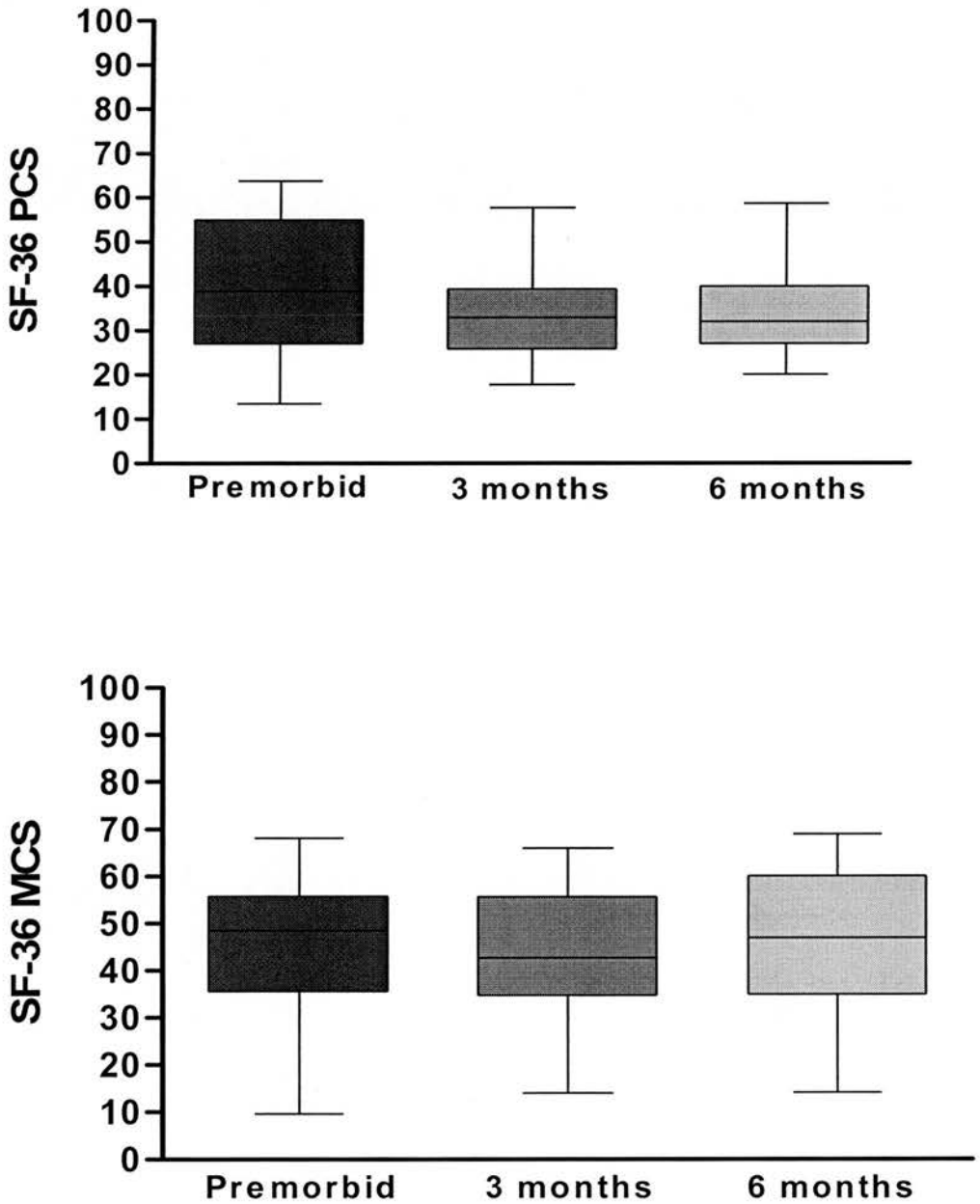



**Figure 3.5 Summary component scores for cohort**

Box and whisker charts showing data for physical component summary score (PCS; upper panel) and mental component summary score (MCS; lower panel) for cohort.

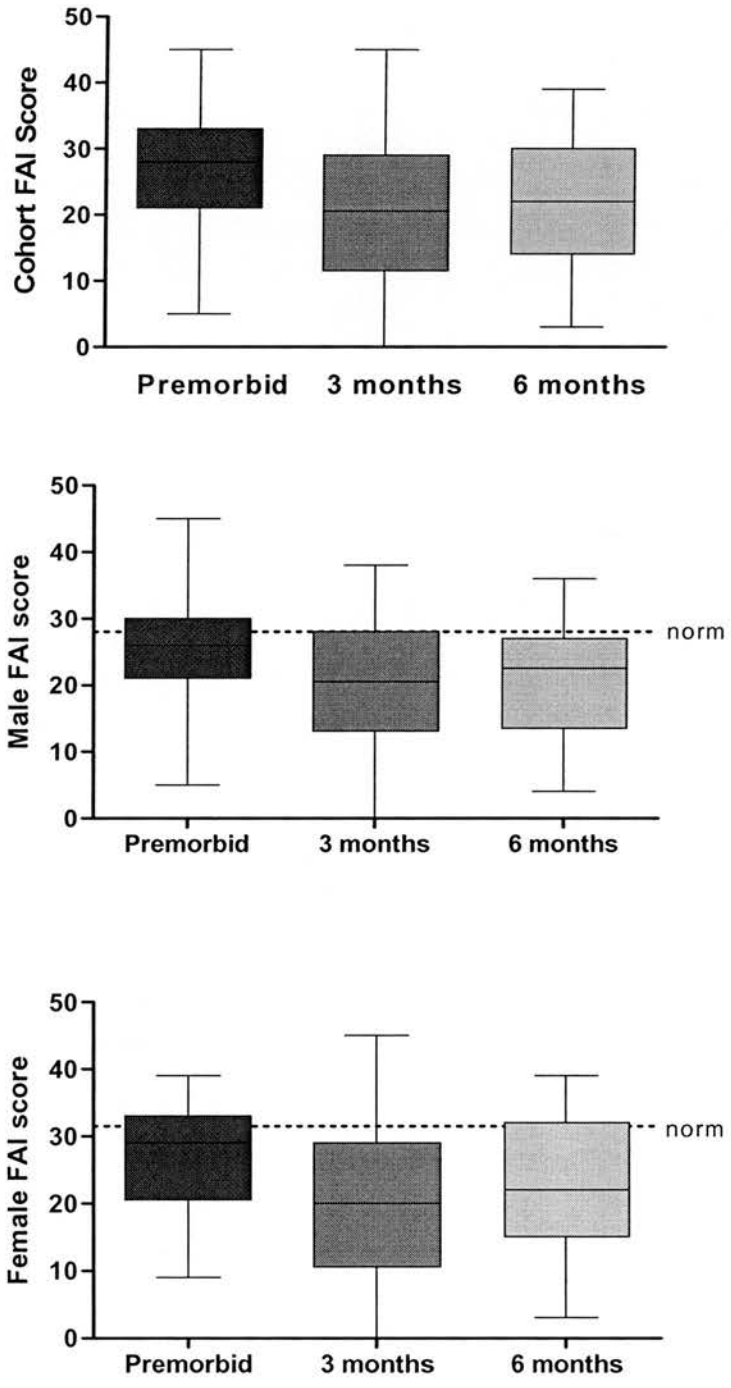



**Figure 3.6 FAI scores for study cohort**

### 3.6.4 Perceived physical function

#### *3.6.4.1 FAI scores for entire cohort*

The FAI data was found to be normally distributed. Figure 3.6 summarises the data for the study population and for the gender groups. Median gender specific values for UK population aged 55-65 years are included (Turnbull, Kersten et al. 2000).

#### *3.6.4.2 Change of FAI scores with time*

There were 25 patients who had completed FAI questionnaires for pre-morbid, 3 and 6 month time points. The mean FAI score was found to change significantly over time ($p<0.05$) with the Bonferroni post test showing the change from pre-morbid to 3 months was significant ($p<0.01$, mean change 7.2, 95% CI of difference 2.1-12.3). The effect size was large for change in FAI pre-morbid to 3 months (0.9), small 3 to 6 months (0.2) and medium pre-morbid to 6 months (0.6) respectively. This suggests that change in FAI score from pre-morbid to 3 months is a useful measure of function as there is a large consistent change throughout our population.

### 3.6.5 Actual physical function

#### *3.6.5.1 Six minute walk test for cohort*

Of the 40 out of 54 patients who were assessed at 3 months performed the test. At 6 months 33 out of 44 patients performed the test. Overall 10 patients did not attempt the test as they were wheelchair bound due to a combination of chronic pain, loss of limbs or unable to take more than a few steps at any time. 2 had unstable angina and were

unwilling to walk. These patients were classed as 0 m walked. 2 patients were too active and busy to attend the clinic and were excluded from analysis!

The 6 MWT data was not normally distributed. For the complete data set (patients who attended both clinics) the difference between the groups was analysed with the Mann-Whitney test. There was no significant difference in the distance walked at 3 compared to 6 months (Figure 3.7). Data for normal population and population with severe heart failure are used for contextual comparison. For patients who attended both clinics 36% (12/33) and 48% (16/33) walked less than 100m and 250m respectively. At 6 months 42% and 48% walked the 100m or 250 m respectively.

#### *3.6.5.2 Hand grip strength for cohort*

The HGS data was found to be normally distributed. Figure 3.8 summarise the data for the cohort. At 3 months only 18% (8/44) of patients had normal HGS. At 6 months 34% (12/35) had normal HGS. For patients with a complete data set the HGS changed significantly ($p=0.04$) for paired results but the effect size was medium (0.4).

### 3.6.6 Organotopic measures

#### *3.6.6.1 Anaemia*

The haemoglobin concentrations for the entire ICU cohort are shown in Figure 3.9. The proportion of patients anaemic at each time point is shown in Table 3.6.

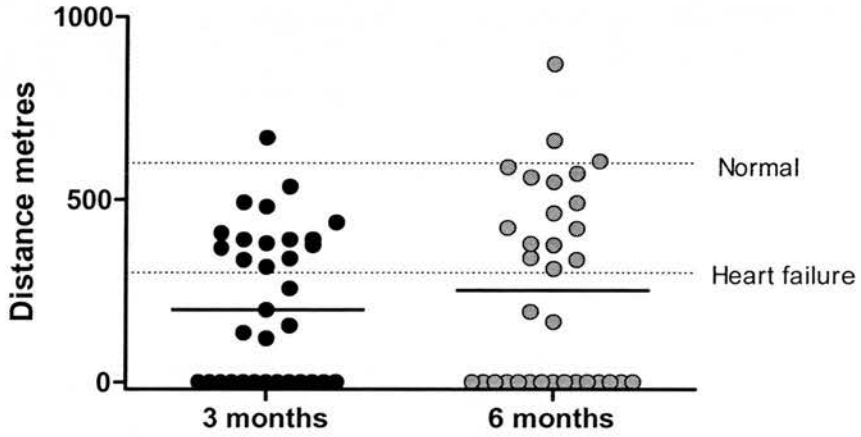



**Figure 3.7 Distance walked in 6 minute walk test**

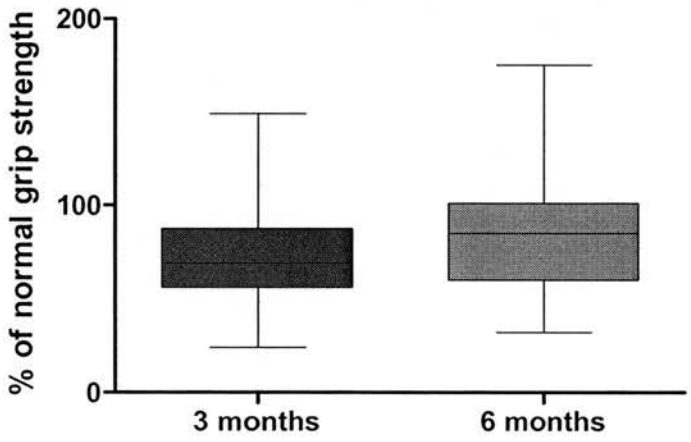



**Figure 3.8 Hand Grip Strength as percentage of normal**

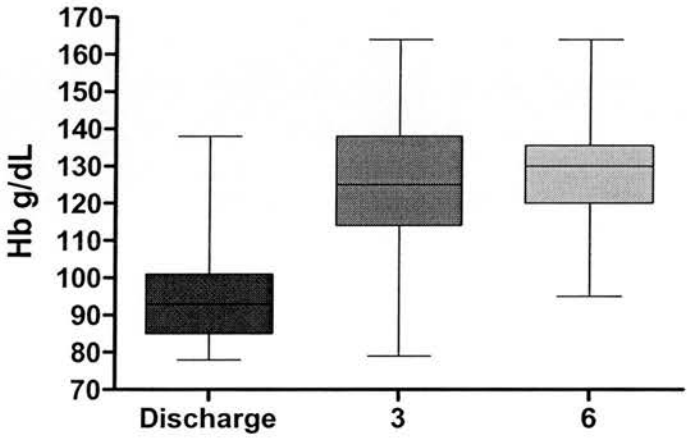



**Figure 3.9 Haemoglobin concentrations for cohort**

**Table 3.6 Proportion of study patients with anaemia at each time point**

| | ICU discharge | 3 month clinic | 6 month clinic |
|---|---|---|---|
| **Number** | 67 | 43 | 28 |
| **Proportion < gender reference range** | 65/68<br>96% | 22/42<br>52% | 9/27<br>33% |
| **Proportion with severe anaemia (Hb <100g/dL)** | 50/68<br>74% | 4/42<br>10% | 1/27<br>4% |

This shows that a third of our cohort was still anaemic at 6 months following ICU discharge.

There were 25 patients who had haemoglobin measures at ICU discharge, 3 and 6 months. The haemoglobin level was found to change significantly over time ($p<0.05$) with the Bonferroni post test showing a significant difference from ICU discharge to 3 months. The analysis for the anaemia subgroups is included in Chapter 4.

#### *3.6.6.2 Nutritional measures*

##### *3.6.6.2.1 Weight*

31 patients had weight measurement at 3 months and 34 at 6 months. 28 patients had weight measured at both time points. The median weights and BMI are shown in Figure 3.10. BMI calculated using height and weight as recalled by proxy for pre-morbid state and at each clinic. 12% (8/67) pre-morbidly, 21% (9/42) at 3 months and 12% (4/34) at 6 months had a BMI <20. The data show that 12.5% of the patients lost weight during recovery.

##### *3.6.6.2.2 Anthropometry*

The values for mid arm circumference are shown in Figure 3.10. The circumferences did not change significantly from 3 to 6 months. Using MUAC as a method of determining BMI thresholds we noted that 16% (7/44) patients would be expected to have BMI <20 $kg/m^2$ at 3 months and 11% (4/35) at 6 months.

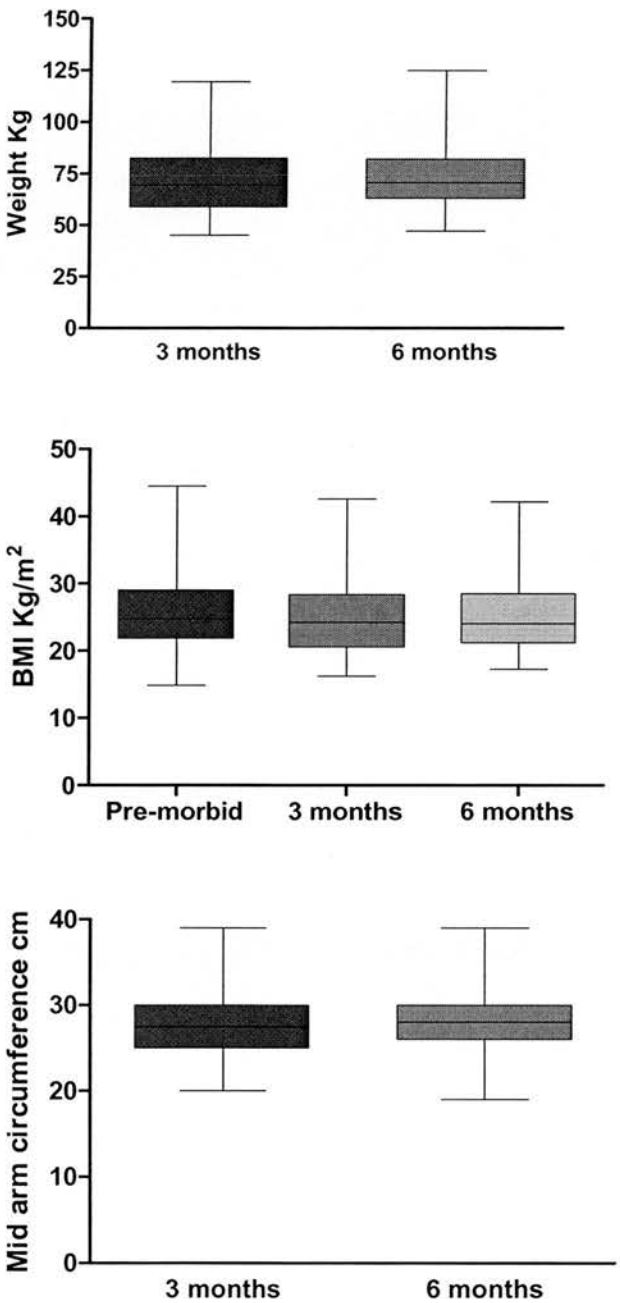



**Figure 3.10 Weight, BMI and mid arm circumference during recovery**

#### *3.6.6.2.3 HGS as measure of nutritional state*

Hand grip strength as a percentage of normal is shown in Table 3.7. These results show that 73% of our cohort at 3 months had values of hand grip strength suggestive of protein malnutrition and 49% at 6 months.

#### *3.6.6.2.4 Albumin*

Albumin concentrations for the study cohort are shown in Figure 3.11. The albumin at ICU discharge was significantly lower than at 3 and 6 months ($p<0.001$).

### *3.6.6.3 Renal Function*

eGFRs for entire cohort were calculated and are shown in Figure 3.12. The number of patients with eGFR below 60 (chronic kidney disease grade 3) was 24%(16/68) at ICU discharge, 23% (10/44) at 3 months and 20% (5/25) at 6 months. There was no statistical difference in the proportion of patients with an eGFR <60 at ICU discharge compared to 3 and 6 months.

### *3.6.6.4 Markers of inflammation*

The CRP data was not normally distributed. The median values ($1^{st}$ and $3^{rd}$ quartiles; range) were 7.5 (5.0, 24.5; 5-290) and 5.0 (5.0, 27.0; 5-232) respectively at 3 and 6 months. There was no difference between the groups either for whole cohort data or for complete data analysis only. 52% (17/33) of patients had an elevated CRP at 3 months and 43% (10/23) at 6 months.

**Table 3.7 Hand grip strength and protein malnutrition**

| | 3 months | 6 months |
|---|---|---|
| **Number of patients** | 44 | 35 |
| **Hand Grip strength, Kg** | 22.0; 14.0-30.0, 6.0-54.0 | 25.0; 19.0-34.0, 13.0-70.0 |
| **Proportion of cohort with abnormally low HGS** | 32/44 (73%) | 17/35 (49%) |

Data expressed as median, inter-quartile range and range. Values for hand grip strength (in Kg) and proportion of cohort with HGS <85% of gender and age adjusted normal values. An HGS < 85% of normal suggests protein malnutrition.

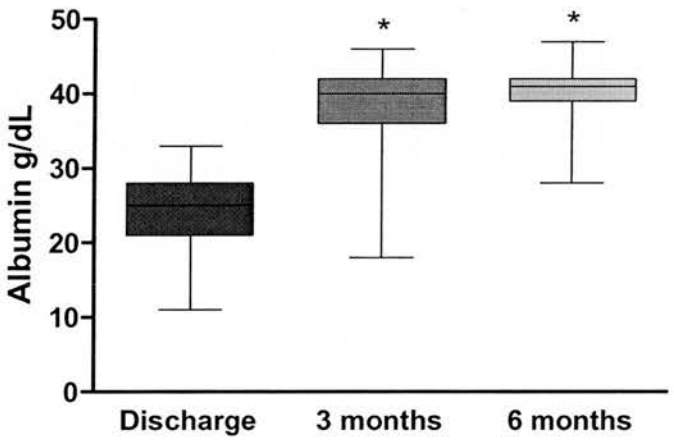



**Figure 3.11 Albumin concentrations for study cohort**
*p<0.001 compared with albumin concentration at ICU discharge

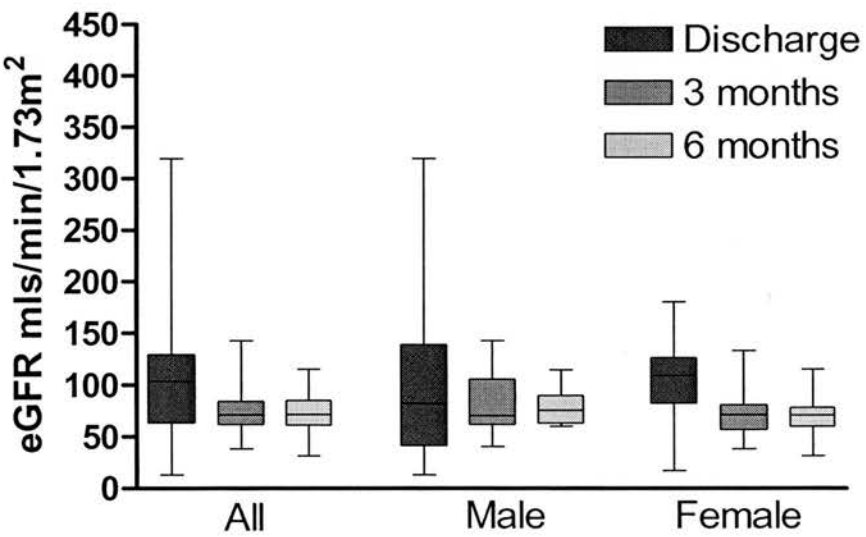



**Figure 3.12 Renal function, expressed as eGFR, for study cohort**

#### *3.6.6.5 Hepatic function*

There was no evidence of an elevated Bilirubin within our population at any time point and further analysis relating to hepatic function and primary outcome measures was therefore not carried out.

### 3.6.7 Post Traumatic Stress Disorder

Results for Davidson's Trauma Score are shown in Figure 3.13. These results show that at 3 months 17/48 (35%) patients had threshold symptoms for PTSD and 14/48 (29%) reached diagnostic criteria for PTSD. At 6 months 9/36 patients (25%) met diagnostic criteria for PTSD.

### 3.6.8 Visual analogue scores

The results are shown in Figure 3.14. The results show that most patients had a good appetite, 50% had moderate pain and 25% severe pain, more than 50% had reported significant fatigue and the majority of patients reported impaired general health.

### 3.6.9 Associations between quality of life and physical function

#### *3.6.9.1 Correlation between PCS score and FAI*

The physical component score (PCS) of the SF-36 quality of life measure correlated with the perceived physical function (FAI) Table 3.8 and Figure 3.15. The results show that there was significant correlation between the physical measures of quality of life and perceived physical function at all time points. The $R^2$ values suggest that the relationship between these variables is not strong.

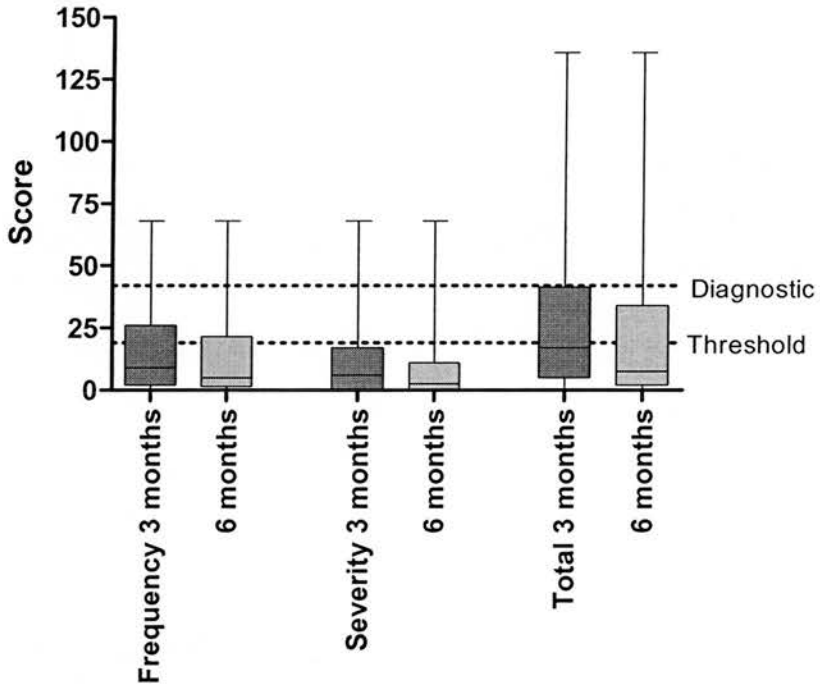



**Figure 3.13 Davidson's Trauma Scores**
Davidson's Trauma Score value for cohorts at 3 and 6 months, shown as frequency score, severity score and total trauma score.

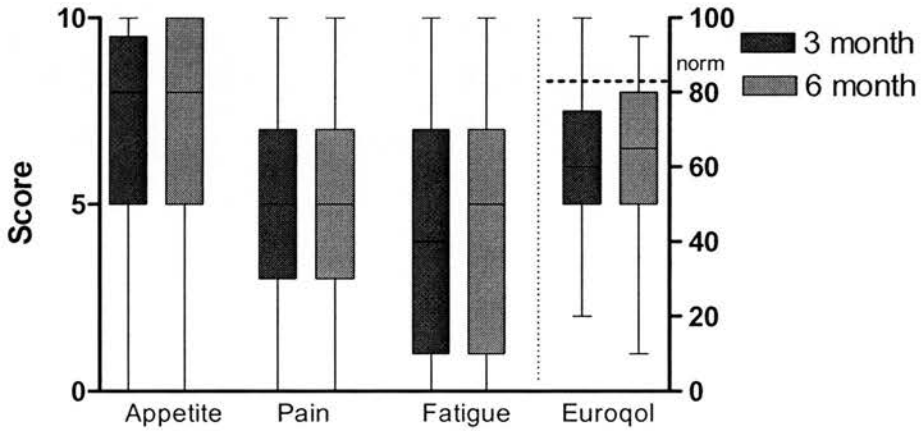
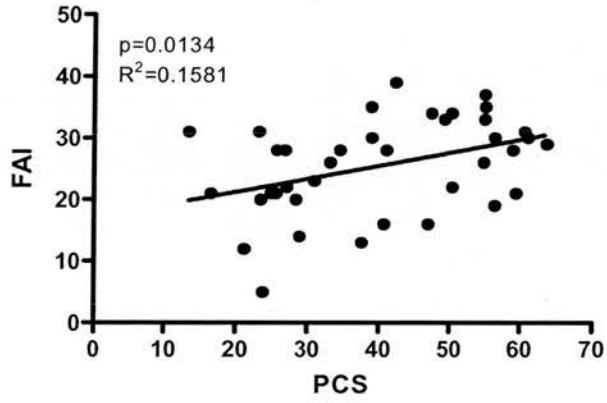


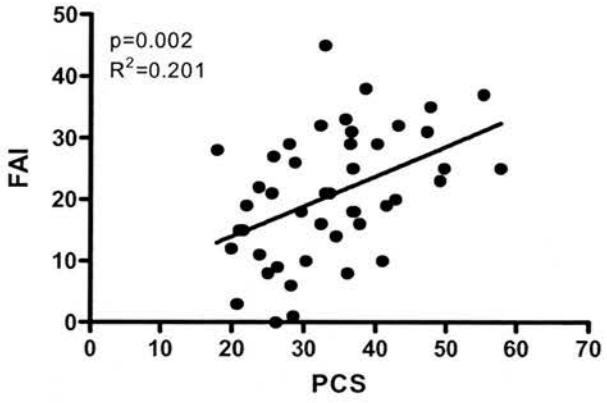

**Figure 3.14 Visual analogue scores**
For appetite the higher score reflects higher appetite levels. For pain and fatigue scores the higher score reflects increased levels of pain and fatigue. The EuroQol scale reflects higher general perceived health the higher the value.

