The relationship between anxiety during critical illness and adverse emotional outcomes

By

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Abstract

Objective: Survivors of critical illness experience compromised psychological health including the development of symptoms of anxiety, depression and post-traumatic stress. The aims of this study were to: (1) describe the magnitude and patterns of state anxiety reported by patients throughout their ICU stay; (2) identify factors associated with patients’ state and trait anxiety during critical illness; (3) determine factors associated with symptoms of anxiety and depression over six months after intensive care unit (ICU) discharge; and, (4) determine factors associated with post-traumatic stress symptoms (PTSS) over six months after ICU discharge.

Design: Prospective longitudinal cohort study.

Setting: One mixed medical/surgical/trauma ICU in an adult tertiary hospital in Brisbane, Australia.

Patients: Participants (n=141) were adult survivors of intensive care admitted ≥24 hours to the ICU.

Measurements: The study outcome of anxiety during critical illness was assessed using the Faces Anxiety Scale (FAS) to assess the state component of anxiety and the trait component of the State-Trait Anxiety Inventory (STAI) Form Y-2 to assess the trait component of anxiety. The study outcomes of symptoms of anxiety, depression and post-traumatic stress over six months after ICU discharge were assessed using the Hospital Anxiety Depression Scale (HADS) and the Post-traumatic Stress Syndrome 10-Questions (PTSS-10) Inventory, respectively. Other measures included the
Multidimensional Scale of Perceived Social Support (MSPSS), the Life Orientation Test-Revised (LOT-R) and Medical Outcome Study Cognitive Functioning Scale (MOS COG). Clinical and demographic data were obtained from patients and medical records. Ethical approval and informed consent were gained. Multiple linear regression modelling process was used to determine factors associated with state anxiety and trait anxiety. Mixed effect regression models with a random intercept per subject were used to determine factors associated with symptoms of anxiety, depression and post-traumatic stress over six months after ICU discharge.

**Main Results:** Of the 141 participants in this study, 98 (70%) were male with an average age of 54 (standard deviation, SD±15) years and stayed in ICU for about 4 (interquartile range, IQR: 3-7) days. The majority (n=115, 82%) of participants reported state anxiety at least once during their stay in ICU with 81 (57%) reporting moderate to severe levels. Although some fluctuations in state anxiety occurred over time, moderate levels were predominantly reported on days 6 to 12. The levels of trait anxiety in these participants (36, IQR: 29-47) were similar to the ones found in the Australian population. Multiple linear regression modeling process identified that factors related to state anxiety in ICU were pain and trait anxiety. Factors associated with trait anxiety were trait optimism, state anxiety, previous mental health treatment, and age.

Of the 141 participants assessed in ICU, 120 completed the follow-up in the hospital wards, 101 the three-month follow-up and 92 the six-month follow-up. Symptoms of anxiety were reported by 42% of the participants while in the hospital wards, 26% at three months and 28% at six months after ICU discharge. Factors significantly associated with symptoms of anxiety were trait anxiety (0.6, 95%CI: 0.2, 1.1, p=0.004), symptoms of depression after ICU discharge (0.4, 95%CI: 0.3, 0.5,
cognitive functioning (-0.4, 95%CI: -0.6, -0.2, p<0.0001), PTSS at six months (0.6, 95%CI: 0.3, 1.0, p<0.0001), post-ICU memories of Intra-ICU anxiety (0.8, 95%CI: 0.2, 1.5, p=0.014) and evidence of mental health treatment prior to the ICU admission (-0.9, 95%CI: -1.8, -0.1, p=0.029).

Symptoms of depression were reported by 37% of the participants while in the hospital wards, 19% at three months and 23% at six months after ICU discharge. Factors significantly associated with symptoms of depression were trait anxiety (0.8, 95%CI: 0.3, 1.2, p<0.001), symptoms of anxiety after ICU discharge (0.4, 95%CI: 0.3, 0.5, p=0.0001), cognitive functioning (-0.5, 95%CI: -0.7, -0.2, p<0.0001), PTSS at three months (0.5, 95%CI: 0.2, 0.9, p=0.003), and ICU admission due to trauma (1.7, 95%CI: 0.6, 2.9, p=0.003).

High levels of PTSS occurred in 19% of participants at three months and 17% at six month after ICU discharge. Mixed effect regression models showed that factors independently associated with PTSS over six months after ICU discharge were trait anxiety (2.2, 95%CI: 0.3, 4.1, p=0.023), symptoms of anxiety after ICU discharge (0.6; 95%CI: 0.2, 1.1; p=0.005), younger age (-1.4, 95%CI: -2.6, -0.2, p=0.024) and evidence of mental health treatment prior to the ICU admission (5.2, 95%CI: 1.5, 8.9, p=0.006).

**Conclusion:** Symptoms of anxiety, depression and post-traumatic stress during recovery are a significant issue for general ICU survivors. Trait anxiety was significantly associated with adverse emotional outcomes over six months after ICU discharge. There was also a significant relationship between memories of anxiety during ICU treatment and anxiety during recovery. High levels of PTSS over time were significantly associated with younger age, evidence of mental health treatment prior to the ICU admission, higher levels of trait anxiety and more symptoms of anxiety after...
ICU discharge. In addition, both components of anxiety (state and trait) were significantly associated with each other. Early assessment and interventions directed to reduce state and trait anxiety in the ICU patient and survivor might decrease the risk of symptoms of anxiety, depression and post-traumatic stress after critical illness.
Statement of originality

This work has not previously been submitted for a degree or diploma in any university. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.

___________________________
Maria Isabel Castillo Escobar
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List of abbreviations

AB                   Abstract
ADL                  Activities of Daily Living
AGFI                 Adjusted Goodness of Fit Index
AIC                  Akaike Information Criteria
ALI                  Anxiety Level Index
ALI                  Acute Lung Injury
ANOVA                Analysis of Variance
APACHE II            Acute Physiology and Chronic Health Evaluation II
APACHE III           Acute Physiology and Chronic Health Evaluation III
ARDS                 Acute Respiratory Distress Syndrome
BIC                  Bayesian Information Criterion
BSI                  Brief Symptoms Inventory
CAM-ICU              Confusion Assessment Method for the ICU
CES-D                Centre for Epidemiologic Studies Depression Scale
CI                   Confidence Interval
CINHAL               Cumulative Index of Nursing and Allied Health Literature
CPOT  Critical-Care Pain Observation Tool

dL  Deciliter

DSI  Daily Sedation Interruption

DSM-IV  Diagnostic and Statistical Manual of Mental Disorders 4th Edition

DSM-V  Diagnostic and Statistical Manual of Mental Disorders 5th Edition

DTS  Davidson Trauma Scale

E  Exclusion criteria

EQ-5D  European Quality of Life-5 Dimensions

ETIC-7  Experience after Treatment in Intensive Care 7-Item Scale

FAS  Faces Anxiety Scale

GFI  Goodness of Fit Index

GHQ28  General Health Questionnaire 28-item version

GP  General Practitioner

HADS  Hospital Anxiety and Depression Scale

HPA  Hypothalamic-pituitary-adrenal axis

hr.  Hour

HREC  Human Research Ethics Committee

HRQoL  Health-related Quality of Life
<table>
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<tr>
<td>I</td>
<td>Inclusion criteria</td>
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<tr>
<td>ICC</td>
<td>Intraclass Correlation Coefficient</td>
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<td>ICEQ</td>
<td>Intensive Care Experience Questionnaire</td>
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<td>ICU</td>
<td>Intensive Care Unit</td>
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<td>ICUM Tool</td>
<td>Intensive Care Unit Memory Tool</td>
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<td>IES</td>
<td>Impact of Event Scale</td>
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<tr>
<td>IES-R</td>
<td>Impact of Event Scale-Revised</td>
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<tr>
<td>IQR</td>
<td>Interquartile Range</td>
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<tr>
<td>Kg</td>
<td>Kilogram</td>
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<tr>
<td>KW</td>
<td>Key word</td>
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<tr>
<td>LASS</td>
<td>Linear Analogue Scales</td>
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<tr>
<td>LOT-R</td>
<td>Life Orientation Test-Revised</td>
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<tr>
<td>m²</td>
<td>Square meter</td>
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<tr>
<td>MCS</td>
<td>Mental Component Summary</td>
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<tr>
<td>MEDLINE</td>
<td>Medical Literature Analysis and Retrieval System Online</td>
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<tr>
<td>mg</td>
<td>milligrams</td>
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<tr>
<td>MOS COG</td>
<td>Cognitive Functioning Scale Medical Outcome Study 6-Item</td>
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<td>MSPSS</td>
<td>Multidimensional Scale of Perceived Social Support</td>
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</table>
MV  Mechanical Ventilation

n    number of patients

n/a  Not applicable

Nos Numbers

NRS Nursing

OR   Odd Ratio

p    p-value

PaO2/FiO2 Ratio of Arterial Oxygen Tension to Inspired Oxygen Fraction

PCS  Physical Component Summary

PsycINFO Psychological Information Database

PTSD  Post-Traumatic Stress Disorder

PTSS Post-Traumatic Stress Symptoms

PTSS-10 Post-Traumatic Stress Syndrome 10-Questions Inventory

PTSS-14 Post-Traumatic Stress Syndrome 14-Questions Inventory

PubMed Public/Publisher MEDLINE

r    Pearson’s correlation;

RCT  Randomised Controlled Trial

RMSEA Root Mean Square Error of Approximation
RR     Relative risk
SAI    State Anxiety Inventory
SCID   Structured Clinical Interview for DSM-IV
SD     Standard Deviation
SF-12  Short Form 12-question Health Survey
SF-36  Short Form 36-question Health Survey
STAI   State-Trait Anxiety Inventory
TI     Title
TISS   Therapeutic Intervention Scoring System
UK     United Kingdom
USA    United States of America
VAS    Visual Analog Scale
VIF    Variance Inflation Factor
vs.    versus
\chi^2  Chi-square
Dissemination of study results

Publications


Conference Presentations


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Included in this thesis are four manuscripts in Chapter 4 and Appendix 1, which are co-authored with my supervisors and another researcher. My contribution to each co-authored paper is outlined at the front of the relevant chapter. The status and bibliographic details for these papers including all authors are:

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Chapter 1: Introduction

1.1 Introduction

Survival from critical illness has improved significantly over the years with most patients surviving to hospital discharge. However, in conjunction with a higher survival rate, short-and-long term physical and emotional problems can also be seen in these patients (Deja et al., 2006; Girard et al., 2007; Hopkins, Orme, Weaver, & Chan, 2004; Kapfhammer, Rothenhausler, Krauseneck, Stoll, & Schelling, 2004; Sukantarat, Greer, Brett, & Williamson, 2007; Weinert, Gross, Kangas, Bury, & Marinelli, 1997). Several studies have reported on the emotional problems that patients experience after critical illness, amongst which are symptoms of anxiety, depression and post-traumatic stress. Since these emotional problems affect about one third of intensive care unit (ICU) survivors, the identification of factors associated with these problems is vital. A factor repeatedly suggested as being important during critical illness is anxiety (Girard et al., 2007; Nelson, Weinert, Bury, Marinelli, & Gross, 2000).

This prospective study addressed the issue of adverse emotional outcomes and the role of anxiety among ICU survivors. In this chapter, an introduction to the study including background, the research problem, and significance of this study are presented as well as an overview of the chapters comprising this thesis.
1.2 Background

Adverse emotional outcomes in survivors of critical illness include symptoms of anxiety, depression and post-traumatic stress (Rattray, Crocker, Jones, & Connaghan, 2010; Rattray & Hull, 2008). Systematic reviews published in 2008 and 2009 reported on the prevalence of these symptoms in this population, with symptoms of anxiety ranging from 23% to 48%, depressive symptoms from 17% to 43% and post-traumatic stress symptoms (PTSS) from 21% to 35% (Davydow, Desai, Needham, & Bienvenu, 2008; Davydow, Gifford, Desai, Bienvenu, & Needham, 2009; Davydow, Gifford, Desai, Needham, & Bienvenu, 2008).

A number of risk factors have been identified for these adverse emotional outcomes in survivors of the ICU. These risk factors can be classified into three categories, pre-ICU factors, intra-ICU factors and post-ICU factors. Pre-ICU potential risk factors correspond to a group of patient’s characteristics and conditions that are present before the ICU admission. The most common pre-ICU factors associated with adverse emotional outcomes are demographic characteristics such as age and gender; mental health history such as pre-morbid anxiety, depression and psychiatric illness; history of alcohol dependence, smoking, personality trait of pessimism versus optimism and level of education (Hopkins, Key, Suchyta, Weaver, & Orme, 2010; Jones et al., 2007; Myhren, Ekeberg, Tøien, Karlsson, & Stokland, 2010; Rattray, Johnston, & Wildsmith, 2005; Weinert & Meller, 2006).

Intra-ICU potential risk factors that have been linked to emotional outcomes after critical illness include sedation, duration of mechanical ventilation, length of ICU stay and neurobiologic factors such as neuroendocrine deregulation, hypoglycaemia and...
hypoxemia (Dowdy et al., 2008; Girard et al., 2007; Hopkins et al., 2010; Kapfhammer et al., 2004; Nelson et al., 2000; Schelling et al., 2001). The presence of anxiety during ICU stay has been identified as a frequent and serious problem for critically ill patients, which could be another possible factor related to adverse emotional outcomes (Girard et al., 2007; Nelson et al., 2000). Post-ICU potential risk factors include memories of the ICU, neurocognitive impairment, lack of social support, early depression symptoms post-ICU discharge, decreased physical function and poor physical health (Deja et al., 2006; Jackson et al., 2003; Samuelson, Lundberg, & Fridlund, 2007; Sukantarat et al., 2007; Weinert & Meller, 2006).

Sedation is one intra-ICU risk factor that has been consistently associated with the development of adverse emotional outcomes. Because sedation and analgesia are an essential part of the intensive care treatment, a significant amount of research exploring this area has been carried out over the years (Brush & Kress, 2009; Kress et al., 2003; Nelson et al., 2000). More than ten years ago, researchers exploring the association between sedation and adverse emotional outcomes hypothesised that anxiety during critical illness might play an important role in the development of these outcomes. In fact, they thought anxiety was the actual risk factor and sedation was an indicator of the amount of anxiety (Nelson et al., 2000). However, the relationship between this emotion during critical illness and adverse emotional outcomes remains unknown.

Some evidence regarding anxiety during critical illness is available today. Anxiety is a complex phenomenon that comprises of two components: state and trait (Spielberger, 1983). To achieve a comprehensive understanding of anxiety during critical illness both components of anxiety (state and trait) were explored in this current study. State anxiety is defined as a normal and temporary emotion that involves
physiological arousal and feelings of tension, apprehension, nervousness and worry when a stressful situation is perceived. Trait anxiety on the other hand, corresponds to a person's tendency to become state anxious as part of their personality trait (Spielberger, 1966, 1983).

Although there has been some exploration of anxiety in the critically ill patient, the majority of the evidence available provides information only about the state component of anxiety. There is a lack of evidence about the trait component of anxiety in critically ill patients. Some aspects of state anxiety that have been reported in the literature are prevalence, levels of state anxiety, assessment and treatment.

It is known that state anxiety is highly prevalent in critically ill patients, especially in those requiring mechanical ventilation (Chlan, 2003). In an American prospective study of patients’ symptoms including 171 seriously ill patients, the prevalence of state anxiety was 57% (Puntillo et al., 2010). In Australia, an investigation including 106 ICU patients found some level of state anxiety in 85% of them (McKinley, Stein-Parbury, Chehelnabi, & Lovas, 2004). The level of state anxiety reported is usually moderate to severe despite receiving sedation and/or analgesia (McKinley et al., 2004).

It is also known that state anxiety during critical illness is either poorly assessed or not assessed at all. The assessment of this emotion in critically ill patients is quite difficult because most patients admitted to the ICU require ventilatory support; therefore, the ability to verbalise their feelings is abolished due to endotracheal intubation. Thus, clinicians often identify state anxiety by observation of behavioural
(e.g. restlessness) and physiological (e.g. tachycardia) manifestations (McKinley et al., 2004; Tate, Devito Dabbs, Hoffman, Milbrandt, & Happ, 2011).

Unfortunately, clinicians’ observations of these two components (behavioural and physiological) are unreliable indicators of state anxiety in ICU settings since common conditions such as delirium or pain share similar physiological and behavioural characteristics which may lead to erroneous symptom interpretation (Tate et al., 2011). Moreover, it has been found that state anxiety may not always be accompanied by physiological changes. Another factor that has made the assessment difficult is the lack of appropriate instruments to assess anxiety in ICU patients. Specifically designed tools for the assessment of this emotion in seriously ill patients have been recently available, although these are not yet part of the routine clinical practice (De Jong, Burns, Campbell, & Chulay, 2005; McKinley et al., 2004; Moser et al., 2003; O'Brien, Moser, Riegel, Frazier, & et al., 2001).

Current knowledge regarding anxiety during critical illness and adverse emotional outcomes during recovery has contributed to the background of this study. It is essential to understand the relationship between anxiety during critical illness and emotional recovery in ICU survivors so as to improve clinical practice and health outcomes as well as to inform education and future research.

1.3 Research Problem

There is sufficient related evidence to propose that there is a relationship between anxiety during critical illness and adverse emotional outcomes during recovery. Patients presenting with higher levels of anxiety during critical illness might be at a
higher risk for developing symptoms of anxiety, depression and post-traumatic stress than those with low or no anxiety. This relationship may be through a direct link and/or an indirect link involving sedation.

As both components of anxiety (state and trait) are poorly assessed during critical illness, anxiety might not be detected in a timely manner and, therefore, remains untreated for long periods of time. This situation may have a direct impact on the development of adverse emotional outcomes in the longer term. On the other hand, if anxiety progresses to extreme levels and patients exhibit psychomotor agitation, the use of increased doses of sedation may be necessary. Thus, sedation could represent an indirect link to post-ICU adverse emotional outcomes.

1.4 Significance of the study

This study contributes new evidence-based knowledge that can be used to inform education, clinical practice and research. Within the literature, no contemporary study has explored the relationship between anxiety (state and trait) during critical illness and emotional outcomes including symptoms of anxiety, depression and post-traumatic stress during recovery. In this study these relationships were examined and new evidence regarding the issue of adverse emotional outcomes among ICU survivors was established.

These findings are important for a number of reasons. First, this new knowledge provides educationalists, clinicians and healthcare managers with objective data that could aid their decisions regarding the implementation of new interventions in ICU settings to improve care during critical illness and health outcomes after the ICU.
experience. Second, a better understanding regarding the association between risk factors and anxiety permits improvements in the management of this emotion with a possible reduction in adverse emotional outcomes. Finally, while the economic impact of these adverse outcomes in ICU survivors needs to be more fully understood, the findings of this study contribute objective data that can be used to explore this area in the future.

Overall, the findings of this study are valuable because they have the potential to help to improve care during critical illness and reduce adverse outcomes during recovery. These improvements should decrease unnecessary suffering, promote comfort and improve long-term recovery.

1.5 Structure of this document

This thesis is presented in five chapters, as follows:

Chapter one: the background of this study, the research problem and significance of the study are provided.

Chapter two: a comprehensive and critical appraisal of the literature addressing the issue of adverse emotional outcomes in ICU survivors is presented. This literature review is organised in five main sections, an introduction to the topic, the methods used to carry out the literature review, the potential risk factors associated with adverse emotional outcomes in survivors of critical illness (pre-ICU, intra-ICU and post-ICU risk factors), the description of the conceptual model of this study and the conclusions to the chapter.
Chapter three: the research aims and research questions addressed in this study are outlined in this chapter. The research design, the methods used to answer the research questions, characteristics of the sample (inclusion/exclusion criteria) and setting, the data collection plan, the data analysis plan and the ethical considerations for this study are described.

Chapter four: the results and discussion of this study are presented. This section comprises an introduction to the results and discussion chapter, three manuscripts that are under peer review processes with scientific journals and a conclusion to the chapter.

Chapter five: the recommendations for clinical practice, education and future research, and the conclusions of this study are provided.

1.6 Summary

In summary, an introduction to this study has been provided in this chapter, which explored the issue of adverse emotional outcomes among ICU survivors. The research problem was presented outlining that anxiety during critical illness may be related to symptoms of anxiety, depression and post-traumatic stress after the ICU experience, and this has not been investigated to date. The significance of this study for clinical practice, education and future research was also presented. Last, an overview of chapters two, three, four and five were provided.
Chapter 2: Literature review

2.1 Introduction

In this chapter the study is located within the context of what is known about adverse emotional outcomes after the intensive care experience of survivors of critical illness. The literature related to symptoms of anxiety, depression and post-traumatic stress in survivors of intensive care unit (ICU) is analysed and synthesised.

The aims of this literature review were to:

1. Examine published evidence pertaining to adverse emotional outcomes after the ICU experience
2. Identify relevant factors associated with symptoms of anxiety, depression and post-traumatic stress in the survivors of critical illness
3. Situate the study within the context of a conceptual model.

2.2 Methods

This integrative literature review was structured following the theoretical framework outlined by Whittemore & Knafl (2005). In this framework the following stages are included: problem identification, literature search, data evaluation, data analysis and discussion. In addition, some components of the process of a systematic review such as search strategy and development of a flow diagram were adapted and
used to produce a rigorous and objective analysis of the evidence related to the adverse emotional outcomes in survivors of critical illness.

2.2.1 Problem identification

Two clinical problems were identified to guide the literature review process: (1) anxiety is a serious problem during critical illness despite pharmacological and non-pharmacological interventions; (2) there are a number of factors associated with symptoms of anxiety, depression and post-traumatic stress during recovery. Based on the problems the search was designed to identify evidence about:

1. Anxiety during critical illness,
2. Factors that may affect the emotional recovery in ICU survivors.

2.2.2 Literature search

In order to identify literature relevant to the problems, the following databases were searched: Cumulative Index of Nursing and Allied Health Literature (CINHAL), Medical Literature Analysis and Retrieval System Online (MEDLINE), Psychological Information Database (PhycINFO), Cochrane Library, Google Scholar and ProQuest. The keywords used were: anxiety, depression, post-traumatic stress, state anxiety, critically ill patients, seriously ill patients, intensive care unit, intensive care, survivors of intensive care, stress, fear, and adverse emotional outcomes. In addition, ancestry searching and journal hand searching were also used. Inclusion criteria included papers that were published in peer-reviewed journal (research articles, systematics reviews) and government reports addressing the aims of this review. The search was limited to literature in English and Spanish, published between January 2000 to April 2014, and including only adult patients (>16 years). A detailed search strategy is presented in Appendix 1 and a flow diagram of this process is presented in Figure (2.2.1).
2.2.3 Data evaluation

Once the literature was accessed, titles and abstracts were scanned for possible inclusion. After selecting the relevant pieces of work to be included in this literature review, they were classified into three major topic categories:

1. Anxiety in ICU: stressors in ICU, pharmacologic and non-pharmacologic interventions to treat anxiety during critical illness and assessment of anxiety during critical illness
2. Adverse emotional outcomes after the ICU experience: symptoms of anxiety, depression and post-traumatic stress

Data from relevant papers were organised and summarised using data extraction sheets, which contained the following items: date, author, country, aims, design (randomisation procedures), sample characteristics (sample size, inclusion and exclusion criteria), data collection strategies measures used (validity and reliability), findings, strengths and limitations (Appendix 2). The Journal of the American Medical Association User's Guide to Medical Literature framework as outlined by Cullum et al. (2008) was used to inform the critical appraisal process of the literature included in this thesis (Cullum, Ciliska, Haynes, & Marks, 2008).

2.2.4 Data analysis

The data were analysed in order to reveal the current state of knowledge, identify gaps in the literature and formulate the research aims and question for this study. In the next section, adverse emotional outcomes after the ICU experience: symptoms of anxiety, depression and post-traumatic stress are examined and discussed.

2.3 Adverse emotional outcomes after the ICU experience: symptoms of anxiety, depression and post-traumatic stress

Adverse emotional outcomes are common in survivors of critical illness. Three systematic reviews reporting the prevalence of these emotional problems in the ICU population were published in 2008 and 2009. In a review exploring post-traumatic stress symptoms (PTSS) in general ICU survivors (n=1,104), data from 15 studies were reported. Clinically significant PTSS were found in 22% (range 10%-39%) of
participants among 12 studies when standardised questionnaires were used to assess these outcomes. A median point prevalence of 19% among three studies assessing 93 patients through clinical interview was reported (Davydow, Gifford, et al., 2008). The same group of researchers reported data from 14 studies (n=1,213) regarding symptoms of depression in general ICU patients in 2009. The median point prevalence of clinically significant symptoms of depression was 28% (range 8%-57%) (Davydow et al., 2009). In the third systematic review data from 10 observational studies in Acute Lung Injury (ALI)/Acute Respiratory Distress Syndrome (ARDS) patients (n=331) were included. In these studies the point prevalence for anxiety ranged from 23% to 48%, for depressive symptoms from 17% to 43% and for PTSS from 21% to 35% (Davydow, Gifford, et al., 2008).

It is important to note that in most of the studies exploring emotional outcomes in ICU survivors, self-report measures have been used to screen for possible or probable cases. Only a few studies have used structured clinical interview to diagnose psychological morbidity. In general, these reviews included and analysed data from studies performed in the United Kingdom (UK), United States of America (USA), Australia and European countries. Symptoms of anxiety, depression and PTSD have a high prevalence among ICU survivors and may represent a significant problem for these patients during recovery. Given this high prevalence, factors associated with adverse emotional outcomes in survivors of critical illness were examined.
2.4 Factors associated with adverse emotional outcomes in survivors of critical illness

A number of factors have been associated with the development of adverse emotional outcomes in survivors of critical illness. As these factors relate to three different time periods, they can be classified into three groups: pre-ICU, intra-ICU and post ICU factors. Pre-ICU risk factors include demographic characteristics, mental health history; history of alcohol dependence and smoking; personality traits of optimism and educational level. Intra-ICU factors include sedation; neurobiologic factors such as neuroendocrine deregulation, hypoglycaemia and hypoxemia; duration of mechanical ventilation and length of intensive care unit stay. Post-ICU factors include memories of the ICU, neurocognitive impairment, lack of social support, and other post-ICU factors.

2.4.1 Pre-ICU potential risk factors

Pre-ICU potential risk factors correspond to a group of patient’s characteristics and conditions that are present before the ICU admission. These variables may influence the development of symptoms of anxiety, depression and post-traumatic stress after critical illness. The most common pre-ICU factors associated with adverse emotional outcomes are demographic characteristics such as younger age and female gender; and mental health history such as pre-morbid anxiety, depression and psychiatric illness. Less frequently, history of alcohol dependence and smoking; personality trait of pessimism versus optimism and level of education have been mentioned.
2.4.1.1 Gender and age

The effect of gender and age on adverse emotional outcomes after critical illness has been investigated in several published reports. There is some evidence supporting that female gender and younger age may be associated with symptoms of anxiety, depression and post-traumatic stress during recovery, although these relationships are not consistent across studies. For example, a prospective longitudinal study explored the contribution of gender and age, among other factors, to post-ICU emotional outcomes in 80 general ICU patients (Rattray et al., 2005). A significant association between age and symptoms of anxiety at twelve months ($t=-2.102$, $p=0.039$) and age and PTSS (avoidance symptoms) at 6 months ($t=-2.26$, $p=0.048$) and twelve months ($t=-2.513$, $p=0.014$) was identified (Rattray et al., 2005). Similar results were found in Acute Respiratory Distress Syndrome (ARDS) survivors where female gender ($t=2.0$, $B=4.44$, $B=0.23$, $p=0.05$) and younger age ($t=-1.77$, $B=-0.12$, $B=-0.20$, $p=0.08$) were associated with depression at one year post hospital discharge, and female gender was associated with anxiety at two years post hospital discharge ($t=2.36$, $B=5.68$, $B=0.28$, $p=0.02$) (Hopkins et al., 2010).

Older patients were less likely to develop PTSS than younger ones in 108 patients with abdominal sepsis (OR=0.74 per 10 years increase in age, $p=0.084$), suggesting a protective effect of older age against PTSS (Boer et al., 2008). It is thought that older patients might not consider critical illness as a traumatic experience since they might have been exposed to chronic diseases and previous hospitalisations. In addition, elderly patients might not receive as aggressive ICU treatment as younger ones, interventions that may predispose them to adverse emotional outcomes (Hamel et al., 1999). Similarly, PTSS were found to be significantly associated with female gender.
(OR 4.74, 95%CI: 1.44, 15.5, p=0.005) in 226 mechanically ventilated patients (Samuelson, Lundberg, & Fridlund, 2007). Other groups of researches have reported similar findings (Cuthbertson, Hull, Strachan, & Scott, 2004; Girard et al., 2007).

As described significant associations between these two demographic factors (female gender and younger age) and symptoms of anxiety, depression and post-traumatic stress after the intensive care experience have been found. Nonetheless, there are also other researchers reporting having found no such associations. Age and gender were not significant independent predictors for symptoms of anxiety, depression or post-traumatic stress in a retrospective study, which examined the effect of these two variables on emotional recovery after the intensive care experience in 80 general ICU survivors (Scragg, Jones, & Fauvel, 2001). In addition, neither gender nor age was a predictor of symptoms of depression in a prospective study designed to identify predictors of depression and antidepressant medication in a cohort of 277 survivors of the ICU who required ventilatory support (Weinert & Meller, 2006).

Despite the fact that there is inconsistency in findings regarding the effect of gender and age on adverse emotional outcomes, these two characteristics may still be considered predictors of PTSS when looking at the literature as a whole (Davydow, Gifford, et al., 2008).

2.4.1.2 Mental health history

Premorbid anxiety, depression and psychiatric illness are common exclusion criteria in studies exploring the effects of the intensive care treatment on adverse emotional outcomes. The objective of excluding patients presenting with these conditions is to reduce bias when assessing the effects of the intensive care therapy. Common exclusion criteria are attempts of suicide, pre-morbid psychotic illness and
previous or ongoing psychiatric illness (Jones, Griffiths, Humphris, & Skirrow, 2001; Jones et al., 2003; Ringdal, Plos, Lundberg, Johansson, & Bergbom, 2009). Nevertheless, a few studies have included these patients and assessed the relationship between premorbid psychological/psychiatric history and adverse emotional outcomes. In this literature review, three studies examining this association were located.

Short-and-medium-term psychiatric outcomes and predictors of depression and antidepressant medication use in 277 mechanically ventilated patients were examined in a prospective cohort study. Proxies were interviewed to assess the patient’s functional status in the month prior the ICU admission and prescription or use of psychiatric medications (medical records were also reviewed). This study found that proxy-reported premorbid depression was an independent predictor for depression at two and six months after intensive care. In addition, poor physical functioning was also independently associated with higher depressive symptoms (Weinert & Meller, 2006).

A multicentre prospective study proposed a three-path model of factors associated with PTSD (Jones et al., 2007). One of the paths started from premorbid psychological problems that were assessed 1-2 weeks after ICU discharge by asking the patient about premorbid history of anxiety, depression and previous traumatic event (to detect pre-ICU PTSS). The prevalence of premorbid psychological problems was as high as 24%. In the proposed model, premorbid psychological problems contribute to prolonged use of sedatives and opioids in the ICU. This prolonged analgosedation administration would enhance the recall of delusional memories of the ICU, leading to PTSD. A second path identified was directly through prolonged sedation and opioid administration to PTSD (where delirium may be involved). The third path argued is from physical restraint with inadequate or no sedation through to PTSD. This model
demonstrated a good fit to the data \( \chi^2=7.88, p=0.72, \text{RMSEA}=0.0001 \) (90%CI: 0.0001, 0.05); comparative fit=1.00, GFI 0.90, AGFI=0.75]. However, there is an important issue to consider. No information regarding use of psychotropic or antidepressant medications prior to ICU admission was incorporated into this study. Patients, who had previously been taking these medications may have experienced withdrawal symptoms if ceased in ICU. In this hypothetical scenario, it is likely that exhibition of high levels of anxiety and agitation could have led to a prolonged sedation and subsequent recall of delusional memories and PTSS.

In another prospective study patients (n=78) were assessed for mental health history by asking them whether they had seen a general practitioner or mental health professional due to psychological distress before being seriously ill. Patients with mental health history (14% of the patients) had significantly higher levels of PTSS than those without such history (p=0.005) after three months of ICU discharge (Cuthbertson et al., 2004).

Overall, only a few studies have assessed the association between premorbid psychological history and adverse emotional outcomes after intensive care. However, the small amount of evidence unanimously supports that survivors of ICU with premorbid psychological history are at higher risk for the development of symptoms of depression and post-traumatic stress than those without such a condition.

### 2.4.1.3 Alcohol dependence and smoking

Both history of alcohol dependence and smoking have also been suggested as possible predictors of subsequent negative emotional outcomes. Only one study assessing this relationship was identified in this review. It found that history of alcohol dependence was a predictor of depression at one \( \beta=0.32, B=7.74, t=2.71, p=0.0009 \)
and two (β=0.31, B=8.36, t=2.42, p=0.02) years post hospital discharge and anxiety at two (β=0.29, B=7.51, t=2.44, p=0.02) years post hospital discharge. History of smoking was a predictor of anxiety at one (β=0.27, B=5.28, t=2.33, p=0.02), and two (β=0.20, B=3.97, t=1.87, p=0.06) years post hospital discharge. This study included a small sample of ARDS survivors (n=66); therefore, the generalisability of its findings is limited (Hopkins et al., 2010).

2.4.1.4 Personality traits and educational level

Personality traits and educational level were assessed as potential risk factors for the development of adverse emotional outcomes after the ICU experience in a Norwegian study (Myhren et al., 2010; Myhren et al., 2009). In this study 255 ICU patients (medical, surgical and trauma patients) were enrolled, and followed up at 4-6 weeks, 3 and 12 months post-ICU discharge. One hundred ninety-four patients completed the 12-month assessments. Personality trait was defined as optimism versus pessimism and measured by the Life Orientation Test-Revised (LOT-R) and educational level was defined as high or low.