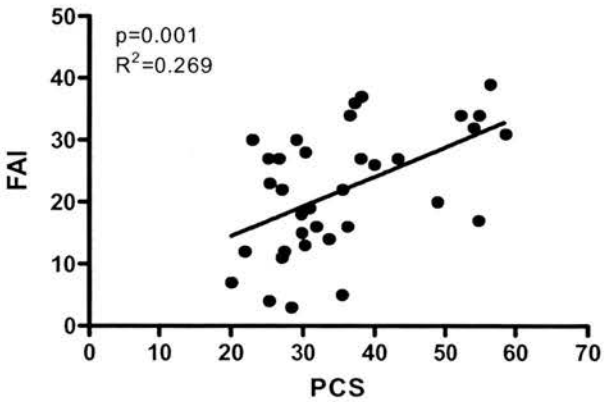
**Table 3.8 Correlation between Physical Component Summary scores (PCS), perceived physical function (FAI) and actual physical function (distance walked in 6MWT)**

| **PCS v FAI** | Number | Pearson r | 95% CI | p-value | $R^2$ |
|---|---|---|---|---|---|
| Premorbid | 38 | 0.398 | 0.089-0.636 | 0.013 | 0.158 |
| 3 months | 45 | 0.449 | 0.179-0.656 | 0.002 | 0.202 |
| 6 months | 35 | 0.518 | 0.224-0.726 | 0.001 | 0.269 |
| **PCS v 6MWT** | Number | Spearman r | 95% CI | p-value | n/a |
| 3 months | 42 | 0.495 | 0.216-0.700 | 0.001 | - |
| 6 months | 33 | 0.437 | 0.010-0.684 | 0.011 | - |

**Figure 3.15 Correlation between quality of life and perceived physical function.**



### 3.6.9.2 Analysis of the proportion of patients with impaired PCS and FAI

The proportion of patients with abnormal PCS scores and FAI scores less than gender and age normal values are shown in Table 3.9a, 3.9b and 3.9c. The proportion of patients with abnormal PCS and FAI were found not to be different for pre-morbid scores and values at 3 months. At 6 months there was a significant difference in the proportions of patients with abnormal PCS and abnormal FAI compared to those who did not ($p=0.025$ males, $p=0.021$ females, $p<0.001$ for entire cohort). These results suggest that a greater proportion of patients with persisting perceived impairment also have an impaired physical quality of life compared to those patients whose perceived physical function had returned to normal.

### 3.6.9.3 Correlation between PCS and 6 minute walk test distance walked

There was significant correlation between PCS and distance walked at 3 and 6 months Table 3.8 and Figure 3.16. The Spearman R value suggests that the strength of this association is poor. Interestingly there were some patients who reported a good physical quality of life but were unwilling to attempt this test.

**Table 3.9a, 3.9b and 3.9c.**
**Proportion of patients with normal and abnormal PCS score, and abnormal and abnormal FAI scores.**

Table 3.9a Premorbid values. No significant difference was noted between the groups

| | FAI score < gender normal value | FAI score ≥ gender normal value |
|---|---|---|
| PCS score <50 | 17 | 9 |
| PCS score ≥50 | 5 | 7 |

Table 3.9b 3 month values. No significant difference was noted between the groups

| | FAI score < gender normal value | FAI score ≥ gender normal value |
|---|---|---|
| PCS score <50 | 34 | 9 |
| PCS score ≥50 | 1 | 1 |

Table 3.9c 6 month values. There was a significant difference between the groups p=0.0004

| | FAI score < gender normal value | FAI score ≥ gender normal value |
|---|---|---|
| PCS score <50 | 26 | 4 |
| PCS score ≥50 | 0 | 5 |

**Table 3.10a and 3.10b.**
**Proportion of patients with normal and abnormal PCS score, and abnormal and abnormal distance walked in 6MWT.**

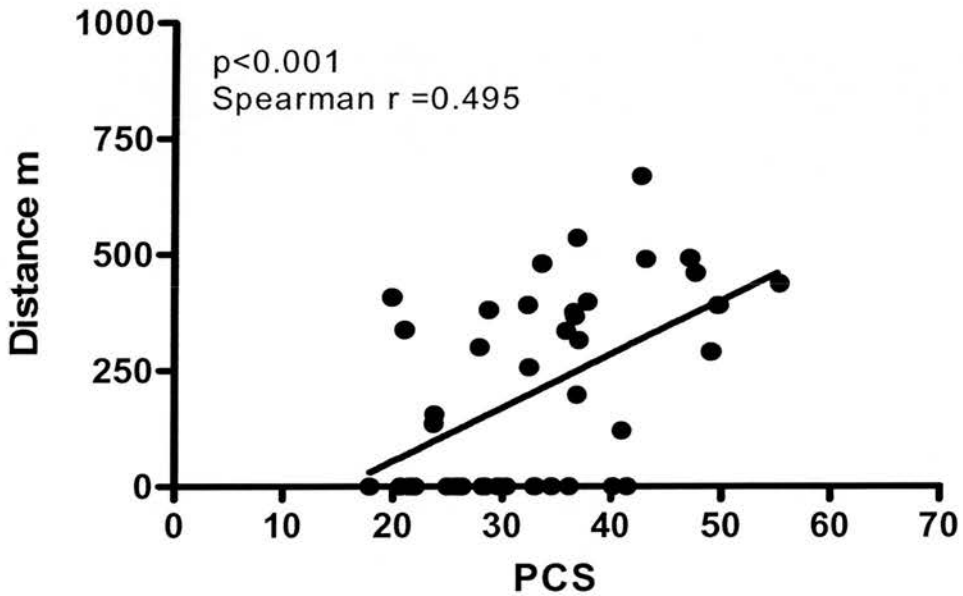
3.10a 3 month values. No significant difference was noted between the groups

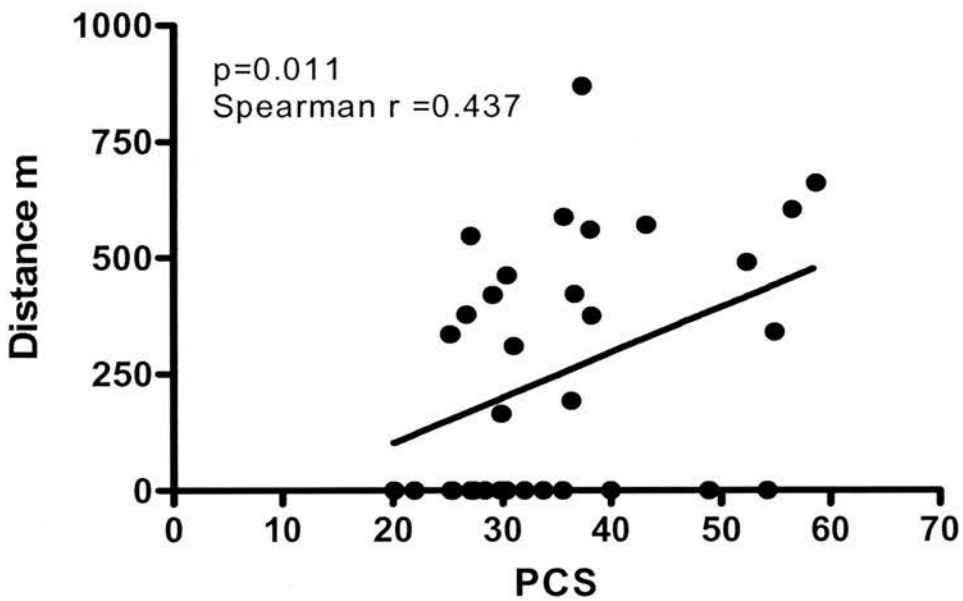
| | 6MWT < 200m | 6MWT ≥ 200m |
|---|---|---|
| PCS score <50 | 23 | 18 |
| PCS score ≥50 | 0 | 1 |

3.10b 6 month values. No significant difference was noted between the groups

| | 6MWT < 400m | 6MWT ≥ 400m |
|---|---|---|
| PCS score <50 | 21 | 8 |
| PCS score ≥50 | 1 | 3 |

**Figure 3.16 Correlation between quality of life and distance walked at 3 and 6 months.**



#### 3.6.9.4 Analysis of the proportion of patients with impaired PCS and reduced distances walked in 6 MWT

The proportions of patients with abnormal PCS score and impaired actual physical function, as determined by a distance less than the mean distance walked by a cohort of ARDS survivors at 3 and 6 months following ICU discharge, is shown in Tables 3.10a and 3.10b. There was no significant difference in the proportion of patients with reduced PCS and a reduced distance walked as part of the 6 minute walk test compared to those who did not.

#### 3.6.9.5 Analysis of the magnitude of change in PCS and change in FAI score

The magnitude of change in PCS and FAI score correlated significantly from premorbid to 3 months ($p=0.038$ and $R^2$ 0.096) and from 3 months to 6 months ($p<0.001$ and $R^2$ 0.376) Figure 3.17. The $R^2$ values suggest that the actual association may not be that strong especially at pre-morbid to 3 months. The scatter of the points suggest that some patients have increased their PCS score with a decline in FAI score. Relatively few patients had a decline in PCS with an improvement in FAI score. This suggests that a change in FAI score (a measure of the ability to perform the activities of daily living) is not well reflected in a change in physical quality of life as measured by the PCS score of the SF-36 questionnaire. The improved correlation at 6 months suggests that the ability to perform the activities of daily living is more important as recovery progresses and therefore may have greater impact on physical quality of life.

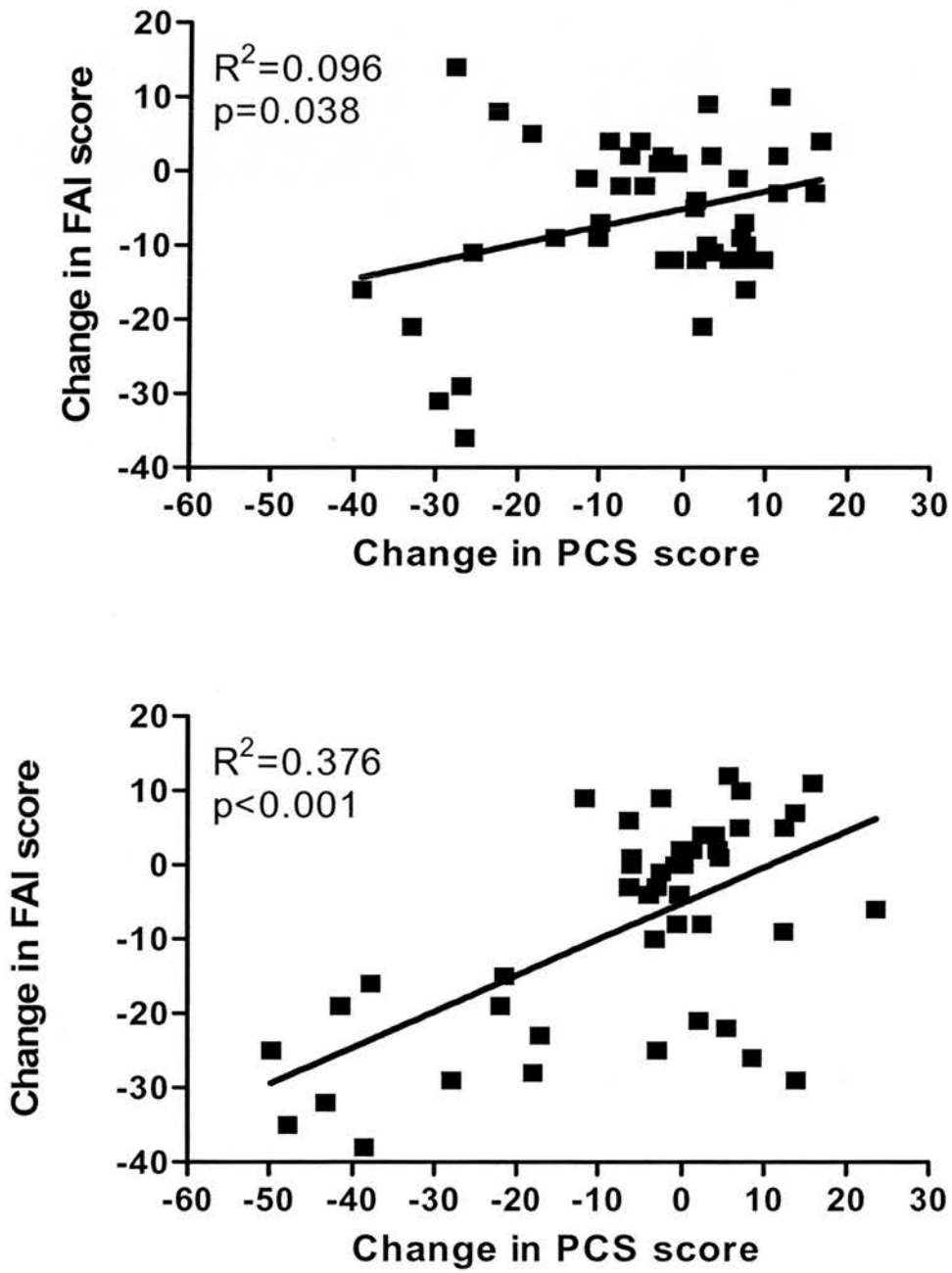



Figure 3.17 Correlation between change in PCS and FAI score from pre-morbid to 3 months (top panel) and from 3 to 6 months (bottom panel)

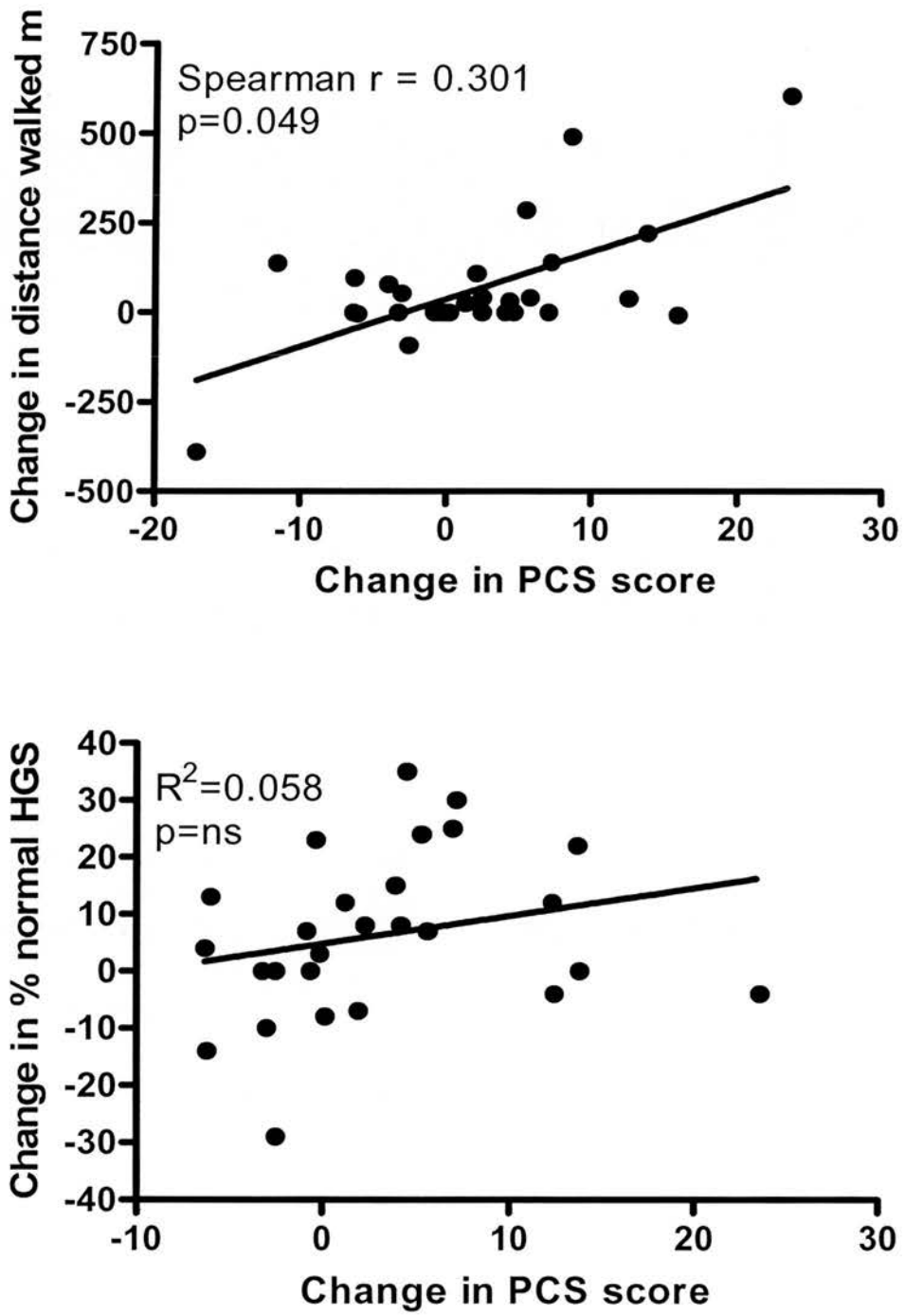



Figure 3.18 Correlation between change in PCS score and actual measures of physical function. Data for 6 minute walk test distance (top panel) and percentage normal hand grip strength (lower panel) shown

### 3.6.9.6 Analysis of the magnitude of change in PCS score and distance walked in 6MWT

The magnitude of change in PCS score and 6MWT distance correlated significantly from 3 to 6 months (p=0.049) Figure 3.18. The Spearman R value suggests that the association may not be that strong. This suggests that the change in 6MWT does not reflect the change in physical quality of life in our cohort. This is likely to be due to the number of patients who did not attempt the test due to co-morbidity such that there is a clustering of patients with 0 distance walked with variable reported PCS scores. The magnitude of change in 6MWT may not therefore be a useful measure of functional activity in a general ICU cohort.

### 3.6.9.7 Analysis of the magnitude of change in PCS score and %HGS

There was no correlation between change in HGS and change in PCS score, which suggests that PCS scores do not reflect the change in actual physical function as measured by % HGS. This may be due to the %HGS being prone to ceiling effects as it is unlikely that patients will continue to improve when they have reached normal values.

### 3.6.9.8 Analysis of the proportion of patients with a significant improvement in FAI score in groups of normal and abnormal PCS score

The proportion of patients with a significant improvement in FAI score was not different between groups of normal and abnormal PCS score Table 3.11a. The analysis was repeated for any improvement in FAI score and again there was no difference in the proportion of patients with any change in FAI score in groups of normal and abnormal

PCS score, Table 3.11b. This suggests that the PCS score does not reflect significant change in FAI score.

#### *3.6.9.9 Analysis of the proportion of patients with a significant improvement in 6MWT distance in groups of normal and abnormal PCS score*

The proportion of patients with an increase in 6MWT distance of 100m was not different between groups of normal or abnormal PCS score Table 3.12a. A further analysis for a change of only 50m was performed and again there was no difference in proportions Table 3.12b. This suggests that the PCS score does not reflect clinically significant changes in actual physical function.

#### *3.6.9.10 Analysis of correlation between PCS, FAI and 6MWT and organotopic measures*

The results from correlation analysis for the primary outcome measures, PCS, FAI and 6 MWT and organtopic measures are shown in Table 3.13, Table 3.14 and Table 3.15 respectively.

##### *3.6.9.10.1 Analysis of serum albumin concentration*

Serum albumin concentration was found to correlate with distance walked at 3 and 6 months. It correlated with PCS at 6 months and almost reached significance at 3 months. It correlated with FAI at 3 months and almost reached significance at 6 months.

**Table 3.11a, 3.11b**
**Proportion of patients with normal and abnormal PCS score, and significant increase in FAI score**

Table 3.11a. Values from 3 to 6 months. For a clinically significant increase in FAI score of 4

| | FAI score not increased by 4 | FAI score increased by 4 |
|---|---|---|
| PCS <50 at 6 months | 18 | 8 |
| PCS ≥50 at 6 months | 2 | 2 |

Table 3.11b. Values from 3 to 6 months for any increase in FAI score

| | FAI score not increased by 4 | FAI score increased by 4 |
|---|---|---|
| PCS <50 | 13 | 13 |
| PCS ≥50 | 2 | 2 |

**Table 3.12a, 3.12b**
**Proportion of patients with normal and abnormal PCS score, and significant increase 6MWT distance**

Table 3.12a. Values from 3 to 6 months for a clinically significant increase in 6MWT of 100m

| | 6MWT not increased by 100m | 6MWT increased by 100m |
|---|---|---|
| PCS <50 | 21 | 5 |
| PCS ≥50 | 2 | 2 |

Table 3.12b. Values from 3 to 6 months for a clinically significant increase in 6MWT of 50m

| | 6MWT not increased by 50m | 6MWT increased by 50m |
|---|---|---|
| PCS <50 | 19 | 7 |
| PCS ≥50 | 1 | 3 |

**Table 3.13 Correlation of PCS with organotopic measures**

| | Number | Pearson r | 95% CI | p-value | $R^2$ |
|---|---|---|---|---|---|
| **Albumin 3** | 42 | 0.303 | -0.001-0.556 | 0.051 | 0.092 |
| **Albumin 6** | 27 | 0.408 | 0.033-0.682 | **0.0345** | 0.167 |
| **CRP 3** | 41 | -0.171 | -0.454-0.145 | 0.286 | 0.029 |
| **CRP 6** | 26 | -0.248 | -0.580-0.154 | 0.222 | 0.062 |
| **% HGS 3** | 42 | 0.496 | 0.226-0.695 | **0.001** | 0.246 |
| **% HGS 6** | 27 | 0.527 | 0.184-0.756 | **0.005** | 0.278 |
| **Creatinine 3** | 42 | 0.242 | -0.066-0.509 | 0.121 | 0.059 |
| **Creatinine 6** | 26 | 0.030 | -0.412-0.362 | 0.885 | 0.001 |

**Table 3.14 Correlation of FAI with organotopic measures**

| | Number | Pearson r | 95% CI | p-value | $R^2$ |
|---|---|---|---|---|---|
| **Albumin 3** | 43 | 0.426 | 0.145-0.644 | **0.004** | 0.182 |
| **Albumin 6** | 21 | 0.429 | -0.003-0.727 | 0.052 | 0.184 |
| **CRP 3** | 42 | -0.126 | -0.414-0.186 | 0.426 | 0.016 |
| **CRP 6** | 20 | -0.517 | -0.781-0.097 | **0.020** | 0.268 |
| **% HGS 3** | 42 | -0.014 | 0.316-0.292 | 0.932 | 0.0001 |
| **% HGS 6** | 21 | 0.440 | 0.009-0.732 | **0.046** | 0.193 |
| **Creatinine 3** | 43 | 0.221 | -0.085-0.489 | 0.155 | 0.049 |
| **Creatinine 6** | 20 | 0.292 | -0.173-0.651 | 0.212 | 0.085 |

**Table 3.15 Correlation of 6MWT with organotopic measures**

| | Number | Spearman r | 95% CI | p-value |
|---|---|---|---|---|
| **Albumin 3** | 42 | 0.402 | 0.103-0.635 | **0.008** |
| **Albumin 6** | 26 | 0.406 | 0.001-0.602 | **0.040** |
| **CRP 3** | 41 | -0.371 | -0.62- -0.06 | **0.017** |
| **CRP 6** | 25 | -0.621 | -0.82- -0.29 | **0.001** |
| **% HGS 3** | 42 | 0.504 | 0.228-0.705 | **0.001** |
| **% HGS 6** | 26 | 0.562 | 0.212-0.785 | **0.003** |
| **Creatinine 3** | 42 | 0.251 | -0.067-0.522 | 0.110 |
| **Creatinine 6** | 25 | -0.145 | -0.520-0.277 | 0.490 |

Overall these results suggest that serum albumin concentration is a useful marker of physical function during recovery from critical illness.

#### *3.6.9.10.2 Analysis of percentage of normal hand grip strength*

Hand grip strength correlated with PCS and distance walked at 3 and 6 months. It also correlated with FAI at 6 months. This suggests that %HGS is also a useful marker of physical function.

#### *3.6.9.10.3 Analysis of serum CRP concentration*

CRP did correlate with distance walked at both 3 and 6 months but only with FAI at 6 months. It did not correlate with quality of life at any time point.

#### *3.6.9.10.4 Analysis of serum creatinine*

There was no correlation between serum creatinine and any primary outcome measure at any time point.

### *3.6.9.11 Analysis of correlation between PCS score and DTS and proportion of patients with threshold and diagnostic symptoms of PTSD at 3 and 6 months*

There was no correlation between PCS and DTS at 3 or 6 months (Spearman r -0.089 and 0.152 respectively). The proportion of patients with threshold and diagnostic symptoms of PTSD and an abnormal PCS was found not to be significantly different at

any time-point. We therefore found no association between psychological morbidity and the physical aspects of quality of life.

## 3.7 Discussion

This prospective observational study evaluated the impact of critical illness on quality of life and physical function. We investigated whether perceptions of physical ability reflected actual physical functioning and whether it was the change in perception of physical ability or the actual level of physical functioning which determined the quality of life during recovery. We also examined the effects of the common complications of critical illness; malnutrition, anaemia, persisting inflammation, hepatic and renal dysfunction, on physical function and physical quality of life.

### 3.7.1 Strengths and Weaknesses

#### *3.7.1.1 Discussion of Recruitment and methodology.*

Recruitment and follow up was difficult in our cohort of patients. Despite keeping an accurate follow up log, contacting patients both by telephone and letter prior to follow up appointments, and even offering to visit patients in their own home, our drop out rate was high. Only 68% and 55% of eligible patients were assessed at 3 months at 6 months respectively. The problems with recruitment were due to the heterogeneity of the ICU population. In our cohort, alcohol and drug problems were common. Follow up studies in such populations are therefore prone to relatively high drop out rates due to the chaotic lifestyles of many of the patients. The face to face nature of the follow up

assessments with the added 'physical assessment' probably added to the drop out rate, as our patients were often already burdened with a significant post ICU morbidity and multiple other medical appointments making demands upon them.

This was compounded further for the measure of actual physical function, the 6MWT which was universally disliked by our patients, even those with good actual physical function. Landmark ICU follow up studies which have used the 6MWT have been in specific groups within the ICU survivor population, such as patients with ARDS (Herridge, Cheung et al. 2003). Though patients with ARDS do represent a well characterised cohort, have the most extensive and intensive follow up to date, and set the standards for other ICU follow up studies, the results cannot be easily generalised. The patients were younger, with much less pre-morbid impairment than our general cohort. In undergoing an intensive period of follow up during recovery it is likely that the ARDS cohort would become actively involved in the follow up process due to the potential for non-specific benefits of participation. Patients could potentially see the research assessments as ways of benchmarking their progress and obtaining reassurance and advice on their recovery as part of an informal ICU follow up / research clinic. This concept of a patient's ownership of their rehabilitation and dual benefit from the research process, although promoted to our cohort, did not appear to help retention within the study. As a consequence, our patients found the 6MWT intrusive and were very anxious that they would be perceived as failures, or that in some way it would cause them to be considered as not being as 'disabled' as they felt they were. The data for actual physical function therefore represents a small number of our cohort and we had to include the data of patients who refused to take the test due to pain or severe co-

morbidity by scoring them as 0 m walked. Despite the small numbers the data does describe a very severe degree of actual physical limitation in our cohort, much more than we expected, and is an interesting result with our patients potentially having worse physical function than patients with end stage heart failure. However, as a result of our experience with the 6MWT we would not recommend it for assessment in general cohorts of ICU survivors.

We did find that hand grip dynamometry was an acceptable, portable test which, as discussed later reflected physical function well in our cohort, and we would aim to continue to utilise this measure in future studies.

Despite these weaknesses our cohort recruitment and demographics were similar to other Scottish ICU follow up studies (Cuthbertson, Scott et al. 2005).

The questionnaires used in this study were easy to administer and helped reduce drop out rates for certain aspects of the study, as patients would often complete the questionnaires by telephone interview or by post even though they were unwilling to attend for formal assessment either in their homes or at the follow up clinic.

#### *3.7.1.2 Discussion of Analyses*

We attempted to use standard statistical measures which had been established in other ICU follow up studies as well as measures which hoped to clarify the clinical significance of such a change, such as calculating effect size and assessing correlation

between factors at each time point. The use of correlation in our analyses did provide statistically significant p-values but often with test specific measures, such as $R^2$, suggesting that the strength of such associations was small. To overcome this problem we sought to establish groups in which clinically significant change had occurred. Despite these problems with recruitment, retention and inherent complexities in describing the population and change within it we believe that this data describes a general cohort of ICU survivors in terms of their physical functioning and provides some indication as to magnitude of change in function and the relative impact change in physical function has on post ICU quality of life.

### 3.7.2 Results

For clarity, the results from the study will be discussed with reference to the research questions posed in the methods section of the study

#### *3.7.2.1 Quality of life*

*3.7.2.1.1 What is the pre-morbid physical quality of life in a cohort of general ICU survivors?*

The results show that our patients have recalled quality of life prior to the development of their critical illness that was impaired, especially in the physical domains.

*3.7.2.1.2 What is the impact of critical illness on physical components of quality of life?*

The physical component summary score (PCS) declined significantly to 3 months post ICU discharge and did not improve at 6 months. The mental summary scores did not

change significantly. As discussed in Section 3.2.1 this is consistent with other larger ICU follow studies and supports the hypothesis that it is the physical rather than psychological morbidity which is contributing to the overall reduction in quality of life.

#### *3.7.2.1.3 What is the time course of recovery of physical components of quality of life?*

There was little evidence of recovery of PCS score up to 6 months following ICU discharge. Only 27% (9/33) had a increase in PCS score of 5 and in fact 45% (15/33) showed no change or a decline in PCS score from 3 to 6 months.

### *3.7.2.2 Perceived physical function*

#### *3.7.2.2.1 What is the pre-morbid perceived physical function in a cohort of general ICU survivors?*

The pre-morbid perceived physical function of the cohort was reduced compared to gender and age matched values for a normal UK population.

#### *3.7.2.1.2 What is the impact of critical illness on perceived physical function*

For the whole population there was a significant decline in FAI score from pre-morbid values to 3 and 6 months and remained reduced at 6 months following ICU discharge. This shows that there is a marked reduction in perceived physical function caused by critical illness.

#### *3.7.2.1.3 What is the time course of recovery of perceived physical function*

There was little evidence of recovery in perceived physical function up to 6 months following ICU discharge. Only 33% (11/33) showed a clinically significant increase of an increase in total score of 4 or more (Harrington, Taylor et al.) from 3 to 6 months.

### *3.7.2.3 Actual physical function*

#### *3.7.2.3.1 What is the 6MWT distance in a general cohort of ICU survivors?*

The actual distances walked by our cohort was much lower than expected with the median values of the cohort being well below that expected of patients with significant heart failure.

#### *3.7.2.3.2 What is the time course of recovery of actual physical function in a general cohort of ICU survivors?*

There was little evidence of improvement in distance walked from 3 to 6 months with only 26% (8/30) showing an increase of more than 50m from 3 to 6 months

### *3.7.2.4 Description of the cohort in terms of PCS, FAI and 6MWT*

These results describe a cohort with a reduced pre-morbid physical quality of life which is further impaired by the critical illness. The impairment although improving, persists to 6 months. The individual mental components and mental summary scores of quality of life were near normal and remained robust throughout the follow up period. The activities of daily living as measured by FAI score were less than the normal population pre-morbidly and again were severely impaired by the event of critical illness. This is

reflected by severe impairment in the measured actual physical function at 3 and 6 months. This suggests that in our cohort there is a significant level of pre-morbid impairment of physical function with a further dramatic impairment as a consequence of critical illness and that ongoing physical morbidity plays a large role in the impaired quality of life seen in survivors of critical illness.

### 3.7.3 Discussion of the results of correlation analysis

#### *3.7.3.1 Does physical quality of life correspond to perceived physical function?*

The PCS score did correlate with FAI score. The $R^2$ value for the results of correlation tests was low. This suggests that PCS may not accurately reflect measures of impaired activities for daily living which are measured by the FAI.

#### *3.7.3.2 Does physical quality of life correspond to actual physical function?*

The PCS score did correlate with the 6MWT distance but the Spearman R values were low. The correlation, though weak, was stronger compared to correlation of the FAI score with PCS. This suggests that actual physical function may be better reflected in the PCS score.

#### *3.7.3.3 Does perceived physical function correspond to actual physical function?*

The FAI score correlated well with the 6 MWT distance suggesting that perceived physical function corresponds to measures of actual physical function. It is interesting to note from the plots that several patients are unable to complete the 6MWT but have moderate to good FAI scores. This suggests that the 6MWT as a measure of physical function may not be sensitive to levels of activity required for the execution of the activities of daily living assessed by the FAI score.

#### *3.7.3.4 Discussion of the result of the analysis of the proportions of patients with impaired perceived and actual physical function in groups of normal and abnormal PCS score*

##### *3.7.3.4.1 Proportions of patients with impaired FAI scores in groups of normal or abnormal PCS score*

The finding that patients with an impaired FAI score were more likely to have impaired PCS scores at 6 months only reinforces that concept that as recovery progresses the importance of being able to carry out the activities of daily living becomes more important and has the potential to affect the physical component and therefore overall quality of life following critical illness

#### *3.7.3.4.2 Proportions of patients with less than expected 6 MWT distances in groups of normal or abnormal PCS score*

There was no difference in the proportion of patients with impaired 6MWT distances in groups of normal and abnormal physical quality of life. This suggests that the actual physical function as measured by 6MWT does not affect physical quality of life.

#### *3.7.3.4.3 Discussion of the results of the additional exploratory analyses*

The finding that impaired perceived physical function (i.e. the ability to carry out activities of daily living) was more common in patients with less than normal PCS score whereas the patients with less than expected 6MWT distances did not more commonly have impaired physical quality of life. This suggests that the ability to carry out the activities of daily living is more important to quality of life than regaining actual physical ability.

### 3.7.4 Discussion of the results of analysis of change in parameters during follow-up

#### *3.7.4.1 Does a change in perceived physical function correspond to a change in PCS score?*

The magnitude of change in PCS scores did correlate with the change in FAI score. The patients with the biggest decline in PCS score were also noted to have an associated large decline in FAI score. For the cohort as a whole the measures at 3 months had a weak association whilst the strength of the association looked much stronger from 3 to 6 months. This suggests that an improving FAI score is reflected in the physical aspects of

quality of life. In conjunction with the finding above 3.7.3.4.1 it reinforces the concept that as recovery progresses, the importance of being able to perform the activities of daily living and therefore its impact on quality of life increases.

#### *3.7.4.2 Does a change in actual physical function correspond to a change in PCS score?*

The magnitude of change in PCS score did correlate with the magnitude of change in 6MWT data but the strength of the association was weak. Examining the plotted data it could be seen that at the extremes of the data patients who had the greatest improvement in distance also had the greatest improvement in quality of life. The converse was also true. In the majority of cases however there was little change in the 6MWT distance despite varying degrees of change in PCS score. This may reflect an inherent insensitivity of the 6 MWT for use in ICU survivors as there are too many potential reasons why a test would not be attempted at a given time which was not related to overall physical activity.

#### *3.7.4.3 Discussion of the results of the analysis of the proportions of patients with significant change in perceived and actual physical function in groups of normal and abnormal PCS score*

*3.7.4.3.1 Proportions of patients with significant increase FAI scores in groups of normal or abnormal PCS score*

There was no difference in the proportions of patients with a significant increase (or in fact with any increase – data not shown) in groups determined by normal or abnormal PCS score.

#### *3.7.4.3.2 Proportions of patients with an increase 6MWT distance of 100m in groups of normal or abnormal PCS score*

There was no difference in the proportions of patients with an increase of 100m (or in fact with any increase – data not shown) in groups determined by normal or abnormal PCS score.

#### *3.7.4.3.3 Discussion of the effects of change in outcome measure on physical quality of life scores*

We were unable to answer this research question adequately due to the severity of impairment and lack of improvement within the cohort. However it would appear that patients with improving FAI scores or improving 6MWT distances were no more likely to have a normal PCS score suggesting that it is not the change in a parameter but the actual level attained which determines the impact on quality of life. This further supports the concept that within our cohort being able to carry out the activities of daily living rather than the actual level of physical function is the important determinant of quality of life.

### *3.7.5 Discussion of the potential for %HGS to be a useful measure of actual physical function*

#### *3.7.5.1 The magnitude of change in PCS score and change in %HGS*

Disappointingly there was no obvious correlation between the magnitude of change in PCS score and HGS. We had found this measure much more acceptable to our population and the preliminary findings that the percentage scores correlated with PCS scores, 6MWT distances and FAI at 6 months. It may therefore be that hand grip strength reflects the degree of physical impairment but improvement of this score (as it is a percentage of normal already) is prone to ceiling effects.

### 3.7.6 Discussion of the effects of common complications of critical illness on physical functioning and quality of life

In considering the common organotopic sequelae of critical illness it can be seen that over 50% of our cohort were anaemic at 3 months and 33% at 6 months supporting the findings of the TRAC study that anaemia is common and persistent complication of critical illness. Haemoglobin and physical quality of life on this initial analysis were found not to be correlated. There was no statistical difference in the proportion of patients with an eGFR <60 at ICU discharge compared to 3 and 6 months.73% of our cohort at 3 months had values of hand grip strength suggestive of protein malnutrition and 49% at 6 months. Albumin levels were impaired at ICU discharge but had recovered to normal levels by 3 months. There was little evidence of ongoing inflammation. Albumin may therefore be a useful measure of global recovery following critical illness. Certainly an improving serum albumin concentration is a good indicator of the potential

to survive critical illness (Blunt, Nicholson et al. 1998) and to have the physical reserve to wean from ventilation (Sapijaszko, Brant et al. 1996).

Serum albumin concentration and % HGS both seem to reflect actual and perceived physical function as well as physical quality of life and would appear to be useful markers of physical function status in survivors of critical illness.

### 3.7.7 The effects of PTSD on physical quality of life

Our results show that although there is a significant prevalence of psychological morbidity it has no influence on physical or indeed overall quality of life in our cohort. At 3 months 17/48 (35%) patients had threshold symptoms for PTSD and 14/48 (29%) reached diagnostic criteria for PTSD and at 6 months 9/36 patients (25%) met diagnostic criteria for PTSD which shows that there is a significant burden of psychological morbidity which may either be poorly assessed by the SF-36 measure of quality of life or in this relatively short follow up time frame is masked by the relief of having survived the critical illness.

The findings of a major UK ICU follow up study (The Practical Study) (Cuthbertson, Rattray et al. 2007; Cuthbertson, Rattray et al. 2009) have found that ICU follow up clinics and measures focused on psychological morbidity have little effect on quality of life after critical illness. It may be that focusing on physical rehabilitation may make the biggest impact on quality of life following critical illness but the significant psychological burden present within the population still needs to be addressed.

## 3.8 Conclusions

Physical aspects of quality of life are impaired before the development of critical illness but are significantly worse after critical illness and have not recovered by 6 months after ICU discharge. There is impairment in both subjective physical function and actual physical function following critical illness and these measures correlate with the physical summary score of the SF-36 quality of life measure suggesting that it is physical morbidity rather than psychological morbidity contributing to the impaired quality of life as psychological measures of quality of life are not impaired during recovery. However the strength of this association may not be strong. The change in perception of physical function especially at 6 months appears to be reflected in quality of life scores. The association between actual physical function is less strong but this may be due to the small numbers and inclusion of patients who did not attempt the test for valid reasons as 0 distance walked on both occasions. This may be a reflection of the severity of impairment of actual physical function in our cohort or due to the insensitivity of the 6MWT in our cohort.

If FAI is considered a measure of the ability to execute the activities of daily living then it would appear that recovery of these basic measures is the most important determinant of quality of life in survivors of critical illness.

Analysis of the organotopic measures show that serum albumin concentration and hand grip strength are useful markers of physical function and should be included into future

studies. There is significant and persisting anaemia and there are some measures suggesting malnutrition up to 6 months after ICU discharge. However there is little evidence of ongoing actual organ failure.

These findings suggest that the greatest area for potential impact on improving quality of life following critical illness is to focus upon physical rehabilitation. Such studies should consider using alternative measures of quality of life as the SF-36 score as it may not reflect changes within the activities of daily living that are important determinants of physical function quality of life. The FAI score may represent an alternative to the SF-36 score as it is a linear scale within each domain and was responsive in a general cohort of ICU survivors. It was also quicker to administer than the SF-36.

The 6 MWT is not an ideal measure of actual physical function and the use of hand grip dynamometry should be considered as an alternative. Other measures such as 'activity meter' could become the gold standard for determining actual physical function in the future.

The most striking finding of our research was the magnitude of physical impairment and highlights the need for rehabilitation strategies to be focused upon this group of patients.

# Chapter 4

# Anaemia, Quality of Life and Physical Function

## 4.1 Introduction

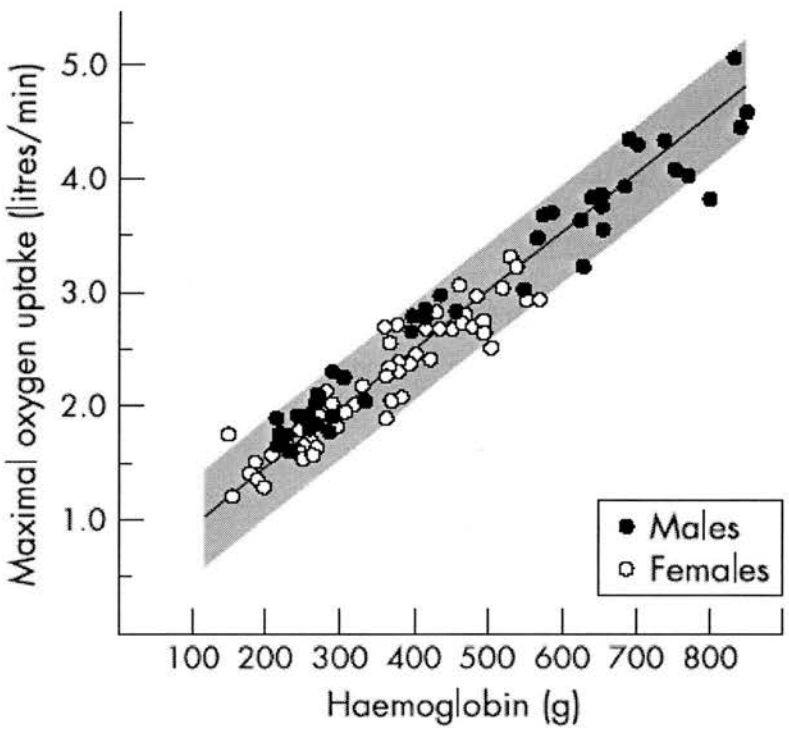
As haemoglobin concentration is one of the prime determinants of oxygen carriage in the blood it is reasonable to expect that impairment of physical function would occur in the presence of abnormally low haemoglobin levels. Certainly looking at athletes, especially in cycling and endurance sports, high haemoglobin level is perceived as desirable. Thus increasing haemoglobin levels either by training, especially at altitude, or by other artificial means such as erythropoietin use ('blood doping') or transfusion ('blood boosting') are sought as a means of improving physical performance. The scientific basis for this has been established (Figure 4.1) (Astrand 1953; Joyner 2003).

### 4.1.1 The effects of haemoglobin on physical performance

Maximal oxygen consumption, $VO_2$ max, is the maximum capacity of an individual's body to transport and utilize oxygen during incremental exercise and reflects the physical fitness of an individual. In athletes an acute reduction of circulating haemoglobin concentration even when blood volume is maintained results in a lower$VO_2$ max and a reduced endurance performance due to the reduction in the oxygen carrying capacity of the blood. Conversely, an increase in haemoglobin concentration is associated with enhanced $VO_2$ max and endurance capacity that is proportional to the increase in oxygen capacity of the blood. The observed effects on endurance capacity seem more pronounced than the effect on $VO_2$ max (Gledhill, Warburton et al. 1999). Thus the reinfusion of blood, increasing haemoglobin levels above an individual's normal value increases $VO_2$ max and enhances physical performance.

**Figure 4.1 Relationship between $VO_2$ max and haemoglobin concentration**

Classic data showing the relationship between total body haemoglobin and $V0_2$ max for 94 subjects aged 7 – 30 years. *Adapted from Joyner (Joyner 2003), illustrating work by Astrand (Astrand 1953).*



During sub maximal exercise the reinfusion of blood to produce supra-physiological haemoglobin levels reduces heart rate and blood lactate levels suggesting improved oxygen delivery and tissue perfusion (Ekblom 2000). The use of erythropoietin to increase haemoglobin has been shown to increase$VO_2$ max and physical performance in athletes (Joyner 2003). In non-elite athletes these effects may be more pronounced as the elite are looking for a tiny competitive edge in an almost optimal physiological machine. In us, less than perfect mortals, the ability to increase $VO_2$ max produces relatively more effect.

### 4.1.2 Anaemia in illness

What do we know about the effects of haemoglobin concentration in poor health? Because anaemia is a common complication of illness, and is potentially treatable, there is a large body of work investigating the consequences of anaemia in different medical conditions. These conditions can be broadly considered as:

1. normal individuals developing a transient anaemia secondary to a reversible cause
2. individuals who develop anaemia secondary to a chronic medical condition

Another population group in which anaemia is common and highly relevant to survivors of critical illness (due to the prevalence of co-morbidity) is the elderly.

#### *4.1.2.1 'Transient anaemia'*

##### *4.1.2.1.1 Anaemia associated with the peri-operative period*

Most studies investigating peri-operative physical function and anaemia have come from trials evaluating the use of erythropoietin in the peri-operative period. Generally the results have shown that erythropoietin affords a measurable improvement in fatigue, exercise capacity, muscle strength and the activities of daily living (Carson, Terrin et al. 2003). It was suggested that improved haemoglobin levels in the severely anaemic patients facilitated participation in rehabilitation programmes and led to greater functional independence. The effects were most pronounced in studies investigating the treatment of severe anaemia (haemoglobin levels less than 100 g/L and even 80 g/L) and it was suggested that 'the rule of diminishing returns' applied in treating haemoglobin levels that approached normal such that treating mild anaemia (below gender reference range) or attempting to achieve high normal haemoglobin concentration produced relatively little observed benefit.

##### *4.1.2.1.2 Post partum anaemia*

In the early post partum period women are generally anaemic. 43% of non-pregnant women in developing countries and 12% in industrialized countries are anaemic during pregnancy, rising to 56% and 18% respectively by the third trimester. In a study comparing vaginal delivery against elective and emergency caesarean section it was found that haemoglobin concentration correlated with the physical aspects of quality of life within the first week post partum. Patients who had a vaginal delivery were less anaemic and had better actual physical function than the caesarean cohorts but the

difference in quality of life scores had resolved by 1 week post partum (Jansen, Duvekot et al. 2007). This is typically when haemoglobin levels return to the non-pregnant range (Milman 2006). In patients who remain anaemic, the anaemia is associated with higher levels of fatigue until the anaemia resolves (Lee and Zaffke 1999).

#### *4.1.2.1.3 Iron deficiency anaemia*

In 'normal' otherwise healthy patients with iron deficiency anaemia in Japan it was found that patients with iron deficiency anaemia had reduced quality of life compared to the normal population especially in the physical domains of quality of life. Treating the anaemia with iron supplementation restored the quality of life of these individuals to the same or better than the normal population. This effect was most pronounced in women of childbearing age with no co-morbidity, which would suggest that it was the anaemia and the impaired physical performance which was most affecting quality of life.(Ando, Morita et al. 2006). Generally, in populations of low co-morbidity, anaemia is associated with decreased physical function and decreased quality of life. Resolution of the anaemia is associated with improved quality of life.

### 4.1.2.2 Anaemia secondary to chronic conditions

#### *4.1.2.2.1 Anaemia and renal disease*

There has been a great deal of research into anaemia associated with renal failure. In patients with chronic severe kidney disease but not requiring dialysis, health related quality of life is impaired compared to the normal population, but is better than those patients on dialysis. Anaemia was ubiquitous in the non-dialysis dependent patients and

treatment of the anaemia improves quality of life especially in the physical function domains (Alexander, Kewalramani et al. 2007). In patients on dialysis it was also found that anaemia was associated with a poor quality of life and treatment of the anaemia improved quality of life in multiple domains.

The treatment of anaemia in renal failure is a quality of care indicator and the Renal Association consider treatment of anaemia to have a profound influence on morbidity and mortality in chronic renal failure such that standards for treatment have been set for haemoglobin levels to be more than 100 g/L. In the US similar guidelines recommend levels more than 110 g/L. The anaemia of chronic kidney disease results in fatigue, reduced exercise capacity, impaired cognition and reduced quality of life and exacerbates existing co-morbidities and increases the risk of death and its treatment is considered of paramount importance (Locatelli, Covic et al. 2009).

#### *4.1.2.2.2 Anaemia and cancer*

Anaemia is very common in cancer patients and is dependent upon the type and stage of the tumour and of the associated treatments (e.g. chemotherapy) received. The clinical effects of anaemia often overlap with tumour related symptoms but the overall symptom burden has been shown to be related to haemoglobin level. Anaemia is associated with impaired functional capacity and quality of life in cancer patients and treatment of the anaemia improves quality of life and functional ability (Bokemeyer, Aapro et al. 2007; Pelegri 2007). A meta-analysis of 5 randomised controlled clinic trials of darbepoietin alfa in a variety of tumours (solid tumour, lung cancer, non-myeloid haematological

malignancy and lymphoproliferative malignancy) showed that a response in haemoglobin levels to darbepoietin alfa treatment was associated with a meaningful clinical improvement in fatigue which in turn was associated with improved physical function (Cella, Kallich et al. 2004).

#### *4.1.2.2.3 Chronic Obstructive Pulmonary Disease*

Anaemia is common in patients with COPD. Studies estimate a prevalence of significant anaemia between 36% to 48 % (Stanbrook 2003). There was also a correlation between the severity of anaemia and the severity of COPD (Park 2003). In patients with COPD, anaemic patients have lower scores in the physical function domains of the SF-36 score than the non-anaemic patients. It is also interesting to note that the control group without COPD who were also anaemic also had a reduced physical component scores on assessment. Further analysis of the cohort in the Park *et al* study showed that there was an association between anaemia and the physical function components of quality of life. Other studies suggest it may be that there was a greater degree of co-morbidity in patients who were anaemic and had moderate to severe COPD and that it was the co-morbidities that were contributing to this observed reduction in quality of life (Krishnan, Grant et al. 2006).

#### *4.1.2.2.4 Anaemia in cardiac failure*

At least 20% of patients with cardiac failure have anaemia and it is an independent marker for increased mortality. Anaemia is also more prevalent in those patients with advanced age and more severe limitations of functional capacity (Tang and Katz 2008).

The study by Silverberg *et al* investigating the effects of erythropoietin in patients with heart failure was one of the most important papers for bringing this problem of anaemia to light. They found a prevalence of 55% for significant anaemia and treatment of this anaemia reduced the severity grade of the heart failure (i.e. improved physical function) and reduced hospitalizations (Silverberg, Wexler et al. 2000). Since then there have been many studies investigating the effects of anaemia in heart failure which have consistently shown an association between anaemia, poor functional status and higher risk of hospitalisation and death (Murphy and McMurray 2008; Tang and Katz 2008).

#### *4.1.2.2.5 Anaemia and diseases associated with chronic inflammation*

Patients with rheumatoid arthritis are commonly anaemic with a prevalence of 33-60%. Resolution of anaemia improves symptoms and quality of life in these patients.
A third of patients with inflammatory bowel disease have recurrent anaemia and it is associated with a chronic fatigue state which has significant impact upon physical function and quality of life. The majority of patients with inflammatory bowel disease are younger than most chronic illness groups and the expectations of health in this patient group are higher. Again, treating anaemia has been shown to improve physical function and quality of life (Gasche, Lomer et al. 2004; Wells, Lewis et al. 2006). In patients with liver disease due to hepatitis C virus and receiving haemodialysis it has been noted that HRQL was not associated with the severity of liver disease but was associated with anaemia (Afsar, Ozdemir et al. 2009).

#### *4.1.2.3 Anaemia in the elderly*

Anaemia is common in the elderly (~10% of individuals rising to 20% in those over 85 years) and is linked to an increase in morbidity and mortality. It is an independent variable associated with poor outcomes such as poor physical function and quality of life (Gabrilove 2005). The prevalence of mobility problems increases as haemoglobin levels fall (Penninx, Guralnik et al. 2003) and may be due to the reduced muscle strength in anaemic elderly patients (Penninx, Pahor et al. 2004); additionally, anaemia was consistently associated with significant impairments of the activities of daily living. The functional decline seen in anaemic elderly patients has been found to be associated with significant impairments in multiple domains of quality of life measures, especially in the physical domains (Thein, Ershler et al. 2009).

### 4.1.3 Rationale for the investigation of anaemia in critical illness

The consistent theme from studies of anaemia in other patient groups is that anaemia is common, has profound effects on physical function, quality of life, morbidity and mortality, and is potentially treatable with improvements in all of these domains. A recent panel of experts produced a series of recommendations aimed at treating anaemia with a view to restoring physical function and quality of life in chronic medical conditions which highlights the importance of anaemia treatment (Cavill, Auerbach et al. 2006). There have been few studies into the effects of anaemia during rehabilitation from critical illness and we therefore believed that the further analysis of the anaemic patients in our cohort could provide useful information to guide the development of further focused studies into anaemia and potential treatments in this group.