The first report was a cross sectional study and found that personality trait of pessimism was a strong independent predictor of anxiety symptoms (β=−0.33, 95%CI: -0.44, -0.22, p<0.001) depression symptoms (β=−0.38, 95%CI: -0.48, -0.27, p<0.001), and PTSS (β=−0.87, 95%CI: -1.27, -0.46, p<0.001). In addition, patients with a lower educational level had significantly higher depression scores (β=−1.13, 95%CI: -1.86, -0.40, p≤0.003) in the Hospital Anxiety and Depression Scale (HADS) than patients with a higher education. A positive correlation between higher educational levels and optimism was found (r=0.20, p=0.002), suggesting that patients with higher education tended to be more optimistic and vice versa (Myhren et al., 2009). At one year post-ICU
discharge, the second prospective cohort study reported that optimistic patients had significantly lower levels of anxiety symptoms (OR=0.8, 95%CI: 0.8, 0.9, p<0.001), depression symptoms (OR=0.8, 95%CI: 0.7, 0.9, p<0.001) and PTSS (OR=0.9, 95%CI: 0.8, 1.0, p=0.029), than the pessimistic ones, and a association between lower educational level and PTSS (OR=0.38, 95%CI: 0.15, 0.95, p=0.038) was observed (Myhren et al., 2010).

It is possible that patients’ level of education affected the manner in which they saw the future. Thus, patients with high education tended to be more optimistic while their counterparts with less education were more pessimistic. It is logical to think that patients with higher education might have a better economic situation, therefore, better opportunities for recovering (e.g. more options for healthcare treatment, less worry about family economy and more options for returning to work) than the less educated ones. These advantages may have contributed to diminished emotional distress and negative emotional outcomes after the ICU experience.

These findings suggest that these two variables, optimism and high educational level, have a positive effect on emotional recovery whereas pessimism and lower education have a negative effect. In addition, optimism together with high education could be a combination that may situate the patients at a lower risk for adverse emotional outcomes after the intensive care experience.

In conclusion, while there is limited and inconsistent evidence in some areas, there is evidence that age, gender, mental health history, alcohol dependence, smoking, education level and personality traits all have the potential to be important predictors of emotional health. In general, more research is needed to understand the effects of pre-
ICU factors on the subsequent development of negative emotional outcomes as well as to identify others that might be involved.

2.4.2 Intra-ICU potential risk factors

Certain aspects of intensive care treatment have been identified as potential risk factors for the development of symptoms of anxiety, depression and post-traumatic stress in survivors of intensive care. Factors that have been linked to these emotional outcomes are sedation, duration of mechanical ventilation, length of ICU stay and neurobiologic factors such as neuroendocrine deregulation, hypoglycaemia and hypoxemia. In this literature review, the presence of anxiety during critical illness has been identified as a frequent and serious problem for critically ill patients, which could be another possible factor for adverse emotional outcomes.

2.4.2.1 Anxiety during critical illness

Critically ill patients are constantly exposed to a great variety of stressors while receiving intensive care treatment and anxiety is a common issue in this population. Anxiety during critical illness has been suggested to be a potential risk factor for adverse emotional outcomes after the ICU experience. In this section, the evidence currently available about anxiety during critical illness was examined.

Anxiety was conceptualised as state anxiety and trait anxiety by Spielberger in the sixties (Spielberger, 1966). This distinction has provided a better understanding of this complex phenomenon and this approach has been recognised in much literature and research. State anxiety is defined as a normal and temporary emotion that involves physiological arousal and feelings of tension, apprehension, nervousness and worry when a stressful situation is perceived. Trait anxiety, on the other hand, corresponds to
The person's tendency to become state anxious as part of their personality trait (Spielberger, 1983; Spielberger & Reheiser, 2009).

State anxiety alerts the individual of imminent danger enabling them to prepare and deal with the threat (Doenges, Moorhouse, & Murr, 2010). Despite anxiety being a normal adaptive mechanism in human beings that helps the body to respond to stressful situations, however it can also become detrimental if it impairs an individual’s ability to function (Steimer, 2002). Further, anxiety can progress to agitation or panic and even modify physiological function (e.g. promote the formation of gastric ulcers or dysrhythmias); becoming pathological and representing a clinical concern (Doenges et al., 2010; Steimer, 2002). High levels of anxiety, particularly when sustained, are less adaptive and might contribute to the development of adverse emotional outcomes after the ICU experience (Nelson et al., 2000).

A high prevalence of state anxiety has been identified in critical ill patients, especially in those requiring mechanical ventilation. In a descriptive study including 192 ventilated patients state anxiety was found in all of them, with low levels in 20% (n=38), moderate to severe levels in 62% (n=119) and high levels in 18% (n=35) of the patients (Chlan, 2003). In addition, a significantly higher prevalence of anxiety was reported in mechanically ventilated patients than in non-ventilated (74.2% versus (vs.) 25.8% respectively, p=0.02) in seriously ill ICU patients at risk of dying (Puntillo et al., 2010). In a recent qualitative investigation exploring this emotion in 30 ICU patients, all the patients exhibited anxiety at some stage during the study (Tate et al., 2011).

A high proportion of ICU patients usually report moderate to high levels of anxiety despite receiving sedation and/or analgesia. In 106 Australian patients (89% ventilated) severe anxiety was reported by 35% of patients who received sedation
(n=45) and 66% of patients who did not (n=61) (McKinley et al., 2004). Several years later, using similar measurement instruments, McKinley and Madronio (2008) reported lower levels of anxiety in 100 non-ventilated patients. However, more than a quarter (28%) of patients still reported moderate to severe anxiety, and half of them (14%) had received sedation (McKinley & Madronio, 2008). Both studies included patients from the same three ICUs (general, cardiothoracic and neurosurgical) of a tertiary metropolitan Australian hospital, with the aim of validating the Faces Anxiety Scale (FAS). The FAS is an instrument designed to assess state anxiety during critical illness in ICU settings. In both studies, the assessment of state anxiety was performed daily. In the study published in 2004, where most patients were ventilated (89%), state anxiety was assessed by the FAS and the interviewer’s clinical judgment which was guided by the anxiety scale of the Profile Mood State (a validated instrument). The study published in 2008 included non-ventilated patients only, and the assessment was made by using the FAS and the State Anxiety Inventory (SAI) of the Spielberger State-Trait Anxiety Inventory (STAI). Both studies concluded that the FAS was a valid instrument to assess self-reported state anxiety in ICU patients, both ventilated and non-ventilated.

Undeniably, the need for intensive care treatment is accompanied by several physical, psychological and environmental sources of distress. Physical sources of distress such as invasive mechanical ventilation, may lead to physiologically and psychologically distressing experiences since the patients are not able to verbalise their feelings, symptoms or wants. In fact, spells of terror, nervousness when left alone, and sleeping disturbances have been associated with endotracheal intubation (Rotondi et al., 2002). Psychological sources of distress such as confusion, fear, panic, and frustration are common while receiving intensive care (Puntillo et al., 2010; Tate et al., 2011).
Examples of environmental sources of distress are noise, lights and lack of privacy (Yava, Tosun, Ünver, & Çiçek, 2011).

**Assessment of state anxiety during critical illness:** the assessment of state anxiety in critically ill patients is quite difficult for several reasons. Most patients admitted to the ICU require ventilatory support; therefore, the ability to verbalise their feelings is abolished due to endotracheal intubation. Thus, state anxiety is usually detected by observation of its physiological and behavioural manifestations (McKinley et al., 2004; Tate et al., 2011). Unfortunately, clinicians’ observations of these two components are limited since common conditions such as delirium or pain share similar physiological and behavioural characteristics with anxiety which may lead to erroneous symptom interpretation (Tate et al., 2011). Moreover, when the emotional component (e.g. feelings of apprehension, fear and panic) is assessed, patient's self-reported levels of anxiety are usually in disagreement with clinicians’ observations (O'Brien et al., 2001).

Vocabulary differences between clinicians and patients could interfere with an accurate assessment. According to a qualitative investigation, the term “anxiety”, used by health professionals, is not commonly used by patients when expressing feelings or emotions; instead, they use words related to this concept such as fear, panic, frustration, anger and withdrawal (Tate et al., 2011). In addition, patients’ ability to interact with the environment could play a fundamental role in the expression of anxiety. For example, it has been found that patients with a low level of interaction usually exhibited agitation (hyperactive psychomotor movements) whereas more interactive patients, tended to verbally express their feelings (e.g. feelings of apprehension, fear and panic) (Tate et al., 2011).
A further consideration that makes assessment difficult is that state anxiety may not always be accompanied by physiological changes (De Jong et al., 2005). In fact, changes in vital signs such as heart rate and blood pressure were not associated with the self-reported emotional experience of anxiety in a sample of 106 ICU patients (McKinley et al., 2004). Similar findings were reported in a sample of 117 patients (n=54 acute myocardial infarction, n=32 heart failure and n=31 healthy individuals) in a descriptive study (Chlan, 2003). Inconsistent evidence of a relationship between anxiety and increased heart rate and blood pressure is possible due to the fact that the physiological response to anxiety would vary from person to person; therefore, some patients would respond with an increase in heart rate and blood pressure while others would not exhibit haemodynamic changes. In addition, differential responses, depending on the brain hemisphere stimulated, would be involved. Further, the physiological component of state anxiety may be disrupted by critical illness and/or intensive care treatment. For example, critically ill patients receiving medications such as beta-blockers may not respond to anxiety with changes in blood pressure and heart rate. Finally, adaptive mechanisms could be activated to mediate the physiological response when stressors and anxiety persist over time. Thus, anxiety would not be reflected in haemodynamic changes (Chlan, 2003).

There have been a number of instruments developed to aid the assessment of anxiety. At least nine instruments were identified amongst 18 studies included in a literature review exploring anxiety in ICU settings (Perpiñá-Galvañ & Richart-Martínez, 2009). Multi-item instruments were: the state component of the STAI (20 items); the anxiety subscale of the HADS (7 items); the Experience After Treatment in Intensive Care 7-Item anxiety scale (ETIC-7); the shortened version of the STAI (6 items); and
the anxiety subscale of the Brief Symptoms Inventory (BSI) (6 items). Amongst single-item scales were the FAS, the Visual Analog Scale (VAS), the Linear Analogue Scales (LASS), and the Anxiety Level Index (ALI) (Perpiñá-Galvañ & Richart-Martínez, 2009). Despite a number of instruments available, these are not yet part of routine clinical practice (De Jong et al., 2005; McKinley et al., 2004; Moser et al., 2003; O'Brien et al., 2001). Should the state anxiety assessment be incorporated into clinical practice, clinicians should consider the communication difficulties and energy limitations that ICU patients may have, which are likely to interfere with patient’s capacity to complete a lengthy instrument.

**Management of anxiety in the ICU:** strategies to manage anxiety and agitation in the ICU include use of pharmacologic therapy with anxiolytics, sedatives and opioids (sedation and analgesia in the ICU is discussed in the next section), and non-pharmacological interventions such as reassurance; encouragement or coaching; and music therapy (Han et al., 2010; Moser et al., 2003; Tate et al., 2011). New non-pharmacological strategies such as early intra-ICU psychological intervention have been studied recently (Peris et al., 2011). This intervention included education, counseling, stress management, psychological coping support approaches at the bedside from clinical psychologists. The findings from this study are promising with a lower prevalence of adverse emotional outcomes and less pharmacological psychiatric treatment one-year post ICU discharge. The possible negative effects form these interventions are currently being investigated (Peris et al., 2011). The management of anxiety in critical illness is vital to avoid or reduce the deleterious consequences that this emotion may have such as complications after acute myocardial infarction (Moser & Dracup, 1996).
The gaps in the literature: while state anxiety is acknowledged in a number of studies as constituting a serious problem for ICU patients that may lead to adverse consequences, no study examining the relationship between state anxiety during ICU stay and adverse emotional outcomes has been found in this literature review. There is evidence, however, that a prolonged stress response may lead to the development of PTSD through changes and adaptation of the Hypothalamic-pituitary-adrenal (HPA) axis (the allostatic response to stress will be discussed later in this review).

Although some research has been performed on anxiety in the critically ill patient, the majority of the evidence available provides information only about the state component of anxiety. There is little research exploring trait anxiety in the ICU patient. In other populations such as survivors of rectal cancer, a relationship between trait anxiety and emotional health has been shown (Ristvedt & Trinkaus, 2009). However, it is unclear if this association applies to the ICU population. As current research in the field of psychology suggests that trait anxiety can be modified using tailored interventions, it seems beneficial to also explore trait anxiety in ICU patient (Clark, Clark, Ehlers, McManus, & Hackmann, 2003; Jackson, Hill, Payne, Roberts, & Stine-Morrow, 2012; Tang et al., 2009).

2.4.2.2 Sedation and analgesia

Sedation and analgesia are an essential part of the intensive care treatment since critically ill patients are constantly exposed to various sources of pain and anxiety, especially those patients requiring mechanical ventilation. Not only are pharmacological therapies needed to manage these symptoms, but also to meet goals of care in ventilated patients such as, amnesia when neuromuscular blockage is used or reduce patient oxygen consumption in ARDS or shock (Brush & Kress, 2009; Kress et al., 2003;
Nelson et al., 2000; Puntillo et al., 2010; Rotondi et al., 2002). Sedation practices have changed over the last decade, as has the goal of sedation. The current trend is to provide a level of sedation that enables the patient to be alert and interact with the environment, instead of a deeply sedated patient as in previous years (Barr et al., 2013; Boer et al., 2008; Elliott et al., 2013; O'Connor, Bucknall, & Manias, 2010).

In Australian ICUs, an important proportion of patients are treated with light sedation levels, with propofol and midazolam the preferred pharmacologic agents administered by continuous infusion and bolus doses. Morphine and fentanyl are the preferred opioids (Elliott et al., 2013).

Sedatives and analgesics have many desirable and valuable benefits such as relieving pain, anxiety and agitation associated with critical illness and intensive care treatment. Nevertheless, it is vital to consider that they also have significant adverse effects such as prolonging the ventilatory support, the ICU stay and increasing the risk of infections and mortality (O'Connor et al., 2010; Rattray et al., 2005). In addition, sedation has been associated with physical (neuromuscular weakness) and psychological (symptoms of anxiety, depression and post-traumatic stress) morbidity after the intensive care experience (Brush & Kress, 2009; Kress, 2013; Kress et al., 2003; Nelson et al., 2000).

To understand the mechanisms by which this pharmacologic treatment would affect the patients’ emotional outcomes, different aspects of sedation and analgesia have been studied. Thus, factors such as the use of certain drugs, total drug doses, duration of sedation and administration methods (continuous venous infusion, intermittent sedation and daily sedative interruption) have been found to have a significant influence. A group of researchers prospectively explored the impact of sedation on the development
of PTSS in 238 mechanically ventilated patients from five different European ICUs. They found a significant association between the use of benzodiazepines and PTSS (Jones et al., 2007). This was supported by a significant correlation between the total dose of lorazepam and PTSS (for every 10mg increase in cumulative lorazepam dose, PTSS-10 score increased by 0.39 (95%CI: 0.17, 0.61, p=0.04) as reported in another study (Girard et al., 2007). Duration of sedation during the ICU stay and its relationship to adverse emotional outcomes has also been found to be statistically significant. A significant correlation between days of sedation and depression symptoms (r=0.30, p=0.007) and PTSS (r=0.32, p=0.006) was reported in a small American study including 24 ALI patients (Nelson et al., 2000).

A randomised controlled trial with a small sample size (n=32) explored the long-term psychological effects of DSI in mechanically ventilated patients (Kress et al., 2003). Some participants (n=18), seven from the control group and eleven from the intervention group had been enrolled and randomised in a previous study exploring DSI (Schelling et al., 1999). The intervention group was treated with DSI and reported lower average total Impact of Event Scale (IES) scores than the control group (intervention group n=13, scores 11.2±14.9 vs. n=19 scores 27.3±19.2, p=0.02). The IES is a self-report questionnaire used to measure PTSS. In addition, six patients from the control group were diagnosed with PTSD versus none of the intervention group (6 of 19 vs. 0 of 13, p=0.06). The diagnosis of PTSD was based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) through interview by clinical psychologists. This research also reported lower anxiety and depression scores in the intervention group; however, this difference did not reach statistical significance (Kress et al., 2003). The small sample size in this study should be noted. Although
Daily Sedative Interruption (DSI) has had some support as an effective intervention to achieve low levels of sedation and improve emotional recovery, it has recently been demonstrated to not offer additional benefits for patients when compared with a nurse implemented light sedation protocol (Mehta et al., 2012).

While sedation in the ICU seems to be a predictor of negative emotional outcomes, it is necessary to note that the mechanisms of this relationship remain unclear. This uncertainty has raised the idea that high levels of anxiety in the ICU population is a key factor in this relationship. Sedation is usually administered to manage exhibited anxiety in intensive care patients. Therefore, it has been speculated that those patients who demonstrate greater levels of anxiety could be more vulnerable to receiving higher doses of sedatives than those patients who do not exhibit such distress (Girard et al., 2007; Nelson et al., 2000). Based on this, it has been suggested that the high levels of anxiety experienced when in ICU could be the actual risk factor for the development of adverse emotional outcomes when recovering, instead of the pharmacologic treatment. Thus, sedation could play a secondary role as an indicator of the amount of distress, and anxiety would be the protagonist in this relationship. No study exploring this idea was found in this literature review.

Evidence regarding sedation in intensive care patients is primarily related to patients receiving mechanical ventilation. Little has been reported about intensive care patients in general ICUs who do not require ventilatory support. This is an important issue because ICU patients who are not mechanically ventilated may also be seriously ill and require analgesics and sedatives to relieve pain and distress from trauma, surgical interventions or invasive procedures.
In addition, it is likely that some aspects of the experience of pain and anxiety are similar in ventilated and non-ventilated patients. A recent study found no significant difference in symptom intensity and distress ratings between these two groups (Puntillo et al., 2010). This investigation assessed the symptoms experienced by 171 general ICU patients at risk of dying where only 34% of the patients were mechanically ventilated at the time of the symptoms assessment. The prevalence of anxiety and pain in ventilated and non-ventilated patients were 58% and 40% respectively. Only the prevalence of anxiety was significantly higher in the ventilated patients (74% vs. 26%), however, a quarter (26%) of non-ventilated patients is still considerable. Therefore, non-ventilated and ventilated patients may be exposed to a similar risk of developing anxiety.

In summary, while sedation and analgesia are common and necessary therapies to treat critically ill patients, these medications are not free of adverse effects. Several aspects of sedation management such as the use of benzodiazepines, total dose of lorazepam, duration of sedation and continuous intravenous infusion have been significantly associated with the development of negative emotional outcomes when recovering from critical illness. However, the mechanisms of this association have not been clearly established. In an attempt to explain this relationship, it has been speculated that the presence of high levels of anxiety may be the actual risk factor for the development of these emotional problems, regarding sedation as a secondary factor in this relationship. For these reasons, it cannot be concluded that sedation causes anxiety, depression or post-traumatic stress symptoms following the ICU experience (Girard et al., 2007; Nelson et al., 2000).
2.4.2.3 Neurobiologic factors

Neurobiologic factors associated with the development of adverse emotional outcomes in ICU survivors include neuroendocrine deregulation, hypoglycaemia, and hypoxemia.

*Neuroendocrine deregulation*: the allostatic response to stress has a very complex physiology, involving the activation of multiple organ systems such as the autonomic nervous system, the HPA axis, and the cardiovascular, immune and metabolic systems (McEwen, 1998). When a stressful or dangerous situation is perceived, the sympathetic nervous system and the HPA axis play a key role in regulating the acute stress response. Stress hormones such as epinephrine or norepinephrine are released to the blood stream producing physiologic changes to adapt to stress and maintain homeostasis. On the other hand, cortisol and other glucocorticoids are released from the adrenal cortex, by the action of the corticotropin hormone, to mediate the termination of this response. When the stressors or danger have passed, and the stress response is terminated, catecholamine and cortisol return to normal levels (McEwen, 1998; Yehuda, Giller, Southwick, Lowy, & Mason, 1991). However, if the down-regulation and termination of the acute stress response is inefficient, catecholamines and cortisol circulate for much longer in the blood stream, overexposing the organism to the effect of these stress mediators which can lead to a number of chronic stresses and disease development such as post-traumatic stress disorder (PTSD) and depression (Holsboer, 2001; Yehuda, Teicher, Trestman, Levengood, & Siever, 1996).

Over the last decades, research exploring biologic changes in patients with depression and chronic PTSD has been performed. As significant variations in the
neuroendocrine function have been found in these patients, it has been suggested a possible physiological adaptation of the HPA axis to chronic stress (Yehuda, 2002). It has also been suggested that a causal relationship between neuroendocrine deregulation and psychopathology exist (Holsboer, 2001). The evidence regarding depression consistently supports this causality, suggesting that its pathophysiology is mediated by an excessive release of cortisol because of an impairment of corticosteroid receptors (Holsboer, 2001). However, this relationship has not been studied in ICU patients.

On the other hand, the published reports on PTSD often show great disparity in their findings, which has led to interesting debates amongst researchers in this arena (Yehuda, 2002). For example, significantly higher levels of catecholamines (norepinephrine and dopamine) in 24-hour urinary excretion were reported in a sample of 22 Vietnam veterans with chronic PTSD, compared with 16 normal controls (Yehuda, Southwick, Giller, Ma, & Mason, 1992). In addition, lower levels of both urinary and plasma cortisol have been reported in male combat veterans with PTSD compared with control subjects (Yehuda et al., 1990; Yehuda et al., 1996).

In contrast, significantly higher levels of 24-hour cortisol urinary excretion were found in 20 combat Vietnam veterans with PTSD compared with 15 non-psychiatric combat control subjects in another investigation. This study also reported having found no significant difference in urinary levels of catecholamines between the PTSD group and the control group (Pitman & Orr, 1990). Several explanations for the inconsistency in findings have been proposed such as differences in subjects studied, presence of comorbid depression or duration of the disorder (Mason et al., 2001; Yehuda, 2002). Even though the evidence regarding neuroendocrinology of PTSD is inconsistent, there
is general agreement that the HPA axis seems to function in a different manner under chronic stress (Yehuda et al., 1991).

Based on the evidence of hypocortisolism in chronic PTSD, some investigators have hypothesised that the exogenous administration of glucocorticoids in similar doses to the ones released under maximal stimulation (stress doses of hydrocortisone) may have a protective effect from PTSD in some sub-sets of ICU survivors (Briegel et al., 1999; Schelling et al., 2001). It is hypothesised that patients who would benefit from cortisol replacement therapy are the ones presenting with systemic inflammatory response such as those with septic shock and cardiac surgery (systemic inflammatory response syndrome after cardiopulmonary bypass) (Kilger et al., 2003). The rationale for this is that patients with septic shock and cardiac surgery usually require exogenous vasopressor support with catecholamines to maintain organ perfusion in peripheral circulatory failure (Briegel et al., 1999). In addition, systemic inflammation causes the release of cytokines, which may cause a concentration-dependent resistance to glucocorticoids by reducing the affinity to glucocorticoid receptors (Kam, Szefler, Surs, Sher, & Leung, 1993). Therefore, the cortisol available in the plasma would not be functional in the presence of supra-physiological levels of stress hormones in the blood stream (Schelling et al., 1999).

There is evidence that this catecholamine-cortisol imbalance in the ICU patient can be corrected by the administration of stress doses of hydrocortisone (Schelling et al., 2001; Schelling et al., 2004; Schelling et al., 1999). There is also some beginning evidence that such treatment contributes to a reduction in duration of critical illness and PTSD (Briegel et al., 1999; Schelling et al., 2001).
The mechanisms by which catecholamines and cortisol influence the development of PTSD are unclear. However, some researchers have hypothesised that one possible mechanism could be the interaction between these stress hormones and the memory process. This argument is based on some essential pieces of evidence; first, patients with PTSD often show an important number of traumatic memories such as panic/anxiety, pain, nightmares and respiratory distress (Schelling et al., 1998). Second, the number of these memories has been significantly associated with the severity of PTSD symptoms (Deja et al., 2006; Schelling et al., 1998). Third, the consolidation of these memories is enhanced by catecholamines and glucocorticoids, but corticoids may also cause temporary impairment of memory retrieval (De Quervain, 2006; De Quervain, Aerni, Schelling, & Roozendaal, 2009).

As the evidence from studies on stress doses of hydrocortisone showed that the exogenous administration of glucocorticoids reduced the incidence of PTSD without significantly affecting the number of memories, the possible protective mechanisms of cortisol replacement therapy are unclear. It has been proposed that glucocorticoid-induced inhibition of traumatic memories may reduce the risk and symptoms of PTSD whereas a low or inefficient serum cortisol level may increase the recollection of them, increasing PTSD incidence (De Quervain, Roozendaal, Nitsch, McGaugh, & Hock, 2000). It has also been thought that increased serum cortisol may have an impact by diminishing the intensity of traumatic memories, therefore, PTSD incidence (Schelling et al., 2001).

The evidence from these studies supports the hypothesis of a protective effect of exogenous glucocorticoids administration from the development of PTSD in patients.
with septic shock and cardiac surgery. However, several aspects of these findings must be considered, for example:

- Although there are a number of studies supporting a neuroendocrine deregulation with low levels of cortisol in patients with chronic PTSD, the findings in this area are still controversial.

- While it may be true that some critically ill patients experience catecholamine-cortisol imbalance because of exogenous administration of catecholamines and/or functional cortisol deficiency, it is also true that the infusion of hydrocortisone may have side effects compromising the renal, hepatic and gastrointestinal functions (Briegel et al., 1999; Fletcher, Creamer, & Forbes, 2010).

- While stress doses of hydrocortisone studies have targeted small sub-sets of ICU patients considered to be at higher risk for neuroendocrine alterations when in ICU, not all patients who present with septic shock or who are post-cardiac surgery necessarily develop PTSD when recovering.

- Information regarding use of sedatives, opioids or beta-blockers was not reported in studies that tested stress doses of hydrocortisone. This is an important issue because some of these drugs are thought to have a protective effect for PTSD, as well. For example, morphine is thought to inhibit the release of norepinephrine (Bryant, Creamer, O'Donnell, Silove, & McFarlane, 2009; Holbrook, Galarneau, Dye, Quinn, & Dougherty, 2010). Propranolol, on the other hand, blocks the norepinephrine reuptake (Fletcher et al., 2010). If morphine or propranolol were administered to some of the
patients studied, it is likely that these drugs had constituted parallel protective mechanisms; therefore, confounding variables might have existed.

- Neuroendocrine deregulation is only one piece of the complex puzzle that is the pathophysiology of septic shock, and as Schelling et al. (2001) explained, it is difficult to attribute these positive outcomes to only one intervention.

Finally, it is important to mention that there is a lack of evidence regarding generalised or unspecific anxiety in ICU patients. No study assessing this particular emotional outcome and its association to neuroendocrine deregulation was found in this review.

**Hypoglycaemia:** metabolic deregulation of blood glucose is common in critically ill patients independently of previous diabetes diagnosis. This condition is characterised by high levels of glucose in blood and has been described as an adaptive mechanism when patients are faced with stress (McCowen, Malhotra, & Bistrian, 2001). However, the benefits of hyperglycaemia as part of the stress response have been seriously questioned since deleterious consequences associated with high levels of glucose in blood have been described in the ICU population (McCowen et al., 2001; Vanhorebeek & Langouche, 2007). ICU patients presenting with this condition, known as glucose intolerance, are normally controlled and treated with insulin with the goal of reaching and maintaining normoglycaemia. However, this pharmacological therapy has the potential risk of leading the patient to a hypoglycaemic state (Griesdale et al., 2009; Krinsley & Grover, 2007). In addition to the use of insulin, several other predisposing factors for hypoglycaemia have been reported; such as sepsis, inotropic support,
bicarbonate-based substitution fluid during continuous venovenous hemofiltration and diabetes mellitus (Vriesendorp et al., 2006).

It is known that patients with diabetes often present with depression associated with both hypoglycaemia and hyperglycaemia (Lustman et al., 2000; Strachan, Deary, Ewing, & Frier, 2000). Therefore, it has been thought that this emotional outcome may also be developed in ICU patients presenting with glucose intolerance while receiving ICU treatment, in both diabetic and non-diabetic patients. In this literature review, only one study examining the relationship between blood sugar levels while in ICU and development of adverse emotional outcomes was found. However, its findings suggest a strong relationship between hypoglycaemia and depressive symptoms in patients with respiratory failure (Dowdy et al., 2008).

In this prospective multicentre study (Dowdy et al., 2008), a cohort of 104 survivors of acute lung injury were studied by measuring their blood sugar levels three times a day and screening for depressive symptoms at the third month after discharge. Low blood glucose levels (100 mg/dl) and hypoglycaemia (<60 mg/dl) were significantly associated with depressive symptoms (mean increase: 2.1, 95%CI: 0.6, 3.7, p=0.006 and mean increase: 2.0, 95%CI: 0.5, 3.5, p=0.007, respectively). Interestingly, no significant association between depressive symptoms and mean or maximum blood sugar levels was reported. In addition, factors such as diabetes diagnosis, premorbid anxiety/depression, length of ICU stay, and benzodiazepine doses seemed not to interact significantly with the impact of minimum glucose levels on depression score (p≥0.3 in every case).

Overall, there is a small amount of published evidence regarding the relationship between metabolic deregulation of glucose while in ICU and subsequent development
of adverse emotional outcomes. Even though the findings of the association between hypoglycaemia and depressive symptoms in ALI survivors are significant, more evidence of this association in other sub-sets of ICU patients is needed for these findings to be generalised to the general ICU population. In addition, there is a lack of evidence regarding the impact of both hypoglycaemia and hyperglycaemia on the subsequent development of anxiety or PTSD in ICU survivors.

**Hypoxemia:** hypoxemia during the ICU stay has also been thought to contribute to the development of adverse emotional outcomes in survivors of the ICU (Davydow et al., 2009; Davydow, Gifford, et al., 2008; Jackson, Mitchell, & Hopkins, 2009). However, little empirical evidence supporting this hypothesis has been reported to date. One group of researchers assessed risk factors for depression and anxiety at one and two years post ICU discharge using stepwise multiple regression analysis (n=66 ADRS survivors) (Hopkins et al., 2010). Anxiety at one year was predicted by low PaO2/FiO2 and duration of mechanical ventilation (R²=0.159, R²adj=0.132, F(2,62)=5.87, p=0.005). Anxiety at year two was predicted by the existence of anxiety at year one. These findings suggest that hypoxemia during critical illness may contribute to the development of anxiety. The PaO2/FiO2 was not associated with depression at either one or two years post discharge.

Overall, although there is some evidence to support the hypothesis that neurobiologic factors contribute to the development of adverse emotional outcomes in ICU survivors, the research in this area is in its early stage (Hopkins et al., 2010; Jackson et al., 2009). More research is needed to establish predictors of negative emotional outcomes in the ICU population as well as possible mechanisms of action and interventions.
2.4.2.4 Length of mechanical ventilation and ICU stay

The evidence available regarding the relationship of length of mechanical ventilation and ICU stay to negative emotional outcomes is unclear. While some studies report a significant association between these two variables and emotional problems, others report no connection at all. Investigations supporting this relationship tend to have samples of patients requiring mechanical ventilation due to respiratory failure.

In two small cohorts of ALI/ARDS patients a significant relationship between length of mechanical ventilation and adverse emotional outcomes (symptoms of depression and post-traumatic stress) was found (Nelson et al., 2000). Length of ICU stay was also significantly associated with depression symptoms and PTSS (Kapfhammer et al., 2004; Nelson et al., 2000). In contrast, some studies have found no correlation between the incidence of symptoms of anxiety, depression and post-traumatic stress with duration of mechanical ventilation or the length of ICU stay (Girard et al., 2007; Scragg et al., 2001; Sukantarat et al., 2007). In general, these studies included general ICU patients, with a shorter duration of ICU stay and mechanical ventilation. Patients with extremely long ICU stay (e.g. >one month) appear to have problems.

In summary, there is evidence to support that the duration of mechanical ventilation and length of ICU stay may be predictors for the development of adverse emotional outcomes in ALI/ARDS patients. However, there is no evidence to support such a relationship in the general ICU population. The findings suggest that ALI/ARDS patients require mechanical ventilation and ICU stay for a longer period than the general ICU patients. Therefore, this subset of patients may be exposed to a higher risk for developing adverse emotional outcomes. Thus, these relationships may only be relevant
for patients with an extremely long ICU stay and prolonged mechanical ventilation and not for general ICU patients.

2.4.3 Post-ICU potential risk factors

A number of factors relating to post-ICU status have been linked to the development of symptoms of anxiety, depression and post-traumatic stress. In order to obtain a thorough understanding of the risks that survivors of the ICU are exposed to, it is essential to examine the most common post-ICU factors described in the literature. This section will explore memories of the ICU, neurocognitive impairment, lack of social support, and other post-ICU factors.

2.4.3.1 Memories of the ICU

The role of memories of the intensive care experience in the development of anxiety, depression and PTSD symptoms in ICU survivors has been of great interest. Memories of the ICU have been found to be significantly associated with adverse emotional outcomes in ICU survivors (Jones et al., 2001; Ringdal et al., 2009; Samuelson et al., 2007). Because of the subjective nature and complexity of these memories, the need for appropriate instruments for assessment has led to the development of a number of them. These instruments are often used to explore different aspects of these memories, for example, whether they correspond to a real event or not, or how the patient perceives and interprets them, or the number of these recollections (Deja et al., 2006; Granja et al., 2008; Jones et al., 2001; Rattray et al., 2005). This variety has the valuable benefit of exploring and providing information about these memories from different perspectives; however, these tools often have different classifications that sometimes overlap, and different terminologies to refer to the same types of memories. These two factors should be taken into consideration when
examining the literature to avoid confusion. For this reason, the next section will examine the memories of the intensive care experience in relation to their respective assessment tool.

The Intensive Care Unit Memory Tool (ICUM tool) is an instrument specifically designed to assess three types of memories of the ICU; delusional, factual and memories of feelings (Jones, Humphris, & Griffiths, 2000). While factual memories of the intensive care experience correspond to the recall of real events such as the presence of an endotracheal tube or the recall of suctioning, delusional memories correspond to the recall of unreal events such as hallucinations, nightmares, and paranoia. Patients may also have recollections of feelings experienced while receiving care such as anxiety/panic, pain, or confusion (Jones et al., 2000; Stoll et al., 1999).

Delusional memories of the intensive care experience are often reported by ICU survivors, with a prevalence varying between 26% and 77% (Jones et al., 2001; Ringdal et al., 2009). Such memories are often described as flashbulb-like quality (vividness, clarity and intensity) and producing great distress at the moment of being experienced (Jones et al., 2001). While their origin is not fully understood, it is probably multifactorial. Factors such as prolonged mechanical ventilation, extended ICU stay, severity of illness, and sedation with propofol have been associated with their development (Ringdal et al., 2009). Personal characteristics such as younger age and premorbid psychological history may also contribute (Jones et al., 2001; Ringdal et al., 2009).