## 4.2 Materials and Methods

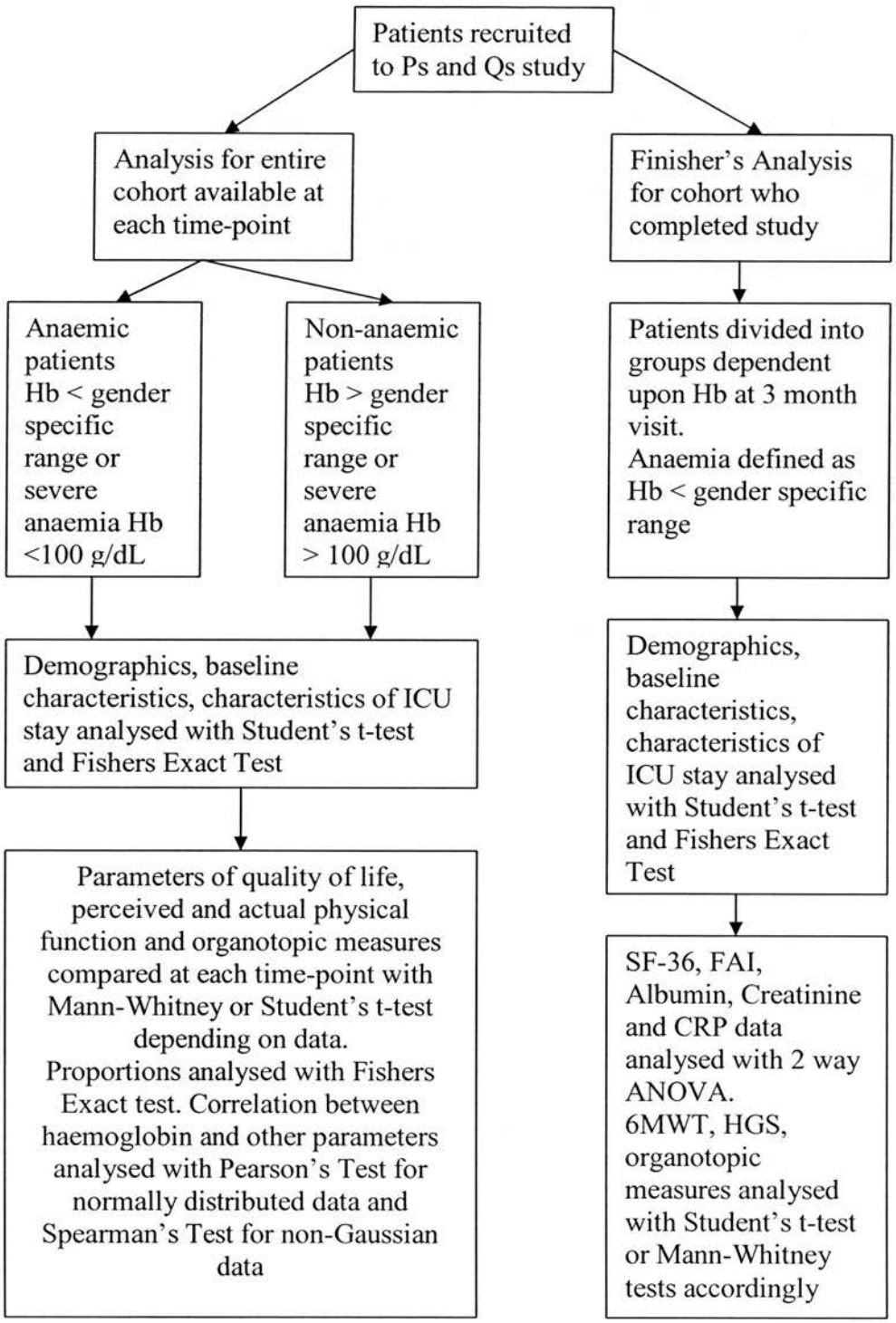
This chapter focuses on a subgroup of the cohort described in Chapter 3 (Sections 3.3 and 3.4). For the purposes of the subgroup analysis the patients were divided into gender specific anaemia groups (haemoglobin concentration less than gender specific reference range) and also severe anaemia groups (haemoglobin concentration less than 100 g/L) as detailed below and Figure 4.2. A further analysis of patients who had a complete data set for the follow up period was also performed (The 'Finisher's Analysis'). For this analysis the patients were divided into 2 groups depending upon whether their haemoglobin concentration was below or within the gender specific reference range at the 3 month follow up visit.

### 4.2.1 Anaemia groups

#### *4.2.1.1 Gender and Severe Anaemia groups*

The study cohort was divided into subgroups at each time point (0 months, 3 months and 6 months) depending upon haemoglobin concentration at this time. The first analysis related to groups determined by whether the haemoglobin concentration of the patient was less than gender specific reference range (120 g/L for females and 130 g/L for males) at the particular time point - 'gender anaemia'. Further analysis was performed for severe anaemia where the group was determined by whether the haemoglobin concentration of a patient was more or less than 100 g/L - 'severe anaemia'.

**Figure 4.2 Flow diagram illustrating patient group selection and analyses**



#### *4.2.1.2 Finisher's Analysis*

A further analysis of patients who remained anaemic (with haemoglobin below gender specific range) at 3 months compared to those who did not was also performed specifically for patients where the complete data set was available for the follow up period. This would allow for changes with time for a given parameter to be analysed within a specific population.

### 4.2.2 Analyses

#### *4.2.2.1 Groups determined by gender anaemia or severe anaemia at each time point*

##### *4.2.2.1.1 Demographics and Baseline Characteristics*

The baseline characteristics (age, ICU length of stay, APACHE II score) of the anaemic and non-anaemic groups were compared using Student's t test. The proportion of patients with severe organ failure (SOFA >3) for each component of the SOFA score was recorded for each group. The proportion of each of the anaemic and non-anaemic subgroup with severe organ failure during ICU stay was then compared using Fisher's Exact Test.

##### *4.2.2.1.2 Anaemia and quality of life*

The cohort was again considered in two sub-groups, gender anaemia and severe anaemia, at each time point. The proportion of each cohort with SF-36 component scores less than mean values for the UK normal population was then calculated and analysed with Fisher's Exact Test. The physical and mental component summary scores for the

cohort were also compared for statistical difference at each time point with Student's t-test.

#### *4.2.2.1.3 Anaemia and perceived physical function*

The cohort was again considered in the two sub-groups. The FAI score for the groups was compared at each time-point (3 and 6 months) using Student's t-test.

#### *4.2.2.1.4 Anaemia and actual physical function*

The results of the 6 minute walk test and hand grip strength measurement of the two subgroups at 3 and 6 months was compared with Mann Whitney U-test and Student's t-test accordingly.

#### *4.2.2.1.5 Anaemia and nutrition as assessed by hand grip strength*

The raw data from the hand grip dynamometer was converted in to a percentage of the normal value for patient's gender and age. A value less than 85% of normal was considered as evidence of protein malnutrition (Klidjian, Foster et al. 1980; Goode 1985). Hand grip strength is an unusual measure of nutritional status and it is possible that other factors such as neuropathy and myopathy could contribute to the development of reduced grip strength. However it has been shown to be a robust predictor of nutritional status in several patient groups and a better marker than the classic laboratory indices of nutritional state (Webb, Newman et al. 1989; Wang, Sea et al. 2005). This is likely to be due to the fact that hand grip strength represents the common easily measured endpoint of the multiple potential factors reflecting a patient's physiological

state (i.e. is a measure of frailty) and that nutritional state is an important determinant in many of these components of physiological state. The proportion of patients with evidence of malnutrition in each group was also compared using Fisher's Exact Test.

#### *4.2.2.1.6 Anaemia and organotopic measures*

The organotopic measures (albumin, CRP, creatinine) were compared using Student's t-test at 0, 3 and 6 months. The creatinine concentrations were converted to estimated glomerular filtration rate (eGFR) for the comparison of proportions to account for differences in age and gender (Burden and Tomson 2005). The proportion of each subgroup who had an abnormal result (either a CRP >10, reduced eGFR (<60ml/min), or an albumin level less than 30g/L) was also recorded and the proportions compared with Fisher's Exact Test.

#### *4.2.2.1.7 Correlation between outcome measures and haemoglobin concentration*

The data for quality of life (SF-36 PCS and MCS score), perceived physical function (FAI), actual physical function (hand grip strength) and organotopic measures (CRP, creatinine, albumin) which were normally distributed, were analysed for correlation with haemoglobin concentration with Pearson's Test. Non-Gaussian data (eGFR, distance walked in 6MWT) were analysed with Spearman's Test.

#### *4.2.2.2 Analysis of data from patients based on subgroups defined by the presence of gender anaemia at 3 months and who completed follow up – The 'Finisher's Analysis'*

##### *4.2.2.2.1 Demographics and baseline characteristics*

The baseline characteristics (age, ICU length of stay, APACHE II score) of these anaemic and non-anaemic groups, as determined by haemoglobin concentration at 3 months, were compared using Student's t test.

##### *4.2.2.2.2 Organotopic measures*

The organotopic measures of the groups were compared at each time point (0, 3 and 6 months for haemoglobin concentration, serum creatinine and albumin and 3 and 6 months for serum CRP concentrations) and the change in these results over time analysed with 2 way ANOVA for creatinine and albumin concentrations comparing anaemic and non-anaemic changes over time and Mann-Whitney U-test for CRP.
The proportion of patients with evidence of protein malnutrition (HGS < 85% of normal) was also compared at 3 and 6 months using Student's t test.

##### *4.2.2.2.3 Measures of quality of life and perceived physical function*

Physical component summary scores and Frenchay Activities Index were analysed for the 2 groups for pre-morbid, 3 and 6 months using 2 way ANOVA.

#### *4.2.2.2.4 Actual physical function*

Results from the 6 minute walk test and hand grip strength were analysed with the Mann Whitney U Test.

## 4.3 Results

### 4.3.1 Gender and severe anaemia groups at ICU discharge, 3 and 6 month follow up visits

The proportion of patients anaemic for gender and severe sub-groups at each time point are shown in Table 4.1.

#### *4.3.1.1 Demographics and clinical characteristics*

The demographic and ICU characteristics of each subgroup are shown in Tables 4.2a, b and c.

##### *4.3.1.1.1 ICU discharge – Table 4.2a*

These results that show that severely anaemic patients at ICU discharge had a significantly longer ICU stay compared to those who were not severely anaemic (14.1 days compared to 4.7 days, p=0.03). This suggests that whilst 'gender anaemia' is a common complication of all ICU stays and not related to the characteristics of ICU stay, 'severe anaemia' at ICU discharge is associated with a longer ICU stay. It may therefore be that it reflects either a greater exposure to the many potential sources of blood loss in ICU or that the underlying illness process resulting in an inability to mount an appropriate response to the anaemia of critical illness is persisting.

**Table 4.1 Proportion of patients anaemic at each time point in the study**

Proportion and 95% confidence interval of the proportion for gender specific anaemia and severe anaemia groups shown

| | Hb < Gender specific range | | | Hb < 100 g/dL | | |
|---|---|---|---|---|---|---|
| | *Number* | *Proportion* | *95% CI* | *Number* | *Proportion* | *95% CI* |
| **Discharge** | 65/68 | 0.96 | 0.87-0.99 | 50/68 | 0.74 | 0.62-0.83 |
| **3 months** | 22/42 | 0.52 | 0.38-0.67 | 4/42 | 0.10 | 0.03-0.23 |
| **6 months** | 9/27 | 0.33 | 0.19-0.52 | 1/27 | 0.04 | <0.001-0.20 |

**Table 4.2a ICU characteristics of anaemia groups at ICU discharge**

| | Gender specific groups | | | Severe anaemia groups | | |
|---|---|---|---|---|---|---|
| | **Less than gender** | **Not anaemic** | **p-value mean diff 95% CI** | **Severe anaemia < 100g/dL** | **Not anaemic** | **p-value mean diff 95% CI** |
| **N (%)** | 65 (95.6) | 3 (4.4) | | 50 (73.5) | 18 (26.5) | |
| **Age (years)** | 60.0<br>48-70<br>18-86 | 70<br>n/a<br>56-74 | 0.2983 | 59.5<br>48.5-70.0<br>18-86 | 65.0<br>41.5-71.5<br>25-76 | 0.9288 |
| **APACHE II** | 19.0<br>15.5-23.0<br>2-36 | 20.0<br>n/a<br>7-27 | 0.7650 | 19.0<br>15.0-23.5<br>10.0-36.0 | 17.5<br>14.0-20.5<br>2-27 | 0.0737<br>3.0 ± 1.7<br>-0.3-6.3 |
| **ICU stay (days)** | 11.5<br>5.9-21.5<br>2.9-67.8 | 4.0<br>n/a<br>3.8-11.5 | 0.2544 | 14.1<br>8.4-24.7<br>3.0-67.8 | 4.7<br>3.3-10.6<br>2.9-64.0 | *0.0323**<br>*9.2 ± 4.2*<br>*0.8-17.6* |
| **Hb (g/dL)** | 93.0<br>85.0-99.0<br>78.0-128 | 134.0<br>n/a<br>128.0-138.0 | n/a | 89.0<br>82.5-94.5<br>78.0-99.0 | 115.0<br>106.0-123.5<br>101-138.0 | n/a |

Data expressed as median, 1st & 3rd quartiles and range (min-max). Groups were tested for statistical significance with student's t-test. Statistically significant result ($p<0.05$) are highlighted*. For non significant results with small values the difference between the means and the 95% confidence of the p-value are included

**Table 4.2b ICU characteristics of anaemia groups at 3 month follow up**

| | Gender specific groups | | | Severe anaemia groups | | |
|---|---|---|---|---|---|---|
| | **Less than gender** | **Not anaemic** | **p-value mean diff 95% CI** | **Severe anaemia < 100g/dL** | **Not anaemic** | **p-value mean diff 95% CI** |
| **N (%)** | 22.0 (52.4) | 20 (47.6) | | 4 (9.5) | 38 (90.1) | |
| **Age (years)** | 66.0<br>59.0-73.5<br>53.0-78.0 | 56.0<br>48.0-64.5<br>34.0-71.0 | *0.0014**<br>*-10.3±3.0*<br>*-16.4- -4.3* | 60.0<br>56.5-67.5<br>55.0-73.0 | 62.0<br>50.0-70.0<br>34.0-78.0 | 0.851 |
| **APACHE II** | 18.5<br>13.5-23.5<br>10.0-31.0 | 18.0<br>15.0-22.0<br>7.0-27.0 | 0.7386<br>-0.57±1.7<br>-4.0 – 2.9 | 20.5<br>17.5-27.0<br>17.0-31.0 | 18.5<br>14.0-23.0<br>7.0-27.0 | 0.187<br>3.8 ± 2.8<br>-1.9 - 9.4 |
| **ICU stay (days)** | 19.2<br>7.9-28.8<br>4.0-67.8 | 9.8<br>4.4-13.3<br>3.0-24.2 | *0.0087**<br>*-12.2 ± 4.4*<br>*-21.2 - -3.3* | 36.9<br>13.8-55.3<br>4.6-59.7 | 10.3<br>5.5-21.1<br>3.0-67.8 | *0.0125**<br>*19.98 ± 7.641*<br>*4.540 - 35.43* |
| **Hb (g/dL)** | 115.5<br>105.0-124.0<br>79.0-129.0 | 138.0<br>128.5-141.5<br>120.0-164.0 | n/a | 89.5<br>84.0-94.0<br>79.0-98.0 | 126.0<br>118.0-138.5<br>104.0-164.0 | n/a |

Data expressed as median, 1st & 3rd quartiles and range (min-max). Groups were tested for statistical significance with student's t-test. Statistically significant result ($p<0.05$) are highlighted*. For non significant results with small values the difference between the means and the 95% confidence of the p-value are included.

**Table 4.2c ICU characteristics of anaemia groups at 6 month follow up**

| | Gender specific anaemia groups | | | Severe anaemia groups | | |
|---|---|---|---|---|---|---|
| | **Less than gender** | **Not anaemic** | **p-value mean diff 95% CI** | **Severe anaemia < 100g/dL** | **Not anaemic** | **p-value mean diff 95% CI** |
| **N (%)** | 9 (33.3) | 18 (66.6) | | 1 (3.8) | 26 (96.2) | |
| **Age (years)** | 63.0<br>57.5-69.0<br>55.0-74.0 | 61.0<br>49.0-70.5<br>34.0-86.0 | 0.4905 | 55 | 62.0<br>55.5-70.0<br>34.0-86.0 | n/a |
| **APACHE II** | 17.0<br>15.0-22.5<br>11.0-27.0 | 16.0<br>12.5-22.0<br>7.0-24.0 | 0.4590 | 17 | 16.0<br>13.5-22.0<br>7.0-27.0 | n/a |
| **ICU stay (days)** | 10.7<br>6.9-19.6<br>4.0-50.9 | 10.5<br>4.4-24.7<br>3.0-67.8 | 0.6234 | 50.9 | 10.3<br>4.9-22.6<br>3.0-67.8 | n/a |
| **Hb (g/dL)** | 117.0<br>102.5-122.5<br>95.0-128.0 | 133.0<br>130.0-144.0<br>121.0-164.0 | n/a | 95 | 130.0<br>120.0-136.0<br>102.0-164.0 | n/a |

Data expressed as median, 1st & 3rd quartiles and range (min-max). Groups were tested for statistical significance with student's t-test. For non significant results with small values the difference between the means and the 95% confidence of the p-value are included.

#### *4.3.1.1.2 3 months – Table 4.2b*

These results show that patients with 'gender anaemia' at 3 months were older (66 years compared to 56 years, p=0.001) and had a longer ICU stay (19.2 days compared to 9.8 days p=0.008) compared to those who were not anaemic at 3 months. The persistence of severe anaemia was again associated with a longer ICU stay.

#### *4.3.1.1.3 6 months – Table 4.2c*

There were no differences in demographics and baseline characteristics for the gender anaemia group at 6 months following ICU discharge. The severe anaemia group was not analysed as only one patient had severe anaemia at this time.

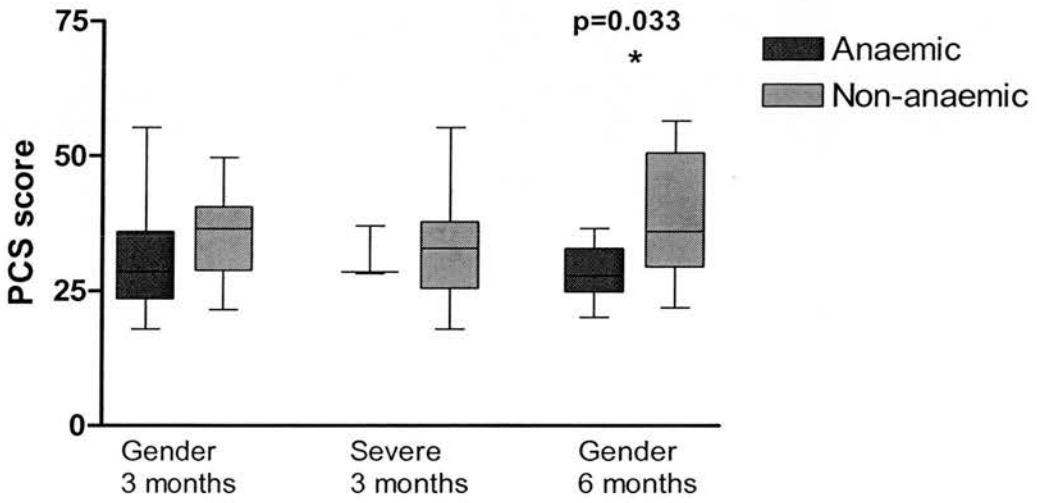
#### *4.3.1.1.4 Proportion of anaemia groups with severe organ failure in ICU*

The proportion of patients in each group (gender and severe anaemia) with severe organ failure during ICU stay was not different at ICU discharge, 3 or 6 month follow up. This suggests that the degree of organ failure during ICU stay does not affect whether patients will remain anaemic following ICU discharge.

### *4.3.1.2 Quality of life*

Figure 4.3a and 4.3b shows the PCS and MCS scores for anaemic and non-anaemic groups at 3 and 6 months with the results summarised in Table 4.3. There is a strong trend at both 3 and 6 months for patients with persisting anaemia to have a significantly reduced physical quality of life and this reached statistical significance at 6 months, median PCS 27.8 compared with 35.6, p=0.032.

**Figure 4.3a Physical (PCS) and 4.3b Mental (MCS) component summary scores for anaemia groups**



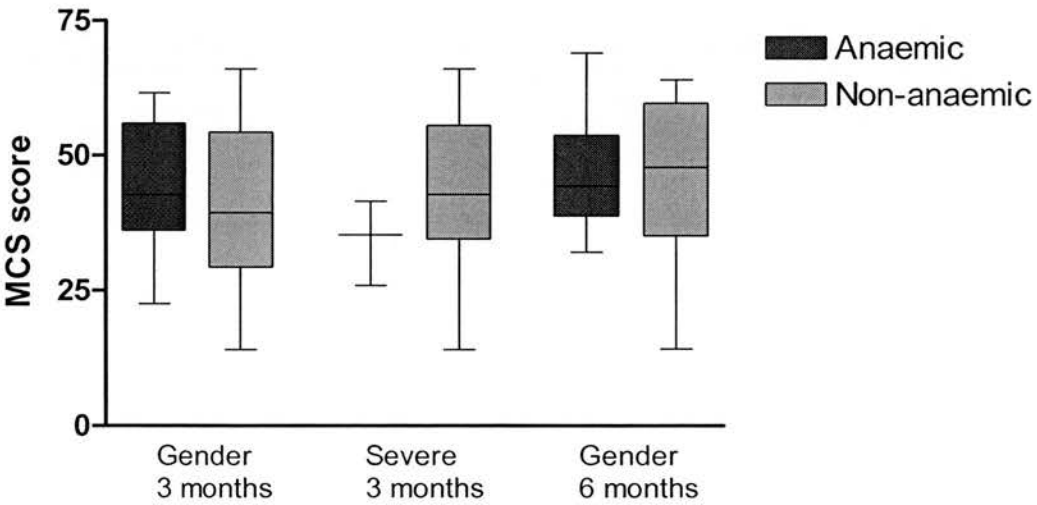



**Table 4.3 Component summary scores for anaemic and non-anaemic subgroups at 3 and 6 months**

| Time Point | | 3 months | | | | | | 6 months | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Group | | Gender | | | Severe | | | Gender | | |
| | | Anaemic | Non-anaemic | p-value | Anaemic | Non-anaemic | p-value | Anaemic | Non-anaemic | p-value |
| Number | | 21 | 21 | | 3 | 39 | | 8 | 20 | |
| PCS | Median | 28.5 | 36.5 | 0.103 | 28.5 | 32.9 | 0.754 | 27.8 | 35.6 | **0.0326** |
| | IQ range | 23.5-36.0 | 28.8-40.6 | | - | 25.5-37.8 | | 24.9-32.9 | 29.5-50.6 | |
| | Range | 17.9-55.3 | 21.5-49.7 | | 28.2-37.0 | 17.9-55.3 | | 20.1-36.6 | 21.9-56.5 | |
| MCS | Median | 42.8 | 39.4 | 0.241 | 35.3 | 42.8 | 0.281 | 44.3 | 47.8 | 0.841 |
| | IQ range | 36.1-56.0 | 29.3-54.3 | | - | 34.5-55.5 | | 38.8-53.7 | 35.2-59.7 | |
| | Range | 22.6-61.6 | 14.1-66.0 | | 25.9-41.5 | 14.1-66.0 | | 32.1-69.0 | 14.2-64.0 | |

Data expressed as median, interquartile range and range. Significant values shown in bold.

**Table 4.4 Proportions of patients in each anaemia group with mean individual component score of SF-36 quality of life measure**

| Time point | 3 months | | 3 months | | 6 months | |
|---|---|---|---|---|---|---|
| Anaemia type | Gender | | Severe | | Gender | |
| Anaemia status | Not anaemic | Anaemic | Not anaemic | Anaemic | Not anaemic | Anaemic |
| Total Number | 23 | 22 | 42 | 3 | 21 | 8 |
| Proportion < UK mean (%) | | | | | | |
| PF | 19 (83) | 19 (84) | 36 (86) | 2 (66) | 16 (76) | 8 (100) |
| PR | 22 (96) | 21 (95) | 40 (95) | 3 (100) | 15 (71) | 8 (100) |
| BP | 17 (74) | 19 (84) | 33 (79) | 3 (100) | 15 (71) | 7 (86) |
| GH | 20 (87) | 21 (95) | 38 (90) | 3 (100) | 16 (76) | 8 (100) |
| Vi | 17 (74) | 19 (84) | 33 (79) | 3 (100) | 14 (66) | 6 (75) |
| SF | 17 (74) | 17 (77) | 31 (74) | 3 (100) | 13 (62) | 6 (75) |
| ER | 17 (74) | 12 (55) | 27 (64) | 2 (66) | 13 (62) | 6 (75) |
| MH | 19 (83) | 17 (77) | 32 (76) | 3 (100) | 12 (57) | 6 (75) |

Actual number of patients shown with percentage shown in brackets

PF = physical function, PR = role physical, BP = bodily pain, GH = general health, Vi = vitality,
SF = social functioning, ER = role emotional, MH = mental health

The proportion of each study cohort with PCS scores less than mean values for UK population were calculated and analysed with Fisher's Exact Test. The results show that the majority (95%; 64/67) of the study cohort had an impaired quality of life prior to ICU admission. In comparing anaemia groups at 3 and 6 months >75% had impaired SF-36 scores especially on the physical domains compared to the normal population. The proportions of patients whose SF-36 parameter was less than the mean normal values was not significantly different in the anaemic or non anaemic groups when compared with Fisher's exact test in either summary scores or individual components. The proportions are shown in Table 4.4

#### *4.3.1.3 Perceived physical function*

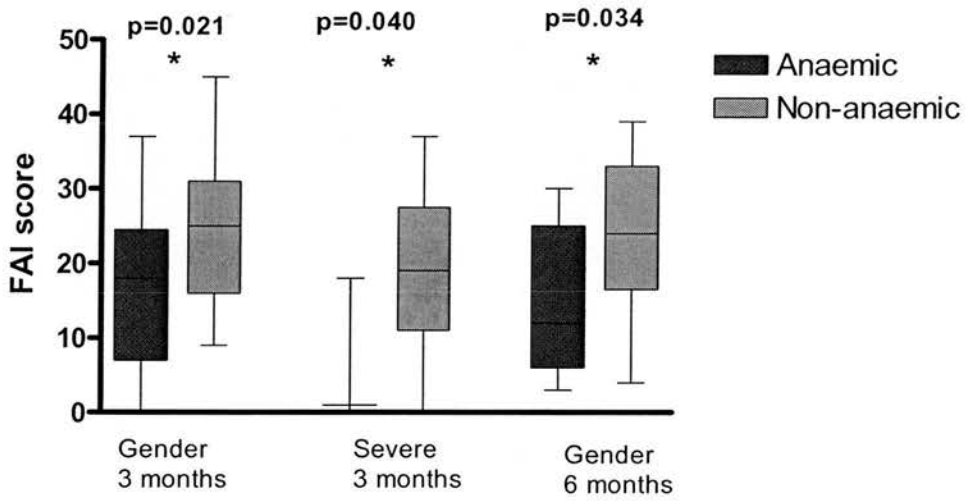
The FAI scores for gender specific anaemia and severe anaemia are shown in Figure 4.4 and Table 4.5. The FAI score was statistically less in the anaemic groups compared to the non-anaemic groups (both gender and severe anaemia groups) at all time points. Median FAI scores were 18 for the gender anaemia groups compared to 25 for the non-anaemic group at 3 months, and 12 compared to 24 for gender anaemia group at 6 months. A change of 4 in FAI score is considered clinically significant (Harrington, Taylor et al.).

#### *4.3.1.4 Actual physical function*

##### *4.3.1.4.1 6 minute walk test*

The distance walked for gender specific and severe anaemia groups are shown in Figure 4.5 and Table 4.6.

**Figure 4.4 FAI for gender and severe anaemia groups**



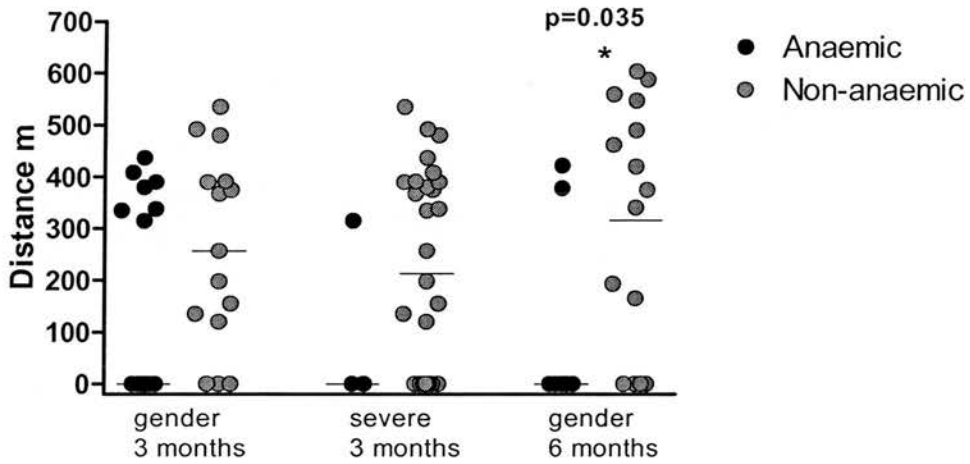

* indicates significant result with p value shown

**Table 4.5 FAI scores for gender and severe anaemia groups**

| **Time Point** | | **3 months** | | | | | |
|---|---|---|---|---|---|---|---|
| **Group** | | **Gender** | | | **Severe** | | |
| | | **Anaemic** | **Non-anaemic** | **p-value** | **Anaemic** | **Non-anaemic** | **p-value** |
| **Number** | | 21 | 21 | | 3 | 26 | |
| **FAI** | **Median** | 18.0 | 25.0 | **0.021** | 1.0 | 19.0 | **0.040** |
| | **IQrange** | 7.0-24.5 | 16.0-31.0 | | - | 11.0-27.5 | |
| | **Range** | 0.0-37.0 | 9.0-45.0 | | 0.0-18.0 | 0.0-37.0 | |
| **Time Point** | | **3 months** | | | | | |
| **Group** | | **Gender** | | | **Severe** | | |
| | | **Anaemic** | **Non-anaemic** | **p-value** | **Anaemic** | **Non-anaemic** | **p-value** |
| **Number** | | 8 | 20 | | - | - | - |
| **FAI** | **Median** | 12.0 | 24.0 | **0.034** | - | - | - |
| | **IQrange** | 6.0-25.0 | 16.5-33.0 | | | | |
| | **Range** | 3.0-30.0 | 4.0-39.0 | | | | |

Data expressed as median, interquartile range and range, and analysed with Student's t-test

**Figure 4.5 Distance walked in 6 minute walk test**




* indicates significant difference with p value shown

**Table 4.6 Distances walked during 6MWT for gender and severe anaemia groups**

| **Time Point** | | **3 months** | | | | | |
|---|---|---|---|---|---|---|---|
| **Group** | | **Gender** | | | **Severe** | | |
| | | **Anaemic** | **Non-anaemic** | **p-value** | **Anaemic** | **Non-anaemic** | **p-value** |
| **Number** | | 17 | 15 | | 3 | 29 | |
| **DIST** | **Median IQ range Range** | 0<br>0-359<br>0-437 | 257<br>120-391<br>0-535 | 0.121 | 0<br>-<br>0-315 | 198<br>0-390<br>0-535 | 0.365 |
| **Time Point** | | **6 months** | | | | | |
| **Group** | | **Gender** | | | **Severe** | | |
| | | **Anaemic** | **Non-anaemic** | **p-value** | **Anaemic** | **Non-anaemic** | **p-value** |
| **Number** | | 8 | 15 | | - | - | - |
| **DIST** | **Median IQ range Range** | 0<br>0-189<br>0-422 | 375<br>0-547<br>0-604 | **0.0355** | - | - | - |

Data expressed as median, interquartile range and range, and analysed with Mann-Whitney U test

For the cohort at 3 months there was no difference in the distance walked between anaemic or non-anaemic patients. At 6 months non-anaemic patients walked significantly further (median 375m compared with 0m, p=0.035). This may reflect a greater degree of co-morbidity in the anaemic group as there were more patients with a 0 distance walked. This may reflect inability to attempt the test rather than actual physical function being reduced.

#### *4.3.1.3.2 Hand grip strength*

The results are shown in Figure 4.6 and Table 4.7. At 3 and 6 months the gender anaemic patients had significantly reduced percentage of normal handgrip strength compared to the non-anaemic patients. This was not present for the severe anaemia group at 3 months.

### *4.3.1.5 Organotopic measures*

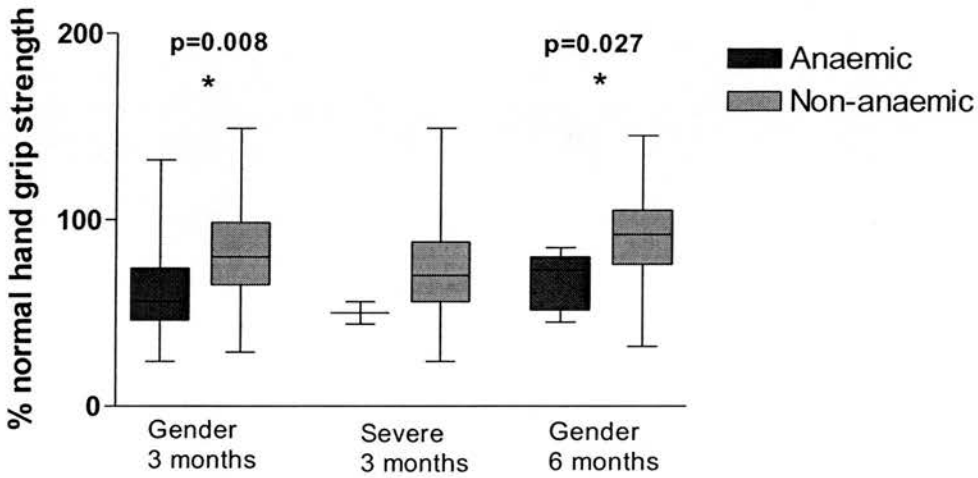
#### *4.3.1.5.1 Nutritional status by hand grip strength*

Hand grip strength as a marker of nutritional state was assessed using Fisher's Exact test for the proportion of each group with HGS less than 85% of normal (Table 4.8). The proportion of patients with evidence of protein malnutrition was significantly greater in the anaemic compared to the anaemic groups at 6 months only.

#### *4.3.1.5.2 Albumin*

Results are shown in Figure 4.7a, Figure 4.7b and Table 4.9. At ICU discharge only the severe anaemia group had a significantly lower albumin concentration.

**Figure 4.6 Percentage of normal hand grip strength**




* indicates significant difference with p value shown

**Table 4.7 Percentage of normal hand grip strength for gender and severe anaemia groups**

| Time Point | | 3 months | | | | | |
|---|---|---|---|---|---|---|---|
| Group | | Gender | | | Severe | | |
| | | Anaemic | Non-anaemic | p-value | Anaemic | Non-anaemic | p-value |
| Number | | 21 | 21 | | 3 | 39 | |
| HGS | Median | 56 | 80 | **0.008** | 50 | 70 | 0.160 |
| | IQrange | 46-74 | 65-99 | | - | 56-88 | |
| | Range | 24-132 | 29-149 | | 44-56 | 24-149 | |
| Time Point | | 6 months | | | | | |
| Group | | Gender | | | Severe | | |
| | | Anaemic | Non-anaemic | p-value | Anaemic | Non-anaemic | p-value |
| Number | | 9 | 19 | | - | - | - |
| HGS | Median | 73 | 92 | **0.027** | - | - | - |
| | IQrange | 52-80 | 76-105 | | | | |
| | Range | 45-85 | 32-145 | | | | |

Data expressed as median, interquartile range and range; analysed with Student's t-test

**Table 4.8 Proportion of patients with gender and severe anaemia and evidence of protein malnutrition (<85% of normal)**

| Time Point | 3 months | | | | | |
|---|---|---|---|---|---|---|
| Group | Gender | | | Severe | | |
| | Anaemic | Non-anaemic | p-value | Anaemic | Non-anaemic | p-value |
| **<85% normal** | 19 | 13 | 0.067 | 3 | 28 | 0.554 |
| **>85% normal** | 2 | 8 | | 0 | 11 | |
| | 6 months | | | | | |
| **<85% normal** | 6 | 7 | **0.0157** | - | - | - |
| **>85% normal** | 1 | 12 | | - | - | - |

Data analysed with Fisher's Exact Test

**Figure 4.7a Albumin levels in gender anaemia group**

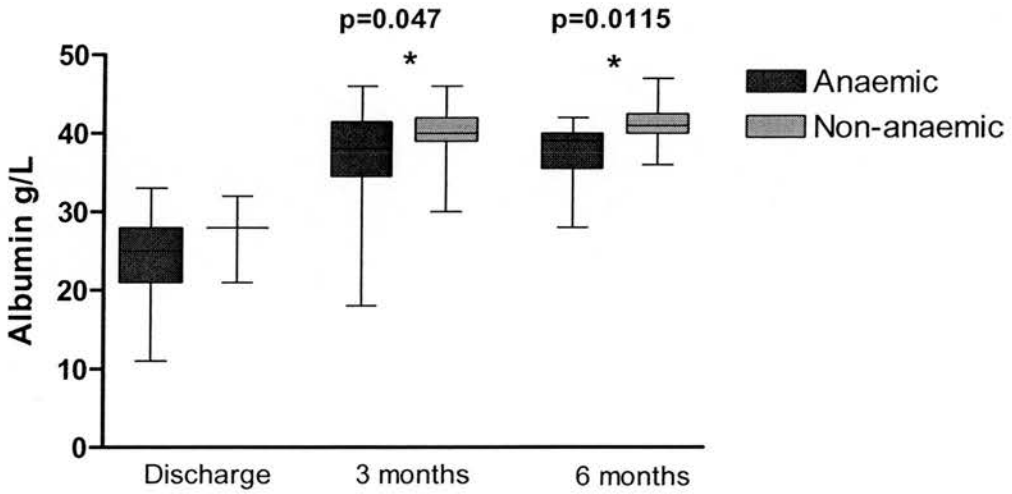



**Figure 4.7b Albumin levels in severe anaemia group**

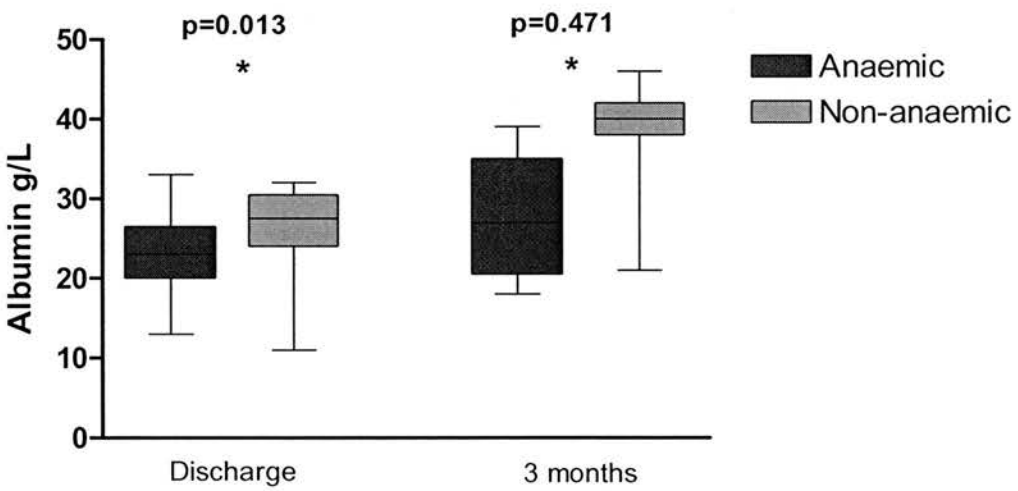


**Table 4.9 Serum albumin concentrations for gender and severe anaemia groups**

| **Time Point** | **Discharge** | | | | | |
|---|---|---|---|---|---|---|
| **Group** | **Gender** | | | **Severe** | | |
| | **Anaemic** | **Non-anaemic** | **p-value** | **Anaemic** | **Non-anaemic** | **p-value** |
| **number** | 65 | 3 | | 49 | 18 | |
| **Median**<br>**IQ range**<br>**Range** | 25.0<br>21.0-28.0<br>11.0-33.0 | 28.0<br>-<br>21.0-32.0 | 0.29 | 23.0<br>20.0-26.5<br>13.0-33.0 | 27.5<br>24.0-30.5<br>11.0-32.0 | **0.013** |

| **Time Point** | **3 months** | | | | | |
|---|---|---|---|---|---|---|
| **Group** | **Gender** | | | **Severe** | | |
| | **Anaemic** | **Non-anaemic** | **p-value** | **Anaemic** | **Non-anaemic** | **p-value** |
| **number** | 22 | 21 | | 4 | 39 | |
| **Median**<br>**IQ range**<br>**Range** | 38.0<br>34.5-41.5<br>18.0-46 | 40.0<br>39.0-42.0<br>30.0-46.0 | **0.047** | 27.0<br>20.5-35.0<br>18.0-39.0 | 40.0<br>38.0-42.0<br>21.0-46 | **<0.001** |

| **Time Point** | **6 months** | | | | | |
|---|---|---|---|---|---|---|
| **Group** | **Gender** | | | **Severe** | | |
| | **Anaemic** | **Non-anaemic** | **p-value** | **Anaemic** | **Non-anaemic** | **p-value** |
| **number** | 9 | 18 | | - | - | - |
| **Median**<br>**IQ range**<br>**Range** | 39.0<br>35.5-40.0<br>28.0-42 | 41.0<br>40.0-42.5<br>36.0-47.0 | **0.0115** | - | - | - |

Data expressed as median, interquartile range and range; analysed with Student's t-test
Significant results highlighted in bold.

At 3 and 6 months albumin concentration was found to be significantly different between the groups both for gender anaemia and severe anaemia groups. The proportion of patients in each group with serum albumin concentration <30 g/L was different at all time points (Table 4.10).

#### *4.3.1.5.3 Creatinine and eGFR*

Results are shown in Figure 4.8a, Figure 4.8b and Table 4.11. Serum creatinine concentration was not different between the groups at any time point. The proportion of patients with severe renal impairment (eGFR<60 or grade 3 renal failure) was not different between the groups.

#### *4.3.1.5.4 CRP*

Results are shown in Figure 4.9 and Table 4.12. CRP concentrations were found not to be different at 3 months but were significantly higher in the anaemic group at 6 months suggesting that the persistence of inflammation is associated with the persistence of anaemia. The proportion of patients with an elevated CRP in each group was significantly higher in the severe anaemia group at 3 months and in the gender group at 6 months (Table 4.13).

### *4.3.1.6 Correlation of parameters with haemoglobin concentration*

Results are summarised in Table 4.14. Haemoglobin concentration did not correlate with quality of life measures. Distance walked in 6 minutes correlated with haemoglobin at 3 months but not at 6 months.

**Table 4.10 Proportion of patients with gender and severe anaemia and with low serum albumin concentration (<30 g/L)**

| Time Point | Discharge | | | | | |
|---|---|---|---|---|---|---|
| Group | Gender | | | Severe | | |
| | Anaemic | Non-anaemic | p-value | Anaemic | Non-anaemic | p-value |
| <30 | 59 | 2 | 0.28 | 48 | 13 | **0.0118** |
| >30 | 6 | 1 | | 2 | 5 | |

| Time Point | 3 months | | | | | |
|---|---|---|---|---|---|---|
| Group | Gender | | | Severe | | |
| | Anaemic | Non-anaemic | p-value | Anaemic | Non-anaemic | p-value |
| <30 | 3 | 20 | 0.24 | 2 | 2 | **0.0193** |
| >30 | 0 | 20 | | 1 | 38 | |

| Time Point | 6 months | | | | | |
|---|---|---|---|---|---|---|
| Group | Gender | | | Severe | | |
| | Anaemic | Non-anaemic | p-value | Anaemic | Non-anaemic | p-value |
| <30 | 1 | 7 | 0.30 | 1 | 0 | **0.037** |
| >30 | 0 | 19 | | 0 | 26 | |

Data analysed with Fisher's Exact Test.

**Figure 4.8a Creatinine concentrations in gender anaemia group**

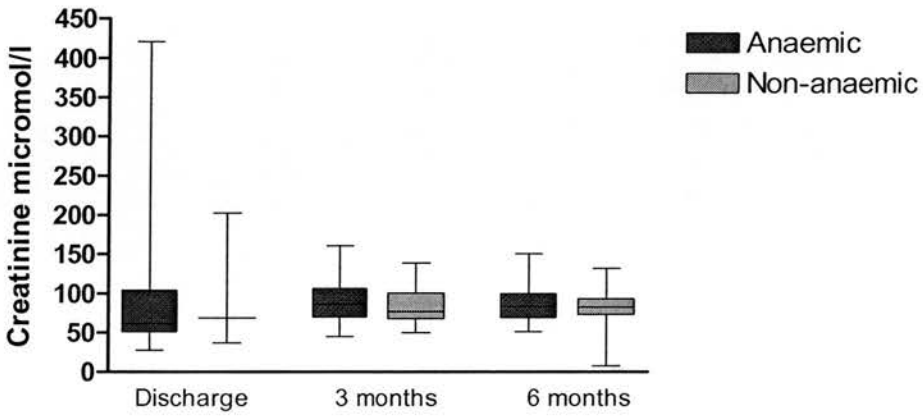



**Figure 4.8b Creatinine concentrations in severe anaemia group**

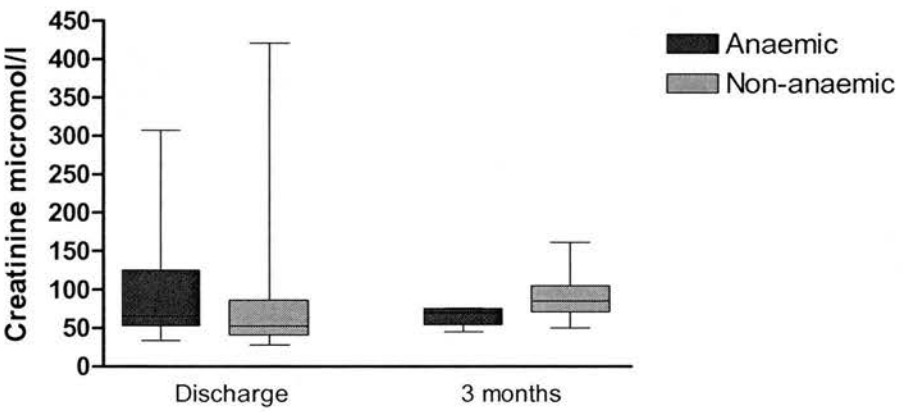


**Table 4.11 Serum creatinine concentrations for gender and severe anaemia groups**

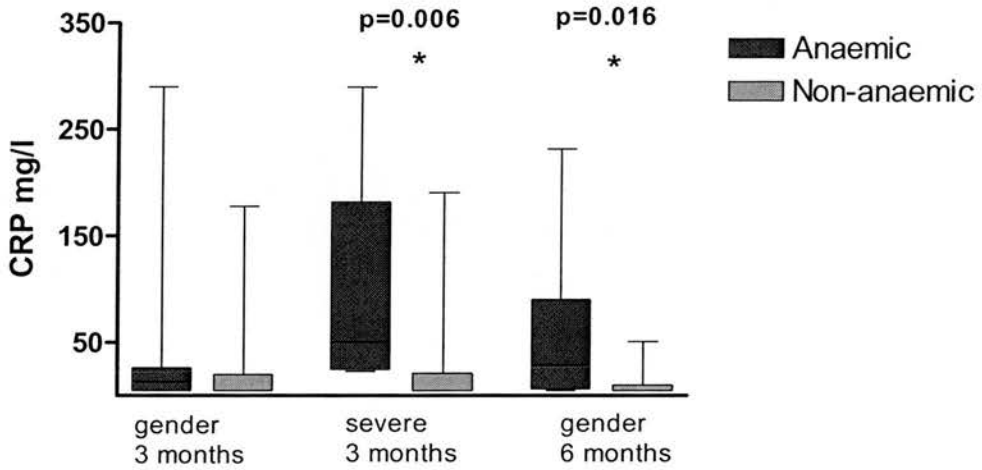
| Time Point | Discharge | | | | | |
|---|---|---|---|---|---|---|
| Group | Gender | | | Severe | | |
| | Anaemic | Non-anaemic | p-value | Anaemic | Non-anaemic | p-value |
| number | 65 | 3 | | 49 | 18 | |
| Median | 63.0 | 69.0 | ns | 65.0 | 52.5 | ns |
| IQ range | 51.0-108.0 | - | | 53.0-125.5 | 41.0-86.5 | |
| Range | 28.0-421.0 | 37.0-203.0 | | 34.0-307.0 | 28.0-421.0 | |

| Time Point | 3 months | | | | | |
|---|---|---|---|---|---|---|
| Group | Gender | | | Severe | | |
| | Anaemic | Non-anaemic | p-value | Anaemic | Non-anaemic | p-value |
| number | 22 | 21 | | 4 | 39 | |
| Median | 86.5 | 77.0 | ns | 69.5 | 85.0 | ns |
| IQ range | 70.0-106.5 | 68.0-100.5 | | 54.5-75.5 | 71.0-105.0 | |
| Range | 45.0-161.0 | 50.0-139.0 | | 45.0-76.0 | 50.0-161.0 | |

| Time Point | 6 months | | | | | |
|---|---|---|---|---|---|---|
| Group | Gender | | | Severe | | |
| | Anaemic | Non-anaemic | p-value | Anaemic | Non-anaemic | p-value |
| number | 8 | 18 | | - | - | - |
| Median | 83.5 | 82.5 | ns | - | - | - |
| IQ range | 69.5-100.0 | 73.5-93.0 | | | | |
| Range | 51.0-151.0 | 8.0-132.0 | | | | |

Data expressed as median, interquartile range and range; analysed with Student's t-test.

**Figure 4.9 CRP concentrations at 3 and 6 months following ICU discharge**




* indicates significant difference with p values shown

**Table 4.12 Serum CRP concentrations for anaemia groups**

| Time Point | 3 months | | | | | |
|---|---|---|---|---|---|---|
| Group | Gender | | | Severe | | |
| | Anaemic | Non-anaemic | p-value | Anaemic | Non-anaemic | p-value |
| number | 22 | 20 | | 4 | 38 | |
| | 13.5<br>5.0-26.5<br>5.0-290.0 | 5.0<br>5.0-20.0<br>5.0-178 | ns | 50.5<br>25.0-182.0<br>23.0-290.0 | 5.0<br>5.0-21.0<br>5.0-191.0 | **0.006** |

| Time Point | 6 months | | | | | |
|---|---|---|---|---|---|---|
| Group | Gender | | | Severe | | |
| number | 9 | 17 | | - | - | - |
| | 29.0<br>6.5-90.5<br>5.0-232.0 | 5.0<br>5.0-10.0<br>5.0-51.0 | **0.016** | - | - | - |

Data expressed asmedian, interquartile range and range; analysed with Mann-Whitney.

**Table 4.13 Proportion of anaemic patients with elevated CRP (>10 g/L )**

| Time Point | 3 months | | | | | |
|---|---|---|---|---|---|---|
| Group | Gender | | | Severe | | |
| | Anaemic | Non-anaem | p-value | Anaemic | Non-anaem | p-value |
| <10 | 9 | 13 | 0.136 | 0 | 22 | **0.043** |
| >10 | 13 | 7 | | 4 | 16 | |

| Time Point | 6 months | | | | | |
|---|---|---|---|---|---|---|
| Group | Gender | | | Severe | | |
| | Anaemic | Nonanaem | p-value | Anaemic | Non-anaem | p-value |
| <10 | 3 | 13 | **0.046** | 0 | 16 | 0.384 |
| >10 | 6 | 4 | | 1 | 9 | |

Data analysed with Fisher's Exact Test.

**Table 4.14 Correlation between quality of life measures, distance walked in 6MWT, organotopic parameters and haemoglobin concentration**

| Parameter | No of pairs | Test | p-value | $R^2$ | Pear /Spr r |
|---|---|---|---|---|---|
| **Hb v PCS 3** | 42 | Pearson | 0.118 | 0.060 | 0.2449 |
| **Hb v PCS 6** | 28 | Pearson | 0.156 | 0.076 | 0.2757 |
| **Hb v MCS 3** | 42 | Pearson | 0.588 | 0.007 | -0.0860 |
| **Hb v MCS 6** | 28 | Pearson | 0.225 | 0.056 | -0.2368 |
| **Hb v dist 3** | 36 | Spearman | **<0.001** | - | 0.6561 |
| **Hb v dist 6** | 26 | Spearman | 0.317 | - | 0.2043 |
| **Hbv CRP 3** | 42 | Pearson | **0.011** | 0.1512 | -0.3888 |
| **Hbv CRP 6** | 26 | Pearson | 0.006 | 0.2787 | -0.5279 |
| **Hbv eGFR 3** | 42 | Pearson | 0.461 | 0.01334 | -0.1155 |
| **Hbv eGFR 6** | 25 | Pearson | 0.994 | 0.000003 | -0.001726 |
| **Hbv creat 3** | 42 | Pearson | 0.267 | 0.03 | 0.1732 |
| **Hbv creat 6** | 25 | Pearson | 0.448 | 0.02525 | -0.1589 |
| **Hbv alb 3** | 42 | Pearson | **<0.001** | 0.3641 | 0.6034 |
| **Hbv alb 6** | 27 | Pearson | **0.002** | 0.3137 | 0.5601 |
| **Hbv %HGS 3** | 42 | Pearson | **0.003** | 0.1993 | 0.4464 |
| **Hbv %HGS 6** | 28 | Pearson | **0.030** | 0.1687 | 0.4107 |

Hb = haemoglobin concentration at timepoint, PCS = physical component summary score, MCS = mental component summary score, dist = distance walked in 6MWT, CRP = C-reactive protein concentration, eGFR = estimated glomerular filtration rate, creat = serum creatinine concentration, alb = serum albumin concentration, %HGS = percentage hand grip strength, 3 = 3 month assessment, 6 = 6 month assessment.

Haemoglobin concentration correlates with hand grip strength and albumin concentration at 3 and 6 months and negatively correlates with CRP at 3 months. There was no correlation with serum creatinine or eGFR.

The results from the correlation analysis showed significant p values but the test specific values of significance, the Pearson $R^2$ or Spearman R values were less than 0.5 for all results suggesting a relatively weak association. The strength of the association was strongest for CRP and serum albumin concentration which is supportive of the link between anaemia and ongoing inflammation.

### 4.3.2 Results for 'Finisher's Analysis' cohort

#### *4.3.2.1 Demographic and Baseline characteristics of cohort of patients who completed the study with complete analysis parameters*

Demographics and characteristics of ICU stay of the 'Finisher's' groups are shown in Table 4.15. Age and ICU length of stay were greater in the anaemic compared to the non-anaemic groups. The proportion of patients with severe organ failure was only different for the SOFA cardiac element. There was a significantly greater proportion of patients requiring inotropic support in the anaemic group p=0.033.