The presence of delusional memories in survivors of the ICU has been strongly associated with the development of adverse emotional outcomes in several investigations. For example, a prospective study examined the association of these
memories with the development of psychological distress at two and eight weeks post-ICU discharge (Jones et al., 2001). This small single centre study (45 mechanically ventilated patients) demonstrated that patients with delusional memories such as paranoid delusions or hallucinations without recall of factual events, had higher anxiety and depression levels than patients with factual memories and delusional memories two weeks after ICU discharge [HADS-anxiety (mean 14.0 vs. mean 6.3; F(4.2) p=0.0001) and HADS-depression (mean 13.0 vs. mean 3.9; F(4.2) p=0.0001)]. They also were more likely to develop PTSS (Impact of Event Scale mean 43.0 vs. mean 15.2; F(12.9), p=0.0001), and panic attacks (Fear Index mean 52.7 vs. mean 13.8; F(17.7), p=0.002) at eight weeks than those patients with factual memories. A similar pattern was seen in a later study in the same ICU where patients with delusional memories had higher levels of anxiety (one-way ANOVA, F(4.28), df=1, p=0.044) and PTSS (one-way ANOVA, F(4.38), df=3, p=0.008) at six months than those without such memories (Jones et al., 2003).

An explorative multicentre study examined the relationship between delusional memories and psychological distress in 239 trauma ICU patients (Ringdal et al., 2009). A significant correlation between these memories and both anxiety (OR: 2.5, CI: 1.4, 4.7, p=0.0026) and depressive symptoms (OR: 2.7, CI: 1.5, 5.0, p=0.0013) was found. The probability that patients with delusional memories present with symptoms of anxiety was 51% vs. 29% in patients without such memories. Patients with delusional memories and head injury had an increased probability of experiencing anxiety (69% vs. 26%) than patients without delusional memories or head injury. The prevalence of delusional memories reported in this study was 26%, compared to 77% reported previously (Jones et al., 2001). This significant difference may be explained by
differences in sample characteristics, mechanical ventilation status and time of memory assessment. In Ringdal et al. (2009), only 25% of trauma patients required mechanical ventilation from which 43% reported delusional memories compared to 19% of the non-ventilated patients (p<0.001). Memories were assessed at six to eighteen months after discharge compared to Jones et al. (2001) where all the general ICU patients (7% trauma patients) included were mechanically ventilated and the memory assessment was at two and eight weeks after discharge.

Factual memories, on the other hand, have been reported as having a protective effect. Even though these memories are considered to be unpleasant (endotracheal tube) and stressful (tracheal tube aspiration), they may be a key element in providing the patient with a sense of reality, which may help them to distinguish between reality and delusion (Granja et al., 2005; Jones et al., 2001). The ability to make such a judgment may provide some protection from anxiety, panic attacks and PTSS (Jones et al., 2001). Therefore, according to this hypothesis, the mechanism by which the psychological distress may generate is through the recall of delusional rather than factual memories. In contrast, a multicentre observational cohort study found that patients reporting both factual and delusional memories together had more PTSS (PTSS-14 median 37, IQR: 21-51, p=0.007) than those without delusional memories or those with delusional but without factual memories (Granja et al., 2008). This study examined the relationship of both factual and delusional memories to the development of PTSD symptoms in 313 general ICU survivors (16% trauma patients) at six months post-ICU discharge. These findings suggest that the recall of adverse experiences (factual or delusional) of the ICU is associated with the development of PTSD symptoms.
The differences in sample characteristics and time of memory assessment may explain contradictions in findings. The study supporting that factual memories may have a protective effect included only ventilated patients who were assessed at two weeks post hospital discharge and reported a prevalence of delusional without factual memories of 20% (Jones et al., 2001). In contrast, the study supporting that it is the recall of adverse experiences regardless of them being factual or delusional that contribute to adverse emotional outcomes included general ICU patients (ventilated and non-ventilated), assessed memories much later (six months post discharge) and reported a much lower prevalence of delusional without factual memories (5%) (Granja et al., 2008).

With regard to changes over time, there is a small amount of evidence suggesting that delusional memories tend to be stable over a short period of time while factual memories and memories of feelings tend to decrease (Jones et al., 2001). This study reported a reduction from the second to the eighth week in the recollection of memories of feelings such as anxiety or pain, and factual events of the ICU stay. Delusional memories, on the other hand, were stable over this time and patients’ descriptions of these memories were similar at the two occasions. Changes in symptoms of anxiety and depression were observed over more than five years in 153 trauma patients with and without delusional memories during the ICU stay (Ringdal, Plos, Ortenwall, & Bergbom, 2010). Patients with delusional memories had an incidence of anxiety and depression significantly higher than patients without delusional memories four years after injury (anxiety 43% vs. 24%, p=0.025; depression: 38% vs. 19%, p=0.021). In addition, no improvement in anxiety and depressive symptoms was seen over this time in patients with delusional memories (Ringdal et al., 2010). It is important
to note that studies using the ICU memory tool usually report findings mainly on delusional, factual and combination between these two types of memories, reporting very little about memories of feelings.

The Post-Traumatic Stress Syndrome 10-Questions Inventory (PTSS-10) is a two-part questionnaire that examines the recall of traumatic memories or memories of adverse events of the ICU experience in the Part (A) and the intensity of PTSS in the Part (B). The purpose of part A is to determine how many of four memories (nightmares, anxiety/panic, pain and suffocation) are recalled by the patient without explicit assessment of their frequency or intensity (Schelling et al., 1998). It can be seen that some of the traumatic memories such as pain and panic/anxiety overlap with memories of feelings, and nightmares with delusional memories of the ICUM Tool (Jones et al., 2000).

The presence of traumatic memories has been consistently associated with PTSS in ICU survivors. A retrospective study including 80 ARDS survivors, found that patients reporting multiple traumatic memories of the ICU experience were more likely to develop PTSS than patients reporting none or one episode (from 17 to 28 points, p=0.015) (Schelling et al., 1998). Two prospective studies including 65 ARDS survivors and 313 general ICU patients confirmed these findings by reporting a significant association between the number of traumatic memories and the development of PTSD symptoms (Deja et al., 2006; Granja et al., 2008). Interestingly, the recollection of having experienced anxiety (one of these four traumatic memories) was significantly correlated with higher risk of developing PTSD ($\chi^2(1)=7.59; p<0.01$) (Deja et al., 2006). These three studies explored the relationship between traumatic memories and
development of PTSD symptoms (Deja et al., 2006; Granja et al., 2008; Schelling et al., 1998). None of them assessed post-ICU symptoms of anxiety or depression.

The Intensive Care Experience Questionnaire (ICEQ) is an instrument designed to examine patients' subjective perceptions of the intensive care experience and its impact on emotional outcomes. This tool examines four components: awareness of surroundings, frightening experiences, recall of experiences and satisfaction with care (Rattray, Johnston, & Wildsmith, 2004). Two of these components (frightening experiences and recall of experiences) have been associated with the development of emotional problems (Rattray et al., 2005). The frightening experiences component has six items (I seemed to have bad dreams, I felt scared, I saw strange things, I felt helpless, I thought I would die, I seemed to be in pain). The recall of experiences has five items (I wish I remembered more about it, most of my memories are blurred, I wish I had known more about what was happening to me, I seemed to sleep too much, I never knew whether it was day or night). Some of the items assessed by this tool are also assessed by others instruments. For example, “bad dreams”, “seeing strange things” or “I seemed to be in pain” would correspond to some of the categories of the ICUM Tool.

The subjective interpretation of the intensive care experience has been speculated as a possible mechanism by which frightening and stressful experiences influence the development of psychological distress (Rattray et al., 2005). This group of researchers explored the effect of patients’ perceptions of the intensive care experience on emotional outcomes in a sample of 80 ICU patients. It was found that the frightening experiences component was consistently associated with higher anxiety, avoidance, and intrusion scores at hospital discharge, at six months and 12 months post discharge. The
recall of experiences component was also associated with higher anxiety and depression scores at six months, and higher intrusion scores at hospital discharge.

Overall, memories of the ICU seem to play an important role in the development of symptoms of anxiety, depression and post-traumatic stress in ICU survivors. Nevertheless, it remains unclear what sort of memories are related to adverse emotional outcomes. While delusional memories without recall of factual events have been associated with post-ICU adverse emotional outcomes, there is evidence supporting that both delusional and factual memory of adverse events contribute to the development of PTSD symptoms. Moreover, the subjective interpretation of the intensive care experience could be the mechanism by which these frightening and stressful experiences (factual or delusional) influence the development of emotional problems. The evidence found in this literature review has found that the relationship between memories of the ICU and the development of negative emotional outcomes has not been well determined.

2.4.3.2 Neurocognitive impairment

Impaired memory, attention, concentration or mental processing speed are some of the symptoms that ICU survivors are usually faced with when recovering. The effects of neurocognitive impairment on the development of symptoms of depression, anxiety and post-traumatic stress in ICU survivors have been assessed in some studies (Hopkins et al., 2004; Hopkins, Weaver, Collingridge, Parkinson, & al, 2005; Jackson et al., 2003).

A prospective cohort study explored neuropsychological function, depression, and quality of life, six months post discharge in 34 mechanically ventilated patients (Jackson et al., 2003). The neuropsychological assessment involved seven cognitive
domains: mental status, psychomotor speed, verbal fluency, working memory, verbal memory, visual memory, and visual-construction, as measured by a set of standardised neuropsychological well-validated instruments. This investigation found that patients who presented with cognitive impairment (32%) were significantly older than the non-impaired group (impaired group mean 60.3, SD±16.2 years; non-impaired group mean 49.2, SD±13.5 years, p=0.07) and had a level of education significantly lower (mean 11.3 vs. 14.1 years, p=0.03). This suggests that younger age and higher level of education may have a protective effect from negative cognitive outcomes. Depressive symptoms were assessed at hospital discharge and six months post hospital discharge. Impaired patients showed significantly higher mean scores of depressive symptoms than non-impaired patients at both occasions (at hospital discharge 6.2 vs. 3.7, p=0.04, and six months after hospital discharge 6.4 vs. 3.0, p=0.02). While these findings suggest a relationship between cognitive impairment and symptoms of depression in general ICU patients, no correlation between cognitive impairment and symptoms of depression and anxiety was found at one year post hospital discharge by other groups of researchers who prospectively studied a sample of 66 ARDS survivors (Hopkins et al., 2004). Intellectual function, attention/concentration, memory, mental processing speed, executive function, verbal abilities, visual-spatial abilities and emotional outcomes were assessed by standardised and well-validated instruments in Hopkins et al (2004). The prevalence of cognitive sequelae was 69.7% at hospital discharge, which diminished to 45.5% in approximately one year. Eventually, this sample of patients was included in another study and followed for another year. The findings were similar to those previously reported, namely, no significant association between depression and anxiety and neurocognitive outcomes at two years post hospital discharge (Hopkins et al., 2005).
It can be seen that there is inconsistency in findings regarding the association between neurocognitive impairment and emotional outcomes after the ICU experience. This difference may be explained by differences in sample characteristics, time of assessment and instruments used. For example, the study where this association was statistically significant had a wider spectrum of patients (all general ICU patients requiring mechanical ventilation versus ARDS survivors only, in the other two studies) was included. The time of neurocognitive assessment may also play a role here, leading to different results. While Jackson et al. (2003) found a significant association at six months after hospital discharge, the other two studies did not find such an association at one and two years post hospital discharge (Hopkins et al., 2004; Hopkins et al., 2005). It can be thought that this association existed at a medium-term (six months) and then, as the symptoms of neurocognitive impairment reduce over time (from 69.7% at hospital discharge to 45.5% one year after hospital discharge) the relationship resolved. While the three studies administered a battery of standardised and well-validated tests for neurocognitive assessment, some of them assessed different cognitive outcomes, which may have also contributed to these differences in findings. The evidence regarding the relationship between neurocognitive impairment and emotional outcomes after the ICU experience includes symptoms of anxiety and depression. No study linking neurocognitive impairment to PTSS was found in this review.

2.4.3.3 Social support

The level of social support available for ICU survivors after the ICU experience has been thought to play a significant role in emotional recovery, reducing and/or preventing symptoms of anxiety, depression and PTSD. In this literature review, two of three studies examining this relationship suggest that an optimal level of social support
may have a protective effect against the development of negative emotional outcomes (Deja et al., 2006; Perrins, King, & Collings, 1998). Perception of social support as assessed by the Questionnaire for Social Support German version (a 22-item questionnaire) was found to have a significant positive impact on psychological well-being, reducing significantly symptoms of PTSD in 65 ARDS patients ($r=-0.31$, $p<0.05$) included in a prospective study (Deja et al., 2006). It was observed that patients with high levels of perceived emotional support and social integrity (two sub-dimensions of the Social Support Questionnaire) reported significantly lower scores in the PTSS-10 (F-Sozu, $t=2.24$, $p<0.05$ and $t=3.53$, $p<0.01$, respectively) (Deja et al., 2006). In addition, a longitudinal study observed psychological recovery patterns over a one year period in a group of 44 ICU patients (Perrins et al., 1998). Psychological well-being (including symptoms of depression and anxiety) was assessed by the General Health Questionnaire 28-item version (GHQ28) and post-traumatic stress symptoms by IES. Patients were categorised into one of the four levels of social support ranging from maximum social support (living with partner/next of kin) to minimal support (patient perceives self to have no/minimal support). It was found that the higher levels of social support the patient received, the better the scores in the GHQ28 and IES (less symptoms) over the year and vice versa. However, this trend failed to reach statistical significance probably due to small sample size ($n=44$) (Perrins et al., 1998).

In contrast, a cross sectional retrospective study found no significant differences between three different subgroups of patients (group with PTSD, group with sub-PTSD and group without PTSD) and level of social support, therefore, no correlation between symptoms of PTSD and social support was reported (Kapfhammer et al., 2004). Some
limitations of this study are a low follow-up rate (58%) and small sample size (n=46 ARDS patients).

Overall, while it is reasonable to think that optimal levels of social support may have a protective effect against the development of negative emotional outcomes in ICU survivors, the evidence supporting this association is limited. Only one study reported a significant protective effect against symptoms of PTSD in a small sample of ARDS patients. Hence, more evidence is needed in order to learn to what extent a high level of social support is beneficial to the general ICU population.

2.4.3.4 Symptoms of emotional distress early post-ICU discharge, decreased physical function and poor physical health

There are other post-ICU factors that have been assessed and associated with the development of adverse emotional outcomes. However, the evidence tends to be small since they are particular to the study assessing them. The lack of replication of these findings makes it difficult to generalise. Factors that have been considered include symptoms of emotional distress early post-ICU discharge, decreased physical functioning and poor physical health. In a prospective study (n=277 ventilated patients), depressive symptoms at two months after ICU discharge were a strong risk factor for depression at the sixth month. This study also assessed the association between physical functioning and depressive symptoms, reporting that improvements in physical functioning (domain from the physical component summary (PCS) of the SF-36 Health Survey) contributed significantly to reduced symptoms of depression as measured by the Centre for Epidemiologic Studies Depression Scale (CES-D) from two to six months (Spearman p=-0.45, p<0.001) (Weinert & Meller, 2006). However, this result should be looked at with caution since no relationship between change in physical
functioning (difference between the baseline and two months post ICU) and the CES-D score at two months after ICU discharge was found in this sample (Weinert & Meller, 2006).

Nevertheless, another prospective study reported that physical functioning was significantly correlated with symptoms of depression and anxiety at three and nine months post-ICU discharge in 51 general ICU patients (Sukantarat et al., 2007). In addition, this study examined the association between levels of anxiety, depression and PTSD, and general health parameters at three and nine months after discharge. The researchers designed an instrument to measure a set of six symptoms (pain, nausea and vomiting, loss of appetite and weight, change of bowel habit, sleep, energy and vitality). The score for every symptom ranged from 0 to 3 (absent to severe), with a maximum score of 18. They also used the EuroQol “thermometer” to measure perceptions of health. At the third month, symptoms of anxiety, depression and avoidance correlated significantly with the EuroQol value and symptoms score. These associations were stable at the ninth month and intrusion symptoms also correlated with the scores of both of these instruments at this time. These findings suggest that decreased physical health and/or physical functioning after ICU admission may have a negative impact on emotional recovery (Sukantarat et al., 2007).

In conclusion, while there is a number of post-ICU factors associated with the development of adverse emotional outcomes, the empirical evidence supporting these associations is limited. Regarding neurocognitive impairment the evidence suggests that there may be medium-term relationships between symptoms of depression and neurocognitive impairment in general ICU survivors. Although optimum levels of social support were seen to have a protective effect against the development of PTSD
symptoms in ARDS patients, more research is needed to understand if a high level of social support is beneficial to the general ICU population. Depressive symptoms early post-ICU discharge seems to be a strong predictor of depression at six months after discharge in the general ICU population. Both decreased physical functioning and physical health after ICU stay may contribute to the development of anxiety and depression in general ICU patients, and poor physical health may also contribute to PTSD symptoms. In general, replication of these findings is needed to understand to what extent these post-ICU factors influence the development of adverse emotional outcomes when recovering. This information would enable development and testing of appropriate interventions to improve recovery after critical illness.

2.5 Conceptual model

The literature review process yielded the development of a conceptual model, which has been incorporated in this study as a framework to drive and organise the entire study. Conceptual models are schematic representations of the possible relationship between factors that are believed to be associated to a particular public health problem (Earp & Ennett, 1991). They are particularly useful to illustrate research questions when investigating specific behaviours in specific context (Earp & Ennett, 1991).

In the conceptual model developed for this research, possible factors associated with adverse emotional outcomes came from the biological, psychological and social spheres, conforming a biopsychosocial model. Potential risk factors were classified into three categories as follows: Pre-ICU, Intra-ICU and Post-ICU factors. Pre-ICU potential
risk factors correspond to a group of patient’s characteristics and conditions that are present before the ICU admission. Intra-ICU factors involve factors associated with critical illness during ICU stay. Post-ICU factors include those conditions present during recovery after the ICU stay. The conceptual model outlined below summarises and integrates the knowledge of the concepts involved in the development of adverse emotional outcomes after the ICU experience from the literature reviewed (Figure 2.5.1).

Figure 2.5.1. Factors associated with adverse emotional outcomes after the ICU experience

The association between anxiety during critical illness, with its state and trait components, and adverse emotional outcomes during recovery has not yet been tested. They appear in this model because they are the factors that we hypothesise to be associated with the outcomes of this study.
2.6 Conclusion

The evidence regarding a number of factors associated with the development of symptoms of anxiety, depression and post-traumatic stress in ICU survivors has been presented in this literature review. The evidence has been analysed, discussed and synthesised in order to identify gaps in current knowledge. During this process, a gap in the literature has been identified. Several aspects of sedation and analgesia have been significantly associated with adverse emotional outcomes. However, the mechanisms of this association have not been clearly established. It is possible that the level of anxiety during critical illness is one mechanism leading to emotional problems when recovering.

Evaluation of the effect of both components of anxiety (state and trait) during critical illness on emotional recovery is vital to inform clinical practice, education and research. This new knowledge will help clinicians to better target interventions to improve care and health outcome. The next chapter outlines the methodological framework used for this study.
Chapter 3: Methods

3.1 Introduction

A number of risk factors for the development of adverse emotional outcomes in intensive care unit (ICU) survivors were presented in Chapter 2. The review of the literature led to the identification of gaps in current knowledge and the formulation of the research questions for this study. The methodological framework to answer these research questions is presented in this chapter. First, the reasons for the design chosen are explained. Second, the characteristics of the sample (inclusion/exclusion criteria), sample size and setting for this study are described. Third, the data collection and data analysis procedures are discussed. Finally, the ethical considerations for this study are presented. The methods of this study were published in 2013 in the Australian Critical Care (Castillo, Aitken, & Cooke, 2013) (see Appendix 3).

3.2 Research aims and questions

The overall aim of this study is to acquire a better understanding about the relationship between anxiety during critical illness and adverse emotional outcomes in survivors of the intensive care.

3.2.1 Aims

The aims of this study were:
1. To describe the magnitude and patterns of state anxiety reported by patients throughout their ICU stay
2. To identify factors associated with patients’ state anxiety and trait anxiety during critical illness
3. To identify factors associated with symptoms of anxiety and depression over six months after the intensive care experience
4. To determine factors associated with PTSS over six months after the intensive care experience.

3.2.2 Research questions

In order to meet the aims of this study the following research questions have been developed:

1. What are the magnitude and patterns of patients’ state anxiety throughout their ICU stay?
2. What factors are associated with state and trait anxiety during critical illness?
3. What factors are associated with symptoms of anxiety and depression in ICU survivors over six months after ICU discharge?
4. What factors are associated with PTSS in ICU survivors over six months after ICU discharge?

3.3 Design

This research was a prospective longitudinal cohort study of ICU survivors. This observational design allowed studying anxiety (state and trait) during critical illness as a factor for the development of adverse emotional outcomes during recovery. In addition,
it also allowed follow up the patients at different time points to determine the effects of anxiety over time.

3.4 Setting

This study was conducted in the adult ICU of a tertiary metropolitan hospital located in Brisbane, Queensland, Australia. This ICU has 25 beds, including general ICU patients and post-cardiac surgery patients. The nurse/patient ratio is 1:1 and in 2013 there were approximately 2000 admissions to this ICU.

3.5 Sample

All adult patients (≥ 18 years of age) admitted to the ICU ≥24hours, who were able to: (1) communicate verbally or non-verbally; (2) understand English; and, (3) open their eyes spontaneously or in response to voice to respond to the Faces Anxiety Scale (FAS) were invited to participate in this study.

3.6 Sample size

In this study, previous research exploring similar research questions in the ICU population were examined to determine the effect size reported and perform power analysis a priori using G*Power 3.1.3 (Faul, Erdfelder, Buchner, & Lang, 2009). The effect size reported in the literature testing correlations in the ICU context is often medium (Davydow, Desai, et al., 2008; Davydow et al., 2009; Davydow, Gifford, et al.,
Therefore, a medium effect size and a selected power of 80% with a significance of \( \alpha=0.05 \) were used to estimate the sample size for this study.

The number of predictors to be entered into the model was unknown at the stage of power analysis, but based on the number variables that were going to be controlled for the number of predictors expected was seven. By convention, a moderate effect size for multiple regression is \( R^2=0.15 \), therefore, using power of 80\% and \( \alpha=0.05 \), the number of participants needed was 104 (Polit-O'Hara, 2010; Polit-O'Hara & Beck, 2012).

Because longitudinal research in the ICU population often reports a number of patients lost to follow-up, it was estimated that 170 patients needed to be enrolled during their ICU stay to obtain a sample of about 104 patients at six month. A 70\% completion of follow up and a mortality rate of 10\% were estimated.

### 3.7 Recruitment process

All ICU patients were screened daily by the principal investigator for potential enrolment, liaising with the ICU Research Nurse to determine eligibility. Each participant was approached at an appropriate time determined in consultation with the bedside ICU nurse. Patients’ assent was required to include patients in this study during the ICU stay, and then when the patients were in the wards (after the ICU stay but prior to hospital discharge), written consent was requested. The relevant Human Research Ethics Committees approved this process.
3.8 Data collection

During the course of this study patients provided information at four time points: in ICU, in the wards, 3 months post ICU discharge and 6 months post ICU discharge. All the data were collected between September 2012 to September 2013.

**In ICU:** the principal investigator and the ICU Research Nurse screened for potential participants every morning. Once patients met the inclusion criteria, the ICU bedside Registered Nurse was approached to discuss the appropriateness of including the patient in this study. After this step, patients were invited to participate in the project. As soon as they agreed, state anxiety assessment commenced. Participants reported their state anxiety levels twice a day using the FAS.

The FAS is a single-item instrument especially designed to measure state anxiety in ICU settings. It consists of a scale showing five faces representing five different levels of anxiety, ranging from no anxiety to extreme anxiety, scoring from one to five. The patient is asked how much anxiety is felt at the moment of assessment and the answer may be a verbal or a nonverbal response, i.e. they can point to the relevant face. The reported criterion validity of this tool was 0.64 (p<0.001) in mechanically ventilated patient (correlation between the self-report of anxiety on the FAS and clinical judgment of anxiety) (McKinley et al., 2004). While its reliability has not been measured because of limitations in reliability methods for a single-item instrument (McKinley & Madronio, 2008; McKinley et al., 2004), the FAS is a practical tool to assess this emotion in critically ill patients.

The time to perform this assessment was approximately two minutes and did not involve any invasive procedure. The researcher approached the patient, explained the
procedure and showed them the FAS with the following instructions:

- These faces are showing different levels of anxiety.

- This face shows no anxiety at all; this face shows a little bit more; a bit more (sweep finger along scale); right up to extreme anxiety.

- Have a look at these faces and choose the one that shows how much anxiety you feel at the moment (McKinley et al., 2004).

The level of state anxiety was measured as a continuous variable (scale from 1 to 5 points), and then the value obtained was categorised into low (1-2) or moderate to severe anxiety (score 3-5), consistent with instructions provided by the scale developer. State anxiety was assessed twice a day (morning 8-11am and afternoon 4-7pm) up to 30 days during ICU stay. These timeframes were selected to identify any difference between morning assessments (usually busier ICU environment) and evening assessments (usually quieter ICU environment). Patient’s competency to report on their level of state anxiety was determined by consultation with the bedside registered nurse and patient’s ability to communicate effectively (verbally or non-verbally) with the researchers.

Clinical and demographic data collected from medical records included: age, gender, type of admission (medical, surgical, trauma, cardiac surgery), delirium (Confusion Assessment Method – ICU: CAM-ICU), hours of mechanical ventilation (invasive and non-invasive), acute physiology and chronic health evaluation III score (APACHE III), length of ICU stay (days), length of hospital stay (days) and pain using the Critical-Care Pain Observation Tool (CPOT) (Cook et al., 2002; Ely et al., 2001; Gelinas, Fillion, Puntillo, Viens, & Fortier, 2006; Gelinas, Harel, Fillon, Puntillo, &
Data on drugs administered included exposure to corticosteroids, opioids, benzodiazepines, anxiolytics, antidepressants, beta-blockers, anesthetic agents and analgesics; length of sedation and analgesia (hours of propofol, midazolam, morphine, fentanyl, ketamine, oxycodone infusion); and total doses of sedatives and analgesics (propofol, midazolam, morphine, fentanyl, ketamine, oxycodone and paracetamol).

**In the wards:** the principal researcher performed daily ward visits to find an appropriate time to approach the participants and obtain written consent. Participants who did not wish to continue in this study were asked permission to use the ICU based-data. If permission to use this information was not given, the data were not used. At this time, trait anxiety was assessed using the trait component of the State-Trait Anxiety Inventory for Adults Form Y-2 (STAI) (Spielberger, 1983). The STAI is a self-report 20-items measure based on a 4-point Likert scale with scoring ranging from 20-80 with higher scores indicating greater levels of trait anxiety. The STAI is a well-validated and recognised tool for the assessment of trait anxiety and has previously been used with survivors of critical illness (Jones et al., 2003; Kress et al., 2003). The trait component of the STAI had good internal consistency in this current study, with a Cronbach alpha coefficient of 0.92. The assessment of trait anxiety was performed once only when participants were in the wards for two reasons: (1) The State-Trait Anxiety Inventory (STAI) Form Y-2 is a 20-Item instrument, with completion requiring a patient to be able to maintain attention for about 10 minutes; and, (2) Trait personalities are stable patterns of cognition, affect and behavior that are relatively consistent across time and situations (American Psychiatric Association, 2013). Thus, trait anxiety would have
been unlikely to change in such a short period (between ICU stay and assessment in the wards).

Symptoms of anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983). The HADS is a widely used self-report questionnaire consisting of 14 statements divided into two seven-statement subscales, one for depression and one for anxiety. The score range for each statement is 0-3, with higher scores indicating greater frequency of the feeling assessed. The total score for each subscale can be classified into four categories: normal [0-7], mild [8-10], moderate [11-14] and severe [15-21] (Zigmond & Snaith, 1983). Both the anxiety and the depression subscales of the HADS had good internal consistency in this current study, with a Cronbach alpha coefficient of 0.83 and 0.81, respectively.

Participants completed a self-reported questionnaire containing questions on current marital status and employment status, highest level of education, evidence of treatment for mental health (self-reported mental health history and use of benzodiazepines, anxiolytics and/or antidepressants medications), current smoking and drinking habits and pre-ICU medication (corticoids, opioids, beta-blockers). They also reported on their levels of trait optimism by completing the Life Orientation Test-Revised (LOT-R) (Scheier, Carver, & Bridges, 1994). This questionnaire contains ten statements with six of them concerning general expectations relative to positive or negative consequences. Four statements are filler items and are not used in the scoring. For each statement, a rating score between 0 and 4 is possible. The total score ranges from 0 to 24 (higher scores indicate greater optimism). Trait optimism was assessed when participants were in the hospital wards.
Three months after ICU discharge: at this time, the questionnaires were sent to study participants by mail or email, together with a cover letter explaining to the participants that the surveys were to be completed by themselves without the help of their relatives or friends. A pre-paid envelope was provided for return of the completed surveys. At this time, participants were reassessed for symptoms of anxiety and depression (HADS), current employment status and smoking and drinking habits (demographic questionnaire). Participants also completed the Post-traumatic Stress Symptoms 10-question inventory (PTSS-10) to self-report post-traumatic stress symptoms (Stoll et al., 1999).

The PTSS-10 is a self-report two-part questionnaire (part A and part B) designed to screen for PTSD in survivors of critical illness. Part A consists in a statement about the patients’ memory of their ICU admission. Two alternatives (Yes/ No) are possible to indicate the presence or absence of the following traumatic memories: nightmares; severe anxiety or panic; severe pain; and, respiratory distress. In part B, the presence and intensity of 10 PTSS are assessed. These symptoms are sleeping disturbance, nightmares, depression, hyperalertness, emotional numbing, irritability, labile mood, guilt, avoidance of activities prompting recall of the traumatising event, and muscular tension. Each symptom can be rated from 1 (never) to 7 (always); therefore, a total score ranging from 10 to 70 points can be obtained. Symptoms of PTSD were classified according the recommended cut-off of 35 points (scale from 10 to 70 points) into two categories, high probability of PTSD (total score >35 points) and low probability of PTSD (<35 points) (Stoll et al., 1999). Part B of the PTSS-10 had good internal consistency in this current study, with a Cronbach alpha coefficient of 0.86.
In addition, participants self-reported on their perceived level of social support and cognitive function. Participants completed the Multidimensional Scale of Perceived Social Support (MSPSS) and the Self-reported Cognitive Functioning Scale-Revised MOS 6-Item (MOS COG-R) (Stewart & Ware, 1992; Zimet, Dahlem, Zimet, & Farley, 1988). The MSPSS is a 12-item measure contains three subscales: family, friends and significant other. For each item a rating score between 1 (very strongly disagree) and 7 (very strongly agree) is possible. Higher scores indicated higher levels of perceived social support. Subscale and total score are obtained by summing the relevant number of items. The reliability and validity of this questionnaire were demonstrated and reported by Zimet et al. (1990). The MOS COG-R contains six questions assessing areas of memory, attention and reasoning. Each item is scored from 1 (all the time) to 6 (none of the time). Summing the individual item scores and transforming the resulting score to a 0-100 scale calculates the total score. Higher scores indicate better cognitive functioning (Stewart & Ware, 1992).

**Sixth month after ICU discharge:** participants completed the HADS, PTSS-10, MSPSS, MOS COG-R and Demographic questionnaire for the last time. The PTSS-10, STAI, HADS, FAS, MSPSS, LOT-R and MOS COG-R were chosen because they are self-reported, well validated and easy to understand instruments, take a few minutes to complete, and with the exception of the MOS COG, have all been used in ICU research. The instruments used in this research are presented in Appendixes 12-22.

The researcher contacted the participants or next of kin to confirm that the participants were alive before posting all the questionnaires. Mortality during the ICU stay, at the third month and sixth month post-ICU discharge was recorded. Most pre-ICU, intra-ICU and post-ICU risk factors from the conceptual model developed in the
literature review chapter were assessed in this study. It should be noted, however, that while neurobiological factors such as hypoglycaemia and neuroendocrine dysregulation were identified in the literature review, these factors were not measured in this study. In the ICU where this study was carried out, there is a tight glycaemic control where patients are monitored hourly and therefore treated immediately. Thus, hypoglycemia would have been rare in these patients. Neuroendocrine dysregulation was not measured because the resources needed to assess this risk factor properly were too extensive for the scope of this PhD program. For the same reason, decreased physical function and poor physical health were also risk factors not assessed in this study. Therefore, these four interesting factors could not be assessed representing a limitation of this research.

3.9 Data analysis

Data were cleaned and checked for missing and invalid values. A random selection (15%) of the database was verified against original questionnaires. Descriptive characteristics are presented using means and standard deviations (SDs) or medians and interquartile ranges (IQRs) for continuous variables and percentages for categorical variables.

The outcome variable “state anxiety” was derived from repeated measures taken during the participants ICU stay (twice a day up to 30 days). The first state anxiety measure in ICU and several aggregate variables were extensively explored to obtain a single value that best represented the level of state anxiety during the patient’s ICU stay. Of all derived (aggregated) measures for anxiety, the mean value was the strongest at accounting for correlations amongst observations in the same cluster.
**State and trait anxiety:** distributions of variables were assessed with frequency histograms and statistical tests for normality. Bivariate relationships were tested between each risk factor and the outcome variables (trait and state anxiety) using appropriate inferential statistics. Continuous, binary and nominal/ordinal risk factors used Spearman's correlation, Mann-Whitney U test, Kruskal-Wallis, respectively. Variables associated at p≤0.2 were then tested in the multivariable analysis.

Multiple linear regression was used to identify factors significantly associated with state anxiety. A stepwise approach with a forward selection of variables, identified in the bivariate analysis, testing the successive addition of each variable into the model was used. This process was repeated until all variables in the model were significant (p<0.05). Variables that had been repeatedly identified in the literature as significant were added and tested in the final model. The same process was used to determine the factors that were significantly associated with trait anxiety.

Regression diagnostics were performed informally (graphical) and formally (statistical) to verify the analysis met the assumptions underlying multiple linear regression. Diagnostic tests included assessing the normality and homoscedasticity of residuals, degree of multicollinearity amongst risk factors, the linearity assumption between the outcome variable and risk factors and identification of outliers.