#### *4.3.2.2 Haemoglobin concentration at ICU discharge and 6 months*

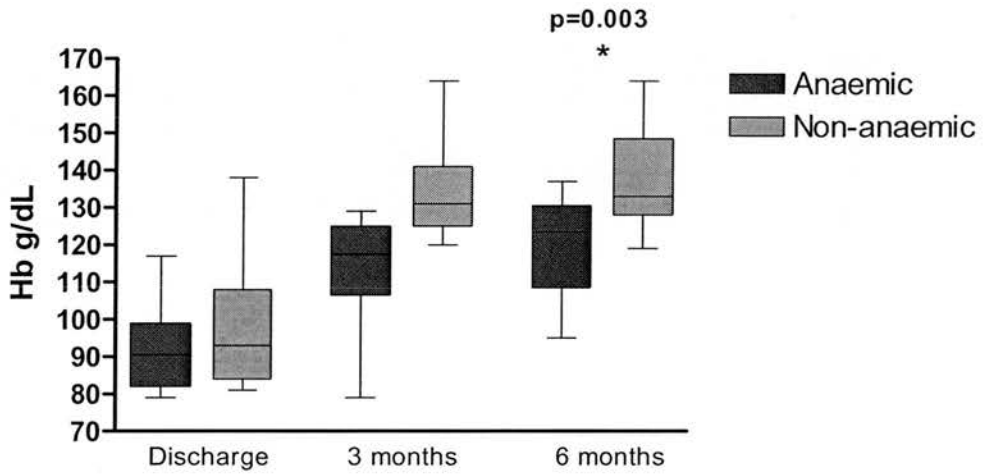
The haemoglobin concentrations of the groups are shown in Figure 4.10 and Table 4.16. The results show that the groups are not significantly different at ICU discharge but the difference at 3 months persists to 6 months.

**Table 4.15 Demographics and baseline characteristics of 'Finishers' cohort**

| Parameter | Anaemic | Non-anaemic | p-value |
|---|---|---|---|
| **Number (male/female)** | 14<br>8/6 | 13<br>2/11 | |
| **Age** | 66; 59.0-71.5, 55-74 | 56; 45.5-67.5, 34-74 | **0.0362** |
| **APACHE II** | 16.5; 13.5-22.5, 12-27 | 18.0; 13.0-21.0, 7-24 | 0.629 |
| **ICU LOS** | 16.3; 8.0-50.1, 4-67.8 | 9.7; 3.8-11.3, 3.0-24.5 | **0.0149** |
| **SOFA max** | 10.5; 7.0-13.0, 4-14 | 8.0; 4.0-12.5, 4-15 | 0.235 |
| **SOFA Cardiac proportions severe/non-severe** | 13/1 | 7/6 | **0.0329** |
| **Hb at ICU discharge** | 90.5; 82.0-99.0, 79.0-117.0 | 93.0; 84.0-108.0, 81.0-138 | 0.244 |

Data expressed as median, IQ range and range. Differences between groups analysed with Student's t test. The proportions of each group with severe organ failure (SOFA >3) and the data for the cardiac component were analysed with Fisher's Exact Test.

**Figure 4.10 Haemoglobin concentrations at ICU discharge, 3 and 6 months for 'Finishers' groups.**




Anaemic and non-anaemic groups defined by haemoglobin concentration at 3 months

**Table 4.16 Serum haemoglobin concentrations**

| Time Point | Discharge | | |
|---|---|---|---|
| | **Anaemic** | **Non-anaemic** | **p-value** |
| **number** | 14 | 13 | |
| **Median**<br>**IQ range**<br>**Range** | 90.5<br>82.0-99.0<br>79.0-117.0 | 93.0<br>84.0-108.0<br>81.0-138.0 | ns |

| Time Point | 3 months | | |
|---|---|---|---|
| | **Anaemic** | **Non-anaemic** | **p-value** |
| **number** | 14 | 13 | |
| **Median**<br>**IQ range**<br>**Range** | 117.5<br>106.5-125.0<br>79.0-129.0 | 131.0<br>125.0-141.0<br>120.0-164.0 | n/a |

| Time Point | 6 months | | |
|---|---|---|---|
| | **Anaemic** | **Non-anaemic** | **p-value** |
| **number** | 14 | 13 | t test |
| **Median**<br>**IQ range**<br>**Range** | 123.5<br>108.5-130.5<br>95.0-137.0 | 133.0<br>128.0-148.5<br>119.0-164.0 | **0.003** |

Pre-morbid, 3 month and 6 month values for 'Finisher' groups analysed with Student's t-test at discharge and 6 months only

#### 4.3.2.3 Quality of life

##### 4.3.2.3.1 Physical component scores

The quality of life PCS scores are shown in Figure 4.11 and Table 4.17. 2 way ANOVA of the cohort shows that the PCS score changes significantly from premorbid to 3 and 6 months but that there is no statistical difference between the patients who were anaemic compared to those who were non-anaemic at 3 months. Post hoc analysis using Student's t-test to verify this result confirms that the PCS scores are not significantly different pre-morbidly or at 3 months between the anaemic and non-anaemic groups. However at 6 months the scores were significantly reduced in the anaemic group compared to the non-anaemic group.

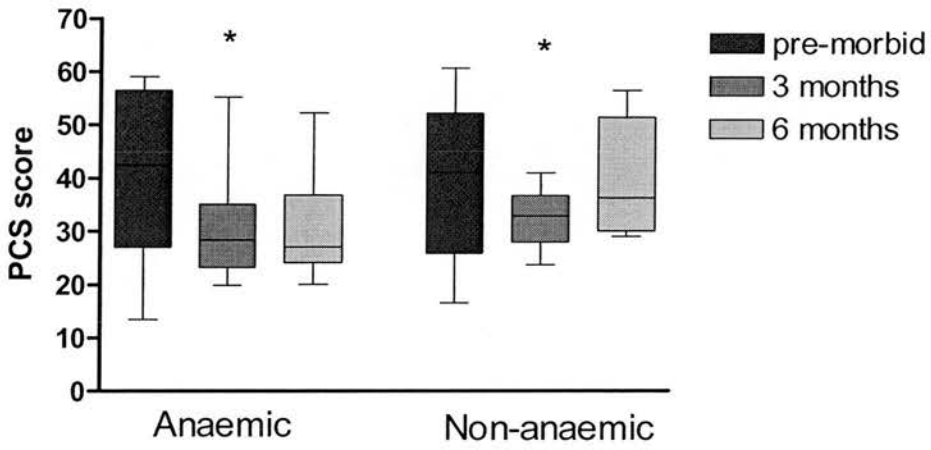
##### 4.3.2.3.2 Mental component scores

The mental component summary scores showed no difference either with time or in relation to anaemia at any time point (Figure 4.12 and Table 4.18).

#### 4.3.2.4 Perceived physical function

The FAI scores are shown in Figure 4.13 and Table 4.19. 2 way ANOVA of the data shows that the FAI scores change significantly with time ($p<0.001$), but there was no statistical difference found between the trajectories in the cohorts dichotomised by anaemia at 3 months. Examining the data further the change in FAI score from pre-morbid to 3 months was analysed with a paired t-test and it was found that there was a significant deterioration in FAI at 3 months (compared with pre-morbid levels; $p=0.003$) for the anaemic group but not for the non-anaemic group, although the trend was the same ($p=0.077$).

**Figure 4.11 Physical component summary scores**




Pre-morbid, 3 and 6 month values for 'Finishers' groups. Anaemic and non-anaemic groups defined by haemoglobin concentration at 3 months. * indicates significant change over time (p=0.017).

**Table 4.17 Physical component summary scores for 'Finisher' groups**

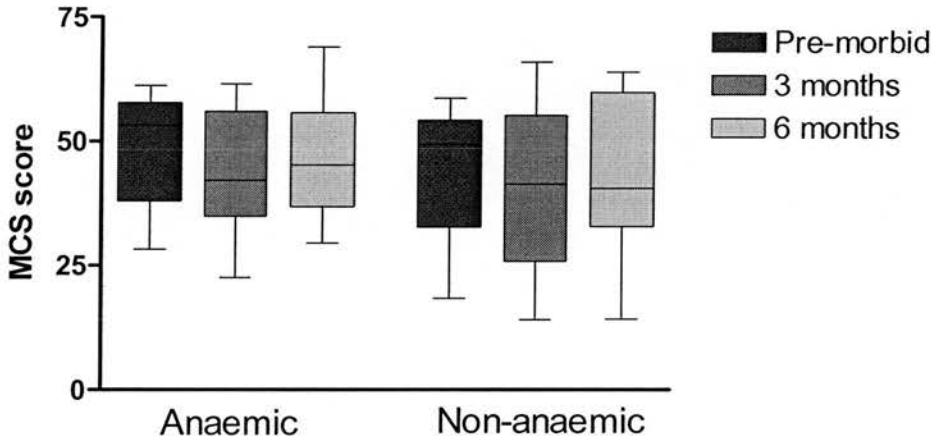
| Time Point | Discharge | | |
|---|---|---|---|
| | **Anaemic** | **Non-anaemic** | **p-value** |
| **number** | 14 | 13 | |
| **Median**<br>**IQ range**<br>**Range** | 42.5<br>27.1-56.5<br>13.5-59.2 | 41.1<br>25.9-52.3<br>16.6-60.7 | ns |

| Time Point | 3 months | | |
|---|---|---|---|
| | **Anaemic** | **Non-anaemic** | **p-value** |
| **number** | 14 | 13 | |
| **Median**<br>**IQ range**<br>**Range** | 28.4<br>23.3-35.2<br>19.9-55.3 | 32.9<br>27.9-36.7<br>23.7-41.0 | ns |

| Time Point | | | | |
|---|---|---|---|---|
| | **Anaemic** | **Non-anaemic** | **p-value anaemia** | |
| **number** | 14 | 13 | ANOVA | t-test |
| **Median**<br>**IQ range**<br>**Range** | 27.1<br>24.2-36.9<br>20.1-32.3 | 36.3<br>30.1-51.5<br>29.1-56.5 | ns | **0.029** |

Data expressed as median, interquartile range and range; analysed with 2 way ANOVA and post hoc Student's t-test for premorbid, 3 months and 6 month values.

**Figure 4.12 Mental component summary score for 'Finisher' groups**




Data expressed as median, interquartile range and range; analysed with 2 way ANOVA and Student's t-test for pre-morbid, 3 months and 6 months values.

**Table 4.18 Mental component summary score for 'Finisher' groups**

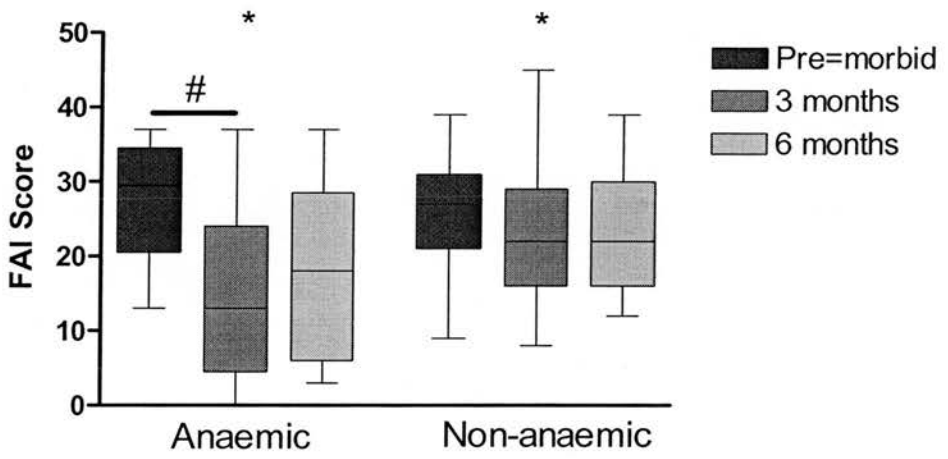
| Time Point | Discharge | | |
|---|---|---|---|
| | **Anaemic** | **Non-anaemic** | **p-value time/anaem** |
| **number** | 14 | 13 | ANOVA/t test |
| **Median**<br>**IQ range**<br>**Range** | 53.3<br>38.0-57.8<br>28.3-61.3 | 49.4<br>32.7-54.4<br>18.4-58.7 | ns |

| Time Point | 3 months | | |
|---|---|---|---|
| | **Anaemic** | **Non-anaemic** | **p-value** |
| **number** | 14 | 13 | |
| **Median**<br>**IQ range**<br>**Range** | 42.2<br>34.9-56.1<br>22.6-61.6 | 41.4<br>25.9-55.3<br>14.1-66.0 | ns |

| Time Point | | | |
|---|---|---|---|
| | **Anaemic** | **Non-anaemic** | **p-value** |
| **number** | 14 | 13 | |
| **Median**<br>**IQ range**<br>**Range** | 45.3<br>36.9-55.8<br>29.5-69.0 | 40.6<br>32.9-59.9<br>14.2-64.0 | ns |

Data expressed as median, interquartile range and range; analysed with 2 way ANOVA and Student's t-test for discharge, 3 months and 6 month values.

**Figure 4.13 Frenchay Activities Index scores for 'Finisher' groups**




Data expressed as median, interquartile range and range; analysed with 2 way ANOVA and Student's t-test for pre-morbid, 3 months and 6 month values.
* indicates significant change with time, $p<0.001$. # indicates significant difference with Student's t-test within group, $p=0.003$.

**Table 4.19 Frenchay Activity Index scores for 'Finisher' groups**

| **Time Point** | **Discharge** | | | |
|---|---|---|---|---|
| | **Anaemic** | **Non-anaemic** | **p-value anaemia** | |
| **number** | 14 | 13 | ANOVA | t-test |
| **Median**<br>**IQ range**<br>**Range** | 29.5<br>20.5-34.5<br>13.0-37.0 | 27.0<br>21.0-31.0<br>9.0-39.0 | ns | ns |

| **Time Point** | **3 months** | | | |
|---|---|---|---|---|
| | **Anaemic** | **Non-anaemic** | **p-value anaemia** | |
| **number** | 14 | 13 | ANOVA | t-test |
| **Median**<br>**IQ range**<br>**Range** | 13.0<br>4.5-24.0<br>0.0-37.0 | 22.0<br>16.0-29.0<br>8.0-45.0 | ns | ns |

| **Time Point** | | | | |
|---|---|---|---|---|
| | **Anaemic** | **Non-anaemic** | **p-value anaemia** | |
| **number** | 14 | 13 | ANOVA | t-test |
| **Median**<br>**IQ range**<br>**Range** | 18.0<br>6.0-28.5<br>3.0-37.0 | 22.0<br>16.0-30.0<br>12.0-39.0 | ns | ns |

Data expressed as median, interquartile range and range; analysed with 2 way ANOVA and Student's t-test at discharge, 3 months and 6 months.

#### 4.3.2.5 Actual physical function

##### 4.3.2.5.1 Six minute walk test

The results for 6 MWT are shown in Figure 4.14 and Table 4.20.There was no difference between anaemic and non-anaemic groups in distance walked at either time-point. The distance walked did not change between 3 and 6 months for the anaemic group but for the non anaemic group it did increase significantly from 3 to 6 months ($p=0.003$). This may suggest that the non-anaemic group are recovering their physical function to a greater degree than the anaemic group.

##### 4.3.2.5.2 Hand grip strength

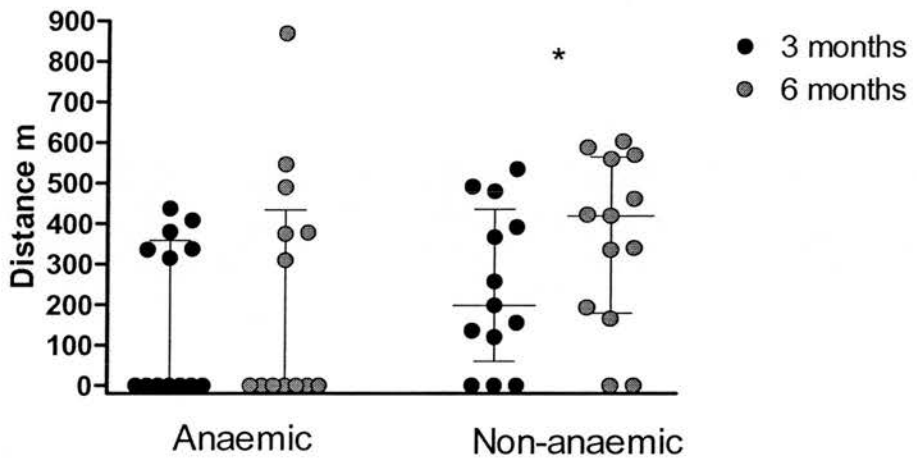
The percentage of normal hand grip strength for each group is shown in Figure 4.15. There was a significantly reduced percentage of normal hand grip strength in the anaemic compared to the non-anaemic group at 3 and 6 months ($p=0.020$ and $p=0.037$ respectively) (Table 4.21). The HGS increased significantly from 3 to 6 months for the anaemic groups but not the non-anaemic group.

#### 4.3.2.6 Organotopic measures

##### 4.3.2.6.1 Hand grip strength

Considering the proportions of each group with evidence of protein malnutrition through measurement of HGS there was significantly greater prevalence of protein malnutrition in the anaemic group at 3 months ($p=0.033$) which was no longer present at 6 months (Table 4.22).

**Figure 4.14 Distance walked in 6 MWT**




* indicates significant change within the group between the two time-points p=0.033

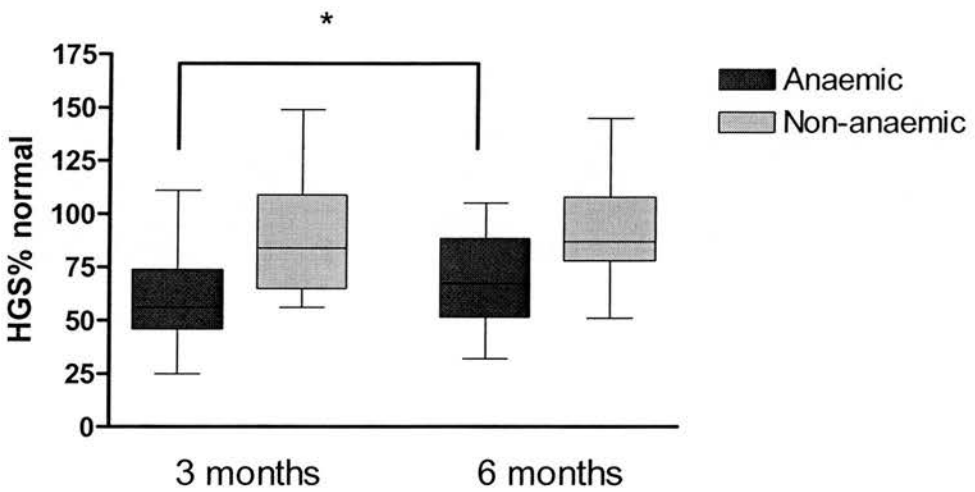
**Table 4.20 Distance walked in 6 MWT for 'Finisher' groups**

| Time Point | 3 months | | |
|---|---|---|---|
| | Anaemic | Non-anaemic | p-value |
| number | 13 | 13 | |
| Median<br>IQ range<br>Range | 0<br>0-359<br>0-359 | 198<br>60-436<br>0-535 | ns |

| Time Point | 6 months | | |
|---|---|---|---|
| | Anaemic | Non-anaemic | p-value |
| number | 13 | 13 | |
| Median<br>IQ range<br>Range | 0<br>0-434<br>0-870 | 420<br>179-565<br>0-604 | ns |

Data expressed as median, interquartile range and range; analysed with Mann-Whitney test for 3 month and 6 month values.

**Figure 4.15 Percentage of normal hand grip strength at 3 and 6 months**




* indicates significant change within the group between the two time-points p=0.033

**Table 4.21 Hand Grip Strength for 'Finisher' groups**

| Time Point | 3 months | | |
|---|---|---|---|
| | Anaemic | Non-anaemic | p-value |
| number | 14 | 13 | |
| Median<br>IQ range<br>Range | 56<br>46-74<br>25-111 | 84<br>65-109<br>56-149 | **0.020** |

| Time Point | 6 months | | |
|---|---|---|---|
| | Anaemic | Non-anaemic | p-value |
| number | 14 | 13 | |
| Median<br>IQ range<br>Range | 68<br>52-89<br>32-105 | 87<br>78-108<br>51-145 | **0.037** |

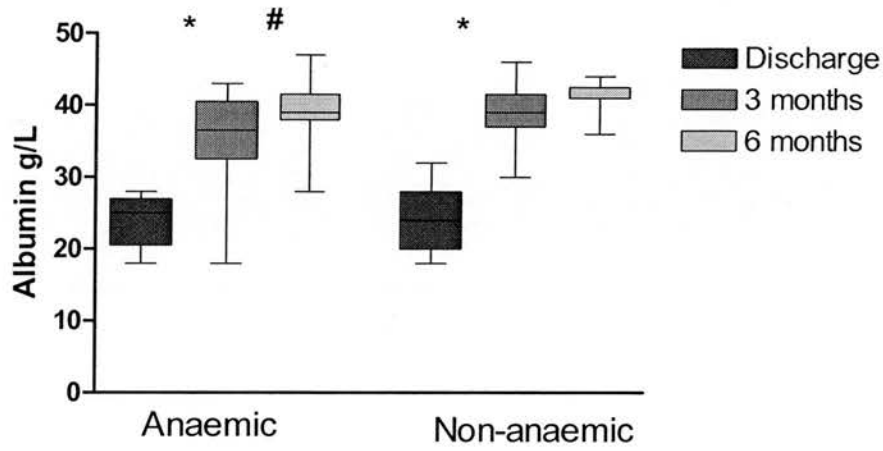
Data expressed as median, interquartile range and range; analysed with Student's t-test at 3 and 6 months.

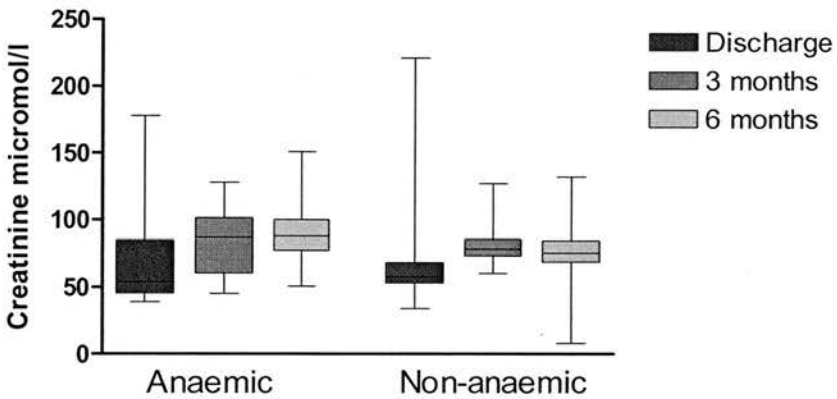
**Table 4.22 Proportion of patients in Finisher group with less than 85% of normal hand grip strength suggesting protein malnutrition**

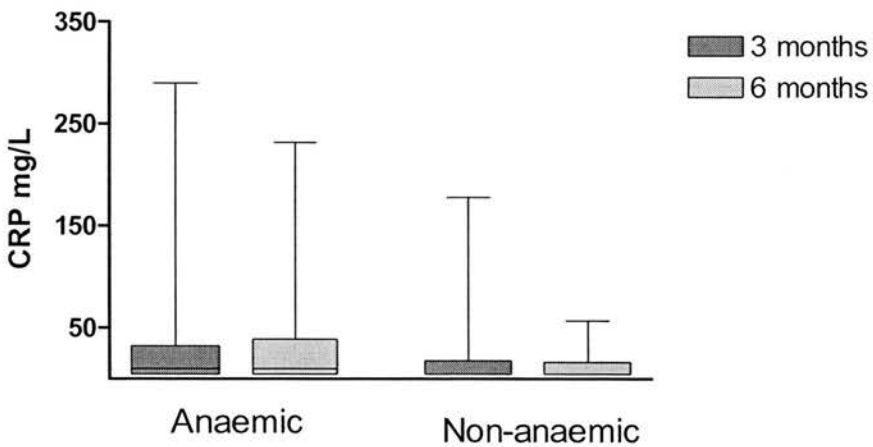
| | | | | | | |
|---|---|---|---|---|---|---|
| Time Point | 3 months | | | 6 months | | |
| | Anaemic | Non-anaemic | p-value | Anaemic | Non-anaemic | p-value |
| <85 | 13 | 7 | **0.033** | 9 | 6 | ns |
| >85 | 1 | 6 | | 5 | 7 | |

Data analysed with Fisher's Exact Test.

**Fig 4.16 Organotopic measures**



#### *4.3.2.6.2 Other measures*

There was no significant difference in albumin, creatinine or CRP between the groups at any time point (Figure 4.16). The albumin concentration did increase significantly from discharge to 3 months in both groups ($p<0.001$) but only increased significantly from 3 to 6 months in the anaemic group ($p=0.03$).

## 4.4 Discussion

In the Ps and Qs Study (Chapter 3) we aimed to investigate the relationship between health related quality of life and physical function. In this subgroup analysis we aimed to explore the potential relationship between anaemia and physical function and quality of life. The 'gender / severe' anaemia analyses aimed to look at the differences between anaemic and non-anaemic patients at each time-point following critical illness. The 'finisher's' analyses aimed to look at a specific cohort of patients who remained anaemic at 3 months following ICU discharge and investigate which factors were associated with and may have contributed to these patients remaining anaemic and how the presence of anaemia affected the patient's actual and perceived physical function and quality of life. We also investigated which factors may be associated with improvement of the anaemia by 6 months.

### 4.4.1 Study design and limitations

The relationship between anaemia, physical function and quality of life in patients recovering from critical illness has never been investigated previously. We gathered appropriate data in a complex cohort of paints with acceptable levels of recruitment and loss to follow up during the study (discussed in Chapter 3). The major limitation of this analysis was of relatively small patient numbers particularly at 6 months; this was addressed in the 'gender / severe' analyses by looking at all available data at each time point. However this had the potential to confound the results as the loss to follow up and incomplete data available for all patients who were assessed could mean that the cohort of patients at 3 months were distinct from those at 6 months. This potential bias also existed in the 'finisher's' analysis which only included patients who had a complete dataset for the whole study. In conjunction with the 'gender / anaemia' study it was believed that this was a useful exploration of potential factors affecting recovery following critical illness, though it was recognised that the statistical significance and clinical significance of such an analysis should be interpreted with caution especially because of the risk of type II error.

### 4.4.2 Gender and severe anaemia analysis

Anaemia was prevalent at ICU discharge: 97% of our entire cohort was 'gender' anaemic and 73% had severe anaemia at ICU discharge. This anaemia persisted with 52% and 33% of patients remaining anaemic at 3 and 6 months respectively.

#### *4.4.2.1 Factors associated with the persistence of anaemia*

The presence of severe anaemia during recovery from critical illness was associated with a longer ICU stay, increased age but not with a greater illness severity or a greater development of organ failure during ICU stay. This was different from other studies within our population where renal failure and thrombocytopenia were associated with an increased risk of being anaemic at ICU discharge(Walsh, Lee et al. 2006). By 6 months the possible contribution of age and length of stay to the presence of anaemia has diminished. Patients who were anaemic at 6 months had a reduced hand grip strength and serum albumin concentration and elevated CRP suggesting that malnutrition and the persistence of inflammation contribute to the persistence of anaemia. Renal function does not appear to influence the development or persistence of anaemia during recovery, though very few of the cohort had significant renal impairment during follow up.

#### *4.4.2.2 The effects of anaemia on quality of life and physical function*

##### *4.4.2.2.1 Quality of life and anaemia*

Anaemia at 6 months was associated with a reduced physical 'quality of life'. The reduced quality of life prior to 6 months may therefore be due to other factors such as pain and muscle weakness which have a greater direct impact upon physical function compared to the less obvious effect of anaemia on patients who are likely to be inherently less active (i.e. the type of petrol in a car does not affect the performance when it has broken down!).

#### *4.4.2.2.2 Perceived physical function and anaemia*

Anaemia was associated with a worse perceived physical function as measured by Frenchay's Activity Index.