**Symptoms of anxiety, depression and post-traumatic stress:** linear mixed models using a single variable and alpha level (p < 0.2) was performed to identify variables with a potential longitudinal relationship with the outcome variables (symptoms of anxiety, depression and post-traumatic stress). The selected variables were checked against one another for multicollinearity using Spearman correlations and Chi-square, then entered into the model based on level of significance.
Repeated measures analysis using mixed models with a random intercept per subject was performed to determine variables independently and significantly associated with the outcomes of symptoms of anxiety, depression and post-traumatic stress over a six-month period. Significance level of 5% and the Akaike Information Criteria (AIC) were used to identify robust and parsimonious models. Model diagnostics included assessment of influential observations, multicollinearity amongst variables and residual checks. Theory-grounded factors were added into the ‘final set’ of variables to check whether they influenced the model (i.e. were significant and/or decreased/improved the AIC).

The analysis of PTSS data had some differences compared to anxiety and depression symptom because PTSS were assessed for the first time three months after the intensive care experience and not in the hospital wards. The timing for the first assessment of PTSS was based on the definition of PTSD outlined in the Diagnostic and statistical manual of mental disorders 5th edition (DSM-V) (American Psychiatric Association, 2013). Linear mixed models in the case of PTSS allowed the identification of factors, at baseline and three months, which were significantly associated with PTSS scores over a period of 6 months post ICU discharge. Model results are expressed as unstandardized coefficients, 95% confidence intervals and p-values. The Statistical Package for the Social Sciences version 20.0 (SPSS IBM Corp. in Armonk, NY) and Stata version 13 (Statacorp, College tation, Texas) were used to analyse the data (IBMCorp, 2013; StataCorp, 2013).
3.10 Ethical Considerations

As the participants in this research were human beings, several ethics issues were considered to conduct this investigation in Australia. In this study, the general values and principles set out in the National Statement on Ethical Conduct in Human Research were applied (NHMRC & AVCC, 2007). These principles are respect for human beings, research merit and integrity, justice and beneficence. In this study, this includes informed consent, data storage, anonymity and confidentiality, and beneficence and non-maleficence.

3.10.1 Informed consent

Verbal or nonverbal assent was sought from each participant during the ICU stay prior to collection of data. Then, when the participants were in the wards, written informed consent was sought from each participant. Participants who did not give consent were asked permission to use the ICU based-data. If permission to use this information was not given, the data was destroyed. The consent was voluntary and might have been withdrawn at any time without penalty, repercussion or reason. This process followed the guidelines on Informed Consent in Human Research booklet set out in The Griffith University Research Ethics Manual (Griffith University Human Research Ethics Committee & Office for Research, 2003), and the Queensland Health guidelines. The participant information and consent form used in this research is presented in Appendix 8.
3.10.2 Data storage

All data are being stored in locked facilities at Griffith University, with identifying and contact details stored separately to study data. Five years post completion of the study, the data will be destroyed.

3.10.3 Anonymity and confidentiality

The data were collected in a potentially re-identifiable manner and then, were de-identified for analysis, reporting and publication purposes. Patient’s key was stored separately to the data and all data sheets only contained study ID. Only the researcher and research advisors had access to the patient’s information. This is to ensure anonymity and confidentiality. Publications and presentations are being prepared in such a manner as to maintain the confidentiality and anonymity of all study participants.

3.10.4 Beneficence and Non-maleficence

In this study, participants were required to complete questionnaires, which might have lead the participants to experience mild distress or discomfort. Participants were advised of their ability to withdraw consent at any time without reprisal. Further, if participants indicated their desire, details of general counselling services were provided. The benefits of this study, to improve the care, recovery and wellbeing of ICU patients, justified the small amount of risk of discomfort participants might have experienced.

3.10.5 Ethics review

The approval of the Human Research Ethical Committees of Griffith University and Princess Alexandra Hospital were obtained prior to the commencement of this study (see Appendix 9).
In this chapter the methodological framework used for this study was presented.

Chapter four presents the findings and discussion of this research through three manuscripts currently under review.
Chapter 4: Results and discussion

Statement of contribution to co-authored published papers

This chapter includes three co-authored papers. The first co-authored paper in this chapter has been submitted for publication to the *Journal of Critical Care* and is undergoing peer review. The details of the co-authored paper, including all authors, are:


My contribution to the paper involved:

- Critical review of the literature to inform the design of the study
- Enrolment of participants
- Data collection
- Data analyses
- Data interpretation
- Writing of the manuscript
- Revision of the manuscript for important intellectual content
- Approval of the final version

I completed the research and writing of the paper with methodological and editorial advice from my PhD supervisors Professor Marie Cooke and Professor Leanne Aitken as well as Bonnie Macfarlane.
Student: Maria Isabel Castillo Escobar

Co-author of the paper and supervisor: Professor Leanne Aitken

Co-author of the paper and supervisor: Professor Marie Cooke

Co-author of the paper: Bonnie Macfarlane
The second co-authored paper in this chapter has been submitted for publication to *Critical Care Medicine* and is undergoing peer review. The details of the co-authored paper, including all authors, are:


*My contribution to the paper involved:*

- Critical review of the literature to inform the design of the study
- Enrolment of participants
- Data collection
- Data analyses
- Data interpretation
- Writing of the manuscript
- Revision of the manuscript for important intellectual content
- Approval of the final version

I completed the research and writing of the paper with methodological and editorial advice from my PhD supervisors Professor Leanne Aitken and Professor Marie Cooke as well as Bonnie Macfarlane.
Student: Maria Isabel Castillo Escobar

Co-author of the paper and supervisor: Professor Leanne Aitken

Co-author of the paper and supervisor: Professor Marie Cooke

Co-author of the paper: Bonnie Macfarlane
The third co-authored paper in this chapter has been submitted for publication to *Critical Care and Resuscitation* and is undergoing peer review. The details of the co-authored paper, including all authors, are:


**My contribution to the paper involved:**

- Critical review of the literature to inform the design of the study
- Enrolment of participants
- Data collection
- Data analyses
- Data interpretation
- Writing of the manuscript
- Revision of the manuscript for important intellectual content
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Co-author of the paper: Bonnie Macfarlane
4.1 Introduction

In this chapter, the findings of this investigation are presented. The research aims of this study were:

To describe the magnitude and patterns of state anxiety reported by patients throughout their intensive care unit (ICU) stay

To identify factors associated with patients’ state and trait components of anxiety during critical illness

To identify factors associated with symptoms of anxiety and depression over six months after the intensive care experience

To determine factors associated with post-traumatic stress symptoms (PTSS) over six months after the intensive care experience.

Three co-authored manuscripts comprise this chapter. These papers have been submitted for publication and are undergoing peer review. In the first paper the findings regarding the magnitude and patterns of state anxiety throughout patients’ ICU stay, and the risk factors associated with state and trait anxiety during critical illness are reported. This paper is currently under review with the Journal of Critical Care. In the second paper, the findings related to factors associated with symptoms of anxiety and depression over six months after the intensive care experience are reported. This paper is currently under review with Critical Care Medicine. Findings regarding factors associated with PTSS over six months after the intensive care experience are presented in the third paper. This third manuscript is currently under review with Critical Care and
Publication 1: Factors Associated with Anxiety In Critically Ill Patients

**Publication status:** submitted for publication

4.2 Publication 1: Factors Associated with Anxiety In Critically Ill Patients

Authors:

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Abstract

Purpose: To describe the magnitude and patterns of state anxiety reported by patients in an intensive care unit (ICU), and identify factors associated with state and trait anxiety.

Materials and Methods: Prospective follow-up study including 141 patients from one mixed ICU in Brisbane, Australia. Outcomes were state anxiety as measured by the Faces Anxiety Scale (FAS) and trait anxiety as measured by the Trait component of the State-Trait Anxiety Inventory Form Y-2 (STAI). Clinical and demographic data were obtained from patients and medical records. Multivariable regression analysis was used to identify factors significantly associated with state and trait anxiety.

Results: Of 141 participants, 98 (70%) were male with an average age of 54 (SD±15) years and stayed in ICU for about 4 (IQR: 3-7) days. The majority (n=115; 82%) of participants experienced state anxiety at least once during their stay in ICU, with 57% reporting moderate to severe levels. Although some fluctuations in state anxiety occurred over time, moderate levels were predominantly reported on days 6 to 12. After adjustment factors related to state anxiety in ICU were pain and trait anxiety. Factors associated with trait anxiety were trait optimism, state anxiety, evidence of mental health treatment and age.

Conclusion: Anxiety is a significant issue for many ICU patients. Both state and trait anxiety were significantly associated with each other. State anxiety persists throughout the ICU stay and interventions designed to prevent or reduce state and trait components in ICU should be tested.

Keywords

Intensive care unit, state anxiety, trait anxiety, critically ill.
Introduction

Anxiety is an unpleasant emotion that most intensive care unit (ICU) patients experience [1]. This emotion is an important issue in ICU settings because of its prevalence, adverse effects and severity [1-4]. Charles D. Spielberger, a famous psychologist, described the modern concept of anxiety where the distinction between state and trait anxiety was made [5-7]. State anxiety is defined as a temporary and normal emotion that manifests in response to a perceived threat, involving physiological arousal, as well as feelings of tension, apprehension, nervousness and worry. Trait anxiety, on the other hand, corresponds to a person’s tendency to experience state anxiety due to their personality characteristics [7].

Although there is some description of anxiety in the critically ill population, the majority of the evidence available provides information only about the state component. In other populations such as survivors of rectal cancer, a relationship between trait anxiety and emotional health has been shown [8]. However, it is unclear if this association applies to the ICU population. As current research in the field of psychology suggests that trait anxiety can be modified using tailored interventions, it seems beneficial to also explore trait anxiety in the ICU patient [9-11].

Since trait anxiety has been associated with the development of adverse emotional outcomes, the investigation of anxiety in the critically ill patient is imperative. Findings from this investigation could inform the development of interventions to manage anxiety early during hospitalisation and, as a result, reduce the risk of adverse emotional outcomes during recovery. The aims of this study were to: (1) describe the magnitude and patterns of state anxiety reported by patients
throughout their ICU stay, and (2) identify factors associated with both state and trait components of anxiety.

Abbreviations

FAS: Faces Anxiety Scale; STAI: State-Trait Anxiety Inventory Form Y-2 (STAI); LOT-R: Life Orientation Test Revised; APACHE III: Acute Physiology and Chronic Health Evaluation III; CAM-ICU: Confusion Assessment Method for the ICU; CPOT: Critical-Care Pain Observation Tool; AIC: Akaike Information Criteria; Intraclass Correlation Coefficient (ICC).
Materials and methods

Participants in this analysis were enrolled in a prospective follow-up study that investigated long-term emotional outcomes in ICU survivors [12]. Participants (n=141) were from one closed mixed medical/surgical/trauma ICU of a tertiary metropolitan public hospital located in Brisbane, Australia. This 25-bed ICU provides 24-hour intensivist led care, with a registered nurse/patient ratio of 1:1. Data were collected prospectively between September 2012 and February 2013. The study protocol has previously been published [12], but a summary of the methods is provided below. The current study is a preplanned sub-study analysis of this research.

Inclusion criteria were adult patients (≥18 years), admitted to the ICU for ≥24 hours; able to communicate verbally or non-verbally; understand English; and, open their eyes spontaneously or in response to voice. Patients were invited to participate in the project as soon as meeting the inclusion criteria and their assent was required to start data collection in ICU.

Written consent was sought once the patients were in the hospital wards, and able to provide written informed consent. As patients woke up and became interactive at different times, they were not recruited on a particular day of their ICU stay. The Griffith University (NRS/35/12/HREC) and Princess Alexandra Hospital Ethics Committees (HREC/12/QPAH/173) approved this research.

Clinical and demographic data collected in the hospital wards using a set of questionnaires included: marital status, employment status and level of education, pre-ICU medications (benzodiazepines, anxiolytics, antidepressants, corticoids, opioids, and beta-blockers), smoking status, personality trait of optimism (Life Orientation Test-Revised: LOT-R), personality trait of anxiety (Trait component of
the State-Trait Anxiety Inventory Form Y-2 (STAI) and evidence of mental health treatment [6, 13]. Participants who answered “Yes” to either of the following two questions was considered to have positive evidence of mental health treatment prior to the ICU admission: (1) Have you ever visited a general practitioner (GP) or a mental health professional for symptoms of psychological distress or emotional problems? (2) Were you taking benzodiazepines, anxiolytics or antidepressants medications within the 12 months prior to the ICU admission? Information about pre-ICU medications (corticoids, opioids and beta-blockers) and personality trait of optimism were collected because the literature suggests a possible association between these factors and adverse emotional outcomes after ICU [14-17].

Clinical and demographic data collected from electronic patient notes held in the ICU included: age, gender, type of admission (medical, surgical, trauma, cardiac surgery), delirium (Confusion Assessment Method – ICU: CAM-ICU), hours of mechanical ventilation (invasive and non-invasive), acute physiology and chronic health evaluation III score (APACHE III), length of ICU stay (days), length of hospital stay (days) and pain using the Critical-Care Pain Observation Tool (CPOT) [18-21]. Data on drugs administered included exposure to corticosteroids, opioids, benzodiazepines, anxiolytics, antidepressants, beta-blockers, anesthetic agents and analgesics; length of sedation and analgesia (hours of propofol, midazolam, morphine, fentanyl, ketamine, oxycodone infusion); and total doses of sedatives and analgesics (propofol, midazolam, morphine, fentanyl, ketamine, oxycodone and paracetamol).

The primary outcomes of this study were both components of anxiety (state and trait) in the critically ill patient. Levels of state anxiety were self-reported twice daily (morning 8-11 am and evening 4-7 pm) using the Faces Anxiety Scale (FAS) [3]. These timeframes were selected because we wanted to identify any difference
between morning assessments (usually busier ICU environment) and evening assessments (usually quieter ICU environment). We selected the FAS because it is a practical tool, specially designed to measure state anxiety in ICU settings. The FAS consists of a scale with five faces with each face representing a different level of anxiety. The score ranges from 1 (no anxiety) to 5 (extreme anxiety). The criterion validity of this scale was 0.64 (p<0.001) in mechanically ventilated patients (Pearson’s correlation coefficient between the self-report of anxiety on the FAS and clinical judgment of patient’s anxiety) [3].

Before approaching for the assessment of anxiety, the following information was recorded: airway status (tracheostomy, endotracheal tube, natural), mechanical ventilation status (invasive, non-invasive, non-ventilation), delirium status (CAM-ICU), oxygen saturation, pain score (CPOT) and sedation (total dose of sedatives and analgesics as well as total hours of continuous infusion of sedoanalgesia). Then, the participants were shown the FAS and asked to choose the face that better represented how much anxiety they felt at the moment of assessment. The answer could be provided by a verbal or a nonverbal response; i.e. they could point to the relevant face.

Trait anxiety was assessed using the Trait component of the State-Trait Anxiety Inventory for adults Form Y-2 (STAI) [6]. This assessment was performed when participants were in the hospital wards and sufficiently awake to be able to answer questions in this inventory. The STAI is a self-report 20-items measure based on a 4-point Likert scale with scoring going from 20-80 with higher scores indicating greater levels of trait anxiety. The STAI is a well-validated and recognised tool for the assessment of trait anxiety and has previously been used with survivors of critical illness at a similar time point in their recovery process [22, 23]. Trait anxiety was
assessed in the wards and not in ICU for two reasons: completion of the STAI requires a patient able to maintain attention for about 10 minutes; and, trait personalities are stable patterns of cognition, affect and behavior that are relatively consistent across time and situations [24]. Thus, trait anxiety would have been unlikely to change in such a short period (between ICU stay and assessment in the wards) and without a specific intervention to modify this personality trait. The principal investigator and the ICU Research Nurse conducted the state anxiety assessments in ICU and assisted the participants (when needed due to physical impairment) with the surveys in hospital wards.

We performed power analysis a priori using G*Power to determine the sample size needed for this study [25]. Multiple regression test (fixed model, $R^2$ increase) with a power of 80%, a significance level of $\alpha = 0.05$ and a medium size effect (0.15) were used. In addition, we expected a maximum of seven variables to be included in the final model and a mortality rate of 10%. Thus, the estimated sample size for this study was 104 participants.

The outcome variable “state anxiety” was derived from repeated measures taken during the participants ICU stay (twice a day). The first state anxiety measure in ICU and several aggregate variables were extensively explored to obtain a single value that best represented the level of state anxiety during the patient’s ICU stay. Of all derived (aggregated) measures for anxiety, the mean value was the strongest at accounting for correlations amongst observations in the same cluster.

Distributions of variables were assessed with frequency histograms and statistical tests for normality. Bivariate relationships were tested between each risk factor and the outcome variables (trait and state anxiety) using appropriate inferential
statistics. Continuous, binary and nominal/ordinal risk factors used Spearman's correlation, Mann-Whitney U test, Kruskal-Wallis, respectively. Variables associated at p≤0.2 were tested in the multivariable analysis.

Multiple linear regression was used to identify factors significantly associated with state anxiety. A stepwise approach with a forward selection of variables, identified in the bivariate analysis, testing the successive addition of each variable into the model was used. This process was repeated until all variables in the model were significant (p<0.05). Variables that had been repeatedly identified in the literature as significant were added and tested in the final model. The same process was used to determine the factors that were significantly associated with trait anxiety.

Regression diagnostics were performed informally (graphical) and formally (statistical) to verify the analysis met the assumptions underlying multiple linear regression. Diagnostic tests included assessing the normality and homoscedasticity of residuals, degree of multicollinearity amongst risk factors, the linearity assumption between the outcome variable and risk factors and identification of outliers. Statistical analyses were conducted using Stata version 13 (StataCorp, College Station, Texas) and SPSS version 21 [26, 27].

Results

Of 797 patients screened during the enrollment period 600 were excluded: 597 stayed in ICU for less than 24 hours, and three were younger than 18 years old. One hundred and ninety-seven patients assented to participate in this study and reported on their levels of state anxiety during ICU treatment, but only 120 patients completed the
STAI in the wards (Figure 4.2.1). There were no significant differences in baseline demographics (age, gender, APACHE III score, length of ICU stay and hospital stay) or state anxiety between those who assented to ICU data collection and those who completed the STAI.

Participants were predominantly male (70%) and relatively young (mean 54.1±15.3 years). The majority was in a relationship (61%) and worked (57%). Evidence of mental health treatment prior to the ICU admission was reported by 37% of participants and just under a third (28%) smoked. Approximately half of the participants were admitted with medical diagnoses (49%), followed by surgical (21%), trauma (17%) and cardiac surgery (13%). Most participants received mechanical ventilation (82%) for about 52 (IQR: 13-148) hours, and sedation with benzodiazepines and anesthetic agents (Table 4.2.1). Participants stayed in ICU for about four days and fifteen days in hospital.

Eighty-two percent (n=115) of participants reported state anxiety at least once during their stay in ICU, with 57% (n=80) reporting moderate to severe levels. Because most of the participants were unconscious during the first hours in ICU, they were able to report state anxiety status only half of their ICU days. Participants reported moderate to severe state anxiety on 44% of these days. While the levels of state anxiety fluctuated over time, a paired-samples t test showed no significant difference between morning and afternoon assessments (2.4 SD±1.0 vs. 2.3 SD±1.0, t (88) = 0.28, p = 0.779). Moderate levels of anxiety were predominantly reported from days 6 to 12 and then decreased (Figure 4.2.2). The trait component of anxiety in these participants (median 36 [IQR: 29-47]) was very similar to the Australian population [28].
Factors associated with state anxiety on univariate analysis (p≤0.2) included: trait anxiety (\(\rho=0.32, p<0.001\)), evidence of mental health treatment (\(r=-0.22, p=0.01\)), trait optimism (\(\rho=-0.15, p=0.1\)) and pain (\(\rho=0.16, p=0.06\)). After multivariable model adjustment both trait anxiety and pain remained statistically significant. The results indicate trait anxiety was the strongest contributor to state anxiety (beta=0.29, p=0.001) followed by pain (beta=0.18, p=0.043) (Table 4.2.2).

Thirteen factors were significantly associated (p≤0.20) with trait anxiety on univariate analysis: age, evidence of mental health treatment, trait optimism, state anxiety, smoking, length of hospital stay, length of propofol infusion, total dose of propofol, total dose of midazolam, total dose of morphine, length of fentanyl infusion, total dose of oxycodone and pain (Table 4.2.3). Several factors remained significantly associated with trait anxiety after adjustment including age, trait optimism, state anxiety, and evidence of mental health treatment (Table 4.2.4).

**Discussion**

This observational study showed that ICU patients with mixed diagnoses suffer considerable emotional distress during their ICU admission. Despite our participants having similar trait anxiety levels to the Australian norms, the majority of participants experienced moderate to severe levels of state anxiety during ICU treatment. The prevalence and severity of state anxiety found in our sample are comparable to the prevalence and severity reported in other studies [3, 29, 30].

Our participants were able to report state anxiety status half of their ICU days because they were unconscious or too ill to be assessed the other half. Of the days of
assessment, moderate to severe state anxiety was reported by almost half of the participants. Self-reported levels of state anxiety demonstrated minimal fluctuation from days 6 to 12, with average scores showing moderate levels over this period (Figure 4.2.2). During these days, participants might have been capable of perceiving ICU stressors such as pain, noise and endotracheal tube and, therefore, their levels of state anxiety were higher. After the day 12, may have become accustomed to the ICU environment, staff and routine, resulting in a decrease in their anxiety levels. As participants in this study reported state anxiety after 24 hours of being in ICU, levels of state anxiety for the initial 24 hours are unknown. In addition, as this component was only assessed during patient’s ICU stay, state anxiety levels after ICU discharge, but still in hospital wards, are also unknown. Despite these limitations, the information provided about state anxiety in this study is important because this is the second study that has investigated patient’s self-report of state anxiety throughout the ICU stay.

Trait anxiety and state anxiety were significantly associated with each other. Participants who were anxious by nature experienced higher levels of state anxiety in ICU. This finding is consistent with the theory behind the anxiety concept developed by Spielberger [5-7]. Trait anxiety levels in our sample were similar to the ones found in the general Australian population. This finding suggests that anyone with high anxiety personality trait admitted to ICU is at greater risk of experiencing state anxiety during intensive care treatment. Measuring trait anxiety prior to ICU admission in elective patients and as soon as possible after admission in emergency patients might help clinicians to identify patients at risk of experiencing high levels of state anxiety during ICU treatment. During patient’s ICU stay, state anxiety should be
assessed systematically, and clinicians should use this assessment to guide treatment in ICU.

Participants with lower levels of pain reported significantly less state anxiety and vice versa. Because pain may be perceived as a very distressing symptom, it is not surprising that these two unpleasant symptoms were associated with each other in our participants [31]. Effective strategies for pain management are fundamental to alleviate both pain and state anxiety in the critically ill [31]. Trait anxiety and evidence of mental health treatment prior to ICU were also significantly associated. This finding was expected since it is likely that high trait anxious patients had needed some mental health assistance at some stage in their lives.

Lower levels of trait anxiety were observed in older participants, suggesting a protective effect of ageing on anxiety outcomes. To our knowledge, this relationship has not previously been reported in the ICU patient. However, there is evidence that age-related reduced prefrontal-amygdala structural connectivity is associated with lower levels of trait anxiety in healthy adults [32].

Optimistic participants reported significantly lower levels of trait anxiety. The relationship between these two trait personalities has previously been reported in healthy participants and patients hospitalised for chronic diseases [33, 34]. No study reporting this association in the ICU patient was located. This finding is important because trait optimism was identified as a predictor of less anxiety and depression symptoms after one year in ICU survivors [35]. Trait anxiety might also be associated with adverse emotional outcomes after ICU discharge. In addition, the interaction between these two trait personalities in the development of adverse emotional outcomes in the ICU survivor is yet to be tested. Thus, age, trait optimism and
evidence of mental health treatment prior to the ICU admission were all factors significantly associated with trait anxiety, which in turn together with pain were associated with state anxiety in ICU (Table 4.2.2 and 4.2.4).

Although a number of risk factors were examined and tested, no other demographic (age, gender, marital status, etc.) or clinical (sedatives, analgesics, mechanical ventilation, etc.) variable were significantly associated with state anxiety in ICU. Given that sedation is often administered to treat agitation and anxiety, it was anticipated that we would find a significant statistical relationship between sedation and anxiety, but this was not the case [36]. Discrepancies between patients’ self-reported anxiety and clinician’s observations of anxiety might explain this lack of association [37]. The management of anxiety in the ICU is often based on clinician’s detection of it, which is usually done through observation of physiological and behavioural manifestations [38]. Unfortunately, clinicians’ observations of physiological and behavioural manifestations of anxiety are limited since delirium and pain share similar physiological and behavioural characteristics with anxiety. These similarities may lead to erroneous symptom interpretation. It might be the case that the association between state anxiety and sedation was not found in this sample because sedation was not administered to treat anxiety.

These findings further underline the importance of the assessment of both components of anxiety (state and trait) in the critically ill patient. State anxiety can be easily assessed in ICU by the use of self-reported measures such as the Faces Anxiety Scale or the Visual Analog Scale-Anxiety [3, 29]. Trait anxiety could be an assessment performed by the bedside ICU nurse or ICU outreach teams using the trait component of the STAI when the patients are able to respond to this tool. The feasibility of trait anxiety assessment needs to be tested. Early assessment of state and
trait anxiety in ICU patients is vital to put in place simple non-pharmacological interventions to alleviate anxiety in ICU, promote comfort and potentially reduce the risk of adverse outcomes during recovery.

Our study was limited to adult patients who were ≥24 hours in a general ICU and therefore is only generalisable to other cohorts of patients who spend at least 24 hours in ICU. Despite exploring the association between both components of anxiety and a number of potential risk factors, there are still many other causes of anxiety in ICU patients that were not assessed in this study. These include memories of the illness, any traumatic event that precipitated ICU admission, environmental factors such as noise, and longer term concerns such as fear of changes in relationships, physical appearance and loss of job and function.

Although a sub-study, the current analysis was planned at the time of conception of the ICARe study. While we assessed the levels of state anxiety, we did not explore the reasons why patients were anxious. It might have been beneficial to collect this information in a qualitative manner although there are some previous studies examining state anxiety in ICU that are available to aid interpretation of these data.

**Conclusion**

This study provides evidence that both components of anxiety (state and trait) are significant for many critically ill patients. It also demonstrates that clinicians must recognise the importance of anxiety assessment and determine ways to manage this symptom. The findings of this study will enable the informed nurse researcher and
clinician to plan and design interventions to reduce anxiety in the critically ill patient by targeting contributing factors.

Acknowledgements

The Intensive Care Foundation and the Australian College of Critical Care Nurses Novice Researcher Grants funded this study. We thank Dr. Robert Ware for advising on statistical analysis. We also thank the ICU Research Nurses Lena James and Kelly Perkins for their assistance with data collection.
Table 4.2.1. Participant flow through study

- **Screened**
  - $n=797$
- **Eligible & assessed for state anxiety in ICU**
  - $n=197$
  - ICU stay $\leq 24$ hrs ($n=597$)
  - Age $< 18$ ($n=3$)
- **ICU data collected**
  - $n=141$
  - Not consented ($n=17$)
  - Discharged home ($n=19$)
  - Insufficient English ($n=7$)
  - Altered mentation ($n=13$)
- **Completed baseline questionnaires**
  - $n=120$
  - Permission to use ICU information only ($n=10$)
  - Died in the wards ($n=9$)
  - Discharged home ($n=2$)
Faces Anxiety Scale scores from 1 to 5 (1-2 = low anxiety, 3-5 = moderate to severe anxiety)

Figure 4.2.2. Mean state anxiety score and standard deviation for the days of ICU stay
Table 4.2.1. Sedation and analgesia in intensive care unit (n=141)

<table>
<thead>
<tr>
<th></th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Length of sedation and analgesia (hrs)</strong></td>
<td></td>
</tr>
<tr>
<td>Propofol (n=116)</td>
<td>23 (7-83)</td>
</tr>
<tr>
<td>Fentanyl (n=80)</td>
<td>46 (15-94)</td>
</tr>
<tr>
<td>Midazolam (n=47)</td>
<td>36 (15-109)</td>
</tr>
<tr>
<td>Morphine (n=26)</td>
<td>30 (15-85)</td>
</tr>
<tr>
<td>Ketamine (n=8)</td>
<td>40 (9-80)</td>
</tr>
</tbody>
</table>

| **Total doses of sedatives and analgesics (mg)** |                 |
| Propofol (n=119)        | 2960 (750-11290) |
| Fentanyl (n=111)        | 4 (1-7)          |
| Midazolam (n=49)        | 101 (17-218)     |
| Morphine (n=37)         | 48 (9-161)       |
| Ketamine (n=8)          | 260 (36-350)     |
| Hydrocortisone (n=10)   | 450 (325-588)    |
| Oxycodone (n=38)        | 10 (5-65)        |
| Paracetamol (n=120)     | 7500 (4000-14750)|

IQR: Interquartile Range; hrs: hours; mg: milligrams
Table 4.2.2. Multiple Linear Regression: Factors associated with state anxiety in ICU patients (n=141)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Unstandardised Coefficients</th>
<th>Standardised Coefficients</th>
<th>Sig.</th>
<th>95.0% Confidence Interval for B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>Std. Error</td>
<td>Beta</td>
<td>Lower Bound</td>
</tr>
<tr>
<td>(Constant)</td>
<td>1.204</td>
<td>0.317</td>
<td>0.001</td>
<td>0.577</td>
</tr>
<tr>
<td>Trait anxiety</td>
<td>0.027</td>
<td>0.008</td>
<td>0.294</td>
<td>0.001</td>
</tr>
<tr>
<td>Pain</td>
<td>0.095</td>
<td>0.046</td>
<td>0.180</td>
<td>0.043</td>
</tr>
<tr>
<td>Variables/Trait anxiety score</td>
<td>r value and (p)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>----------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.26 (0.004)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evidence of mental health treatment</td>
<td>0.29 (0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trait optimism</td>
<td>-0.58 (&lt;0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>State anxiety</td>
<td>0.32 (&lt;0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>0.30 (0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital LOS</td>
<td>0.18 (0.04)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of propofol infusion</td>
<td>0.17 (0.053)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total dose of propofol</td>
<td>0.15 (0.09)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total dose of midazolam</td>
<td>0.18 (0.052)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total dose of morphine</td>
<td>-0.16 (0.08)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of fentanyl infusion</td>
<td>0.19 (0.04)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total dose of oxycodone</td>
<td>0.15 (0.094)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>0.17 (0.058)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Spearman's rank correlation coefficients, Mann-Whitney U test, Kruskal-Wallis test were used with, respectively, continuous, binary and categorical risk factors.
Table 4.2.4. Multiple Linear Regression: Factors associated with trait anxiety in ICU patients (n=120)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Unstandardised Coefficients</th>
<th>Standardised Coefficients</th>
<th>95% Confidence Interval for B</th>
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<tr>
<td></td>
<td>B</td>
<td>Std. Error</td>
<td>Beta</td>
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<tr>
<td>(Constant)</td>
<td>62.369</td>
<td>4.209</td>
<td></td>
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<tr>
<td>Trait optimism</td>
<td>-1.549</td>
<td>0.181</td>
<td>-0.563</td>
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<td>State anxiety</td>
<td>2.235</td>
<td>0.728</td>
<td>0.204</td>
</tr>
<tr>
<td>Age</td>
<td>-0.142</td>
<td>0.049</td>
<td>-0.188</td>
</tr>
<tr>
<td>Evidence of mental health treatment</td>
<td>4.186</td>
<td>1.586</td>
<td>0.175</td>
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</table>
References


Publication 2: Anxiety during critical illness is associated with anxiety and depression symptoms over six months after ICU discharge: The ICARE study

Publication status: submitted for publication


Anxiety during critical illness is associated with anxiety and depression symptoms over six months after ICU discharge: The ICARE study Critical Care Medicine.
4.3 Publication 2: Anxiety during critical illness is associated with anxiety and depression symptoms over six months after ICU discharge: The ICARe study

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**Keywords**
Intensive care unit, state anxiety, trait anxiety, critically ill, anxiety, depression.
Abstract

Objective: To identify factors associated with symptoms of anxiety and depression over six months after intensive care unit (ICU) discharge in survivors of intensive care treatment.

Design: Longitudinal cohort study.

Setting: One closed mixed ICU in an adult tertiary hospital in Brisbane, Australia.

Patients: Participants (n=141) were adults (≥18 years), admitted to ICU for ≥24 hours, able to communicate either verbally or non-verbally, understand English, and open their eyes spontaneously or in response to voice.

Measurements and Main Results: The outcomes of symptoms of anxiety and depression over six months after ICU discharge were assessed using the Hospital Anxiety Depression Scale. The primary variable of interest was anxiety during critical illness. Two components of anxiety (state and trait) were assessed during critical illness using the Faces Anxiety Scale and the trait component of the State-Trait Anxiety Inventory. Perceived social support, cognitive functioning and post-traumatic stress symptoms were also assessed using standardised instruments. Clinical and demographic data were obtained from patients and medical records. Participants were followed-up in hospital wards, and at three and six months after ICU discharge.

During ICU treatment, 81 (57%) of the 141 participants reported moderate to severe levels of state anxiety. Of the 92 participants who completed the surveys at the six-month follow-up, 26 (28%) reported symptoms of anxiety and 21 (23%) symptoms of depression. Symptoms of anxiety and depression were strongly correlated in this cohort of survivors. Trait anxiety was significantly associated with both anxiety and
depression symptoms over time, however, state anxiety was not associated with either outcome. Participants who reported post-ICU memories of intra-ICU anxiety were significantly more anxious during recovery over six months. Cognitive functioning and post-traumatic stress symptoms were both significantly associated with anxiety and depression symptoms over time.

**Conclusion:** Symptoms of anxiety and depression are a significant issue for general ICU survivors. Trait anxiety was significantly associated with adverse emotional outcomes over six months after ICU discharge. There was also a significant relationship between post-ICU memories of intra-ICU anxiety and anxiety during recovery. Interventions to reduce anxiety during critical illness need to be considered and evaluated for their longer term benefits for survivors of critical illness.
Introduction

Survival from critical illness has improved significantly over the years with most patients discharged alive from hospital. For some survivors however, the recovery process can be physically and emotionally challenging. Numerous observational studies have reported on the emotional problems, including symptoms of anxiety and depression, that patients experience after critical illness. The prevalence of these emotional problems in intensive care unit (ICU) survivors is relatively high with around a third of patients reporting adverse emotional outcomes (1-5).

The widespread nature of this problem has led researchers to explore factors associated with adverse emotional outcomes (6, 7). Anxiety during critical illness has repeatedly been suggested as important (6, 8, 9). Anxiety is a complex phenomenon that comprises of two components: state and trait (10, 11). State anxiety is defined as a normal and temporary emotion that involves physiological arousal and feelings of tension, apprehension, nervousness and worry when a stressful situation is perceived. Trait anxiety, on the other hand, corresponds to a person's tendency to become state anxious as part of their personality trait (10, 11). To achieve a comprehensive understanding of anxiety during critical illness in our cohort of survivors, both components of anxiety (state and trait) were explored. We hypothesised that state and trait anxiety would be associated with anxiety and depression symptoms over time after ICU discharge.

The aim of this study was to identify factors associated with symptoms of anxiety and depression over six months after ICU discharge in survivors of intensive care treatment.
Materials and Methods

This longitudinal cohort study of general ICU survivors was conducted in one closed mixed medical/surgical/trauma ICU of a tertiary metropolitan public hospital located in Brisbane, Australia. The Intensive Care Unit has 25 beds and provides 24 hours intensivist led care with a registered nurse-patient ratio of 1:1. During the time of enrolment (September 2012–February 2013) there were approximately 1,100 admissions to this ICU. The Princess Alexandra Hospital (HREC/12/QPAH/173) and Griffith University (NRS/35/12/HREC) Ethics Committees approved this research. All participants provided written informed consent. The study protocol has previously been published (12). However, a summary of the methods and modifications made to the published protocol are provided in this section.

Patients

Participants were adults (≥18 years), admitted to the ICU for ≥24 hours, able to communicate either verbally or non-verbally (pointing, gestures, written, mouthing, etc.), understand English, and open their eyes spontaneously or in response to voice (visually intact or sufficient corrected vision).

Data Collection

Study participants provided information in ICU, in the hospital wards, and at three and six months post ICU discharge. Participants were followed-up in the hospital wards (within three weeks of ICU discharge) to confirm their wish to participate in this study, obtain written informed consent and complete the first set of self-reported questionnaires (Table 4.2.1). At three and six-month follow-up participants were contacted by a phone call to remind them about their involvement in this study before
posting the surveys. An appointment for a phone interview was scheduled for those participants who wished to provide the answers to the researcher over the phone. Most participants returned the surveys in the reply paid envelope provided, twelve participants read their answers to the researcher over the phone, and two participants preferred to use email.

State anxiety was assessed twice a day (morning 8-11am and afternoon 4-7pm) up to 30 days during ICU stay. These timeframes were selected to identify any difference between morning assessments (usually busier ICU environment) and evening assessments (usually quieter ICU environment). Patient’s competency to report on their level of state anxiety was determined by consultation with the bedside registered nurse and patient’s ability to communicate effectively (verbally or not verbally) with the researchers.

The assessment of trait anxiety was performed once only when participants were in the wards for two reasons: [1] The State-Trait Anxiety Inventory (STAI) Form Y-2 is a 20-Item instrument, with completion requiring a patient to be able to maintain attention for about 10 minutes. [2] Trait personalities are stable patterns of cognition, affect and behavior that are relatively consistent across time and situations (13). Thus, trait anxiety would have been unlikely to change in such a short period (between ICU stay and assessment in the wards). The principal investigator and the ICU Research Nurse conducted the state anxiety assessments in ICU and assisted the participants (when needed due to physical impairment) with the surveys in hospital wards.

Clinical and demographic data collected from medical records included: age, gender, type of admission (medical, surgical, trauma, cardiac surgery), delirium (Confusion Assessment Method – ICU: CAM-ICU), hours of mechanical ventilation
(invasive and non-invasive), acute physiology and chronic health evaluation III score (APACHE III), length of ICU stay (days), length of hospital stay (days) and pain using the Critical-Care Pain Observation Tool (CPOT) (14-17). Data on drugs administered included exposure to corticosteroids, opioids, benzodiazepines, anxiolytics, antidepressants, beta-blockers, anesthetic agents and analgesics; length of sedation and analgesia (hours of propofol, midazolam, morphine, fentanyl, ketamine, oxycodone infusion); and total doses of sedatives and analgesics (propofol, midazolam, morphine, fentanyl, ketamine, oxycodone and paracetamol).

Data collected in the hospital wards using a questionnaire included: marital status, employment status and level of education, pre-ICU medications (benzodiazepines, anxiolytics, antidepressants, corticoids, opioids, and beta-blockers), smoking status and evidence of mental health treatment. Participants who answered “Yes” to either of the following two question was considered to have evidence of mental health treatment prior to the ICU admission: [1] Have you ever visited a general practitioner or a mental health professional for symptoms of psychological distress or emotional problems? [2] Were you taking benzodiazepines, anxiolytics or antidepressants medications within the 12 months prior to the ICU admission? Mental health history was assessed using this approach to capture any indication of mental health problems prior to the ICU admission more thoroughly than was likely if relying on mental health history from medical records. A similar approach has previously been used in a cohort of ICU patients (18). The demographic questionnaire is provided as Supplementary Material 1.

Instruments used in this study are outlined in Table 4.2.1 and included: the Post-traumatic Stress Symptoms 10-Question Inventory (PTSS-10), trait component of the
State-Trait Anxiety Inventory (STAI) for Adults Form Y-2, Hospital Anxiety and Depression Scale (HADS), Faces Anxiety Scale (FAS), Multidimensional Scale of Perceived Social Support (MSPSS), Life Orientation Test-Revised (LOT-R) and Cognitive Functioning Scale Medical Outcome Study 6-Item (MOS COG). These tools were chosen because they are self-reported, well validated and easy to understand instruments, take a few minutes to complete, and with the exception of Cognitive Functioning Scale Medical Outcome Study 6-Item (MOS COG), have all been used in ICU research (11, 19-24).

Information about pre-ICU medications, social support, cognitive functioning, trait optimism and post-traumatic stress symptom (PTSS) were collected because the literature suggests a possible association between these factors and adverse emotional outcomes after ICU (25-28).

**Data analysis**

Power analysis *a priori* using G*Power was performed to estimate the sample size of this study (29). Multiple regression test (fixed model, $R^2$ increase) with a power of 80%, a significance level of $\alpha=0.05$ and a medium size effect (0.15) were selected. The effect size was estimated from previous research exploring similar research questions (30, 31). In addition, we expected a maximum of seven variables to be included in the final model, a mortality rate of 10% and a dropout of 30% at six months. Thus, it was estimated that we needed 104 participants at six months follow up.

Stata version 13 (Statacorp, College Station, Texas) was used for all analysis (32). Data were cleaned and checked for missing, invalid and outlying values. A random selection (15%) of the database was verified against original questionnaires. Categorical
data were reported as percentages and continuous data as means and standard deviations (SDs) or medians and interquartile ranges (IQRs). Comparisons of the characteristics of responders and non-responders were made using Chi-square or Fisher’s exact test, t-test for differences in means, and nonparametric tests for rank differences.

The independent variable “state anxiety” was derived from repeated measures taken during the participants ICU stay (twice a day up to 30 days). The first state anxiety measure in ICU and several aggregate variables were extensively explored to obtain a single value that best represented the level of state anxiety during the patient’s ICU stay. Of all derived (aggregated) measures for anxiety, the mean value was the strongest at accounting for correlations amongst observations in the same cluster. Participants were categorised as low anxious (state anxiety mean score 1-2) and moderate to severe anxious (state anxiety mean score 3-5) (21).

Variables associated with the outcome (p<0.20) on bivariate analysis were selected for models. Selected variables were checked against one another for multicollinearity using Spearman correlations (>0.6) and Chi-square (>1000). After this process, variables were ranked from most to the least significant and entered into the model. Mixed effect regression models with a random intercept per subject were used to assess the independent association of each factor with symptoms of anxiety and depression while accounting for repeated data from the same participants. Mixed model analysis is used in longitudinal studies to adjust for dependency of repeated observations (account for correlated observations within one subject over time). Time is explicit with observations over time nested within subject (33). In other words, all data from measures obtained serially such as cognitive functioning, PTSS and social support were included in the mixed model analysis and adjusted for dependency over time.
Mixed models also better handle missing data by using available data from all subjects regardless of whether their data are complete.

The Akaike Information Criteria (AIC) along with statistical significance (p<0.05) were used to identify the best set of variables significantly and independently associated with adverse emotional outcomes (symptoms of anxiety and depression). Theory-grounded factors were added into the ‘final set’ of variables to check whether they influenced the model (i.e. were significant and/or decreased/improved the AIC).

Model results are expressed as unstandardized coefficients, 95% confidence intervals and $p$-values. Model diagnostics included assessment of influential observations, multicollinearity amongst variables and residual checks.

**Results**

In total 797 patients were screened with 141 enrolled between September 2012 and February 2013. From 141 participants enrolled, 120 consented to participate in the follow-up. One hundred and one (84%) participants completed three-month follow-up and 92 (77%) completed six-month follow-up (Figure 4.2.1). Participants were a mixed medical (49%), surgical (34%) and trauma (17%) group of ICU patients with an average age of 54 (standard deviation, SD±15) years, and 70% were male. The median length of ICU stay and hospital stay were 4 [interquartile range, IQR: 3-7] days and 15 [10-28] days, respectively. The majority of participants required invasive mechanical ventilation (82%) for about 52 [13-148] hours, and the median APACHE III score of this sample was 58 [43-74].

Symptoms of anxiety (HADS≥8) were reported by 42% of the participants while in the hospital wards, 26% at three-month and 28% at six-month follow-up. Symptoms
of depression (HADS ≥ 8) were reported by 37% of the participants while in hospital wards, 19% at three-month and 23% at six-month follow-up. Symptoms of anxiety decreased significantly from hospital to assessment at three-month after ICU discharge (7.0 [4.0-10.0] vs. 5.0 [2.5–8.0], p<0.001). Symptoms of depression also decreased significantly over the same period (5.5 [3.0–9.0] vs. 3.0 [2.0 – 6.0], p<0.001). No significant change was observed from three to six-month follow-up on either symptoms of anxiety or depression. Participants moved between categories (symptomatic/asymptomatic) of anxiety and depression over time. Some participants who scored within normal limits (HADS < 8) in the wards presented with symptoms of emotional distress at three and or six months and vice versa (Figures 4.2.2 and 4.2.3).

Most participants (82%) reported state anxiety in ICU, with 57% reporting moderate to severe levels (FAS 3-5). When considering the 604 individual anxiety assessments, participants reported some level of anxiety 393 (65%) of the time, with 173 (44%) of these being moderate to severe levels. While the levels of state anxiety fluctuated over time, there was no significant difference between morning and afternoon assessments.

The levels of trait anxiety in the study participants were very similar to the Australian population (36.0 [29.0-47.0]) (34). The mean trait optimism (14.7, SD±4.2) was also similar to population-base norms and another cohort of ICU patients (5, 35). Delirium was present in 11 (8%) participants and pain in 65 (46%) participants. The most common sedatives and analgesics administered were propofol (84%), fentanyl (79%), midazolam (35%) and morphine (26%). Other demographic information and data about medications administered during ICU treatment are presented in Table 4.2.2.
Perceived levels of social support did not change from three months to six months post ICU discharge (6.0 [5.3-6.6] vs. 6.0 [5.0-6.5] p=0.088) and they were similar to the ones reported in other populations (22). On the contrary, perceived cognitive functioning increased significantly from hospital to assessment at three months after ICU discharge (56.7 [40.8-70.0] vs. 63.0 [57.0-77.0] p<0.001). No significant increase was observed from three to six months. Despite the initial increase in perceived cognitive functioning, these levels are well below population-based norms (24). Approximately 58-76% of participants reported traumatic memories of their ICU admission at each of the follow-up points. Changes in the proportion of participants who presented with traumatic memories of the ICU admission across the three-time points measured (in the wards, three and six months after ICU discharge) are presented in Supplementary Material 2 (Figure 4.2.4). The incidence of post-traumatic stress symptoms was similar at three and six months (n=19, 19% vs. n=15, 17%).

Participants who completed six-month follow-up were similar to non-responders in gender, length of ICU stay, length of hospital stay and APACHE III score. Non-responders were younger and reported higher levels of anxiety (state and trait) in hospital than the responders (Table 4.2.3). These differences were similar at three and six-month follow-up.

Linear mixed effect models showed a decline in anxiety symptoms over six months after ICU discharge. The most significant drop occurred from ICU to three months (β=-0.8, 95% CI -1.5, -0.1, p<0.02). Trait anxiety, symptoms of depression during recovery, self-reported cognitive functioning, memories of anxiety in ICU, evidence of mental health treatment prior to the ICU admission and six month PTSS
Symptoms of anxiety during recovery, trait anxiety, self-reported cognitive functioning and reason for ICU admission (trauma patients) were all significantly associated with symptoms of depression over the six months after ICU discharge (Table 4.2.5).

Discussion

In this study, we identified factors associated with symptoms of anxiety and depression over six months after intensive care treatment in survivors of critical illness. The role of anxiety during critical illness on adverse emotional outcomes during recovery was the primary focus of this study.

Symptoms of anxiety and depression decreased significantly from the period in hospital to three months after discharge with no further significant change from three to six months after ICU discharge. These findings are in line with those reported recently in a nonsurgical cohort of critically ill patients (36). Anxiety and depression symptoms were present in around a quarter of our study participants at six months, numbers that were similar to those found in other studies (3, 4, 6, 31, 37). Some participants in this cohort moved between asymptomatic and symptomatic categories over time. These changes showed that symptoms of emotional distress had a delayed onset in some participants, resolved rapidly in others and appeared at varied stages during recovery. Ongoing health issues may be one potential explanation for the delayed onset of these symptoms.
The majority of participants reported some degree of state anxiety while in ICU with over half of these reporting moderate to severe levels. These findings are in line with the current understanding of state anxiety in ICU and highlight the need to improve the assessment and management of this symptom in the ICU setting (21).

Mixed effect regression models revealed that common factors associated with symptoms of both anxiety and depression over six months after ICU discharge in our sample were trait anxiety, cognitive impairment and PTSS. Trait anxiety showed a clear association with symptoms of anxiety and depression; to our knowledge no previous study has reported this association. Impaired cognition has previously been associated with anxiety and depression symptoms in critical illness survivors (38-41).

PTSS were associated with both anxiety and depression, however these associations appeared to be significant at varying time points. PTSS at three months were associated with depression and PTSS at six months with anxiety. These variations also suggest that interventions need to be tailored to individual patients because their need for support is likely to change over time.

Symptoms of depression and anxiety were correlated with each other. While no paper describing this relationship in the ICU population was located, anxiety and depression disorders are often comorbid with each other (42, 43). For the same reason, it is not surprising to have found a relationship between symptoms of anxiety and depression and post-traumatic stress.

Factors associated exclusively with anxiety symptoms over time were post-ICU memories of anxiety during ICU treatment and evidence of mental health treatment prior to ICU admission. Only the recall of extremely stressful ICU experiences had
previously been identified as a factor for anxiety symptoms during recovery (44). Patients with mental health history are commonly excluded from studies in this field to reduce bias when assessing emotional outcomes after ICU discharge. In this study, we chose to include participants who had evidence of mental health treatment prior to the ICU admission and in this cohort this history appears to be an important risk factor. Collecting information about mental health treatment (history and medications) prior to ICU allowed us to identify a negative association between symptoms of anxiety and previous mental health treatment. The continuation of usual treatment received by these participants might have reduced the burden of anxiety symptoms after the intensive care experience but we did not specifically measure ongoing treatment (6, 45). Evidence of mental health treatment was not significantly associated with symptoms of depression in the multivariate analysis. The meaning of this lack of association is unclear.

The only factor associated exclusively with depression symptoms was ICU admission due to trauma. With the design used in this study, it is not possible to distinguish between the effects of the initial trauma and the effects of the health care such as ICU treatment on depression during recovery.

As mentioned previously, only the trait component of anxiety was associated with symptoms of anxiety and depression during recovery, the state component was not associated with either outcome. While there was a moderate correlation between state and trait anxiety, state anxiety did not appear to have any long-term effect on adverse emotional outcomes. This finding was unexpected since we had thought that state anxiety was a hidden factor for symptoms of anxiety and depression after ICU. This rationale was based on the fact that sedation is often regarded as a predictor of adverse emotional outcomes, but with unclear mechanisms for this association. This uncertainty
raised the idea that high levels of state anxiety in ICU might have been a key factor in this relationship (6, 8, 9). Although state anxiety was not a significant factor for anxiety and depression symptoms, the recall of being anxious in ICU was significantly associated with anxiety symptoms over six months after discharge in our participants (44).

A number of studies in this area have incorporated follow-up of patients at varying time points during recovery. However some of these studies have not sufficiently adjusted for dependency of observations over time in their analyses or used techniques that deal with missing values such as mixed model analysis. This has potentially led to results not fully capturing the dynamic nature of the recovery process of these patients. In the present study we adopted statistical techniques that model the sources of variation and correlation that arise in longitudinal data sets with multiple missing data points. Mixed model analysis deals with missing values in such a way that missing scores have no effect on other scores from the same patient. In addition, it includes all data available, not only those cases with complete information.

Potential limitations of this study need to be noted. In this longitudinal study, we identified factors associated with symptoms of anxiety and depression, but this study was not designed to test any causal relationships. In addition, although we assessed symptomatology of adverse emotional outcomes using validated tools, clinical diagnoses of anxiety, depression and post-traumatic stress were not made. While we measured numerous factors previously identified in the literature, it is possible that factors other than those measured here may have influenced the outcomes. The sample size was small, however it represented the Australian ICU population well and was comparable to other studies in this area (1, 6, 21). Although follow-up rates at three and
six months were good, the trend for participants lost to follow-up to be younger and more likely to suffer from higher anxiety levels (state and trait) may have resulted in bias. Participants self-reported cognitive functioning by using the MOS 6-Item Cognitive Functioning Scale, this instrument needs further validation in ICU survivors. Although traumatic memories of anxiety were significantly associated with anxiety symptoms over time, these memories might have been biased by ongoing or current anxiety. While trait anxiety was assessed in hospital, trait anxiety may not represent a factor associated with critical illness, but participant’s individual personality characteristics. It is worth noting that the levels of trait anxiety found in this sample were similar to the general Australian population suggesting that critical illness survivors with high anxiety personality trait may be at greater risk of developing anxiety and depression.

This study adds to the body of research assessing long-term recovery from critical illness, specifically factors related to emotional problems such as anxiety and depression in ICU survivors. Incorporation of these findings into the development and implementation of relevant interventions in acute and post-acute settings has the potential to reduce adverse emotional outcomes in ICU survivors. This research adds to the current literature identifying anxiety and depression symptoms as an important problem for survivors of critical illness and that early detection of these symptoms might be beneficial for long-term recovery.

Conclusions

Findings of this research highlight the ongoing adverse emotional outcomes in survivors of critical illness as well as the need for the development and implementation of strategies to reduce these symptoms. Because of the long-term effects of critical
illness and the delayed onset of symptoms in some patients, not only should these interventions take place during intensive care treatment but also at different time points after ICU discharge. Interventions to address anxiety during critical illness should be directed to target both the state and trait components.

**Acknowledgements**

This study was funded by the Intensive Care Foundation and the Australian College of Critical Care Nurses Novice Researcher Grants. We thank Dr. Robert Ware for advising on statistical analysis. We also thank the ICU Research Nurses Lena James and Kelly Perkins for their assistance with data collection.
Figure 4.3.1. Participant flow through study
Figure 4.3.2. Symptoms of anxiety over six months after ICU discharge in survivors of critical illness.

Participants who reported on the Hospital Anxiety and Depression Scale-Anxiety Subscale (HADS-A) at all time points were included in this diagram (n=89). Participants with missing data on the HADS-A at any time point measurement (n=31) were not included. HADS-A score < 8 = asymptomatic, HADS-A score ≥ 8 = symptomatic.
Figure 4.3.3. Symptoms of depression over six months after ICU discharge in survivors of critical illness.

Participants who reported on the Hospital Anxiety and Depression Scale-Depression Subscale (HADS-D) at all time points were included in this diagram (n=89). Participants with missing data on the HADS-D at any time point measurement (n=31) were not included. HADS-D score < 8 = asymptomatic, HADS-D score ≥ 8 = symptomatic.
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<th>Construct</th>
<th>Instrument</th>
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<th>Possible score</th>
<th>Measurement time points</th>
<th>Comments</th>
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<tr>
<td>State anxiety</td>
<td>Faces Anxiety Scale (FAS)</td>
<td>1</td>
<td>1-5</td>
<td>In ICU Twice a day (morning 8-11 and afternoon 4-7)</td>
<td>Each of the five faces of this tool represents a different level of anxiety ranging from no anxiety (1) to extreme anxiety (5). Patients were shown the FAS and asked to rate their levels of anxiety by indicating the face that better represented how much anxiety they felt at the moment of assessment.</td>
</tr>
<tr>
<td>Trait anxiety</td>
<td>Trait component of the State-Trait Anxiety Inventory (STAI) for Adults Form Y-2</td>
<td>20</td>
<td>For each item, a rating score between 1 and 4 is possible. Total score 20-80</td>
<td>Hospital wards within three weeks after ICU discharge</td>
<td>Higher scores indicate greater levels of trait anxiety.</td>
</tr>
<tr>
<td>Trait Optimism</td>
<td>Life Orientation Test-Revised (LOT-R)</td>
<td>10</td>
<td>For each item, a rating score between 0 and 4 is possible. Total score 0-24</td>
<td>Hospital wards within three weeks after ICU discharge</td>
<td>6 items concerning general expectations relative to positive or negative consequences. 4 filler items not used in the scoring. Higher scores indicate greater optimism.</td>
</tr>
<tr>
<td>Symptoms of anxiety and depression</td>
<td>Hospital Anxiety and Depression Scale (HADS)</td>
<td>This tool has two subscales Depression: 7 items Anxiety: 7 items Total: 14 items</td>
<td>For each item, a rating score between 0 and 3 is possible. Total score 0-21</td>
<td>Hospital wards within three weeks after ICU discharge and at three and six-month follow-ups</td>
<td>The total score for each subscale can be classified into four categories: normal (0-7), mild (8-10), moderate (11-14) and severe (15-21).</td>
</tr>
<tr>
<td>Social support</td>
<td>Multidimensional Scale of Perceived Social Support (MSPSS)</td>
<td>12</td>
<td>For each item a rating score between 1 (very strongly disagree) and 7 (very strongly agree) is possible.</td>
<td>Three and six-month follow-ups</td>
<td>Three subscales: family, friends and significant other. Higher scores indicated higher levels of perceived social support.</td>
</tr>
<tr>
<td>Self-perceived cognitive functioning</td>
<td>Cognitive Functioning Scale Medical Outcome Study 6-Item (MOS COG)</td>
<td>6</td>
<td>Each item is scored from 1 (all the time) to 6 (none of the time). Summing the individual item scores and transforming the resulting score to a 0-100 scale calculate the total score.</td>
<td>Hospital wards within three weeks after ICU discharge and at three and six-month follow-ups</td>
<td>Self-reported cognitive functioning. This tool contains questions assessing areas of memory, attention and reasoning. Higher scores indicate better cognitive functioning.</td>
</tr>
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<td>--------------------------------------</td>
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<tr>
<td>Post-traumatic Stress Symptoms and traumatic memories of the ICU experience</td>
<td>Post-traumatic Stress Symptoms 10-Question Inventory (PTSS-10)</td>
<td>This tool has two parts Part A: 4 memories Part B: 10 symptoms</td>
<td>Part A: for each memory, a Yes (presence of memory) or No (absence of memory) answer can be selected. Part B: for each symptom, a rating score between 1 (never) and 7 (always) were possible. Total score 10 to 70</td>
<td>Part A: Hospital wards within three weeks after ICU discharge and at three and six-month follow-ups Part B: Three and six-month follow-ups</td>
<td>This questionnaire has two-parts (part A and B). Part A consists of four traumatic memories of their ICU stay (memories of nightmares, severe anxiety or panic; severe pain; and feelings of suffocation). In part B, the presence and intensity of 10 post-traumatic symptoms are assessed. Total score can be classified into two categories: high probability of PTSD (total score ≥35 points) and low probability of PTSD (&lt;35 points).</td>
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Table 4.3.2. Demographic and clinical characteristics

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<tr>
<td>Married/De facto</td>
<td>73 (61)</td>
</tr>
<tr>
<td>Never married</td>
<td>24 (20)</td>
</tr>
<tr>
<td>Separated/Divorced</td>
<td>19 (16)</td>
</tr>
<tr>
<td>Widowed</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Level of education</td>
<td></td>
</tr>
<tr>
<td>Primary/secondary school (years 8-10)</td>
<td>47 (39)</td>
</tr>
<tr>
<td>Secondary school (years 11,12)</td>
<td>26 (22)</td>
</tr>
<tr>
<td>Trade/vocational/Diploma</td>
<td>26 (22)</td>
</tr>
<tr>
<td>University</td>
<td>21 (17)</td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
</tr>
<tr>
<td>Full time work</td>
<td>49 (41)</td>
</tr>
<tr>
<td>Part time/casual</td>
<td>19 (16)</td>
</tr>
<tr>
<td>Retired</td>
<td>25 (21)</td>
</tr>
<tr>
<td>Student/other</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Disability benefit</td>
<td>18 (15)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>33 (28)</td>
</tr>
<tr>
<td>No</td>
<td>87 (72)</td>
</tr>
<tr>
<td>Evidence of mental health treatment</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>45 (37)</td>
</tr>
<tr>
<td>No</td>
<td>75 (63)</td>
</tr>
<tr>
<td>Corticoids (prior to ICU admission)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15 (12)</td>
</tr>
<tr>
<td>No</td>
<td>105 (88)</td>
</tr>
<tr>
<td>Opioids (prior to ICU admission)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16 (13)</td>
</tr>
<tr>
<td>No</td>
<td>104 (87)</td>
</tr>
<tr>
<td>Benzodiazepines/antidepressants/anxiolytics (prior to ICU admission)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>24 (20)</td>
</tr>
<tr>
<td>No</td>
<td>96 (80)</td>
</tr>
<tr>
<td>Beta-blockers (prior to ICU admission)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>25 (21)</td>
</tr>
<tr>
<td>No</td>
<td>95 (79)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td></td>
</tr>
<tr>
<td>Length of sedation and analgesia (hours)</td>
<td></td>
</tr>
<tr>
<td>Propofol (n=116)</td>
<td>23 (7-83)</td>
</tr>
<tr>
<td>Fentanyl (n=80)</td>
<td>46 (15-94)</td>
</tr>
<tr>
<td>Midazolam (n=47)</td>
<td>36 (15-109)</td>
</tr>
<tr>
<td>Morphine (n=26)</td>
<td>30 (15-85)</td>
</tr>
<tr>
<td>Ketamine (n=8)</td>
<td>40 (9-80)</td>
</tr>
<tr>
<td>Total doses of sedatives, analgesics and corticoids (milligrams)</td>
<td></td>
</tr>
<tr>
<td>Propofol (n=119)</td>
<td>2960 (750-11290)</td>
</tr>
<tr>
<td>Fentanyl (n=111)</td>
<td>4 (1-7)</td>
</tr>
<tr>
<td>Midazolam (n=49)</td>
<td>101 (17-218)</td>
</tr>
<tr>
<td>Morphine (n=37)</td>
<td>48 (9-161)</td>
</tr>
<tr>
<td>Ketamine (n=8)</td>
<td>260 (36-350)</td>
</tr>
<tr>
<td>Hydrocortisone (n=10)</td>
<td>450 (325-588)</td>
</tr>
<tr>
<td>Oxycodone (n=38)</td>
<td>10 (5-65)</td>
</tr>
<tr>
<td>Paracetamol (n=120)</td>
<td>7500 (4000-14750)</td>
</tr>
</tbody>
</table>
Table 4.3.3. Comparison between responders and non-responders at six months follow up (n=141)

<table>
<thead>
<tr>
<th></th>
<th>Responders</th>
<th>Non-responders</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=92</td>
<td>n=49</td>
<td></td>
</tr>
<tr>
<td><strong>Mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age(^a)</td>
<td>56.8 (13.5)</td>
<td>49.0 (17.3)</td>
<td>0.008(^e)</td>
</tr>
<tr>
<td><strong>Median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APACHE III score(^a,b)</td>
<td>56.0 (41.5-72.7)</td>
<td>62.0 (44.5-75.0)</td>
<td>0.569</td>
</tr>
<tr>
<td>Length of ICU stay (days)(^a)</td>
<td>4.0 (3.0-7.0)</td>
<td>5.0 (2.5-11.0)</td>
<td>0.219</td>
</tr>
<tr>
<td>Length of Hospital stay (days)(^a)</td>
<td>14.5 (9.3-25.8)</td>
<td>17.0 (9.2-29.0)</td>
<td>0.456</td>
</tr>
<tr>
<td>FAS State Anxiety in ICU(^a,b)</td>
<td>2.0 (1.2-3.0)</td>
<td>3.0 (1.7-3.5)</td>
<td>0.029(^c)</td>
</tr>
<tr>
<td>STAI Form –Y Trait anxiety(^b,d)</td>
<td>35.0 (28.0-42.0)(^e)</td>
<td>45.5 (34.5-51.5)(^e)</td>
<td>0.001(^c)</td>
</tr>
<tr>
<td><strong>Frequency (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender(^a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>66 (72)</td>
<td>32 (65)</td>
<td>0.550</td>
</tr>
<tr>
<td>Female</td>
<td>26 (28)</td>
<td>17 (35)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Calculated from baseline (ICU) data
\(^b\) APACHE: Acute Physiology and Chronic Health Evaluation System; STAI: State and Trait Anxiety Inventory; FAS: Faces Anxiety Scale; HADS: Hospital Anxiety Depression Scale
\(^c\) Significant ≤ 0.05
\(^d\) Calculated from assessment in the hospital wards (n=121)
\(^e\) Responders=90 Non-responders=31

T-test for normally distributed (age), Mann-Whitney test for not normally distributed (APACHE III score, length of ICU stay, Length of hospital stay, state anxiety in ICU, HADS-Anxiety and HADS-Depression) and Chi-Square test for categorical variables (gender).
Table 4.3.4. Linear Mixed Model: factors associated with symptoms of anxiety over six months after ICU discharge (n=120)

<table>
<thead>
<tr>
<th>Factors</th>
<th>Coefficient (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>2.90 (0.77, 5.01)</td>
<td>0.007</td>
</tr>
<tr>
<td>Time 2 (3 months)</td>
<td>-0.83 (-1.49, -0.16)</td>
<td>0.015</td>
</tr>
<tr>
<td>Time 3 (6 months)</td>
<td>-0.55 (-1.21, 0.10)</td>
<td>0.100</td>
</tr>
<tr>
<td>Cognitive functioning (per 10 units) (score range 0-100)</td>
<td>-0.41 (-0.64, -0.19)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Symptoms of depression (per unit) (score range 0-21)</td>
<td>0.37 (0.27, 0.48)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Trait anxiety (per 10 units) (score range 20-80)</td>
<td>0.63 (0.20, 1.06)</td>
<td>0.004</td>
</tr>
<tr>
<td>Post-traumatic stress symptoms at 6mo (per 10 units) (score range 10-70)</td>
<td>0.63 (0.30, 0.97)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Memories of experiencing anxiety during ICU stay

<table>
<thead>
<tr>
<th></th>
<th>Coefficient (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.84 (0.17, 1.51)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Evidence of treatment for Mental health prior to ICU admission

<table>
<thead>
<tr>
<th></th>
<th>Coefficient (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>-0.92 (-1.8, -0.09)</td>
<td>0.029</td>
</tr>
</tbody>
</table>

**AIC for base model=1612, n=310; AIC for best model= 1235, n=264**
Table 4.3.5. Linear Mixed Model: factors associated with symptoms of depression over six months after ICU discharge (n=120)

<table>
<thead>
<tr>
<th>Factors</th>
<th>Coefficient (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>1.13 (-1.11, 3.38)</td>
<td>0.323</td>
</tr>
<tr>
<td>Time 2 (3 months)</td>
<td>-0.49 (-1.15, 0.16)</td>
<td>0.145</td>
</tr>
<tr>
<td>Time 3 (6 months)</td>
<td>-0.30 (-0.99, 0.37)</td>
<td>0.373</td>
</tr>
<tr>
<td>Cognitive functioning (per 10 units) (score range 0-100)</td>
<td>-0.46 (-0.68, -0.23)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Symptoms of anxiety (per unit) (score range 0-21)</td>
<td>0.43 (0.33, 0.54)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Trait anxiety (per 10 units) (score range 20-80)</td>
<td>0.75 (0.34, 1.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Post-traumatic stress symptoms at 3mo (per 10 units) (score range 10-70)</td>
<td>0.54 (0.18, 0.89)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Reason for ICU admission

<table>
<thead>
<tr>
<th>Medical</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical (Incl. cardiac surgery)</td>
<td>-0.39 (-1.21, 0.41)</td>
</tr>
<tr>
<td>Trauma</td>
<td>1.72 (0.58, 2.85)</td>
</tr>
</tbody>
</table>

AIC for base model=1612, n=310; AIC for best model= 1358, n=264
Supplementary material 1

Patient demographics questionnaire

Please answer the following questions about yourself by underlying the answer that corresponds to you:

1. **Marital status:**
   
   Married       Never married       De facto       Separated       Divorced       Widowed

2. **Highest level of education completed:**
   
   Primary school
   Secondary school (Grades 8, 9, 10)
   Secondary school (Grades 11, 12)
   Vocational/Apprenticeship/Trade Certificate
   Associate Diploma/Diploma
   Undergraduate Degree
   Postgraduate Degree
   Other (please list) ______________

3. **Employment status before the ICU admission:**
   
   In paid Full time work
   In paid Part time work
   In paid Casual work
   
   **If in paid work, how many hours per week do you usually work? _______**
   
   Retired
   Student
   On Disability Benefit
   Unemployed
   Other (Please specify) ___________
4. Have you ever visited a general practitioner (GP) or a mental health professional for symptoms of psychological distress or emotional problems?
   - Yes
   - No

5. Please record how often in the last 12 months you have smoked (please underline).
   - Daily
   - Weekly
   - Less than weekly
   - Ex-smoker
   - Never-smoker

6. How many cigarettes (manufactured or roll-your own) did you used to smoke per day previous to the ICU stay?___________

7. Where you taking any of the following medications before the ICU admission (12 months?)
   - Corticosteroids replacement therapy (Hydrocortisone, prednisone, prednisolone)
     Other, please list ________________ Yes No
   - Opioids (e.g. morphine, MSContin, OxyContin, fentanyl, methadone)
     Other, please list ________________ Yes No
   - Benzodiazepines, anxiolytics, antidepressant (e.g. diazepam, alprazolam, oxazepam)
     Other, please list ________________ Yes No
   - Beta-blockers (e.g. propranolol, metoprolol)
     Other, please list ________________ Yes No
Figure 4.3.4. Changes in the proportion of patients who presented with traumatic memories of the ICU admission across the three-time point measurement.