#### *4.4.2.2.3 Actual physical function*

Actual physical function as measured by the six minute walk test was impaired in the gender anaemia group compared with the non-anaemic patients at 6 months, although this effect was not present prior to this. Thus it is possible that ongoing physical recovery of the anaemic group was being prevented by the persistence of anaemia, although the possibility that anaemia was an epiphenomenon cannot be excluded. Ongoing inflammation was prevalent in anaemic patients at 6 months which may indicate that anaemia and poor physical function are linked indirectly through the persisting inflammatory state rather than directly. The HGS was also impaired in the anaemic groups, and this was evident as early as 3 months. The use of hand grip dynamometry may therefore be a useful tool in assessing patients following critical illness as it appeared to discriminate well between the anaemic and non anaemic groups at all time points and for both subgroup analyses. It also reflected the differences and changes in serum albumin concentrations reinforcing its use as a marker of nutritional assessment. It was also much more readily accepted and understood by the patients as a form of assessment and subjectively appeared to reflect the 'end of the bed' state of the patient.

### 4.4.3 'Finisher's' Analysis

Again the results show that anaemia is common and persistent. 50% of the 'complete' cohort who were anaemic at 3 months remained anaemic at 6 months. Interestingly, 2 of the patients who were not anaemic at 3 months were subsequently anaemic at 6 months.

#### *4.4.3.1 Factors associated with the persistence of anaemia*

The patients who were anaemic at 3 months were older, had a greater ICU length of stay and a greater requirement for inotropes / vasopressors during ICU stay compared to those who were not. This could potentially reflect that these patients had a greater inflammatory response during their ICU stay which persisted following recovery from the initial illness or that they required greater optimisation of their haemodynamic parameters and of oxygen delivery during ICU stay due to anaemia. Protein malnutrition and inflammation were associated with anaemia. Malnutrition had resolved by 6 months.

#### *4.4.3.2 The effects of anaemia on quality of life and physical function*

##### *4.4.3.2.1 Quality of life and perceived physical function*

Anaemia did not appear to affect the quality of life or the perceived physical function following of critical illness. This is not consistent with the findings for the gender / severe anaemia analysis. This may be due to the 'Finisher's Analysis' representing a self selecting cohort who by virtue of remaining in the study reflect a higher degree of function than one which included all the patients at each time point. However the analysis did show that quality of life and perceived physical function was significantly

affected by the development of critical illness and that this impairment persists to 6 months following ICU discharge.

#### *4.4.3.2.2 Actual physical function*

Actual physical function as measured by the 6MWT was not influenced by the presence of anaemia however the non-anaemic group did increase the distance walked significantly between 3 and 6 months. This could reflect a hierarchy of factors which contribute to impaired physical function following critical illness whereby the effects of anaemia are masked by greater physical complaints. As symptomatology improves, anaemia may then start to be a limiting factor in recovery. It may also reflect that patients who develop critical illness may have significantly impaired actual physical function prior to their critical illness affecting the usefulness of such a measure of physical function during rehabilitation.

## 4.5 Conclusions

There are several important findings from this subgroup analysis, some of which are contradictory depending upon which analysis is considered. The key finding of the Gender / Severe subgroup analysis is that persistent anaemia following critical illness is associated with impaired physical quality of life and impaired perceived AND actual physical function. However this finding is not wholly supported by the data, since the 'finisher's analysis' did not demonstrate a similar effect of anaemia. The finisher's cohort however, contains a smaller number of patients who are subject to self-selection

bias, and as such, the results of this subgroup analysis should be interpreted with caution.

The presence of anaemia during recovery in both analyses was also associated with increased age and a longer ICU stay but not with illness severity during critical illness. Furthermore, malnutrition and persistent inflammation were associated with ongoing anaemia in both studies.

.Assessment of physical function following critical illness is complex and simple measures of physical function such as hand grip strength rather than 'gold standard' assessments such as walk tests may be more sensitive to detecting impairment due to the heterogeneous patients group and the varied potential complications they develop. Physical rehabilitation from critical illness is becoming a cornerstone of ICU follow up care and may be a key determinant of a patients overall recovery from critical illness. Since anaemia may limit this physical recovery, treatment of anaemia may be an adjunct in rehabilitating patients. Further studies are now warranted to confirm the association of anaemia with impaired physical recovery and, if confirmed, randomised controlled trials of treatments for anaemia should be undertaken to translate these research findings into clinical benefits for patients.

# Chapter 5

# Conclusions and Future Directions

## 5.1 The three 'Rs'

'... For the secret of the care of the patient is in caring for the patient'

*Dr Francis Peabody.*

The burden of critical illness begins with the acute physical and psychological distress which develops when the patient's illness requires timely intervention to prevent death. It is increasingly apparent that many patients and their families experience persisting physical, psychological and cognitive dysfunction during recovery. Addressing these long term problems is necessary to allow consideration of the 'real' cost of critical care provision, both in human and financial terms. Although most patients do make a good recovery from critical illness and are satisfied with their new state of (albeit reduced) health, there are a significant number of patients who need **r**ecognition, **r**esources and **r**esearch to improve their quality of life.

The components of long term outcome are multi-factorial and are dependent upon the individuality of the patient's response to illness, the interaction between pre-morbid disease and critical illness, and the heterogeneity of the population, ICU environments and clinical practice. Determining which of the many factors throughout this extended period is responsible for the outcome measure being studied is one of the most challenging aspects of ICU research.

The research presented in this thesis aimed to determine the prevalence, pathophysiology and impact on quality of life of two common and potentially related complications of critical illness in the longer term - anaemia and physical morbidity.

## 5.2 Research in the critically ill

### 5.2.1 Recruitment and retention

One of the greatest problems encountered during this research related to recruitment and retention within the study. In TRAC, recruitment was much slower than anticipated. We recruited ~75% of eligible patients resulting in 30 patients enrolled after 1 year. 6 patients died during follow up and 5 (17%) were 'lost' to follow up. In the Ps and Qs study we recruited 63% of eligible patients resulting in 68 patients enrolled after 1 year. Only 35 patients remained in the study for the full 6 months, with 9 patients dying during follow up and 24 being 'lost'.

These figures are similar to other small ICU cohort studies but are less than the 70-80% retention considered acceptable for social science research and the much higher retention rates seen in the large multicentre ICU trials. This high attrition rate within our studies has the potential to impair the internal and external validity, particularly with bias introduced by 'differential dropout' between comparison groups. Differential dropout describes the evolution of a different study cohort over time due to differences between the patients who remained in the study compare to those who dropped out.

### 5.2.2 Methods used to reduce patient dropout

2 review articles suggest several methods which are believed to improve patient retention (Robinson, Dennison et al. 2007; Tansey, Matte et al. 2007). We utilised many of these strategies: respect for patients, flexibility of researcher hours and patient scheduling and good patient tracking systems. Despite this many patients 'disappeared'. This was partially due to many of the patients admitted to the intensive unit having 'chaotic' lifestyles with alcohol and drug problems. Additionally, one major test, the six minute walk test, had very poor patient acceptability and was potentially a cause for subsequent dropout.

#### *5.2.2.1 Unique methods to improve retention*

We attempted to improve patient retention by flexible scheduling, supported transport and visiting the patients in their own home, even offering to utilise a self powered treadmill at home to assess physical function (although all patients refused this option!). Despite this, retention remained difficult. Anecdotally, the burden of recovery with significant ongoing symptomology and multiple clinic appointments seemed to overwhelm many patients such that the perceived extra burden of ongoing participation in research was too much.

#### *5.2.2.2 The home visit and ICU follow up clinics*

The visiting of patients in their own homes provided a unique insight into the problems faced by the survivors of critical illness. Many of the patients simply wanted ***advice*** on how to get modifications to their home, access to appropriate benefits, and have their

specific problems, mainly muscle weakness and pain, treated by physiotherapy and medication. They also wanted reassurance and a 'medical MOT' by the doctors and nurses who they perceived as having helped them through their illness, as well as explanations for the multiple hospital appointments and investigations they felt they were being subjected to as part of their routine clinical care. This was particularly true for surgical patients who had developed medical complications of their admission. These interventions seem ideally suited to being addressed in the outpatient clinic environment. During the course of my research I have attended several ICU follow up clinics. They have varied from clinics which appeared to be run as data collection exercises (rather than for the benefit of the patient) to the other extreme of indulgence of physician vanity. At their best there have been clinics which have focused on each individual's and their families' specific needs, as well as addressing ICU related complications. Clinics can help to co-ordinate medical follow up in a cohesive manner when multiple specialities are involved in long term follow up. They can also provide social support and benefits advice and perhaps most importantly act as patient advocates in endeavouring to get the simple, but life changing, things done for the patient. Although ICU follow up is well established in the UK, a recent review of current research from ICU follow up clinics and the early findings from the PRACTICAL study found that there was no evidence of benefit from attendance (Williams and Leslie 2008) (Cuthbertson, Rattray et al. 2007; Cuthbertson, Rattray et al. 2009). This may be because chronic symptomatology is not easily addressed by infrequent contact with healthcare professionals and the emphasis may therefore need to be on intensive physical rehabilitation rather than the holistic post ICU care.

Cancellation and non-attendance rates were high for the clinics reinforcing the problems found in retaining patients in research, as it was difficult to retain patients in follow up focused ostensibly on benefiting the patient. The ICU clinic offers the opportunity to address the'three Rs' and focused assessment of the potential benefits of such clinics would be required to establish their role. In patients with chronic complex medical needs such as long term ventilation, the medical aspects of the clinics are run in conjunction with 'complex needs assessment' clinics with involvement of specialist nurses and social work input. These types of clinic have been shown to be effective for the elderly population in reducing hospital and nursing home admission (Beswick, Rees et al. 2008). As the elderly have many problems similar to the survivors of critical illness it could be concluded that such a clinic could have a role post ICU.

### 5.2.3 Methodological conclusions

In summary, ICU research is complex and retaining patients in research studies is often difficult to achieve. Novel methods such as visiting patients in their own homes does not improve retention *per se* but does provide valuable insight in to the lives of the survivors of critical illness. In designing a battery of assessments, it is important that the tests should be acceptable to the patient. In the Ps and Qs study, and potentially in other studies post ICU, the 6 minute walk test was a poor assessment of physical function as many of the patients were immobile through muscle weakness, pain or other co-morbidity. As there were many reasons why patients did not perform the test it does not accurately reflect the physical function of the population. The 6MWT has been established in specific populations (such as patients with ARDS) but not in the

heterogenous critical illness group. The hand grip dynamometry assessment appeared to be a portable, safe and acceptable test, with good clinical relevance and may well have a role in ascertaining physical function in ICU follow up.

Drop out rates could be expected to be high due to the often chaotic lifestyles of many of the patients and the overwhelming burden of symptoms and other medical appointments making further commitment unappealing to the patient. This makes ICU studies prone to drop out bias as only motivated patients remain in studies. Therefore, it is acknowledged that final data sets representing only those patients who completed the entire study may not wholly reflect the original cohort and results should be interpreted with caution.

## 5.3 The TRAC study

The TRAC study showed that anaemia persists up to 6 months following discharge and was associated with evidence of an ongoing inflammatory state and impairment of erythropoiesis. Health related quality of life was also noted to be impaired raising the possibility that anaemia may affect quality of life following critical illness

## 5.4 The Ps and Qs study

The Ps and Qs study showed that survivors of critical illness had a normal pre-morbid perceived physical function but a reduced quality of life. Both were significantly worsened by the critical illness and remained impaired up to 6 months. Actual physical function in our heterogeneous population was reduced to levels associated with very

severe chronic disease. There was evidence of a significant level of post traumatic stress disorder, persisting anaemia and malnutrition but no other organ dysfunction during recovery.

## 5.5 The Ps and Qs anaemia subgroup analysis

Further analysis of the Ps and Qs data was performed to investigate potential links between anaemia, physical function and quality of life. The results showed that persistent anaemia following critical illness was associated with impaired physical quality of life and impaired perceived AND actual physical function in snapshot of all available patients at a given time-point. However, when a cohort of patients who completed follow up was used for analysis such that the change within a cohort could be accurately reflected over time, a link between anaemia and physical function was not established. This could be due to complete cohort being prone to selection bias or the severity of physical impairment was such that the effect of anaemia was overwhelmed. The presence of anaemia during recovery in both analyses was associated with increased age and a longer ICU stay but not with illness severity during critical illness; furthermore, malnutrition and persistent inflammation were associated with ongoing anaemia.

## 5.6 Research conclusions

Anaemia is a common complication of critical illness which is not related to the severity of illness on admission to, or degree of organ failure developed within, ICU. There are obvious strategies for reducing iatrogenic blood loss such as paediatric tubes, return of aspirates and appropriate (rather than regular) blood sampling; modification of these factors could be evaluated to determine whether the prevalence of anaemia at ICU discharge could be reduced.

Since anaemia may contribute to impaired quality of life and physical function, strategies to treat it need to be evaluated. It was surprising how few of our patients received transfusion following discharge to the wards. Consideration of all methods to improve haemoglobin levels such as transfusion, recombinant erythropoietin and modulation of the inflammatory response should be considered despite the attendant risks. There is a suggestion from our research that the physical complications are overwhelming early in the recovery period potentially masking the contribution of anaemia to additional symptomology. As physical recovery improves, the impact of concurrent anaemia becomes apparent and there is a window where effective treatment of anaemia could be of great potential benefit.

Quality of life was dramatically impaired by critically illness, mainly in the physical domains and remained impaired at 6 months. Surprisingly, patients' mental health components of quality of life remained essentially normal. This is despite a significant prevalence of PTSD, which is known to be associated with marked impairment of

quality of life in other patient groups. It may be that "survival euphoria" overcomes any concomitant mental health disturbance.

Actual physical function was severely impaired and showed little signs of improvement by 6 months. However, our research suggests the 6MWT may be a poor assessment tool in the post ICU population and therefore this finding must be interpreted with caution. Perceived physical function although impaired showed signs of recovering with time, perhaps reflecting the resolution of physical symptoms allowing small improvements in what the patient feels they are able to achieve, despite significant persisting actual physical disability. In the longer term, the perception of improvement may be translated into actual physical recovery.

Importantly, our studies showed an association between anaemia and impairment of quality of life and physical function, raising the possibility that treatment of anaemia may be an important strategy in improving physical rehabilitation following critical illness.

## 5.7 Future directions

In conclusion these studies show that physical function and health related quality of life are dramatically affected by critical illness. Anaemia is highly prevalent in this population and is associated with ongoing inflammation and impaired erythropoiesis. Furthermore, anaemic patients potentially have a reduced quality of life and physical

function as compared with non-anaemic survivors. Therefore, treatment of anaemia and early physical rehabilitation may be the key to improving patients' longer term quality of life and physical function especially later in the recover period when the initial impairments preventing physical function are resolving. Physical rehabilitation from critical illness is becoming a cornerstone of ICU follow up care (Tan, Brett et al. 2009) and may be a key determinant of a patients overall recovery from critical illness. Since anaemia may limit this physical recovery, treatment of anaemia may be an adjunct in rehabilitating patients. Further studies are now warranted to confirm the association of anaemia with impaired physical recovery and, if confirmed, randomised controlled trials of treatments for anaemia should be undertaken to translate these research findings into clinical benefits for patients.

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# Appendix One

# Questionnaires

**Frenchay Activities Index**

| In the last **3** months how often have you undertaken: | |
|---|---|
| 1. Preparing main meals<br>2. Washing up after meals | 0 = Never<br>1 = Less than once a week<br>2 = 1-2 times per week<br>3 = Most days |
| 3. Washing clothes<br>4. Light housework<br>5. Heavy housework<br><br>6. Local Shopping<br>7. Social occasions<br>8 Walking outside for > 15 minutes<br>9. Actively pursing hobby<br>10. Driving car/going on bus | 0 = Never<br>1 = 1-2 times in 3 months<br>2 = 3-12 times in 6 months<br>3 = At least weekly |

| In the last **6** months how often have you undertaken: | |
|---|---|
| 11. Travel outing/car ride | 0 = Never<br>1 = 1-2 times in 6 months<br>2 = 3-12 times in 6 months<br>3 = At least weekly |
| 12. Gardening<br>13. Household maintenance | 0 = Never<br>1 = Light<br>2 = Moderate<br>3 = Heavy/All necessary |
| 14. Reading books | 0 = None<br>1 = 1 in 6 months<br>2 = Less than 1 in 2 weeks<br>3 = More than 1 every 2 weeks |
| 15. Gainful work | 0 = None<br>1 = Up to 10 hours/week<br>2 = 10-30 hours/week<br>3 = Over 30 hours/week |

**TOTAL____, Subscale 1____, Subscale 2____, Subscale 3____**

**Revised guidelines for using the Frenchay Activities Index**

The aim is to record activities which require some initiative from the patient. It is important to concentrate upon the patient's actual frequency of activity over the recent past, not distant past performance nor potential performance. One activity can only score on one item.

**Specific item information:**

1. Needs to play a substantial part in the organization, preparation and cooking of main meal. Not just making snacks or reheating prepared food.
2. Must do all or share equally, e.g. washing or wiping and putting away. Not just rinsing an occasional item.
3. Organization of washing and drying clothes, whether in washing machine, or by hand or at laundromat. Sharing task equally, e.g. loading, unloading, hanging, folding.
4. Dusting, polishing, ironing, tidying small objects or bedclothes. Anything heavier is included in item 5.
5. All heavier housework including changing beds, cleaning floors, fires and windows, vacuuming, moving chairs, etc.
6. Playing a substantial role in organizing and buying groceries, whether small or large amounts. Must go to the shop and not just push a cart. Can include collection of pension or going to the Post Office.
7. Going out to clubs, church activities, cinema, theatre, drinking, to dinner with friends, etc. May be transported there, provided patient takes an active part once arrived. Includes social activities at home, initiated by the patient, e.g. visits from family or friends not where main purpose is to provide care.
8. Sustained walking for at least 15 minutes (allowed short stops for breath). About one mile. Can include walking to do shopping, provided walks far enough.
9. Must require some 'active' participation and thought, e.g. propagating or caring for houseplants, knitting, painting, games, sports (not just watching sport on television). Can be mental activities, e.g. reading specialist magazines, doing the stocks and shares or window shopping for pleasure.
10. Must drive a car (not just be a passenger), or get to a bus/coach and travel on it independently.
11. Coach or rail trips or car rides to some place for pleasure. Not for a routine 'social outing' (i.e. shopping, going to local friends). Must involve some organization and decision-making by the patient. Excludes trips organized passively by institutions unless patient exercises choice on whether to go. The common factor is travel for pleasure. Holidays within the six months are divided into days per month e.g. a 7-day holiday equals 1 or 2 days per month.
12. Gardening outside:
    a. Light = occasional weeding or sweeping paths
    b. Moderate = regular weeding, raking, pruning, etc.
    c. Heavy = all necessary work including heavy digging.
13. Household maintenance:
    a. Light = repairing small items, replacing lamp lightbulb or plug
    b. Moderate = spring cleaning, hanging a picture, routine car maintenance
    c. Heavy = painting/decorating, most necessary household/car maintenance.

14. Must be full-length books, not periodicals, magazines or newspapers. Can be talking books.
15. Work for which the patient is paid, not voluntary work. The time worked should be averaged out over six months. For example, one month working for 18 hours/week over the six-month period would be scored as 'up to 10 hours/week'.

**Davidson Trauma Scale**

**Frequency scale**

Scores from 0-4.

| Response | Score |
|---|---|
| Not at all | 0 |
| once only | 1 |
| 2-3 times scores | 2 |
| 4-6 times | 3 |
| every day | 4 |

Have you had painful images, memories or thoughts of the events relating to Intensive Care?

Have you had distressing dreams of the event?

Have you felt as though the event was re-occurring?

Have you been upset by something which reminded you of the event?

Have you been avoiding any thoughts or feelings about the event?

Have you been avoiding doing things or going into situations which remind you of the event?

Have you found yourself unable to recall important parts of the event?

Have you had difficulty enjoying things?

Have you felt distant or cut off from other people?

Have you been unable to have sad or loving feelings?

Have you found it hard to imagine having a long life span fulfilling your goals?

Have you had trouble falling asleep or staying asleep?

Have you been irritable or had outbursts of anger?

Have you had difficulty in concentrating?

Have you felt on edge, been easily distracted, or had to stay on guard?

Have you been jumpy or easily startled?

Have you been physically upset by reminders of the event?

**Severity scale**

Scores from 0-4.

| Response | Score |
|---|---|
| Not at all distressing | 0 |
| minimally distressing | 1 |
| moderately distressing | 2 |
| markedly distressing | 3 |
| extremely distressing | 4 |

Have you had painful images, memories or thoughts of the events relating to Intensive Care?

Have you had distressing dreams of the event?

Have you felt as though the event was re-occurring?

Have you been upset by something which reminded you of the event?

Have you been avoiding any thoughts or feelings about the event?

Have you been avoiding doing things or going into situations which remind you of the event?

Have you found yourself unable to recall important parts of the event?

Have you had difficulty enjoying things?

Have you felt distant or cut off from other people?

Have you been unable to have sad or loving feelings?

Have you found it hard to imagine having a long life span fulfilling your goals?

Have you had trouble falling asleep or staying asleep?

Have you been irritable or had outbursts of anger?

Have you had difficulty in concentrating?

Have you felt on edge, been easily distracted, or had to stay on guard?

Have you been jumpy or easily startled?

Have you been physically upset by reminders of the event?

# Appendix Two

# Publications

# Time course of anemia during six months follow up following intensive care discharge and factors associated with impaired recovery of erythropoiesis*

Anthony P. Bateman, FRCA; Fiona McArdle, MSc; Timothy S. Walsh, MD

***Objectives:*** **Anemia is a common complication of critical illness, but its duration after intensive care discharge and possible contributory factors have not been studied. Our aim was to follow patients discharged anemic from the intensive care unit (ICU) for up to 6 months and determine the duration of and possible reasons for persisting anemia.**

***Design:*** **Prospective observational cohort study of intensive care (ICU) survivors with moderate-severe anemia at the time of ICU discharge. Erythropoietic and inflammatory markers were measured at regular intervals over six months to assess red cell production and factors limiting recovery from anemia.**

***Setting:*** **An 18-bed medico-surgical ICU in a Scottish university teaching hospital.**

***Patients:*** **Patients who required >24 hrs of ventilatory support and were discharged from intensive care with hemoglobin < 100 g/L were studied prospectively over 6 months. 30 patients were recruited; 19 completed 6 months follow-up, 6 died during the study period, and 5 completed part of the follow up. Patients with ongoing renal failure or chronic hematologic disorders were excluded.**

***Measurements and Main Results:*** **47% (9 of 19) of patients completing 6 months follow up recovered from their anemia. The median time to recovery was 11 wks (1st, 3rd quartiles: 9, 26 wks). 10 patients (53%) were still anemic 6 months after ICU discharge. No patients developed iron, vitamin B12 or folate deficiency. An inappropriately low erythropoietin response to anemia was observed in virtually all patients and did not distinguish nonrecovering patients. Patients with delayed recovery or persisting anemia during the 13 wks following ICU discharge had higher levels of circulating inflammatory markers (IL-6 and C-reactive protein) and did not exhibit reticulocytosis during the weeks following discharge.**

***Conclusions:*** **Anemia persists in many patients following critical illness and is associated with ongoing inflammation, inappropriate erythropoietin response and poor marrow red cell production. (Crit Care Med 2009; 37:1906–1912)**

**Key Words: anemia; critical illness; erythropoietin; erythropoiesis**

Anemia is a common complication of critical illness (1, 2). Once present it frequently persists until intensive care unit (ICU) discharge unless modified by blood transfusion or less well established practices such as erythropoietin administration. The Transfusion Requirements In Critical Care (TRICC) study (3) has resulted in a more consistent use of restrictive transfusion practice with typical median pretransfusion hemoglobin values between 78–85 g/L (2) When a restrictive transfusion policy is used the prevalence of anemia at ICU discharge is as high as 80% (4). Recent studies show that anemia is frequently still present at hospital discharge (5), and has normochromic normocytic characteristics similar to the anemia of chronic disease. Other epidemiologic studies followed patients for up to 28–30 days following ICU admission, but did not report anemia outcomes specifically for the post ICU recovery period (1, 6). It is not known how long anemia persists among ICU survivors or what factors influence the rate of recovery.

Many patients suffer reduced quality of life after hospital discharge, often associated with symptoms typical of anemia such as fatigue and breathlessness (7, 8). Many factors could contribute to these symptoms, but in other settings such as chronic renal failure (9), cancer (10) and cardiovascular disease (11, 12) anemia is associated with a poor quality of life and treatment improves symptoms. These observations are consistent with the hypothesis that anemia contributes to morbidity following critical illness.

The primary aim of this exploratory study was to determine the time period between ICU discharge and resolution of anemia in a cohort of patients discharged with significant anemia (hemoglobin <100 g/L). Our secondary aims were to study the components of erythropoiesis during recovery from critical illness and explore factors that might contribute to persistent anemia.

## MATERIALS AND METHODS

### Design and Setting

We performed a prospective cohort study following patients over a 6 months period following ICU discharge. The study received local ethics committee approval; informed consent was obtained from the patients. Patients were recruited from the 18-bedded medico-surgical ICU of the Royal Infirmary of Edinburgh, a university hospital receiving acute admissions

*See also p. 2108.

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Support and Funding: Chief Scientist's Office Project Grant CZG/1/97, Lothian University Hospitals Division Small Project Grant, Unrestricted Educational Grant, Orthobiotech Ltd.

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The authors have not disclosed any potential conflicts of interest.



DOI: 10.1097/CCM.0b013e3181a000cf

for all specialities except neurosurgery, colorectal surgery and urology.

## Recruitment

We planned to recruit all eligible patients over a 6 months period. We estimated a recruitment rate of 1–2 patients per week and a total study cohort of 40 patients. All 412 patients discharged alive from the ICU during an 11 month period were screened for inclusion to the study. Inclusion criteria were: Patients requiring more than 24 hrs advanced physiologic support (invasive ventilation alone or noninvasive ventilation plus support for an additional organ failure); hemoglobin concentration <100 g/L at ICU discharge; age >16 yrs. Exclusion criteria were: preexisting hematologic disorder; treatment with immunosuppressant or cytotoxic drugs; acute or chronic renal failure requiring renal replacement therapy at time of discharge; patients residing outwith reasonable geographical follow up; patients discharged for palliative care or not expected to survive to hospital discharge, and patients unable to give informed consent.

## Patient Characteristics

We recorded demographic data, clinical diagnosis, Acute Physiology and Chronic Health Evaluation II (APACHE II) score and worst Sequential Organ Failure Assessment (SOFA) score during ICU stay, hemoglobin concentration on admission to ICU and ICU length of stay. Although we excluded patients who required renal replacement therapy at the time of ICU discharge, we calculated the eGFR for all patients at study entry using the Modification of Diet in Renal Disease standard formula (13). At follow-up we recorded whether patients had received blood transfusions, iron, vitamin $B_{12}$ or folate supplements during the study period.

## Study Protocol

Patients were followed up at 1, 3, 6, 9, 13 and 26 wks post ICU discharge either in hospital or their homes. We measured hemoglobin concentration (Hb), mean cell hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) and mean red cell volume (MCV) at all visits. We used locally defined population reference ranges for hemoglobin to define anemia (male <130 g/L; female <115 g/L). We obtained advice from an expert group before the study (see acknowledgments) and established a range of measures to assess erythropoiesis by group consensus. We defined the following abnormalities *a priori*:

*Absolute iron deficiency* was defined as plasma ferritin concentration of <12 μg/L or <100 μg/L in the presence of elevated inflammatory markers. Patients with ferritin >100 μg/L were defined as having no evidence of iron deficiency irrespective of inflammatory markers (14).