Participants who reported on Part A of the Post-traumatic Stress Symptoms 10-Question Inventory (PTSS-10) at all time points were included in this analysis (n=88). Participants with missing data on the Part A of the PTSS-10 at any time point measurement (n=32) were not included.
References


Publication 3: Factors associated with post-traumatic stress symptoms over six months after ICU discharge: A prospective study

Publication status: submitted for publication

4.4 Publication 3: Title: Factors associated with post-traumatic stress symptoms over six months after ICU discharge: A prospective study

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**Institution where work was conducted:**

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**Conflict of interest**

The authors declare that they have no conflicts of interest.
Abstract

Objective: To determine factors associated with posttraumatic stress symptoms (PTSS) over six months after discharge in critical illness survivors.

Design: Prospective study

Setting: Closed mixed adult ICU in a tertiary hospital

Participants: Patients (n=141) admitted ≥24 hours to the ICU

Main outcomes measures: Posttraumatic stress symptoms were measured at three and six months after ICU discharge using the Post-traumatic Stress Symptoms 10-Question Inventory. State anxiety in ICU was assessed with the Faces Anxiety Scale during ICU stay. Trait anxiety was measured with the State-Trait Anxiety Inventory Form Y-2. Clinical and demographical data were also collected. Mixed effect regression models were used to determine the factors significantly associated with PTSS over time.

Results: Moderate to severe levels of state anxiety in ICU were reported by 81 (57%) participants. Levels of trait anxiety (median 36 IQR:29-47) were similar to the Australian population. High levels of PTSS occurred at three (n=19, 19%) and six months (n=15, 17%). Factors independently associated with PTSS were trait anxiety (2.2; 95% CI, 0.3-4.1; p=0.023), symptoms of anxiety after ICU discharge (0.6; 95% CI, 0.2-1.1; p=0.005), younger age (-1.4; 95% CI, -2.6--0.2; p=0.024) and evidence of mental health treatment prior to the ICU admission (5.2; 95% CI, 1.5-8.9; p=0.006).

Conclusions: PTSS occurred in a significant proportion of ICU survivors and were significantly associated with younger age, mental health treatment prior to the ICU admission, higher levels of trait anxiety and more symptoms of anxiety after ICU
discharge. Early assessment and interventions directed to reduce state and trait anxiety in ICU survivors may be of benefit.

**Keywords**

Intensive care unit, state anxiety, trait anxiety, critically ill, posttraumatic stress symptoms
Introduction

Survivors of critical illness experience compromised psychological health including the development of posttraumatic stress symptoms (PTSS). Clinically significant PTSS have been found in 22% (range 10-39%) of ICU survivors. A number of factors have been identified as consistent predictors of the development of PTSS following treatment in an intensive care unit (ICU). Factors including premorbid psychopathology, greater benzodiazepines administration during ICU treatment, post-ICU memories of frightening experiences and psychotic experiences during ICU treatment, younger age and female gender have been identified.

In the general literature of posttraumatic stress disorder (PTSD), it can be observed that individual differences in personality traits contribute significantly to the development of this condition. Specific personality traits of anxiety and hostility/anger have been associated with PTSD. In contrast, personality traits that seem to have a protective effect from PTSD are hardiness and optimism.

In the ICU context, the exploration of the role of personality in the development of PTSS is at the early stages. There is beginning evidence regarding two relevant personality traits: trait optimism and trait anxiety. Trait optimism was found to be an independent predictor of reduced PTSS after ICU treatment in a study exploring adverse emotional outcomes after ICU. Trait anxiety was moderately correlated (rho=0.49, p=0.007) with intrusion symptoms (one of the four distinct diagnostic clusters of PTSD described in the DSM-V) at eight weeks after ICU discharge. However, this finding needs further consideration and statistical approaches such multivariate analysis to determine unique contributions and rule out the influence of confounding factors. In addition, it is unclear if this association would persist over a longer period of time. The
state component of anxiety has also been proposed as a possible risk factor for the development of PTSS during recovery.\textsuperscript{10}

The distinction between PTSS and the fully activated disorder (PTSD) needs to be made. Unlike PTSS, PTSD is a psychiatric diagnosis that impairs patients’ ability to function. Most research in ICU survivors has explored PTSS, rather than PTSD. In this study, we hypothesised that anxiety during critical illness would be associated with the development of PTSS over six months after ICU discharge. Data about social support, cognitive functioning, optimism and medications such as corticoids, opioids and beta-blockers were also collected because they appear in the literature as possible risk factors for adverse emotional outcomes.\textsuperscript{7,11-15}

The purpose of this research was to determine factors associated with PTSS over six months after intensive care unit (ICU) discharge in survivors of intensive care treatment.

**Methods**

**Settings**

This prospective study was carried out at one mixed medical/surgical/trauma adult ICU in a tertiary hospital located in Brisbane, Australia. There were approximately 1130 admissions to this ICU during the six-month enrolment period (September 2012 to February 2013). This 25-bed closed ICU had a registered nurse-patient ratio of 1:1. The Griffith University (NRS/35/12/HREC) and Princess Alexandra Hospital Ethics Committees (HREC/12/QPAH/173) approved this research, and the study protocol was
published elsewhere. A summary of the methods and modification to the published protocol are provided below and in Table 4.4.1.

**Patients**

Adult patients (≥18 years of age) who stayed in ICU for ≥24 hours, were able to communicate verbally or non-verbally; understand English; and, open their eyes spontaneously or in response to voice were invited to participate in this study. A sample size of 104 participants was needed for this study. We performed power analysis a priori using multiple regression test (fixed model, R² increase), power of 80%, significance level of α = 0.05, medium size effect (0.15) and a maximum of seven variables. An in-hospital mortality rate of 10% and a dropout of 30% at six months were estimated.

**Data collection**

As soon as patients agreed to participate in this study, the principal investigator or the ICU research nurse commenced the state anxiety assessments in ICU. Participants reported on their levels of state anxiety twice a day (morning 8-11am and afternoon 4-7pm) up to 30 days. Clinical data collected twice a day at the moment of state anxiety assessment included: Delirium status (The Confusion Assessment Method for the ICU: CAM-ICU), airway status (tracheostomy, endotracheal tube), mechanical ventilation status (invasive, non-invasive, non-ventilation), oxygen saturation, pain score (Critical-Care Pain Observation Tool: CPOT) and sedation (total dose of sedatives and analgesics as well as total hours of continuous infusion of sedoanalgesia). ICU diagnosis, Acute Physiology and Chronic Health Evaluation (APACHE) III, mental health history, gender and age were also collected from medical records.
Marital status, level of education, employment status, evidence of mental health treatment prior to the ICU admission, current smoking habits as well as pre-ICU medications (opioids, beta-blockers and corticoids) were obtained through a demographic questionnaire administered when participants were in the hospital wards. Participants who answered “Yes” to either of the following two question was considered to have evidence of mental health treatment prior to the ICU admission: (1) Have you ever visited a general practitioner (GP) or a mental health professional for symptoms of psychological distress or emotional problems? (2) Were you taking benzodiazepines, anxiolytics or antidepressants medications within the 12 months prior to the ICU admission? Trait anxiety was assessed using the Trait component of the State-Trait Anxiety Inventory (STAI) for adults Form Y-2.  

In the hospital wards, participants confirmed their wish to participate in this project by giving written informed consent and completing the questionnaires. The principal investigator or the ICU research nurse assisted the participants (when needed due to physical impairment) with the surveys in hospital wards. The Posttraumatic Stress Symptoms 10-Question Inventory (PTSS-10), trait component of the State-Trait Anxiety Inventory (STAI) for Adults Form Y-2, Hospital Anxiety and Depression Scale (HADS), Faces Anxiety Scale (FAS), Multidimensional Scale of Perceived Social Support (MSPSS), Life Orientation Test-Revised (LOT-R) and Cognitive Functioning Scale Medical Outcome Study 6-Item (MOS COG) were chosen because they are self-reported, well validated and easy to understand instruments, take a few minutes to complete, and with the exception of Cognitive Functioning Scale Medical Outcome Study 6-Item (MOS COG), have all been used in ICU research. A description of these instruments as well as the time point measurements is presented in Table 4.4.1.
At three and six-month follow-up, participants were mailed the surveys after a phone call to remind them about their involvement in this study. Most participants returned the surveys in the reply paid envelope provided, twelve participants read their answers to the researcher over the phone, and two participants preferred to use email.

**Data analysis**

All data were cleaned and checked for missing and invalid values. Descriptive characteristics are presented using means and standard deviations (SDs) or medians and interquartile ranges (IQRs) for continuous variables and percentages for categorical variables.

Linear mixed models using a single variable and alpha level (p<0.2) was performed to identify variables with a potential longitudinal relationship with PTSS. The selected variables were checked against one another for multicollinearity using Spearman correlations and Chi-square, then entered into the model based on level of significance.

Repeated measures analysis using mixed models with a random intercept per subject was performed to determine variables independently and significantly associated with PTSS over a six-month period. Significance level of 5% and the Akaike Information Criteria (AIC) were used to identify a robust and parsimonious model. Model diagnostics included assessment of influential observations, multicollinearity amongst variables and residual checks. Stata version 13 (StataCorp, College Station, Texas) was used for statistical analysis. 27
Results

In total 1130 patients were admitted to the ICU between September 2012 and February 2013. Of the 1130 patients, 797 were screened for possible inclusion in this study, 141 provided data while in ICU, 120 completed the follow-up in the hospital wards, 101 completed three-month follow-up and 92 six-month follow-up (Figure 4.4.1). Participants were aged 54 (SD±15) years and 70% male. The majority (61%) was in a relationship and working (57%). Forty-five (37%) participants reported some evidence of mental health treatment prior to critical illness. The median score for the trait component of the STAI Form-Y was 36 (IQR: 29-47) and the mean score for the LOT-R (trait optimism) was 15 (SD±4). Participants stayed in ICU for about 4 (IQR: 3-7) days and 15 (IQR: 10-28) days in hospital. Most participants required invasive mechanical ventilation (82%) for 52 (IQR: 13-148) hours; and, 81 (57%) participants reported moderate to severe levels of state anxiety. Most participants received propofol (84%), fentanyl (79%), midazolam (35%) and morphine (18%). Other clinical and demographic characteristics are presented in Table 4.4.2.

There were no significant differences in gender, length of ICU stay, length of hospital stay and APACHE III score between those who completed the study (n=92) and those who were lost to follow-up at six months (n=49). Participants lost to follow-up were significantly younger (mean 49 SD±17 vs. 57 SD±14, p=0.008) and reported significantly higher levels of state anxiety (median 3.0 IQR: 1.7-3.5 vs. 2.0 IQR: 1.2-3.0, p=0.029) and trait anxiety (median 46 IQR: 35-52 vs. 35 IQR: 28-42, p=0.001) at baseline than those who completed the study.

At the third-month follow-up, 19 (19%) participants scored ≥35 (high levels of PTSS) on the PTSS-10. Of these 19 participants, 14 (74%) reported at least one
traumatic memory of their ICU admission. Of the 15 (17%) participants who reported high levels of PTSS (>35 on PTSS-10) at the sixth-month follow-up, 14 reported at least one traumatic memory. Traumatic memories of pain, difficulty breathing and anxiety were significantly associated with higher scores on PTSS-10 at six months follow-up (Table 4.4.3). The association of social support, cognitive functioning, and anxiety and depression symptoms with PTSS at six months after ICU discharge are presented in Table 4.4.4.

Numerous factors were associated with PTSS-10 score on univariate analyses (Table 4.4.5). When simultaneously entered into a mixed effect model trait anxiety, symptoms of anxiety after ICU (HADS), age and mental health history remained significantly (p<0.05) associated with PTSS score over six months after ICU discharge (Table 4.4.6). State anxiety during ICU stay (FAS) no longer had a significant association to PTSS after ICU discharge in the full model.

**Discussion**

The presence of PTSS in survivors of critical illness has been well documented. Our study confirms these findings, with PTSS prevalence of 19% at three-month and 17% at six-month follow-up. We investigated factors potentially related to PTSS after ICU, with the primary focus on anxiety (state and trait) during critical illness. Numerous factors were significantly associated with PTSS in the univariate analyses. After multivariate analysis only trait anxiety, symptoms of state anxiety after ICU discharge (HADS), younger age and evidence of mental health treatment prior to the ICU admission remained significantly associated with PTSS over six months after ICU discharge.
In this cohort, the levels of trait anxiety were similar to those found in the general Australian population. Mixed effects analysis showed that personality trait of anxiety contributed significantly to the development of PTSS in the ICU survivor. This finding is in line with the general literature on PTSD. It also confirms previous reports suggesting this association in the ICU survivors.

The assessment of trait anxiety prior to hospital discharge could help clinicians to identify patients at higher risk of developing PTSS during recovery. There is growing evidence supporting that trait personalities can be modified with interventions such as cognitive behavioural therapy, educational programs, cognitive training intervention and combination of psychological interventions and medications, to mention but a few. However, these have not been tested in the critically ill population.

The assessment of state anxiety was performed at multiple time points and using two instruments. The FAS was used in ICU and HADS (anxiety subscale) in hospital wards and at three-month follow-up. We treated state anxiety as measured by the FAS as a different variable from the state anxiety measured by the HADS and not as repeated measure of the same variable because we wanted to test if state anxiety in ICU alone had a long term effect on PTSS. Only symptoms of state anxiety measured with the HADS were significantly associated with PTSS over time.

Younger survivors were more likely than older survivors to have high levels of PTSS. The association between younger age and PTSS has been reported previously as well as possible explanations for this relationship. Older patients might not consider critical illness as a traumatic experience since they might have been exposed to chronic diseases and previous hospitalisations. In addition, more elderly patients might not receive as aggressive ICU treatment as younger ones, interventions that may predispose...
Evidence of mental health treatment prior to the ICU admission was also associated with PTSS. Pre-ICU psychopathology was considered to be a consistent predictor of PTSD after ICU in a systematic literature review. It is also a consistent predictor in the general literature of PTSD.

No intra-ICU factor such as sedation, mechanical ventilation and ICU diagnosis were significantly associated with PTSS over time. In the literature of PTSS after ICU, greater benzodiazepines administration during ICU treatment is considered to be a consistent predictor of PTSS. In our research, we did not find this association. This inconsistency may be explained by the current sedation practices, where light sedation with a more interactive patient is the goal in contrast to a deeply sedated patient in past years.

Findings of this study suggest that the strategies addressing PTSS after ICU should be focused on the assessment and management of state anxiety during and after critical illness. Patients’ trait anxiety levels could be assessed in ICU or prior to hospital discharge to identify patients at higher risk, and individuals could be helped through interventions such as cognitive bias modification therapy and cognitive behavioural therapy to reduce trait anxiety and therefore the risk of PTSS. However, while these interventions have been proven to be effective in other populations, they need to be tested in the ICU survivor population to determine benefit and ensure no harm. In addition, future research should investigate a broader spectrum of personality traits (e.g. openness, conscientiousness, extroversion and agreeableness) as predictors of emotional wellbeing in survivors of critical illness since contemporaneous work suggest that personality traits are potentially modifiable factors.
Limitations of this study include the assessment of PTSS using a questionnaire instead of formal diagnosis of PTSD through clinical interview. There is a possibility that the prevalence of PTSS might have been underestimated if participants experiencing most avoidance symptoms were lost to follow-up. In addition, we did not assess if participants sought mental health assistance after ICU; therefore, it is unknown if participants on mental health treatment during recovery experienced a decrease in PTSS.

Participants lost to follow-up were significantly younger and reported significantly higher levels of state anxiety and trait anxiety than those who completed the study. However, these three factors were still significantly associated with PTSS over time.

Conclusion

This study confirms that PTSS occur in an important proportion of survivors of ICU. Early assessment and interventions directed to reduce state and trait anxiety in the ICU patient and survivor might reduce the risk of PTSS after critical illness.

Acknowledgements

We thank the Intensive Care Foundation and the Australian College of Critical Care Nurses for supporting this research. We thank Dr. Robert Ware for advising on statistical analyses. We also thank the ICU Research Nurses Lena James and Kelly Perkins for their assistance with data collection.
Tables and figures

Figure 4.4.1. Participant flow through study
<table>
<thead>
<tr>
<th>Construct</th>
<th>Instrument</th>
<th>Number of items</th>
<th>Possible score</th>
<th>Measurement time points</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>State anxiety</td>
<td>Faces Anxiety Scale (FAS)</td>
<td>1</td>
<td>1-5</td>
<td>During ICU stay Twice a day (morning 8-11 and afternoon 4-7)</td>
<td>5 faces representing different levels of anxiety ranging from no anxiety to extreme anxiety.</td>
</tr>
<tr>
<td>Trait anxiety</td>
<td>Trait component of the State-Trait Anxiety Inventory (STAI) for Adults Form Y-2</td>
<td>20</td>
<td>For each item, a rating score between 1 and 4 is possible. Total score 20-80</td>
<td>Hospital wards within three weeks after ICU discharge.</td>
<td>Higher scores indicate greater levels of trait anxiety.</td>
</tr>
<tr>
<td>Trait Optimism</td>
<td>Life Orientation Test-Revised (LOT-R)</td>
<td>10</td>
<td>For each item, a rating score between 0 and 4 is possible. Total score 0-24</td>
<td>Hospital wards within three weeks after ICU discharge.</td>
<td>6 items concerning general expectations relative to positive or negative consequences. 4 filler items not used in the scoring. Higher scores indicate greater optimism.</td>
</tr>
<tr>
<td>Symptoms of anxiety and depression</td>
<td>Hospital Anxiety and Depression Scale (HADS)</td>
<td>Depression: 7 items Anxiety: 7 items Total: 14 items</td>
<td>For each item, a rating score between 0 and 3 is possible. Total score 0-21</td>
<td>Hospital wards within three weeks after ICU discharge and three-month follow-up</td>
<td>The total score for each subscale can be classified into four categories: normal (0-7), mild (8-10), moderate (11-14) and severe (15-21)</td>
</tr>
<tr>
<td>Social support</td>
<td>Multidimensional Scale of Perceived Social Support (MSPSS)</td>
<td>12</td>
<td>For each item a rating score between 1 (very strongly disagree) and 7 (very strongly)</td>
<td>Three-month follow-up</td>
<td>Three subscales: family, friends and significant other. Higher scores indicated higher levels of</td>
</tr>
<tr>
<td><strong>Self-perceived cognitive functioning</strong></td>
<td><strong>Cognitive Functioning Scale Medical Outcome Study 6-Item (MOS COG)</strong></td>
<td><strong>6</strong></td>
<td>Each item is scored from 1 (all the time) to 6 (none of the time). Summing the individual item scores and transforming the resulting score to a 0-100 scale calculate the total score.</td>
<td><strong>Hospital wards within three weeks after ICU discharge. Three-month follow-up</strong></td>
<td><strong>Self-reported cognitive functioning including areas of memory, attention and reasoning. Higher scores indicate better cognitive functioning.</strong></td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>---------------------------------------------------------------</td>
<td>-----</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Post-traumatic Stress Symptoms</strong></td>
<td><strong>Post-traumatic Stress Symptoms 10-Question Inventory (PTSS-10)</strong></td>
<td><strong>Part A: 4 memories Part B: 10 symptoms</strong></td>
<td>Part A: for each memory, a Yes (presence of memory) or No (absence of memory) answer can be selected. Part B: for each symptom, a rating score between 1 (never) and 7 (always) were possible. Total score 10 to 70</td>
<td><strong>Three and six-month follow-ups</strong></td>
<td><strong>Two-parts instrument: Part A consists of four traumatic memories of their ICU stay (memories of nightmares, severe anxiety or panic; severe pain; and feelings of suffocation); Part B, the presence and intensity of 10 post-traumatic symptoms are assessed. Total score can be classified into two categories: high probability of PTSD (total score ≥35 points) and low probability of PTSD (&lt;35 points)</strong></td>
</tr>
</tbody>
</table>
| Table 4.4.2. Clinical and demographic characteristics
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n=120 (%)</td>
<td></td>
</tr>
<tr>
<td>Employment status pre-ICU</td>
<td></td>
</tr>
<tr>
<td>Full time work</td>
<td>49 (41)</td>
</tr>
<tr>
<td>Part time/casual</td>
<td>19 (16)</td>
</tr>
<tr>
<td>Retired</td>
<td>25 (21)</td>
</tr>
<tr>
<td>Student/other</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Disability benefit</td>
<td>18 (15)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Level of education pre-ICU</td>
<td></td>
</tr>
<tr>
<td>Primary/secondary school (years 8-10)</td>
<td>47 (39)</td>
</tr>
<tr>
<td>Secondary school (years 11-12)</td>
<td>26 (22)</td>
</tr>
<tr>
<td>Trade/vocational/Diploma</td>
<td>26 (22)</td>
</tr>
<tr>
<td>University</td>
<td>21 (17)</td>
</tr>
<tr>
<td>Smoking status pre-ICU</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>33 (28)</td>
</tr>
<tr>
<td>No</td>
<td>87 (72)</td>
</tr>
<tr>
<td>Corticoids pre-ICU</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15 (12)</td>
</tr>
<tr>
<td>No</td>
<td>105 (88)</td>
</tr>
<tr>
<td>Opioids pre-ICU</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16 (13)</td>
</tr>
<tr>
<td>No</td>
<td>104 (87)</td>
</tr>
<tr>
<td>Benzos/anxiolytics/antidepressants pre-ICU</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>24 (20)</td>
</tr>
<tr>
<td>No</td>
<td>96 (80)</td>
</tr>
<tr>
<td>Beta-blockers pre-ICU</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>25 (21)</td>
</tr>
<tr>
<td>No</td>
<td>95 (79)</td>
</tr>
<tr>
<td>Reason for ICU admission</td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>30 (21)</td>
</tr>
<tr>
<td>Medical</td>
<td>69 (49)</td>
</tr>
<tr>
<td>Cardiotoracic surgery</td>
<td>18 (13)</td>
</tr>
<tr>
<td>Trauma</td>
<td>24 (17)</td>
</tr>
<tr>
<td></td>
<td>n=141 Median (IQR)</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td><strong>APACHE III score</strong></td>
<td>58 (43-74)</td>
</tr>
<tr>
<td><strong>Length of sedation and analgesia in ICU (hrs)</strong></td>
<td></td>
</tr>
<tr>
<td>Propofol (n=116)</td>
<td>23 (7-83)</td>
</tr>
<tr>
<td>Fentanyl (n=80)</td>
<td>46 (15-94)</td>
</tr>
<tr>
<td>Midazolam (n=47)</td>
<td>36 (15-109)</td>
</tr>
<tr>
<td>Morphine (n=26)</td>
<td>30 (15-85)</td>
</tr>
<tr>
<td>Ketamine (n=8)</td>
<td>40 (9-80)</td>
</tr>
<tr>
<td><strong>Total doses of sedatives and analgesics in ICU (mg)</strong></td>
<td></td>
</tr>
<tr>
<td>Propofol (n=119)</td>
<td>2960 (750-11290)</td>
</tr>
<tr>
<td>Fentanyl (n=111)</td>
<td>4 (1-7)</td>
</tr>
<tr>
<td>Midazolam (n=49)</td>
<td>101 (17-218)</td>
</tr>
<tr>
<td>Morphine (n=37)</td>
<td>48 (9-161)</td>
</tr>
<tr>
<td>Ketamine (n=8)</td>
<td>260 (36-350)</td>
</tr>
<tr>
<td>Hydrocortisone (n=10)</td>
<td>450 (325-588)</td>
</tr>
<tr>
<td>Oxycodone (n=38)</td>
<td>10 (5-65)</td>
</tr>
<tr>
<td>Paracetamol (n=120)</td>
<td>7500 (4000-14750)</td>
</tr>
</tbody>
</table>

*APACHE: Acute Physiology and Chronic Health Evaluation System*
Table 4.4.3. Relationship between traumatic memories and post-traumatic stress symptoms at six months after ICU discharge (n=90)

<table>
<thead>
<tr>
<th>Group</th>
<th>PTSS-10 score (Median IQR)</th>
<th>Traumatic memories Part A PTSS-10</th>
<th>Pain</th>
<th>Difficulty breathing</th>
<th>Nightmares</th>
<th>Anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>22 (15-31)</td>
<td></td>
<td>30 (33)</td>
<td>39 (43)</td>
<td>34 (38)</td>
<td>34 (38)</td>
</tr>
<tr>
<td>Symptomatic for PTSS</td>
<td>47 (44-55)</td>
<td></td>
<td>9 (60)</td>
<td>12 (80)</td>
<td>8 (53)</td>
<td>11 (73)</td>
</tr>
<tr>
<td>Asymptomatic for PTSS</td>
<td>18 (14-27)</td>
<td></td>
<td>21 (28)</td>
<td>27 (36)</td>
<td>26 (35)</td>
<td>23 (31)</td>
</tr>
<tr>
<td>Difference between symptomatic and asymptomatic patients</td>
<td>$X^2=4.410; p=0.036$</td>
<td>$X^2=8.145; p=0.004$</td>
<td>$X^2=1.144; p=0.285$</td>
<td>$X^2=7.951; p=0.005$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PTSS-10: Post-traumatic Stress Symptoms 10-Question Inventory

Symptomatic for PTSS = PTSS-10 score ≥35
Asymptomatic for PTSS = PTSS-10 score <35
Table 4.4.4. Effect of cognitive functioning, perceptions of social support, and anxiety and depression symptoms on post-traumatic stress symptoms at six months after ICU discharge (n=92)

<table>
<thead>
<tr>
<th>Group</th>
<th>Anxiety symptoms (HADS)</th>
<th>Depression symptoms (HADS)</th>
<th>Cognitive functioning (MOS COG scale)</th>
<th>Perceptions of social support (MSPSS scale)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>5 (2-8)</td>
<td>3 (1-7)</td>
<td>67 (53-76)</td>
<td>6 (5-7)</td>
</tr>
<tr>
<td>Symptomatic for PTSS&lt;sup&gt;d&lt;/sup&gt;</td>
<td>10 (8-12)</td>
<td>10 (6-14)</td>
<td>47 (27-70)</td>
<td>5 (3-6)</td>
</tr>
<tr>
<td>Asymptomatic for PTSS</td>
<td>4 (2-7)</td>
<td>2 (1-5)</td>
<td>67 (57-77)</td>
<td>6 (5-7)</td>
</tr>
<tr>
<td>Difference between symptomatic and asymptomatic patients</td>
<td>$t=-5.615; p&lt;0.0001$</td>
<td>$t=-7.196; p&lt;0.0001$</td>
<td>$t=3.893; p&lt;0.0001$</td>
<td>$t=2.790; p=0.012$</td>
</tr>
</tbody>
</table>

<sup>a</sup>HADS: Hospital Anxiety Depression Scale. Score range (1-14), higher scores, indicate greater symptoms of anxiety

<sup>b</sup>MOS COG: Cognitive Functioning Scale Medical Outcome Study 6-Item. Score range (0-100), higher scores indicate better cognitive functioning

<sup>c</sup>MSPSS: Multidimensional Scale of Social Support. Score range (1-7), higher scores indicate greater perceived social support

<sup>d</sup>PTSS: Post-traumatic Stress Symptoms

Symptomatic for PTSS = PTSS-10 score ≥35

Asymptomatic for PTSS = PTSS-10 score < 35
Table 4.4.5. Factors associated with post-traumatic stress symptoms on univariate analysis

<table>
<thead>
<tr>
<th>Variables being tested for an association with post-traumatic stress symptoms over time (p&lt;0.20)</th>
<th>Univariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B (95% CI)</td>
</tr>
<tr>
<td>Cognitive functioning (score range 0-100)</td>
<td>-0.2 (-0.3, -0.09)</td>
</tr>
<tr>
<td>Depression symptoms (HADS score range 0-21)</td>
<td>1.1 (0.7, 1.5)</td>
</tr>
<tr>
<td>Anxiety symptoms (HADS score range 0-21)</td>
<td>1.1 (0.7, 1.5)</td>
</tr>
<tr>
<td>Trait optimism (score range 0-24)</td>
<td>-1.1 (-1.6, -0.6)</td>
</tr>
<tr>
<td>Trait anxiety (per 10 units) (score range 20-80)</td>
<td>5.1 (3.4, 6.8)</td>
</tr>
<tr>
<td>Memories of anxiety (yes)</td>
<td>4.6 (1.4, 7.8)</td>
</tr>
<tr>
<td>Pain (yes)</td>
<td>1.6 (0.4, 2.9)</td>
</tr>
<tr>
<td>Age (per 10 units) (range 18-84 years)</td>
<td>-2.0 (-3.5, -0.5)</td>
</tr>
<tr>
<td>Benzodiazepines (yes)</td>
<td>3.9 (-0.3, 8.2)</td>
</tr>
<tr>
<td>Oxycodone total dose during ICU stay (range 5-65 mg)</td>
<td>0.03 (0.01, 0.06)</td>
</tr>
<tr>
<td>Ketamine infusion (range 9-80 hours)</td>
<td>0.3 (0.03, 0.5)</td>
</tr>
<tr>
<td>Fentanyl total dose during ICU stay (range 1-7mg)</td>
<td>0.3 (0.03, 0.6)</td>
</tr>
<tr>
<td>ICU diagnosis</td>
<td>Reference group</td>
</tr>
<tr>
<td>Surgical</td>
<td>-5.1 (-10.3, 0.05)</td>
</tr>
<tr>
<td>Medical</td>
<td>-9.8 (-16.9, -2.7)</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>-1.1 (-8.2, 5.9)</td>
</tr>
<tr>
<td>Trauma</td>
<td>-6.2 (-12.1, 0.4)</td>
</tr>
<tr>
<td>Non-invasive mechanical ventilation (yes)</td>
<td>-0.4 (-0.7, -0.01)</td>
</tr>
<tr>
<td>Non-invasive mechanical ventilation (range 7-20 hours)</td>
<td>Reference group</td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
</tr>
<tr>
<td>Full time work</td>
<td>6.4 (-0.5, 13.2)</td>
</tr>
<tr>
<td>Part-time/casual</td>
<td>-0.8 (-7.6, 5.9)</td>
</tr>
<tr>
<td>Retired</td>
<td>2.7 (-4.8, 10.3)</td>
</tr>
</tbody>
</table>
| Student/other                                                                            | 174
Disability benefit: -2.3 (-9.4, 4.8) 0.521
Unemployed: 3.5 (-2.9, 9.9) 0.292
Social support at three months (score range 12-84): -1.8 (-3.7, 0.01) 0.052
Ketamine/total dose during ICU stay (range 36-350mg): 0.04 (-0.003, 0.08) 0.067
Paracetamol/total dose during ICU stay (4,000-14,750mg): Too small to report 0.070

Marital status

<table>
<thead>
<tr>
<th>Marital status</th>
<th>Reference group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Married/defacto</td>
<td>Reference group</td>
<td>-</td>
</tr>
<tr>
<td>Never married</td>
<td>2.8 (-3.1, 8.7)</td>
<td>0.354</td>
</tr>
<tr>
<td>Separated/divorced</td>
<td>7.7 (1.7, 13.8)</td>
<td>0.012</td>
</tr>
<tr>
<td>Widowed</td>
<td>-2.8 (-13.4, 7.9)</td>
<td>0.612</td>
</tr>
</tbody>
</table>

Invasive mechanical ventilation (range 12-148 hours): 0.01 (-0.002, 0.03) 0.081
State anxiety (score range 1-5): 1.9 (-0.3, 4.0) 0.097
Memories of difficulty breathing (yes): 2.8 (-0.6, 6.2) 0.111
Length of ICU stay (range 3-7 days): 0.2 (-0.06, 0.5) 0.118
First state anxiety assessment in ICU (score range 1-5): 1.4 (-0.4, 3.2) 0.132
Fentanyl infusion (range 15-94 hours): 0.02 (-0.01, 0.1) 0.134
Memories of pain (yes): 2.5 (-0.8, 5.8) 0.134
Propofol/total dose during ICU stay (range 750-11,290mg): Too small to report 0.196
Evidence of mental health treatment (yes): 6.7 (2.4, 11.1) 0.002

ICU: Intensive Care Unit; HADS: Hospital Anxiety and Depression Scale
Table 4.4.6. Linear Mixed Model: factors associated with post-traumatic stress symptoms over 6 months after ICU discharge (n=120)

<table>
<thead>
<tr>
<th>Factors</th>
<th>Coefficient (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>17.4 (7.0, 27.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Time (6 months)</td>
<td>2.0 (-0.5, 4.5)</td>
<td>0.112</td>
</tr>
<tr>
<td>Symptoms of Anxiety (per unit) (score range 0-21)</td>
<td>0.6 (0.2, 1.1)</td>
<td>0.005</td>
</tr>
<tr>
<td>Trait anxiety (per 10 units) (score range 20-80)</td>
<td>2.2 (0.3, 4.1)</td>
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Akaike Information Criterion/Bayesian Information Criterion for model= 1394/1423
References


4.5 Conclusion

The results presented and discussed in these three papers confirm that anxiety in ICU is a significant symptom experienced by a high proportion of patients. The majority of participants in this study experienced state anxiety during their stay in ICU with more than a half reporting moderate to severe levels. The risk factors significantly associated with state anxiety during ICU treatment were pain and trait anxiety. Trait anxiety levels in these participants were similar to the Australian population. Factors significantly associated with trait anxiety were trait optimism, state anxiety, age and evidence of mental health treatment prior to ICU admission.

The results of this research also demonstrate that many ICU survivors experience compromised emotional outcomes of anxiety, depression and PTSS. Symptoms of anxiety were reported by 42% of the participants while in the hospital wards, 26% at three months and 28% at six months after ICU discharge. Symptoms of depression were reported by 37% of the participants while in the hospital wards, 19% at three months and 23% at six months after ICU discharge. High levels of PTSS occurred in 19% of participants at three months and 17% at six month after ICU discharge.

Factors significantly associated with poor emotional outcomes for participants in this study were trait anxiety, cognitive functioning, memories of intra-ICU anxiety, age, ICU admission due to trauma and evidence of mental health treatment prior to the ICU admission. In addition, adverse emotional outcomes of symptoms of anxiety, depression and PTSS were significantly associated with each other demonstrating significant comorbidity in these participants. The state component of anxiety during ICU treatment
did not have an independent significant effect over time on any of the emotional outcomes. However, it was significantly associated with trait anxiety, which was a significant risk factor for all of them. Early assessment and interventions directed to reduce state and trait anxiety in the ICU patient and survivor might decrease the risk of adverse emotional outcomes after the intensive care experience.
Chapter 5: Conclusions and recommendations

5.1 Introduction

Adverse emotional outcomes in survivors of critical illness were investigated in this study. The literature review process identified numerous risk factors for symptoms of anxiety, depression and post-traumatic stress in the ICU survivors. These risk factors provided valuable information for the development of the conceptual model for this research and provided a framework to guide and organise the study. In addition to the risk factors identified from the literature to be investigated in this research, discussion with experienced critical care clinicians saw the addition of delirium, pain, APACHE III score and ICU diagnosis added to the model. Figure 5.1.1 presents the risk factors and adverse emotional outcomes during recovery examined in this research.

Figure 5.1.1. Factors associated with adverse emotional outcomes after the ICU experience
The evidence related to sedation in ICU, suggested that anxiety during critical illness needed to be investigated as another possible risk factor for adverse emotional outcomes. Thus, the aims of this study were:

1. To describe the magnitude and patterns of state anxiety reported by patients throughout their ICU stay
2. To identify factors associated with patients’ state anxiety and trait anxiety during critical illness
3. To identify factors associated with symptoms of anxiety and depression over six months after the intensive care experience
4. To determine factors associated with PTSS over six months after the intensive care experience.

In this chapter, the conclusions and recommendations of this prospective study are presented. First, an overview of the study methods and findings of this investigation is provided. Then, the recommendations for clinical practice, future research and education are suggested. Finally, the conclusions of this prospective study are stated.

5.2 Overview of study methods and findings

In this prospective study conducted in a mixed ICU, with 141 participants reported on their levels of state anxiety twice daily during their ICU stay using the FAS. Participants were followed up to the hospital wards where they self-reported on their levels of trait anxiety, and symptoms of anxiety and depression by completing the trait component of the STAI and the HADS, respectively. Participants reported on symptoms of anxiety and depression again at three and six months after ICU discharge using the
HADS. At the three and six months follow-up, they also completed the PTSS-10 to report on symptoms of post-traumatic stress. Clinical and demographic data were obtained from patients and medical records. Multiple linear regression modelling process was used to determine factors associated with state anxiety and trait anxiety. Mixed effect regression models with a random intercept per subject were used to determine factors associated with symptoms of anxiety, depression and post-traumatic stress over six months after ICU discharge.

The study presented in this thesis confirms that ICU patients suffer considerable emotional distress during their ICU admission. The majority (n=115; 82%) of participants experienced state anxiety at least once during their stay in ICU, with 57% reporting moderate to severe levels. Although some fluctuations in state anxiety occurred over time, moderate levels were predominantly reported on days 6 to 12. The prevalence and severity of state anxiety found in this sample were comparable to what has been reported previously (Chlan & Savik, 2011; Chlan, 2004; McKinley et al., 2004). Participants in this current study reported levels of trait anxiety (36, IQR: 29-47) similar to the ones found in the general Australian population (Crawford, Cayley, Lovibond, Wilson, & Hartley, 2011). After adjustment, factors related to state anxiety in ICU were pain and trait anxiety. Factors associated with trait anxiety were trait optimism, state anxiety, evidence of mental health treatment and age. In this current study the levels of trait optimism were also similar to those found in the general population (Glaesmer et al., 2012). To our knowledge these associations have not previously been reported in the ICU population. However, the associations between age and trait anxiety, and optimism and trait anxiety have been explored in other cohorts with findings similar to those found in this current research (Clewett, Bachman, &
This study also confirmed that symptoms of anxiety, depression and post-traumatic stress were an important issue in survivors of critical illness. Of the 141 participants assessed in ICU, 120 completed the follow-up in the hospital wards, 101 the three-month follow-up and 92 the six-month follow-up. Symptoms of anxiety were reported by 42% of the participants while in the hospital wards, 26% at three months and 28% at six months after ICU discharge. Symptoms of depression were reported by 37% of the participants while in the hospital wards, 19% at three months and 23% at six months after ICU discharge. PTSS were reported by 19% of the participants at three months and 17% at six month after ICU discharge. Although the prevalence of anxiety and depression symptoms reduced significantly from the period in hospital to three months after discharge, no further significant change from three to six months was observed with around a quarter of participants reporting these symptoms at six months. These findings are in line with those reported in recently published articles (Davydow Dimitry S., Zatzick Douglas, Hough Catherine L., & Katon Wayne J., 2013; Wunsch et al., 2014). No significant reduction over time was seen in PTSS with 17% of participants reporting PTSS at the six-month follow-up. Some participants in this cohort moved between asymptomatic and symptomatic categories over time. These changes showed that symptoms of emotional distress had a delayed onset in some participants, resolved rapidly in others and appeared at varied stages during recovery. Ongoing health issues may be one potential explanation for the delayed onset of these symptoms.

The association between anxiety during critical illness and symptoms of anxiety, depression and post-traumatic stress was tested using mixed effects regression models.
The results of these analyses showed that only the trait component of anxiety was significantly associated with symptoms of anxiety, depression and post-traumatic stress over six months after the ICU experience. To our knowledge, no previous study has reported these relationships. The state component was not significantly associated with either outcome. However, state and trait anxiety were significantly associated with each other. In addition, the recall of being anxious in ICU was significantly related to anxiety symptoms over six months after discharge in our participants. These findings suggest that state anxiety during critical illness plays a role in the development of adverse emotional outcomes. However, the precise pathway of this role was not elucidated in this study but may influence outcome via an intermediate factor.

Another interesting finding of this research was that symptoms of anxiety, depression and post-traumatic stress were all associated with each other, suggesting significant comorbidity in this sample. While no paper describing this relationship in the ICU population was located, anxiety and depression disorders are often comorbid with each other (Brown, Schulberg, Madonia, Shear, & Houck, 1996; Brown, Campbell, Lehman, Grisham, & Mancill, 2001). Self-reported history of mental health treatment prior to the ICU admission was significantly associated with anxiety symptoms and PTSS over time, but not depression. Premorbid mental health history has previously been associated with PTSS, but no study reporting on the association between premorbid mental health history and symptoms of anxiety after the ICU experience was located (Cuthbertson et al., 2004; Jones et al., 2007). The lack of association between history of mental health treatment and depression is difficult to explain because there is little evidence to compare the results of this current study to others. This is due to the fact that pre-ICU mental health history is a common exclusion criteria in studies in this
area (Jones et al., 2001; Jones et al., 2003; Ringdal et al., 2009). The evidence available reporting a significant relationship might not be comparable to the results of this current study because of differences in the manner in which mental health history was collected (Jackson et al., 2014; Weinert & Meller, 2006). In this current study, participants self-reported on their previous history of having visited a health professional for symptoms of distress or emotional problems at any time prior to the ICU admission and the use of medications (anxiolytics, antidepressants and benzodiazepines) versus proxy-reported premorbid depression and review of medical records (Weinert & Meller, 2006). Overall, the results of this current study are congruent with the findings previously reported in the literature. However, the lack of association between symptoms of depression and mental health history prior to the ICU admission in this current study is not clear.

Self-reported cognitive impairment was another factor significantly associated with symptoms of anxiety and depression over time, but not PTSS. Impaired cognition has previously been associated with symptoms of anxiety and depression as well as in-hospital acute stress symptoms (PTSS that develop less than one month after the experience of a traumatic event) (Davydow D. S., Zatzick D., Hough C. L., & Katon W. J., 2013; Hopkins et al., 2010; Jackson et al., 2003; Jackson et al., 2009). In this current study, self-reported cognitive functioning was not significantly associated with PTSS. Differences in the presence of delirium during hospitalisation might have contributed to the differences in findings since in the current study only 8% of participants presented with delirium versus 51% in Davydow et al. (2013). In addition, the differences in time of PTSS and cognitive functioning assessments between this current study and Davydow et al. (2013) might also explain the differences in findings as well as the instruments used to assess these variables. PTSS was assessed at three and six months
after ICU discharge using the PTSS-10 in this current study versus prior to hospital discharge using the PTSD Checklist-civilian version in Davydow et al. (2013) Impaired cognition was assessed in hospital, at three months and six months in this current study using a self-report tool (MOS COG) versus 12 months after discharge using the modified Telephone Interview for Cognitive Status in Davydow et al. (2013). No study exploring the association between PTSS after three months of ICU discharge was located.

ICU admission due to trauma was associated with depression symptoms, but not symptoms of anxiety and post-traumatic stress. Little evidence exists about these relationships in the literature of ICU survivors. Only one small study (n=45) exploring ICU admission diagnosis as a risk factor for symptoms of anxiety, depression and post-traumatic stress was located. No significant associations between diagnostic groups and any of the outcomes were found (Jones et al., 2001). However, there are studies exploring adverse emotional outcomes in ICU trauma survivors where symptoms of anxiety, depression and post-traumatic stress were significant issues (O'Donnell et al., 2013; Ringdal et al., 2009). In addition, these emotional problems were common and usually comorbid after a traumatic event in other populations (Shalev et al., 1998; Shih, Schell, Hambarsoomian, Belzberg, & Marshall, 2010). The reasons why ICU admission due to a trauma was not associated with symptoms of anxiety and post-traumatic stress in this current study are not clear. It could be that the small number of participants in this category (n=24, compared with surgical n=48 and medical n=69 patients) had influenced the results and the associations were not detected due to a type II error.

Younger age was associated with PTSS, but not anxiety and depression symptoms. These findings are in line with the literature. The association between age
and PTSS has been reported in several studies, and the cumulative evidence suggests that younger age is a significant risk factor for PTSS after the ICU experience (Davydow, Gifford, et al., 2008). The evidence about the association between symptoms of anxiety and age is inconsistent with studies reporting having found no such association, and a systematic review reporting that age was not a consistent predictor of depression (Davydow et al., 2009; Scragg et al., 2001; Weinert & Meller, 2006).

Factors that were tested in this study but did not have a significant association with any adverse emotional outcome were: state anxiety, gender, type of admission (medical, surgical, cardiac surgery), delirium, hours of mechanical ventilation (invasive and non-invasive), APACHE III, length of ICU stay (days), length of hospital stay (days) and pain. Data on drugs administered during ICU treatment included exposure to corticosteroids, opioids, benzodiazepines, anxiolytics, antidepressants, beta-blockers, anesthetic agents and analgesics; length of sedation and analgesia (hours of propofol, midazolam, morphine, fentanyl, ketamine, oxycodone infusion); and total doses of sedatives and analgesics (propofol, midazolam, morphine, fentanyl, ketamine, oxycodone and paracetamol). Marital status, employment status, level of education, current smoking and drinking habits, pre-ICU medication (corticoids, opioids, beta-blockers), trait optimism, traumatic memories of the ICU admission (nightmares; severe pain; and, respiratory distress) and social support were also tested. Some of the variables listed here and not included in the conceptual model (Figure 5.1.1) such as delirium, pain, APACHE III and ICU diagnosis did not come from the literature review process but from discussion with experienced critical care clinicians who saw the addition of these variables added to the model.
Sample size was determined *a priori* with a sample size of 104 participants required at six months follow-up. This number could not be achieved because of the time constraints of the PhD program. In spite of the enrollment process having to stop at 141 participants instead of the 170 previously estimated, this study had a good follow-up rate with a final sample size of 92 participants at six months (difference of 12 participants from the *a priori* estimated sample size=104). This final number (n=92) provided sufficient power for the modeling process of the outcomes of state and trait anxiety. However, this might not have been the case for the outcomes of symptoms of anxiety, depression and post-traumatic stress that were assessed at six-month follow-up after some study participants were lost to follow-up. In addition, sample size calculations were performed in light of using multiple linear regression approach. The data analysis approach was changed on advice from an expert statistician to a more sophisticated approach to analyse the existing data. A mixed effects regression approach was used to build the models for symptoms of anxiety, depression and post-traumatic stress. This improvement provided more robust and stable models.

In the present study the sources of variation and correlation that arise in longitudinal data sets with multiple missing data points were modeled by using mixed model analysis. This statistical technique also deals with missing values in such a way that missing scores have no effect on other scores from the same patient. It also includes all data available, not only those cases with complete information. These are significant advantages when comparing this current study with others that have incorporated follow-up of patients, but have not sufficiently adjusted for dependency of observations over time in their analyses or used techniques that deal with missing values. These fundamental differences in statistical approaches might explain why some of the factors
that were found to be significantly associated with adverse emotional outcomes in other
studies and were not in this current one.

A third reason for the lack of association could be explained by the risk factors
explored in this current study. The literature review process allowed the identification of
numerous risk factors for adverse emotional outcomes in the ICU survivors, and despite
inconsistent findings in the literature, most of them were explored in this research. It
might be the case that some of the variables that had been significant in other studies
were not significant in this one because of type II error. Finally, the differences in the
sample characteristics, the settings, and the instruments used to collect the data or
timeframes to do so amongst different studies could also explain the inconsistency in
findings.

Factors identified in the literature review but not measured in this research were:
hypoglycaemia, neuroendocrine dysregulation, physical function and physical health.
Hypoglycaemia was not measured because of the tight control used in the ICU where
this study was carried out. Since patients’ glycaemia is monitored second-hourly and
treated immediately, hypoglycemia would have been rare in these patients.
Neuroendocrine dysregulation was not measured because the resources needed to assess
this risk factor properly were too extensive for the scope of this PhD program. For the
same reason, physical function and physical health were also risk factors not assessed in
this study. Other factors neither measured in this research nor explored in previous
research, but with proposed theoretically as potentially influencing these relationships
include memories of the illness; any traumatic event that precipitated ICU admission;
environmental factors such as noise; and, over time fear of changes in relationships,
physical appearance and loss of job and function. It is recommended that all these factors be considered in future research.

### 5.3 Recommendations for clinical practice

The identification of risk factors for symptoms of anxiety, depression and post-traumatic stress in survivors of critical illness may inform and facilitate the development of strategies to prevent or reduce these adverse emotional outcomes during recovery. In this study, trait anxiety was identified as a factor independently associated with symptoms of anxiety, depression and post-traumatic stress over six months after the ICU experience. State anxiety during critical illness was a significant problem for patients enrolled in this research and significantly associated with trait anxiety. These findings highlight the need to improve the assessment and management of this emotion in the ICU setting.

Results of this study suggest that the strategies addressing symptoms of anxiety, depression and post-traumatic stress after ICU discharge should be focused on the early assessment and management of state and trait anxiety during and after critical illness. Early assessment could help clinicians to identify patients at higher risk of experiencing high levels of state anxiety during ICU treatment but also those at higher risk of developing adverse emotional outcomes during recovery. State anxiety should be assessed systematically during patients' ICU stay, and clinicians should use this assessment to guide treatment in ICU with the aim that it improves long-term recovery. The assessments of state and trait anxiety should be performed using well-validated tools such as the FAS and the trait component of the STAI. The bedside ICU nurse
could perform daily state anxiety assessments during patients’ ICU stay. In this study, no significant differences between morning and afternoon assessments were observed to justify several assessments per day. Trait anxiety could be assessed prior to ICU admission in elective patients or during ICU stay in patients who are able to answer lengthy instruments such as the STAI. Outreach teams could assess participants who are unable to report on their levels of trait anxiety during ICU treatment. The feasibility of trait anxiety assessment needs to be tested. Early assessment and interventions directed to reduce state and trait anxiety in patients who experience critical illness might decrease the risk of adverse emotional outcomes during recovery.

Interventions to address anxiety during critical illness should be directed to target both the state and trait components. Strategies to manage state anxiety in ICU patients include use of pharmacologic therapy with anxiolytics, sedatives and opioids. Non-pharmacological interventions such as reassurance; encouragement or coaching; music therapy and psychological interventions can be found in the literature (Moser et al., 2003; Peris et al., 2011; Tate et al., 2011). However, these have not been incorporated into clinical practice, probably due to the lack of clinical guidelines including the assessment and management of this symptom in the ICU.

Evidence about interventions targeting the trait component of anxiety in the ICU patient was not found in this research. However, current research in the field of psychology suggests that trait anxiety can be modified using tailored interventions, such as cognitive bias modification therapy, cognitive behavioural therapy, educational programs, cognitive training intervention and combination of psychological interventions and medications, to mention but a few (Clark et al., 2003; Jackson J. J. et al., 2012; Krasner et al., 2009; Tang et al., 2009). Although these interventions have
been proven to be effective in other populations, they need to be tested in the ICU survivor population to determine benefit and ensure no harm. The identification of effective interventions targeting trait anxiety in the ICU population is vital since their implementation might reduce the risk of developing symptoms of anxiety, depression and post-traumatic stress after the ICU experience. Research is needed in this area so that effective interventions could be incorporated in future clinical guidelines and implemented early in the ICU and continue throughout the recovery process.

Results of this study also confirm that impaired cognitive functioning after critical illness is a significant risk factor for adverse emotional outcomes (Wunsch et al., 2014). As such, interventions directed to improving cognitive functioning in the ICU survivor might be beneficial in reducing the risk of developing adverse emotional outcomes. Cognitive rehabilitation programs have been developed and tested recently. However, more evidence is needed in order to incorporate these interventions into clinical practice (Brummel et al., 2012; Jackson J. C. et al., 2012).

Knowledge about non-modifiable risk factors such as younger age, ICU admission due to trauma and evidence mental of health treatment prior to the ICU admission should be used to encourage modification of other risk factors. In addition, patients with increased risk of developing adverse emotional after ICU discharge, such as trauma patients, should be screened at different time points because of their risk status, and also because of the delayed onset of symptoms in some patients observed in this current study and others (Bryant, O'Donnell, Creamer, McFarlane, & Silove, 2013; O'Donnell et al., 2013). For example, trauma patients may be encouraged to complete screening instruments such as the HADS while in hospital and at various time points during recovery. Thus, symptoms of emotional problems could be detected early and
prevented from progressing to the full clinical diagnoses. Clinicians should consider the incorporation of screening as a protective behaviour against adverse emotional outcomes in survivors of critical illness.

5.4 Recommendations for future research

Findings from this study warrant further investigation into the area of emotional recovery in survivors of critical illness. Results of this study confirm that individual differences in personality traits contribute significantly to the development of adverse emotional outcomes (Bartone, 1999; Jaksic, Brajkovic, Ivezic, Topic, & Jakovljevic, 2012; Ouimette, Cronkite, Prins, & Moos, 2004; Thomas, Britt, Odle-Dusseau, & Bliese, 2011). Theoretical frameworks on personality traits could be used in future studies to explore a broader spectrum of personality traits (e.g. openness, conscientiousness, extroversion and agreeableness) as potential risk factors for adverse emotional outcomes. Such investigations might contribute valuable information about trait personalities as predictors of emotional wellbeing in the ICU population. This evidence is important because contemporaneous work suggests that personality traits are potentially modifiable factors (Brosan, Hoppitt, Shelfer, Sillence, & Mackintosh, 2011; Coppola & Montanaro, 2013; Krasner et al., 2009; Magidson, Roberts, Collado-Rodriguez, & Lejuez, 2014; Nabi et al., 2013; Orme-Johnson & Barnes, 2014).

The assessment of self-reported state anxiety in this study was limited to a quantitative measure. Future studies might benefit from assessing state anxiety during critical illness both qualitatively and quantitatively in order to obtain a more comprehensive understanding of this emotion in the ICU patient. In this study, surveys
were used to assess symptoms of adverse emotional outcomes. Clinical interviews to establish the clinical diagnosis anxiety, depression and PTSD may strengthen the design of future research. More research into correctly predicting patients who are going to have psychological problems after critical illness is needed (Wade et al., 2014).

While interventions directed to improve cognition after critical illness have been developed and tested, more evidence is needed in order to validate these interventions and implement them into clinical practice (Brummel et al., 2012; Jackson J. C. et al., 2012). Future research in this area should investigate strategies and interventions to improve cognitive functioning in the ICU survivor.

The traumatic memory of experiencing anxiety during ICU treatment was another factor associated with adverse emotional outcomes in this current study. Post-ICU memories of the ICU experience (e.g. traumatic, delusional, and factual) have been investigated in several studies and there is a significant amount of evidence suggesting that they are associated with adverse emotional outcomes after the ICU experience. Future research should focus on the development and testing of interventions to prevent these memories from being harmful. The use of diaries in the ICU has been suggested as a possible intervention to improve emotional recovery, but the evidence to support the implementation of this strategy is deficient (Aitken et al., 2013; Ullman et al., 2014). More research is needed to determine the effectiveness of this, and other psychological interventions on the emotional recovery of the ICU survivors.
5.5 Recommendation for education

Results from this study suggest that the assessment and management of anxiety during critical illness might be beneficial in reducing the risk of adverse emotional outcomes during recovery. It is therefore recommended that clinicians and educators collaborate in developing, testing and implementing protocols for the assessment and management of this emotion in the ICU patients.

Educational programs on anxiety in the critically ill should include knowledge of the importance of the systematic assessment of anxiety in the ICU patient; how to assess anxiety in the critically ill and interventions to manage this symptom. These educational programs should be available to all clinicians in the ICU settings, especially to the nursing and medical staff. It is also recommendable that these educational programs be incorporated into undergraduate and post-graduate speciality curricula.

5.6 Concluding statement

Findings of this research highlight the importance of adverse emotional outcomes in survivors of critical illness as well as the need for the development and implementation of strategies to reduce these symptoms. Because of the long-term effects of critical illness and the delayed onset of symptoms in some patients, not only should these interventions take place during intensive care treatment but also at different time points after ICU discharge. Early assessment and interventions directed to reduce state and trait anxiety in the ICU patient and survivor might decrease the risk of adverse emotional outcomes after critical illness. The findings of this study may help nurse researchers and clinicians to plan and design interventions to reduce anxiety in the
critically ill patient and the subsequent development of adverse emotional outcomes. This research adds to the current literature identifying symptoms of anxiety, depression and post-traumatic stress as significant problems for survivors of critical illness, and that early detection of these symptoms might be beneficial for long-term recovery.
Appendix 1: Literature search

Search strategy

In order to identify relevant literature to the topics, the following databases were searched: Cumulative Index of Nursing and Allied Health Literature (CINHAL), Medical Literature Analysis and Retrieval System Online (MEDLINE), Psychological Information Database (PhycINFO), Cochrane Library, Google Scholar and ProQuest. The keywords used were: anxiety, depression, post-traumatic stress, state anxiety, critically ill patients, seriously ill patients, intensive care unit, intensive care, survivors of intensive care, stress, fear, and adverse emotional outcomes. In addition, ancestry searching and journal hand searching were also used. Inclusion criteria included papers that were published in peer-reviewed journal (research articles and systematics reviews) and government reports addressing the aims of this review. The search was limited to literature in English and Spanish, published between January 2000 to April 2014, and including only adult patients (>16 years). A detailed search strategy and a Prisma flow diagram are presented below:

After selecting the relevant pieces of work to be included in this literature review, they were classified into categories as per topic. This categorization yield three major topics to be developed:

1. Adverse emotional outcomes after the ICU experience: symptoms of anxiety, depression and post-traumatic stress
2. Potential risk factors associated with adverse emotional outcomes in survivors of critical illness
3. Anxiety in ICU: stressors in ICU, pharmacologic and non-pharmacologic interventions to treat anxiety during critical illness and assessment of anxiety during critical illness.
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AB: abstract; TI: title; Nos: numbers; KW: key word

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TI: title; AB: abstract; KW: key word

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TI: title; AB: abstract; KW: key word
Appendix 2: Literature review

Table 1. Adverse emotional outcomes in ICU survivors and risk factors

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<th>Outcome measure</th>
<th>Findings</th>
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<td>Bienvenu et al (2012)</td>
<td>To evaluate the 2-year incidence and duration of depressive symptoms and physical impairment after ALI, as well as risk factors for these conditions.</td>
<td>Prospective, longitudinal cohort study</td>
<td>n=186 ALI survivors E: pre-existing illness with a life expectancy less than 6 month, primary neurologic disease, cognitive impairment or communication barriers, no fixed address, more than 5 days of mechanical ventilation before ALI, and a physician order for no escalation of ICU care.</td>
<td>HADS Impaired physical function.</td>
<td>The point prevalence of depressive symptoms at the four follow-up time points ranged from 24 to 32%. Education 12 or fewer years was significantly associated with incident depressive symptoms (OR 1/4 3.1; 95% CI: 1.5, 6.6).</td>
<td>Use of self-report measure to assess depression symptoms. Baseline depression determined by use of medical chart.</td>
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<td>Kiekkas et al (2010)</td>
<td>To investigate and synthesise published literature about psychological distress associated with delusional memories of adult ICU survivors.</td>
<td>Literature review</td>
<td>Using key terms, a search was conducted in CINAHL, PubMed, Web of Science and PsycInfo focusing on articles published between 1990 and 2009 in English-language journals.</td>
<td>Ten articles met the inclusion criteria.</td>
<td>Recall of delusional memories at various intervals after ICU discharge was associated with post-traumatic stress disorder (PTSD)-related symptoms in many studies, while associations with other aspects of psychological distress, mainly feelings of fear, anxiety and depression, were also reported. Recent studies did not seem to confirm the protective role of factual memories.</td>
<td>Search terms used may have missed relevant articles. Relatively small number of original studies included and methodological weaknesses identified in some of them.</td>
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| Myhren et al.    | One ICU in Oslo, Norway | To study the level and predictors of PTSD, anxiety and depression symptoms in medical, surgical and trauma patients during the first year post ICU discharge. | Prospective cohort study | n=194  
I: 18–75 years old, ICU ≥24 hrs.  
E: serious psychiatric problems, severe head injury or cognitive failure. | LOT-R, IES, HADS, ICU memory tool  
Memory of pain, distress from lack of control, and inability to express needs (five-point Likert-scale from 0 to 4). | Independent predictors of PTSS at one year were high educational level (OR 0.4, 95%CI: 0.2, 1.0), personality trait (optimism) OR 0.9, 95%CI: 0.8, 1.0), factual recall (OR 6.6, 95%CI: 1.4, 31.0) and memory of pain (OR 1.5, 95%CI 1.1, 2.0). Optimism was a strong predictor for less anxiety (OR 0.8, 0.8, 0.9) and depression symptoms (OR 0.8, 0.8, 0.9) after one year. | No assessment of prior psychological history, medication during ICU stay, delirium during hospital stay or cognitive failure post-ICU discharge was performed. |
| Hopkins et al.  | One ICU in USA | To evaluate risk factors for depression and anxiety at 1 and 2 years after hospital discharge in ARDS survivors. | Prospective study | n=66 ARDS survivors at first year and 62 at the second year.  
I: >16 years. | Beck Depression Inventory  
Beck Anxiety Inventory  
Standardized Neurocognitive tests  
SF-36. | Predictors of depression at one year were alcohol dependence, female gender and younger age. Predictors of anxiety at one year were PaO2/FiO2 ratio and duration of mechanical ventilation. Predictors of depression at two years were depression at one year and cognitive sequelae. Predictor of anxiety at two years was anxiety at one year. | Small number of ARDS patients. Lack of premorbid psychiatric data. The use of self-report measures to assess depression and anxiety. |
| Rattray et al.   | Six ICUs in UK | To assess patients’ perceptions of their ICU experience and the effect of these on anxiety, depression and post-traumatic stress up to 6 months after discharge. | Prospective longitudinal study | n=103 MV  
I: ICU≥24 h, MV, ≥18 years.  
E: head injury, neurosurgery, or unable to give informed consent. | ICEQ  
HADS  
IES | Perceptions of the intensive care experience were significantly associated with anxiety, depression, avoidance and intrusion scores at hospital discharge. | Loss to follow up may have resulted in this study being underpowered. Attrition bias may have occurred. Heterogeneous and relatively small sample. Previous psychiatric history no assessed. |
<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Details</th>
<th>Sample Details</th>
<th>Measures and Findings</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myhren et al (2009)</td>
<td>To compare patients’ psychological distress and memories from ICU treatment 4–6 weeks after ICU discharge with expectations of their relatives. To explore the relationship between personality traits and ICU memories with psychological distress.</td>
<td>n=255 ICU patients. I: 18–75 years old, ICU ≥24 hrs, E: serious psychiatric problems, severe head injury or cognitive failure. n=298 relatives.</td>
<td>LOT-R, IES, HADS, ICU memory tool Memory of pain, distress from lack of control, and inability to express needs (five-point Likert-scale from 0 to 4). Personality trait of pessimism was a strong independent predictor of anxiety, depression and PTSD symptoms. Low level of education correlated significantly with anxiety and depression scores. Positive correlation between higher educational levels and personality trait of optimism (r=0.20, p=0.002). Higher age, unemployment, respiratory treatment, pessimism, memory of pain, lack of control and inability to express needs were independent predictors of PTSS.</td>
<td>No assessment of prior psychological history, medication during ICU stay, delirium during hospital stay or cognitive failure post-ICU discharge was performed.</td>
</tr>
<tr>
<td>Ringdal et al (2009)</td>
<td>To examine the relationship between delusional memories from the ICU, HRQoL, anxiety, and depression in patients with physical trauma, 6 months to 18 months after their ICU stay.</td>
<td>n=239 Trauma admission. I: &gt;18 years old, E: attempted suicide, intellectual impairment. Completing follow up 70%.</td>
<td>SF-36 (Swedish version) HADS ICUM Tool Higher probability of anxiety (51% vs. 29% p=0.0028) and depression (48% vs. 26% p=0.0022) in patients with delusional memories. Head injury correlated significantly with anxiety (p=0.017). Significant less depression in patients who discussed their ICU experiences with someone else. Delusional memories were significantly associated with younger age, longer ICU stay, MV, total dose of propofol, severity of illness and decreased HRQoL.</td>
<td>No power analysis included. Data collected on one single occasion. Too much time between discharge from ICU and memory assessment.</td>
</tr>
<tr>
<td>Dowdy et al (2009)</td>
<td>To evaluate ICU-related factors as predictors of depressive symptoms.</td>
<td>n= 160 ALI survivors. E: cognitive impairment.</td>
<td>12 features of critical illness and ICU care Depressive symptoms were significantly associated with surgical (vs. medical/trauma) ICU admission (RR: 2.2, 95%)</td>
<td>Loss to follow up may have resulted in this study not being representative of all</td>
</tr>
<tr>
<td>USA Thirteen ICUs in four hospitals</td>
<td>symptoms 6 months after acute lung injury (ALI).</td>
<td>Mood symptoms before hospital admission (retrospective patient interview): depression/anxiety dimension of the EQ-5D quality of life instrument. HADS (score &gt;8).</td>
<td>CI: 1.1–4.2), maximum daily Sequential Organ Failure Assessment Score of &gt;10 (RR: 2.1, 95% CI: 1.1–3.5), and mean daily ICU benzodiazepine dose of &gt;75 mg of midazolam equivalent (RR: 2.1, 95% CI: 1.1–3.5). Significantly higher mean HADS scores in patients with education &lt;12 years (1.7 points; 95% CI 0.3–3.0). Preadmission depression and anxiety were significantly associated with a positive screening test (RR: 2.0; 95% CI: 1.1–3.6).</td>
<td>ALI survivors.</td>
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<tr>
<td>Dowdy et al (2008) USA Twelve ICUs in four hospitals</td>
<td>To evaluate the association between ICU blood glucose levels and depression after acute lung injury.</td>
<td>Prospective cohort study Completing follow up: 77%.</td>
<td>Patients with a mean daily minimum glucose level &lt;100 mg/dL had significant increases in mean depression score (2.1 points, 95% CI: 0.6–3.7) and in the likelihood of a positive depression screening test (RR: 2.6, 95%CI: 1.2–4.2). Greater symptoms of depression in patients with hypoglycemia &lt;60 mg/dL (2.0 points, 95%CI: 0.5–3.5; RR: 3.6, 95%CI: 1.8–5.1). Other factors independently associated with depression included body mass index &gt;40 kg/m², baseline depression and anxiety, and mean daily ICU benzodiazepine dose &gt;100 mg of midazolam-equivalent agent.</td>
<td>All relevant events of hypoglycemia might not have been captured.</td>
</tr>
<tr>
<td>Granja et al</td>
<td>To assess the factual and Multicenter observational</td>
<td>n=313</td>
<td>ICUM tool PTSS-14</td>
<td>The number of adverse experiences was significantly Neurologic or psychiatric disorders</td>
</tr>
<tr>
<td>(2008)</td>
<td>Nine ICUs in Portugal</td>
<td>delusional memories reported by ICU survivors and its relationship with PTSS at 6 months post-ICU discharge.</td>
<td>cohort study</td>
<td>I: All adult patients (&gt;18 yrs.), admitted to any of the nine ICUs with a stay of &gt;48 hrs. Completing follow up 52%</td>
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<tr>
<td>Sukantarat et al (2007)</td>
<td>One ICU in UK</td>
<td>To measure levels of anxiety, depression and PTSD among survivors of a critical illness and to relate these symptoms to general health parameters.</td>
<td>Prospective study</td>
<td>Follow-ups at 3 and 9 months after discharge.</td>
</tr>
<tr>
<td>Girard et al (2007)</td>
<td>Two ICUs in USA</td>
<td>To identify factors associated with PTSS in patients following critical illness requiring MV.</td>
<td>Prospective study</td>
<td>Follow-up at 6 month after hospital discharge</td>
</tr>
<tr>
<td>Jones et al (2007)</td>
<td>To explore the relationships between PTSD, memories of the ICU and sedation practices.</td>
<td>Prospective multicentre Follow-up study 3 months after ICU discharge.</td>
<td>n= 238 MV I: ≥18 years, MV, ICU ≥48 h E: suicide attempt, pre-existing or concomitant psychotic illness, anxiety or depression were not excluded, (but recorded).</td>
<td>ICUM Tool PTSS-14 Delusional memories, prolonged sedation and opiates, and physical restraint without sedation were associated with PTSS. Structural equation modeling: (1) from a history of psychological problems to prolonged sedation and opiates, to recall of delusional memories for ICU to PTSD; (2) from prolonged sedation and opiates to PTSD; (3) from physical restraint with little or no sedation to PTSD. This model showed a good fit to the data [chi-square=7.88, p=0.72, RMSEA=0.0001 (90%CI: 0.0001, 0.05); comparative fit=1.00, GFI 0.90, AGFI=0.75]. Patients with history of psychological problems were more likely to receive prolonged sedation (Mann–Whitney U, p=0.0001).</td>
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<td>Samuelson et al (2007)</td>
<td>Two ICUs in Sweden To investigate psychological distress in relation to memory and stressful experiences in the ICU and to identify early predictors for high levels of acute PTSS.</td>
<td>Prospective cohort study Patients were interviewed 5 days and 2 months post-ICU.</td>
<td>n= 226 MV I: intubated mechanically ventilated adults admitted &gt; 24 hrs.</td>
<td>ICU Memory Tool, ICU Stressful Experience Questionnaire HADS IES-R Symptoms of anxiety, depression and PTSD two months post-ICU were significantly associated with the recall of extremely stressful ICU experiences and with high levels of anxiety and depression 5 days post-ICU, but not with amnesia or delusional memories without factual recall of the ICU. Patients scoring &gt;30 in the IES- The ICU Stressful Experience Questionnaire and IES-R need to be validated further in critically ill patients. Attrition bias may have existed since the trend for patients lost to follow-up to be older and.</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Sample</td>
<td>Measures</td>
<td>Findings</td>
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<tr>
<td>Deja et al (2006)</td>
<td>One ICU in Germany</td>
<td>To evaluate HRQoL as a long-term outcome in ARDS survivors, and the relationship between PTSS and HRQoL. It was investigated whether perceived social support during the ICU stay and the rehabilitation process might reduce PTSS and improve HRQoL.</td>
<td>Prospective controlled study</td>
<td>n=65 ARDS survivors I: discharged from the ICU for more than one year. E: history of mental disease such as alcohol or drug abuse.</td>
</tr>
<tr>
<td>Weinert &amp; Meller (2006)</td>
<td>Two ICUs in USA</td>
<td>To describe short- and-medium- term psychiatric outcomes in MV patients and to define predictors of post-ICU depression and antidepressant medication use.</td>
<td>Prospective study</td>
<td>n=277 MV I:≥18yrs, MV&gt;38h E: coma for &gt;24h mental retardation or chronic cognitive dysfunction.</td>
</tr>
<tr>
<td>Rattray et al</td>
<td>To assess changes in anxiety.</td>
<td>Prospective, longitudinal</td>
<td>n=80</td>
<td>ICEQ HADS</td>
</tr>
</tbody>
</table>

R were significantly younger. Female sex, signs of agitation (Motor Activity Assessment Scale scores of 4–6) and feelings of extreme fear were significantly and independently associated with IES-R scores of 30 or more.