*Functional iron deficiency* (impaired incorporation of iron during erythropoiesis despite adequate body iron stores) was defined as the presence of >5% hypochromic red cells (%HYPO) and/or a concentration of hemoglobin in reticulocytes (CHR) of <28 pg/L (15).

*Vitamin $B_{12}$, plasma folate and red cell folate deficiency* were defined as values below the laboratory reference ranges.

*Inappropriate erythropoietin response to anemia* was defined as a circulating erythropoietin concentration that was lower than published values relating hemoglobin with plasma erythropoietin concentration(16, 17). Specifically we defined an abnormal erythropoietin concentration as <40 mIU/mL and <20 mIU/mL for hemoglobin concentrations of <100 g/L and <120 g/L respectively.

*Persistent inflammation* was defined as detectable (>10 pg/mL) circulating interleukin-6 (IL-6) and/or CRP >5 g/L (18).

*Evidence of new erythropoiesis* (a measure of bone marrow responsiveness) was defined as a reticulocyte count above the normal range (>55 × $10^9$) (19) and/or an increase in soluble transferrin receptor (sTfR) concentrations above normal values using a locally determined control distribution.

Analyses of the standard hematologic parameters were carried out in the hospital laboratory. %HYPO, CHR analyses were carried out within 3 hrs of sampling. Samples for serum assays were spun within 2 hrs and stored at −80°C. Serum erythropoietin concentrations were measured by enzyme linked immunosorbant assay (ELISA) at Simbec Research Ltd, Methry Tydfil, UK. Serum IL-6 and sTfR were measured using ELISA kits (Quantikine R&D Systems, Minneapolis, MN).

## Analysis

We plotted hemoglobin values against time and calculated the proportion of anemic patients at each time point. For this analysis we used lower limits for gender specific population reference ranges as cut off values. To assess the rate of recovery from anemia we calculated rates of increase in hemoglobin between visits. An increase of 10 g/L per week is frequently quoted as a healthy response to blood loss. We also included a lower cut off at 5 g/L.

We explored differences between patients who recover more quickly from anemia after ICU discharge ('responders') with those who remained anemic or recovered slowly ('nonresponders') by comparing variables for the subgroups whose hemoglobin was within the reference range at 13 wks with those who remained anemic. We compared patient characteristics at baseline, including measures of illness severity (APACHE II score and worst nonneurologic SOFA score), and ICU length of stay. To explore pathophysiological factors associated with poor recovery we compared variables at the 3 wks visit using the Mann-Whitney test and Fisher's exact test to compare proportions. Week 3 was chosen as it was expected that the greatest divergence between the two groups would be apparent early in those who would recover.

Microsoft Excel and GraphPad Prism (Version 4) were used for analyses.

## Exploratory Assessment of Impact on Health-Related Quality of Life (HRQoL)

We measured HRQoL using the SF-36 self-reporting questionnaire at 3 and 6 months. To explore the possible associations between anemia at ICU discharge and subsequent HRQoL, we compared our data with a previously published nonselected patient cohort of ICU patients followed up in Scotland for HRQoL outcomes (20) and age/gender matched normal population data (21).

# RESULTS

## Study Recruitment

We recruited 30 patients (77% recruitment rate for eligible patients; Fig. 1). Six patients died during the study follow up (20% death rate) and 5 patients dropped out or were lost to follow up (17% drop out rate). Demographic and clinical characteristics for the study cohort and the timing and causes of death during the study are shown in Table 1.

Two of the female patients were premenopausal. One patient had normal menses and was no longer anemic by the third week of follow up. The other patient did not return to normal menses until 3 months following ICU discharge; her hemoglobin returned to normal range by 6 months. No patients received blood transfusions during the study follow up period and none were prescribed iron, folate or vitamin B12 supplements. No patients had known malignancies. No patients received erythropoietin therapy during the study.

## Time Course of Anemia after ICU Discharge

Hemoglobin concentrations over the study period and the proportions of patients remaining anemic at each time point are shown in Figure 2. Among the patients remaining in the study 63% (12 of 19) were anemic at 13 wks and 53% (10 of 19) were anemic at 26 wks compared to gender specific reference ranges. 32% (6 of 19) and 16% (3 of 19) of patients had a

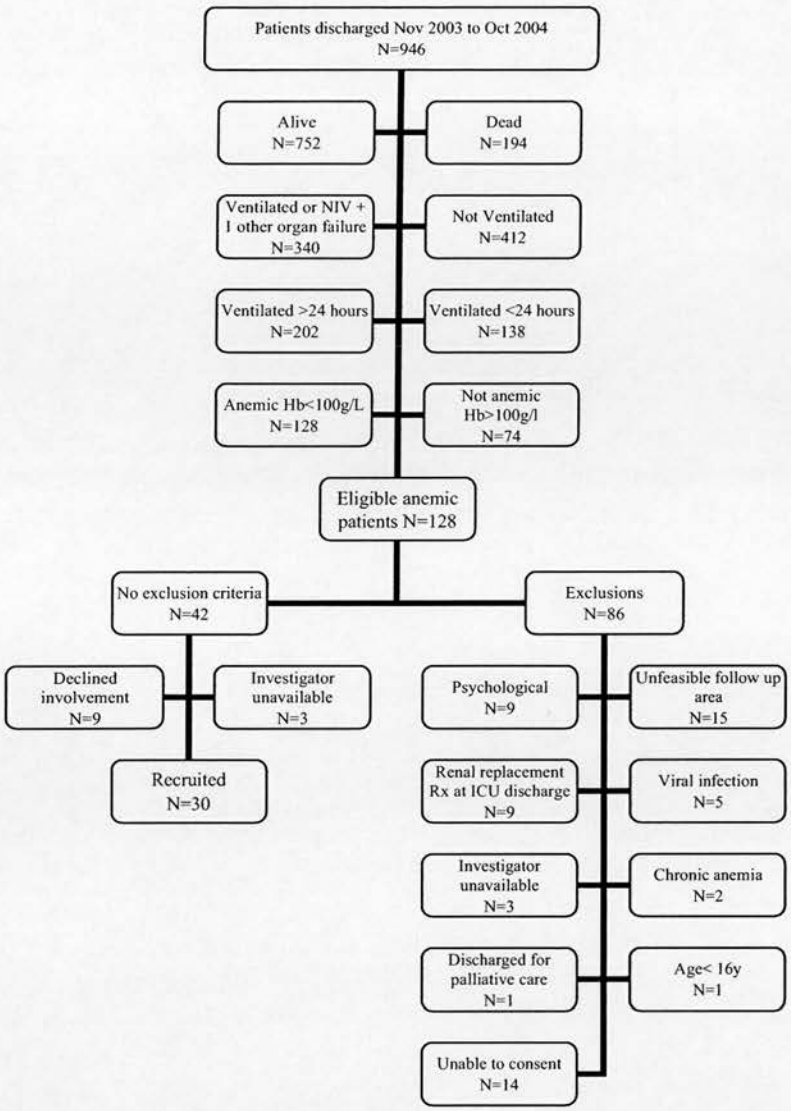


Figure 1. Flow chart of study recruitment. *NIV*, noninvasive ventilation; *Hb*, hemoglobin; *Rx*, prescription; *ICU*, intensive care unit.

hemoglobin concentration <110 g/L at 13 and 26 wks respectively. Among the patients whose anemia recovered during the study period the median time to entering the gender specific reference range was 11 wks (1st and 3rd quartiles 9 and 26; range 1 to 26 wks). Using rates of increase in hemoglobin between visits, from weeks 1 to 3 only 30% (n = 7) patients demonstrated a hemoglobin increase of ≥10 g/L per week and 60% (n = 13) an increase ≥5 g/L per week. Among those patients still anemic at 6 wks post-ICU discharge, none demonstrated an increase ≥5 g/L per week over the remainder of the study period.

## Etiology of Anemia

Baseline hemoglobin levels (median (1st, 3rd quartile)) for patients at recruitment (week 0) were 88.5 g/L (84.0, 95.0). Subsequent values and additional hematologic parameters are summarized in table 2.

*Absolute Iron Deficiency.* Ferritin concentrations were >12 μg/L in all patients throughout the study. Some anemic patients with detectable circulating inflammatory markers had ferritin values 12–100 μg/L, particularly at later time points, but this was unusual. The data suggested that absolute iron deficiency was rare, but may have been present in a small number of patients during the later stages of recovery.

*Functional Iron Deficiency.* The CHR was >28 pg throughout the study in virtually all cases. Some patients had >5% hypochromic red cells early in the study, but this was not seen later in the study. Among patients with >5% hypochromic red cells the mean cell hemoglobin concentration (MCHC) was normal. These data suggested that the detection of functional iron deficiency was test-specific. If present, based on percent hypochromic red cells, it was only present in the early post-ICU period.

*Evidence of Vitamin $B_{12}$ or Folate Deficiency.* Only one patient had a vitamin $B_{12}$ level marginally below the reference range (value 165 ng/L) at week 26. One patient had a folate level marginally below the reference range (value 1.8 μg/L) at week 13, which recovered without treatment by week 26. For all other cases and time points there was no biochemical evidence of vitamin $B_{12}$ or folate deficiency. The data showed that vitamin $B_{12}$ and folate deficiency rarely contribute to anemia after intensive care.

*Persistent Inflammation.* IL-6 and CRP were elevated in most patients at ICU discharge and persisted in many patients at the early evaluation time points (Table 2). There was a highly variable pattern during long-term follow up, but some patients continued to have elevated circulating concentrations of inflammatory markers at 3 and 6 months after ICU discharge.

*Inappropriate Erythropoietin Response.* We found that inappropriately low erythropoietin concentrations were highly prevalent throughout the study, and were present in all patients who remained anemic during the later stages (Table 2). These data showed that the healthy erythropoietin response to anemia was either blunted or absent.

*Evidence of New Erythropoiesis.* A minority of patients (approximately 20%) had elevated sTfR during the study period, but these levels were only modestly increased compared to controls and did not appear to relate to the degree of anemia (Table 2). There was a range in patterns of reticulocyte response. Patients who remained anemic at later time points tended to demonstrate a lack of reticulocyte response to anemia. Together, the data showed a hypo-active bone marrow given the degree of anemia.

## Comparison of Responders and Nonresponders at Week 3 After ICU Discharge

There were no major differences in age, ICU length of stay, admission APACHE II score, and worst nonneuro-

Table 1. Demographics and characteristics of patients recruited to the study

| Demographic | Number. Median (1st and 3rd Quartiles; Range) |
|---|---|
| Gender (♂/♀) | 20/10 |
| Age (yrs) | 66.5 (55, 77; 35–83) |
| APACHE II at admission | 21 (16, 24; 7–38) |
| Worst SOFA score during ICU stay | 9.5 (7.2, 14.0; 5–18) |
| ICU length of stay (days) | 12 (9, 23; 2–46) |
| Hemoglobin at ICU admission (g/L) | 96 (80, 104; 65–164) |
| eGFR at study entry (mL/min/1.73 $m^2$) | 84.9 (53, 102; 13–154) |

| Primary Diagnosis | Number |
|---|---|
| Respiratory | |
| Infective exacerbation of COPD | 7 |
| Pneumonia | 3 |
| Cardiac | |
| Cardiac failure | 3 |
| Post cardiac arrest | 1 |
| GI | |
| Perforated viscous | 4 |
| Alcoholic liver disease | 2 |
| Variceal hemorrhage | 1 |
| Acute pancreatitis | 1 |
| Vascular | |
| Ruptured abdominal aortic aneurysm | 2 |
| Unexpected complication of surgery | |
| Excess bleeding (thyroidectomy) | 1 |
| Protracted surgery (elective abdominal aortic aneurysm repair) | 1 |
| Intraoperative cardiac ischemia | 1 |
| Endocrine | |
| Diabetic ketoacidosis | 1 |
| Other sepsis | |
| Liver abscess | 1 |
| No organism identified | 1 |

Deaths

| Characteristics, Time in Study | Cause of Death |
|---|---|
| Male 85 yrs, 1 wk | Cardiac failure |
| Male 83 yrs, 1wk | Respiratory failure |
| Female 49 yrs, 3 wks | Decompenesated liver failure |
| Male 81 yrs, 9 wks | Respiratory failure |
| Female 62 yrs, 9 wks | Infective exacerbation COPD |
| Female 79 yrs, 9 wks | Pulmonary embolism |

APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal.

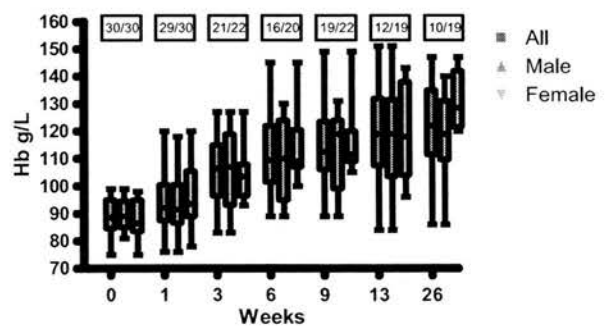


Figure 2. Distribution of hemoglobin concentrations for all patients (*dark gray*) and male and female subset (*mid and light gray, respectively*). Box and whisker plots illustrating median, inter-quartile range and range. The boxes including numbers at each time point represent the number of patients remaining anemic (*numerator*) and the number of samples obtained at each point (*denominator*).

logic SOFA score between responders and nonresponders at 3 months post-ICU discharge (Table 3). Nonresponders received more red blood cell units in ICU. There were no clinically or statistically important differences in measures of absolute or relative iron deficiency, vitamin $B_{12}$ status, red cell folate, or serum folate between responders and nonresponders either at 3 wks after ICU discharge or at any time point over the study period (Table 3). Patients whose anemia did not recover by week 13 had significantly higher CRP concentrations and a trend to higher IL-6 concentrations at week 3 after ICU discharge. These patients had lower reticulocyte counts consistent with persisting marrow hypo-responsiveness in the post-ICU period. Ferritin concentrations were significantly higher in the nonresponder group. There was no difference in circulating erythropoietin concentrations between the groups; both groups had inappropriately low erythropoietin concentrations 3 wks after ICU discharge. Examining trends over time, the nonresponder group tended to have higher CRP and lower reticulocyte counts over the course of the study (data not shown).

### Exploratory Assessment of Impact on Health-Related Quality of Life (HRQoL)

SF-36 questionnaire data are shown for the patients in table 4. Data from a nonselected cohort of ICU survivors from a Scottish ICU with similar case-mix are also included (20), together with age/gender matched UK normal population (21)data. Although numbers in the study cohort were small, patients who were discharged anemic from ICU had a markedly reduced mean SF-36 score at both 3 and 6 months compared to the normal population. Compared to the nonselected ICU cohort data, mean scores were also reduced across all domains, but particularly in the physical function and role physical categories. Formal statistical comparisons were not made.

## DISCUSSION

To our knowledge this is the first study examining the time course and pathophysiology of anemia during long term follow up after intensive care. Anemia recovered at rates expected for healthy individuals in only 30% of cases. In the majority of patients recov-

Table 2. All measured parameters during the study

| Parameter/NR | Week 1 | Week 3 | Week 6 | Week 9 | Week 13 | Week 26 |
|---|---|---|---|---|---|---|
| Hemoglobin (g/L) | 92 (87, 100) | 106 (96, 115) | 109 (101, 122) | 112 (105, 123) | 119 (107, 132) | 122 (111, 135) |
| Ferritin (μg/L) (NR <12 or <100 if CRP >5) | 367 (146, 769) | — | — | — | 130 (44, 386) | 76 (24, 179) |
| CHR pg (NR 28–35) | 32.1 (30.4, 33.9) | 32.0 (30.5, 33.5) | — | 30.8 (29.2, 32.6) | 30.4 (28.9, 31.8) | 31.9 (26.3, 32.9) |
| %HYPO (NR <5%) | 4.05 (2.05, 6.95) | 2.90 (0.75, 6.10) | — | 2.05 (0.70, 5.10) | 1.40 (0.70, 3.20) | 0.70 (0.15, 1.50) |
| STfR nmol/L (NR <51) | 38.4 (19.7, 45.7) | 30.3 (22.8, 50.9) | 37.1 (24.0, 47.8) | 38.2 (27.9, 46.6) | 36.5 (22.3, 48.5) | 42.4 (22.7, 49.1) |
| EPO mIU/mL (NR >40 if Hb <100) | 18.1 (8.8, 25.9) | 14.0 (9.7, 21.6) | — | 17.9 (11.4, 23.7) | 11.3 (8.6, 20.2) | 12.8 (9.9, 21.9) |
| IL6 (pg/mL) (NR <10) | 49.1 (30.9, 99.1) | 29.3 (12.7, 58.8) | 14.8 (9.4, 36.9) | 18.2 (8.9, 39.5) | 12.3 (7.8, 27.1) | 10.9 (8.6, 17.5) |
| CRP (mg/dL) (NR <5) | 51.0 (21.0, 108.0) | 16.5 (5.0, 60.0) | 10.0 (5.0, 23.5) | 15.0 (5.0, 61.5) | 9.0 (5.0, 21.0) | 5.0 (5.0, 11.5) |
| Vit B12 (ng/L) (NR 170–730) | 610 (429, 1279) | — | — | — | 353 (296, 494) | 326 (265, 410) |
| Serum folate (μg/L) (NR 2.0–13.5) | 5.70 (3.70, 7.45) | — | — | — | 7.85 (3.70, 8.85) | 6.50 (3.80, 9.80) |
| Red cell folate (μg/L) (NR 95–570) | 254 (198, 391) | — | — | — | 283 (147, 322) | 237 (164, 398) |
| Reticulocytes $\times 10^{-9}$ (NR <55) | 99.9 (72.8, 140.7) | 72.6 (54.9, 91.0) | — | 63.4 (45.8, 91.3) | 62.4 (46.7, 92.5) | 67.0 (51.9, 96.9) |

NR, normal range; CHR, concentration hemoglobin in reticulocytes; %HYPO, percentage hypochromic red cells; STfR, soluble transferrin receptor; EPO, erythropoietin; IL-6, interleukin-6; CRP, C-reactive protein.

The values are given as median (first, third quartile).

Table 3. Week 3 parameters of inflammation, erythropoietin, and marrow response for "responder" (anemia recovered by week 13) vs. "non-responder" (failure to recover by week 13) groups

| Parameter | Responder Group (N = 7) | Nonresponder Group (N = 12) | p |
|---|---|---|---|
| Baseline characteristics | | | |
| Age (yrs) | 57.2 (54.0–63.0) | 69.9 (64.5–75.5) | 0.075 |
| ICU stay (days) | 11.0 (4.0–12.0) | 14.5 (9.0–17.0) | 0.150 |
| APACHE II (admission) | 23.0 (16.0–28.0) | 20.5 (14.5–25.0) | 0.554 |
| SOFA max (not neuro) | 8.0 (6.0–12.0) | 10.5 (7.5–14.5) | 0.472 |
| ICU Transfusions (units) | 2.0 (0.0–8.0) | 7.0 (4.0–16.0) | 0.188 |
| Proportion of patients with abnormal eGFR (<60 mL/min/1.73 $m^2$) | 2/7 (28.5%) | 5/12 (41.6%) | 0.654 |
| Parameters | | | |
| Hemoglobin (g/L) | 115 (110.0–120.5) | 105 (100.5–115.0) | 0.208 |
| Erythropoietin concentration (mIU/mL) | 14 (10.2–19.25) | 13.2 (10.7–14.2) | 0.690 |
| Number (proportion) with inappropriately low erythropoietin levels | 5/7 (71%) | 8/11 (72%) | 1.000 |
| CRP (mg/dL) | 5 (5–11) | 60 (27.8–124.5) | 0.013[a] |
| Number (proportion) with elevated CRP | 2/7 (28%) | 8/8 (100%) | 0.007[a] |
| IL-6 (pg/mL) | 11.99 (8.01–14.44) | 32.48 (18.03–49.62) | 0.197 |
| Number (proportion) with elevated IL-6 | 1/7 (14%) | 6/9 (66%) | 0.060 |
| Reticulocytes ($\times 10^9$) | 62.1 (53.2–98.0) | 43.6 (33.8–54.8) | 0.014[a] |
| Number (proportion) with reticulocytes $<55 \times 10^9$ | 2/7 (29%) | 9/11 (81%) | 0.049[a] |
| Ferritin 3 months (μg/L) | 90.0 (15.0–130.0) | 365.5 (45.5–512.5) | 0.0312[a] |
| Vitamin $B_{12}$ 3 months (ng/L) | 348 (297–541) | 359 (285–589) | 0.7577 |
| Folate 3 months (μg/L) | 9.4 (6.2–17.1) | 5.8 (2.6–8.1) | 0.0549 |

ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; CRP, C-reactive protein; IL, interleukin.

[a]Significant *p* values. All values median (1st, 3rd quartile) unless stated.

ery was slow or absent such that 63 and 53% of all patients were still anemic at 3 and 6 months respectively, and 32 and 16% respectively had hemoglobin values <110 g/L.

*Strengths and Weaknesses.* Our cohort was an unselected mixed general ICU population with a high illness severity and varied case-mix. Patient numbers were relatively small as the protocol required frequent follow-up either in hospital or at the patients' home and multiple blood analyses. As a result there was a possibility of type II error, so we limited analysis to descriptive methods, with the exception of the exploratory comparison of patients whose anemia recovered at 13 wks versus those with persisting anemia. We achieved high rates of follow-up and sampling, which decreased the chance of bias. The investigations used to describe the etiology of anemia and the definitions of different contributory factors were predefined by an independent expert panel of hematologists. Some important subgroups were excluded, notably patients with persisting acute renal failure or preexisting chronic renal failure. These patients have an independent reason for erythropoietin deficiency and impaired erythropoiesis, and also tend to have greater ongoing blood loss from sampling and dialysis circuits (22). Although treatment decisions were not dictated by the study, no patients received any blood transfusions, iron/folate, erythropoietin or other treatments that might have confounded our findings.

*Meaning of Our Findings.* Our data strongly suggest that recovery was limited primarily by a hypo-reactive bone marrow. This may have been in part a result of inappropriately low circulating erythropoietin levels, although this was a feature of both responders and nonresponders early in the study follow up. It is well documented that circulating erythropoietin concentrations are lower than expected in anemic patients during ICU stay; our data indicate that this persists into the recovery period. The hypo-reactive bone marrow that characterized the nonresponding patients is typical of an anemia of chronic inflammatory disease in which pro-inflammatory mediators inhibit erythrogenesis (23, 24). In the exploratory comparison between patients whose anemia recovered by 3 months and those in whom it persisted we found no obvious differences in the characteristics of ICU stay, although these analyses had a high risk of type II error. Despite the small numbers of patients compared, circulating IL-6 and CRP concentrations were higher in the nonresponder group during this early period of recovery, which supports the conjecture that persistent anemia after critical illness is associated with a chronic inflammatory state.

Table 4. Individual SF-36 parameters for patients in the study group at 3 and 6 months post-ICU (N = 19 at both time points)

| | Physical Function | Role Physical | Bodily Pain | General Health | Vitality | Social Function | Role Emotion | Mental Health |
|---|---|---|---|---|---|---|---|---|
| UK Normal population | 76.2 (22.3) | 75.9 (37.5) | 76.9 (24.0) | 68.1 (21.9) | 61.8 (21.2) | 86.2 (22.7) | 84.8 (30.6) | 76.4 (18.4) |
| 3 months post-ICU discharge | | | | | | | | |
| UK ICU nonselected cohort | 59.4 (24.1) | 47.4 (32.8) | 63.4 (30.2) | 58.0 (23.7) | 48.4 (22.9) | 63.7 (35.7) | 79.3 (28.1) | 75.5 (20.1) |
| Study group | 40.2 (27.3) | 11.9 (26.9) | 49.3 (32.5) | 47.8 (22.5) | 38.1 (20.5) | 54.2 (31.2) | 50.8 (44.2) | 67.2 (18.9) |
| 6 months post-ICU discharge | | | | | | | | |
| UK ICU nonselected cohort | 61.7 (28.7) | 53.1 (34.1) | 66.0 (31.7) | 58.7 (25.4) | 51.9 (24.3) | 69.2 (32.9) | 81.3 (28.0) | 76.8 (19.7) |
| Study group | 44.6 (30.4) | 17.6 (32.8) | 60.6 (26.5) | 43.3 (20.2) | 42.6 (21.4) | 56.6 (25.8) | 49.0 (44.3) | 62.8 (24.1) |

ICU, intensive care unit.

For comparison, UK matched normal population values (21) and values from a nonselected Scottish ICU cohort (20) are included. All values mean (standard deviation).

The nonresponder group also had significantly higher ferritin concentrations, which is most likely an indication of greater inflammation as ferritin is a positive acute phase protein. During follow up, 65% and 60% of patients still had detectable circulating IL-6 at 3 and 6 months respectively after ICU discharge, and 48% and 31% had elevated CRP concentrations. This is a possible explanation for the "inappropriate" erythropoietin response and impaired erythropoiesis. Inflammatory mediators are known to inhibit erythropoietin production and the marrow response to circulating erythropoietin(25, 26). Serum from ICU patients, particularly those with sepsis, directly inhibits erythroid precursors, and can induce apoptosis of red cell precursors (27, 28).

There was little evidence of iron, folate or $B_{12}$ deficiency at any point in the study. In a small number of patients ferritin concentrations fell late in follow up in patients whose anemia recovered, often in association with normalization of inflammatory markers. This could indicate either resolving inflammation or a decrease in iron stores resulting from active erythrogenesis. None of these patients developed evidence of absolute iron deficiency during the study period using our predefined criteria. The interpretation of the indices of functional iron deficiency was difficult and contradictory between methods of assessment. Overall there was little evidence for significant functional iron deficiency. The high percent hypochromic red cells observed in some patients early after ICU discharge was consistent with previously reported findings during ICU stay (29–31). Although this could indicate impaired incorporation of iron into red cells another explanation could relate to red cell shape changes that occur during sepsis and inflammation (8, 32), which are not accounted for in the automated red cell analysis. It is also possible that functional iron deficiency only becomes apparent when the marrow is stimulated with exogenous erythropoietin.

The clinical importance of anemia during recovery from critical illness is unknown. It is well documented that patients suffer fatigue and breathlessness following critical illness even without demonstrable lung pathology (8). It is possible that anemia contributes to these symptoms, but no studies have specifically addressed this question. Our HRQoL data, although exploratory, support the hypothesis that the presence of anemia at ICU discharge is associated with poorer recovery at 3 and 6 months compared to other ICU patients and is associated with markedly reduced HRQoL compared to the general population, especially in physical function domains. Further adequately powered studies are needed to explore whether the relationship between anemia and HRQoL is causative or simply an epiphenomenon. The relationship between anemia and HRQoL reported in other patient groups, such as those with chronic kidney disease and cancer suggest this merits further study (9, 10).

## CONCLUSIONS

We have shown that anemia persists for at least 6 months following intensive care discharge in many patients with no history of preillness anemia. The erythropoietin response to anemia is blunted during this period and bone marrow is hyporeactive in many patients, especially those with persistent systemic inflammation.

## ACKNOWLEDGMENTS

We would like to thank the following expert panel for their invaluable advice: Dr. Ivor Cavill, Senior Lecturer in Haematology, Department of Haematology, University of Wales College of Medicine, Heath Park, Cardiff CF14 4XU, Dr. Huw Roddie, Consultant Haematologist, Department of Haematology, Western General Hospital, Crewe Road, Edinburgh, EH4 2XU, Professor Martin Pippard, Department of Molecular & Cellular Pathology, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY.

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