Note: ICEQ = Impact of Event Scale; HADS = Hospital Anxiety and Depression Scale; SF-36 = Medical Outcomes Study Short-Form 36-Item Health Survey Questionnaire; PTSS = Post-Traumatic Stress Symptoms; ARDS = Acute Respiratory Distress Syndrome; HRQoL = Health-Related Quality of Life; PTSS = Post-Traumatic Stress Disorder; CES-D = Center for Epidemiologic Studies Depression Scale; SF-36 = 36-Item Short-Form Health Survey; SCID = Structured Clinical Interview for DSM-IV Axis I Disorders; ADL = Activities of Daily Living; SCID Mood and alcohol and other substance-use modules.
<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Setting</th>
<th>Objective</th>
<th>Method</th>
<th>Results</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2005) One ICU in Scotland</td>
<td>Depression and PTSS over three occasions (zero, 6 and 12 months) after hospital discharge; and to examine the contribution of objective and subjective indicators of the ICU experience to emotional outcome.</td>
<td>I: ≥18 years, emergency admission, ICU &gt;24 hours.</td>
<td>IES: Three structured interviews. Follow up: before hospital discharge, 6 and 12 months.</td>
<td>and avoidance and intrusion scores at all three interviews. Female gender was associated with anxiety at 6 months and depression at hospital discharge. Longer ICU stay was associated with intrusion at 12 months and longer hospital stay with lower intrusion scores at time of hospital discharge. Anxiety and depression scores significantly reduced between hospital discharge and 6 months, but no further reduction between 6 and 12 months.</td>
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<tr>
<td>Kapfhammer et al (2004) One ICU in Germany</td>
<td>To establish the presence of PTSD and search for an association regarding PTSD diagnostic status</td>
<td>n=46 (ARDS)</td>
<td>PTSS-10 SF-36: The Montgomery-Asberg Depression Rating Scale STAI</td>
<td>Length of ICU stay correlated significantly with the risk for PTSD (Kruskal-Wallis H=7.37, df=2, p&lt;0.04). Retrospective study, follow up rate of 58%. Recall bias may have lowered the reporting of any psychiatric symptom.</td>
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<tr>
<td>Study</td>
<td>Setting</td>
<td>Objective</td>
<td>Study Design</td>
<td>Participants</td>
<td>Measures</td>
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<tr>
<td>Cuthbertson et al (2004)</td>
<td>One ICU in Scotland</td>
<td>To determine the incidence and severity of symptoms related to the diagnosis PTSD in a cohort of general ICU patients.</td>
<td>Prospective cohort study.</td>
<td>n=78 general ICU survivors</td>
<td>DTS</td>
</tr>
<tr>
<td>Jackson et al (2003)</td>
<td>Two ICUs in USA</td>
<td>To explore neuropsychological function, depression, and HRQoL, six months post discharge in patients who received MV in the ICU.</td>
<td>Prospective cohort study</td>
<td>n=34 MV E: mental retardation, cognitive impairment or major psychiatric illness.</td>
<td>Set of standardised neuropsychological well-validated instruments. Depression Scale–Short Form SF-12.</td>
</tr>
<tr>
<td>Jones et al (2003)</td>
<td>Three hospitals (follow up clinics) in UK</td>
<td>To evaluate the effectiveness of a rehabilitation program following critical illness to aid physical and psychological recovery.</td>
<td>The study was a block randomized controlled trial (blind at follow-up) Intervention: routine follow-up plus</td>
<td>n= 126 MV E: ICU&lt;48 hrs. Pre-existing psychotic illness.</td>
<td>STAI HADS IES ICUM Tool SF-36 The revised Norbeck Social Support Questionnaire</td>
</tr>
</tbody>
</table>

with other psychopathologicall y relevant and psychosocial dimensions.
<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Study Setting</th>
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<th>Study Design</th>
<th>Participants</th>
<th>Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kress et al (2003)</td>
<td>One ICI in USA</td>
<td>To search for evidence that daily sedation interruption (DSI) was associated with long-term psychological harm. To look for indicators that DSI leads to improved long-term outcomes, such as decreased PTSD.</td>
<td>RCT</td>
<td>n=32 MV</td>
<td>IES, PTSD, SF-36, STAI, Beck Depression Inventory-2, Psychosocial Adjustment to illness score</td>
<td>Patients on DSI had significantly lower scores on the IES than the control group (11.2 ± 14.9 vs. 27.3 ± 19.2, p=0.02). Six patients of 19 in the control group were diagnosed with PTSD vs. none in the intervention group (n=13) (p=0.06). The duration of MV and ICU stay were shorter in the intervention group (but did not reach statistical significance).</td>
</tr>
<tr>
<td>Schelling et al (2001)</td>
<td>One ICU in Germany</td>
<td>This investigation examines whether increasing serum cortisol levels with hydrocortisone treatment during septic shock reduces the incidence of PTSD in survivors.</td>
<td>Retrospective study</td>
<td>n=20</td>
<td>PTSS-10, SF-36, Traumatic experiences during ICU: structured questionnaire, DSM-IV criteria for diagnosis of PTSD psychiatric assessment (median 31 months).</td>
<td>Significantly lower incidence of PTSD in the hydrocortisone group (p=0.02). Less hours of norepinephrine in the hydrocortisone group 52 hours vs. 120 hours in the control group (median values, p=0.07). All patients with more than three categories of traumatic memory had PTSD (None of them received hydrocortisone). Patients with PTSD (n=5) had significantly lower average serum cortisol levels than patients without PTSD (n=7) (15.7 vs. 55.4 µg/dL, p=0.02). Pain, anxiety/panic and respiratory distress were associated with significantly higher cortisol values measured.</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Setting</td>
<td>Sample Size</td>
<td>Measures</td>
<td>Findings</td>
<td>Limitations</td>
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<tr>
<td>Jones et al. (2001)</td>
<td>Case series cohort</td>
<td>One ICU in UK</td>
<td>n=45 MV</td>
<td>ICU Memory Tool, HADS $\geq$11, STAI, IES, Fear Index</td>
<td>Delusional memories without recall of factual events in the ICU was a predictor for PTSS at the second week post ICU discharge. Trait anxiety was also a predictor for PTSS at the eighth week. Patients with psychiatric history were more likely to suffer from paranoid delusions ($p=0.032$), hallucinations ($p=0.017$), and nightmares ($p=0.017$).</td>
<td>Small sample size.</td>
</tr>
<tr>
<td>Scragg et al. (2001)</td>
<td>Retrospective study</td>
<td>One ICU in UK</td>
<td>n=80 All ICU survivors within a 2 years period. Completing follow up 56%</td>
<td>Trauma Symptom Checklist-33, HADS, IES, ETIC-7</td>
<td>Significant correlation between the ETIC-7 score and time since discharge ($r=0.053$, $p=0.04$) and a significant negative correlation between the ETIC-7 score and age ($r=0.048$, $p=0.05$). In the regression analysis, higher ETIC-7 score was associated with lower age and longer time since discharge. There was no effect of gender or duration of stay on the ETIC-7 score. Age, gender, duration of stay and time since discharge were not significant independent predictor variables for the HADS total score, IES total score or Trauma Symptoms Checklist-33 total score.</td>
<td>Sample may not be representative of the post ICU population. ETIC-7 is a new questionnaire so further validation is needed.</td>
</tr>
<tr>
<td>Nelson et al. (2000)</td>
<td>Cross-sectional mail survey and retrospective</td>
<td>To examine the relationship between the use of sedative and</td>
<td>n=24 ALI patients</td>
<td>CES-D, Seven items related to PTSS</td>
<td>Depressive and PTSS correlated with days of sedation, length of ICU stay and length of MV. PTSD impact score was</td>
<td>Small sample. Specific for ALI patients, no representative of...</td>
</tr>
</tbody>
</table>
ICUs in three teaching hospitals in USA
neuromuscular blocking agents during the ICU stay and subsequent measures of HRQoL.
medical record abstraction
Follow up ranged from 6 to 41 months.
correlated with neuromuscular blockade, but not with initial severity of illness. Depression did not correlate with days of neuromuscular blockade or initial severity of illness.

One ICU in UK
To assess survival, morbidity, HRQoL, and employment status of ICU survivors up to 12 months after ICU discharge.
Prospective study
n=143 general ICU survivors
Completing follow up 63%.
Survival status SF-36, HADS Employment status Clinic interviews at follow up clinic at 3 and 12 months after discharge.
Mortality at 1 year: 43%
Women were more likely to have higher anxiety scores (not statistically significant) 34% women and 21% male patients reported experiencing distressing flashbacks of their ICU experience within the 3 months after discharge.

Schelling et al (1999)
One ICU in Germany
To compare the incidence and intensity of PTSD and HRQoL between patients who received hydrocortisone in addition to conventional treatment of septic shock and those who received conventional treatment only.
Retrospective case-controlled analysis Matched-case study
Control group: 27 patients (standard therapy for septic shock)
Intervention group: 27 patients (standard therapy plus stress doses of hydrocortisone (100 mg bolus, followed by 0.18 mg/kg/hr.).
PTSS-10 SF-36 Traumatic experiences during ICU: structured questionnaire.
Significantly lower incidence of PTSD in the intervention group. Significantly longer ICU treatment in patients with PTSD. Patients who had at least one traumatic experience had significantly higher PTSS-10 scores than those who remembered no traumatic events. From the patients who had traumatic memories, those who received hydrocortisone had significantly lower PTSS-10 scores and a significantly lower incidence of PTSD.

One ICU in Germany
To assess HRQoL in long-term survivors of ARDS and to test the hypotheses that potentially
Retrospective cohort, case-controlled analysis.
n=80 ARDS survivors.
I: >16 years old.
E: pre-existing neurologic or adverse experiences during ICU: structured questionnaire.
Employment status SF-36 PTSS-10 (German version) Adverse Experiences During
Three of 34 patients reporting none, or one, adverse experience had evidence of PTSD vs. 19 of 46 patients remembering multiple traumatic episodes (p=0.007).

Lack of an appropriate instrument to measure PTSD.
| traumatising episodes of respiratory distress, anxiety, or pain during ICU treatment of ARDS can result in PTDS and have adverse effects on HRQoL in long-term survivors. | Follow up 48 months. | psychiatric disease. | Intensive care questionnaire. |

ADL: Activities of Daily Living; AGFI: Adjusted Goodness of Fit Index; ALI: Acute Lung Injury; APACHE II: Acute Physiology and Chronic Health Evaluation II; ARDS: Acute Respiratory Distress Syndrome; CES-D: Centre for Epidemiologic Studies Depression Scale; CES-D: Centre for Epidemiologic Studies Depression Scale; CI: Confidence Interval; CINHAL: Cumulative Index of Nursing and Allied Health Literature; dL: deciliter; DSI: Daily Sedation Interruption; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders 4th Edition; DTS: Davidson Trauma Scale; E: Exclusion criteria; EQ-5D: European Quality of Life-5 Dimensions; ETIC-7: Experience after Treatment in Intensive Care 7-Item Scale; GFI: Goodness of Fit Index; HADS: Hospital Anxiety and Depression Scale; hr: hour; HRQoL: Health-related Quality of Life; I: Inclusion criteria; ICEQ: Intensive Care Experience Questionnaire; ICUM Tool: Intensive Care Unit Memory Tool; IES-R: Impact of Event Scale-Revised; IES: Impact of Event Scale; kg: kilogram; LOT-R: Life Orientation Test-Revised; m²: square meter; mg: milligrams; MV: Mechanical Ventilation; n: number; OR: Odd Ratio; p: p-value; PaO2/FiO2: Ratio of Arterial Oxygen Tension to Inspired Oxygen Fraction; PsycINFO: Psychological Information Database; PTSD: Post-Traumatic Stress Disorder; PTSS-14: Post-Traumatic Stress Syndrome 14-Questions Inventory; PTSS: Post-Traumatic Stress Symptoms; PubMed: Public/Publisher MEDLINE; r: Pearson’s correlation; RCT: Randomised Controlled Trial; RMSEA: Root Mean Square Error of Approximation; RR: Relative risk; SCID: Structured Clinical Interview for DSM-IV; SF-12: Short Form 12-question Health Survey; SF-12: Short Form 12-question Health Survey; SF-36: Short Form 36-question Health Survey; STAI: State-Trait Anxiety Inventory; TISS: Therapeutic Intervention Scoring System; UK: United Kingdom; USA: United States of America; vs.: versus; χ²: Chi-square.
<table>
<thead>
<tr>
<th>Author/year</th>
<th>Aims</th>
<th>Design</th>
<th>I/E criteria</th>
<th>Outcome measure</th>
<th>Findings</th>
<th>Strengths/Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlan 2013</td>
<td>To test whether listening to self-initiated patient-directed music can reduce anxiety and sedative exposure during ventilatory support in critically ill patients.</td>
<td>RCT</td>
<td>Self-initiated patient directed music (n=126) with preferred selections tailored by a music therapist whenever desired while receiving ventilatory support, self-initiated use of noise-canceling headphones (n=122), or usual care (n=125).</td>
<td>n=373</td>
<td>Daily assessments of anxiety (on 100-mm visual analog scale) and 2 aggregate measures of sedative exposure (intensity and frequency).</td>
<td>At any time point, patients in the patient directed music group had an anxiety score that was 19.5 points lower (95% CI, −32.2 to −6.8) than patients in the usual care group (p=0.003). By the fifth study day, anxiety was reduced by 36.5% in patient directed music group. The patient directed music group had reduced sedation intensity by −0.18 (95% CI, −0.36 to −0.004) points/day (p=0.05) and had reduced frequency by −0.21 (95% CI, −0.37 to −0.05) points/day (p=0.01). The patient directed music group had reduced sedation frequency by −0.18 (95% CI, −0.36 to −0.004) points/day vs the noise-canceling headphones group (p=0.04). By the fifth study day, the patient directed music group patients received 2 fewer sedative doses (reduction of 38%) and had a reduction of 36% in sedation intensity.</td>
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<tr>
<td>Study</td>
<td>Setting</td>
<td>Objective</td>
<td>Study Design</td>
<td>Sample Size</td>
<td>Inclusion Criteria</td>
<td>Outcome Measures</td>
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<tr>
<td>Puntillo et al. (2010)</td>
<td>Two ICUs in USA</td>
<td>To provide a focused, detailed assessment of the symptom experiences of intensive care unit patients at high risk of dying and to evaluate the relationship between delirium and patients’ symptom reports.</td>
<td>Prospective, observational study of patient’s symptoms reports</td>
<td>n=171</td>
<td>two intensive care units in a tertiary medical center in the western United States. Inclusion criteria: patients ≥18 yrs. a first 24-hr APACHE II score (8) of ≥20; in the ICU for ≥3 days; and having one or more of the following diagnoses: acute cardiac and/or respiratory failure, chronic liver failure with cirrhosis, multiple organ system dysfunction and sepsis, or any system failure associated with a diagnosis of a malignancy.</td>
<td>Presence, intensity and distress of the following symptoms: pain, tired, short of breath, restless, anxious, sad, hungry, scared, thirsty, confused. Delirium: CAM-ICU</td>
</tr>
<tr>
<td>Han et al (2010)</td>
<td>One ICU in China</td>
<td>To examine the effects of music intervention on the physiological stress response and the anxiety level among mechanically ventilated patients in intensive care unit.</td>
<td>A randomised placebo-controlled trial</td>
<td>A total of 137 I: had to understand Mandarin, be alert, mentally competent and able to communicate by holding up fingers responsive to researchers’ questions; receiving mechanical ventilation were randomly assigned to either music listening group, State-Trait Anxiety Scale and physiological parameters (heart rate, respiratory rate, saturation of oxygen and blood pressure).</td>
<td>A significant reduction in physiological stress response (heart rate and respiratory rate) over time was found in music listening group (p&lt;0·001 for both variables) and a significant increase in heart rate and respiratory rate over time in control group, with no significant change over time in headphone group. Within group pretest-post.</td>
<td>Researchers selected the music instead of the patients. The study only measured the immediate post intervention effect. The presence or absence of any long-term effects was not assessed.</td>
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</tbody>
</table>
### Study Details

**Chlan et al (2010)**

**12 ICUs USA**

To describe anxiety ratings for a subgroup of mechanically ventilated patients over the duration of enrollment in a multisite clinical trial, to discern any pattern of change in anxiety ratings, to determine if anxiety decreases over time, and to explore the influence of sedative exposure on anxiety ratings.

**Secondary analysis of a subgroup of participants enrolled in a multisite RCT**

n=57 mechanically ventilated who were randomly assigned to the usual care group of a randomized controlled trial designed to assess the efficacy of music interventions on anxiety of mechanically ventilated patients in intensive care units.

**Visual Analog Scale-Anxiety.** Anxiety levels were assessed daily for up to 30 days

Participants reported moderate anxiety at study entry (median VAS-A=57.5) with a wide range in anxiety from 0 (not anxious at all) to 96 (near the maximum score of 100). Participants reported varying levels of anxiety over the course of study enrollment. There is no discernible single pattern to the anxiety ratings for those participants who provided at least three anxiety ratings. Reported anxiety ratings decreased for some participants over time; others reported anxiety ratings that fluctuated or increased. The overall pattern of anxiety ratings for this group of participants over the duration of study enrollment suggested a possible slight decline over time with a highly variable pattern of effects was not examined as they focused on a single 30-minute music listening session on MV patients.

**Posttest comparison of the Chinese version of Spielberger State-Trait Anxiety Scale demonstrated a significant reduction in anxiety for the music listening group (p<0.001) and headphone group (p<0.001) but not the control group.**

**Study limitations include the number of missing data points on the VAS-A when participants were too fatigued to complete the assessments, were sedated, or were too ill to provide daily anxiety assessments.**

This study did not attempt to discern the sources of anxiety; anxiety ratings reported here provided only one assessment time point per day. Participants were enrolled at various times during their ICU stay and course.
Participants demonstrated a general pattern of moderate anxiety over the course of study enrollment. Sedative exposure did not significantly influence the participants’ daily anxiety ratings. Neither dose frequency nor sedation intensity explained a statistically significant amount of variance within person or over time on anxiety ratings.

Thus, it is not known how anxious a participant might have been on the first day of receiving mechanical ventilatory support in comparison with their first study enrolled day.

| Perpinan-Galvan et al (2009) | To review studies of anxiety in critically ill patients admitted to an intensive care unit to describe the level of anxiety and synthesize the psychometric properties of the instruments used to measure anxiety | Literature review | Any original or review article in which anxiety in ICU patients was examined by using self-reports was included. | 18 articles, 7 were studies on the validation of instruments, and 11 were studies that used relatively reliable tools | Anxiety levels were moderate for patients admitted to an ICU in most of the studies. Mid-length instruments such as the BAI or the shortened version of the STAI appear to be valid and reliable in ICU patients. | Search terms used may have missed some relevant articles. Relatively small number of original studies included and the methodological weaknesses identified in some of them. |

| McKinley et al (2004) | To assess the validity of the Faces Anxiety Scale in ICU patients, assess the frequency and severity in ICU patients, and explore correlates of anxiety in ICU patients. | Criterion validity of the Faces Scale was assessed in relation to the clinical judgement of patient’s anxiety by a trained research | n=106 Inclusion criteria: any patient in an ICU who could interact even intermittently in order to respond questions, open their eyes in response to hearing their name or spontaneously or were awake. | Criterion validity of the Faces Anxiety Scale (FAS) | The correlation between patients’ self-reports of anxiety on the Anxiety faces Scale and the research assistant’s assessments was 0.64 (p<0.001) Anxiety scores were moderately high. 85% of the patients reported some anxiety (mean level 2.9; DS 1.2). Anxiety levels were lower in patients who had recently received sedatives or opioids but were not included patients from three different settings and pathologies who were and were not receiving respiratory support. | Include patients from three different settings and pathologies who were and were not receiving respiratory support. |
Chlan (2004)  
Nine ICUs in USA  
To discuss the relationship between the Visual Analog Scale-Anxiety (VAS-A) and the Spielberger State Anxiety Inventory (SAI) in patients receiving mechanical ventilatory support. A secondary aim is to provide suggestions for the nurse-researcher to consider when selecting an instrument to measure anxiety.  
**Correlational design**  
- n=200 MV were asked to rate their level of anxiety on the 20-item SAI and a 100-mm VAS-A.  
- 20-item SAI  
- 100-mm VAS-A.  
- Eight participants were unable to complete the Spielberger SAI; 100% completed the VAS-A. The two instruments were found to be significantly correlated at r=0.50; p=0.01.  
- Because of the varying times of anxiety assessment, this could have introduced random measurement error. More than one RA responsible for participant recruitment and instrument administration, and possible measurement error.

Chlan (2003)  
Nine ICUs in USA  
To describe anxiety levels in a sample of mechanically ventilated patients by individual differences (eg, gender or ethnicity) and clinical factors (eg, medical indication for and length of mechanical ventilation)  
This study was a secondary analysis of existing data that used a descriptive design  
- n=200 MV  
- Anxiety was assessed via the 20-item Spielberger State Anxiety Inventory.  
- Participants receiving mechanical ventilatory support reported moderate anxiety (mean=49.2) with comparable levels by gender and ethnicity. Patients receiving ventilatory support for greater than 22 days tended to report slightly higher state anxiety (mean=54.2) compared with those chronically ventilator dependent (mean=45.8).  
- The STAI indicates the presence of anxiety, but does not provide for description of anxiety producing events or conditions and was administered only once during the patient’s stay. Data were not collected about medications.
<table>
<thead>
<tr>
<th>Study</th>
<th>Authors</th>
<th>Methodology</th>
<th>Inclusion Criteria</th>
<th>Findings</th>
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<tbody>
<tr>
<td>McKinley et al. 2003</td>
<td>Development and testing of a Faces Scale for the assessment of anxiety in critically ill patients. To compare the ability of ICU patients to respond to the Faces Anxiety Scale (FAS), the Brief Symptom Inventory (BSI) anxiety subscale and a numerical analogue anxiety scale (VAS); and, to investigate whether the Faces Anxiety Scale yields data of ordinal and interval levels of measurement.</td>
<td>The research was addressed in a series of 4 studies. ICU patients were asked to respond to the FAS, the BSI, and the VAS; and Hospital and University staff and students to place the five faces in rank order. A further 100 staff members and students to place each face at a point on a 60-cm triangular wedge according to the level of anxiety they thought the face showed.</td>
<td>Study 1 and 2, n=20 each (40 patients in total) Study 3 n=75 (hospital and university staff and students) Study 4 n=100 (hospital and university staff and students) Inclusion criteria: ICU patients with score of 3 or better on the Ramsay Sedation Scale; conversant in English; normal or corrected vision; and no apparent neurological impairment.</td>
<td>The FAS elicited more responses from intensive care patients than the numerical analogue anxiety scale or the anxiety subscale of the BSI (36 vs. 25 vs. 17, respectively, p&lt;0.0001). The Scale is easily administered for clinical assessment and research purposes. The results of this research provide support for the application of the FAS as an interval scale measure. The criterion validity of the Scale is to be determined.</td>
</tr>
<tr>
<td>Moser et al. (2003)</td>
<td>To identify the clinical indicators that critical care nurses consider to be the defining attributes of anxiety in critically ill patients.</td>
<td>Descriptive study (survey techniques/open-ended) n= A random sample of 2500 critical care nurses with 593 (31.6%) response</td>
<td>Clinical indicators of anxiety in critically ill patients. 70 individual anxiety indicators and 61 anxiety management strategies were identified by nurses. Categorized into four and</td>
<td>The human expression of emotion in the FAS is more recognizable representations of actual anxiety, which serves to strengthen its construct validity. The results of this research provide support for the application of the FAS as an interval scale measure. The criterion validity of the Scale is to be determined.</td>
</tr>
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</table>
Forty-seven ICUs in USA

anxiety in critically ill patients, and delineate the interventions that critical care nurses use to alleviate anxiety in their patients.

<table>
<thead>
<tr>
<th>Questions</th>
<th>Rate.</th>
<th>Interventions to alleviate anxiety in critically ill patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nurses selected were mailed a survey designed to determine what they considered to be the important attributes of anxiety in their patients and what interventions they commonly used to manage anxiety.</td>
<td>I: critical care nurses (1) work full or part-time in a coronary care unit, medical, surgical, neurological, or trauma intensive care unit (ICU), combined ICU, or a step-down unit; (2) deliver direct bedside patient care at least 8 hours per week; and (3) work primarily in an adult care area.</td>
<td>three major categories, respectively. Anxiety assessment categories: Physical/physiological; behavioural; psychological/cognitive; and Social (Physiological and behavioural, are the most commonly used indicators) Anxiety management strategies: care techniques; improving knowledge and communication; and support. Numerous and distinctive anxiety indicators and management strategies were reported. Further research is needed.</td>
</tr>
</tbody>
</table>

Nurses selected were mailed a survey designed to determine what they considered to be the important attributes of anxiety in their patients and what interventions they commonly used to manage anxiety.

Endler & Kocovski (2001)

State and trait anxiety revisited.

Review of the state and trait anxiety theory and assessment.

State and trait anxiety theory and assessment

Anxiety should be viewed as a dimensional construct and that the multidimensionality of state and trait anxiety should be considered in both theory and assessment. Levels of state anxiety are dependent upon both the person (trait anxiety) and the stressful situation.

Endler & Kocovski (2001) Literature review

Nurses’ descriptions about assessment and management of anxiety depended on respondents’ memory of a specific patients’ anxiety. Recall of past experience can limit the accurate and complete description of incidents. Failure to describe evaluation of the effectiveness of the management strategies that were used by nurses. (Usable data).

Moser et al. (1996)

15 coordinators in USA of an international multicentre study

To determine the association between early anxiety in the AMI patient and the incidence of subsequent in-hospital AMI complications.

Prospective, multicenter study. Assessment of anxiety level within 48 hours of patient arrival at the hospital in confirmed

n=86 patients 15 GUSTO coordinators in North America participated in this study. Inclusion criteria: patients hemodynamically stable and capable of completing a

Myocardial infarction complications.

More complications were seen in patients with higher vs. lower levels of anxiety (19.6% years 6%; p=0.001). Patients with higher anxiety levels were 4.9 times (p=0.001) more likely to have subsequent complications. Anxiety early after myocardial infarction onset is associated with

The homogeneity of clinical data. It was a substudy of an international randomized thrombolytic trial, the Global Utilization of Streptokinase and Tissue Plasminogen 230
| Myocardial infarction patients, using the Brief Symptom Inventory. Myocardial infarction complications were defined as reinfarction, new onset ischemia, ventricular fibrillation, sustained ventricular tachycardia, or in-hospital death. | questionnaire within 48 hours of admission to the emergency room. Presented to the hospital less than 6 hours after the onset of AMI symptoms and had chest pain lasting longer than 20 minutes along with 0.1 mV ST-segment elevations in two or more electrocardiogram (ECG) limb leads or 0.2 mV ST-segment elevations in two or more contiguous precordial ECG leads. Exclusion criteria: the contraindications to thrombolytic therapy. | increased risk of ischemic and arrhythmic complications. | Activator for Occluded Coronary Arteries (GUSTO) trial. Direct comparison of the odds ratios reported in this study should be done with caution. Although the highest odds ratio was associated with anxiety, this was likely due to the homogeneity of the clinical characteristics of the sample (which limits generalizability). Confirmation of the association between anxiety and complications is needed in other AMI groups. |

AMI: Acute Myocardial Infarction; APACHE II: Acute Physiology and Chronic Health Evaluation II; BAI: Beck Anxiety Inventory; CPAP: Continuous Positive Airway Pressure; CVM: Continuous Mandatory Ventilation; E: Exclusion criteria; ECG: Electrocardiogram; FAS: Faces Anxiety Scale; GUSTO: Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial; I: Inclusion criteria; ICU: Intensive Care Unit; ICUM Tool: Intensive Care Unit Memory Tool; MV: Mechanical Ventilation; n: number of patients; p: p-value; RCT: Randomised Controlled Trial; SAI: State Anxiety Inventory; STAI: State-Trait Anxiety Inventory; USA: United States of America; VAS-A: Visual Analog Scale-Anxiety; vs.: versus.
Appendix 3: Study Protocol: Intensive Care Anxiety And Emotional Recovery (Icare) – A Prospective Study

Statement of contribution to co-authored published paper

This appendix includes a co-authored published paper. The bibliographic details of the co-authored paper, including all authors, are:


My contribution to the paper involved:

- Critical review of the literature to inform the design of the study
- Enrolment of participants
- Data collection
- Data analyses
- Data interpretation
- Writing of the manuscript
- Revision of the manuscript for important intellectual content
- Approval of the final version

I completed the research and writing of the paper with methodological and editorial advice from my PhD supervisors Professor Leanne Aitken and Professor Marie Cooke.
Publication 4: Study Protocol: Intensive Care Anxiety And Emotional Recovery (Icare) – A Prospective Study

Publication status: Published

Publication 4: Study Protocol: Intensive Care Anxiety And Emotional Recovery (Icare) – A Prospective Study

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Keywords: Nursing, critical care, anxiety, depression, post-traumatic stress disorder.
Abstract

Background: Survivors of intensive care units (ICUs) commonly present with symptoms of anxiety, depression and post-traumatic stress disorder (PTSD) during recovery. A number of factors have been identified as predictors of these adverse emotional outcomes, but the role of state anxiety during critical illness in the development of these emotional problems remains unknown.

Purpose: The ICARe (Intensive Care Anxiety and Emotional Recovery) study protocol propose the development of an statistical model to determine the relationship between state anxiety during ICU stay and symptoms of anxiety, depression and PTSD at three occasions; after ICU discharge but prior to hospital discharge and at the third and sixth months post ICU discharge.

Methods: Prospective study including adult patients admitted to the ICU of a tertiary metropolitan Australian hospital for ≥24 hours who are able to: (1) communicate verbally or nonverbally; (2) understand English and (3) open their eyes spontaneously or in response to voice to respond to the Faces Anxiety Scale (state anxiety assessment). One hundred and seventy patients will be assessed for their levels of state anxiety during their ICU stay to achieve a sample size of about 104 patients prior to hospital discharge. The outcomes of the ICARe study will include symptoms of anxiety, depression and PTSD assessed by standardised and well validated questionnaires widely used in intensive care research. Demographic, clinical, and social support information will also be collected.

Results: The projected sample size will provide sufficient power to evaluate the association between state anxiety and adverse emotional outcomes, as well as a variety of variables that will be entered into a multivariate regression analysis.
Conclusion: This study will provide new evidence to improve care during critical illness and reduce adverse outcomes during recovery with the potential to decrease unnecessary suffering, promote comfort and improve long-term recovery.

Introduction

Advances in research, technology and expert care have permitted continuous improvements in the survival of intensive care patients. However, these survivors commonly present with symptoms of anxiety, depression and post-traumatic stress disorder (PTSD) during recovery. Systematic reviews including studies of survivors of the ICU; mainly from developed countries such as the United Kingdom (UK), United States of America (USA), Australia and some European countries, have reported that the prevalence of these emotional problems in the ICU population is relatively high (1-3). When looking at the literature as a whole, it can be observed that approximately 25% of ICU survivors experience some emotional problem, either symptoms of anxiety, depression or PTSD. Further, it has been suggested that these emotional problems after the ICU experience may negatively affect these survivors’ health-related quality of life (HRQoL) (4-9).

A number of factors have been identified as predictors of these adverse emotional outcomes in ICU survivors (7, 9-19). In the Intensive Care Anxiety and Emotional Recovery (ICARe) study, these risk factors have been classified into three categories: prior to critical illness, during intensive care treatment and after ICU discharge risk factors (Fig.1). Prior to critical illness risk factors include demographic characteristics such as female gender and younger age, low level of education, history of smoking and alcohol dependence, mental health history (premorbid anxiety,
depression and psychiatric illness) and personality trait of pessimism. During intensive care risk factors include sedation, duration of mechanical ventilation, length of ICU stay and neurobiological factors such as hypoxaemia, hypoglycaemia and neuroendocrine dysregulation; and after ICU risk factors include memories of the ICU, neurocognitive impairment and lack of social support. The presence of state anxiety during ICU stay has been identified as a frequent and serious problem for critically ill patients, which could be another possible during intensive care treatment factor, related to adverse emotional outcomes, however, the relationship between this emotion during critical illness and adverse emotional outcomes remains unknown (20).

Anxiety was conceptualised as state anxiety and trait anxiety by Spielberger in the sixties (21). This distinction has provided a better understanding of this complex phenomenon and this approach has been recognised in much literature and research. State anxiety is defined as a normal and temporary emotion that involves physiological arousal and feelings of tension, apprehension, nervousness and worry when a stressful situation is perceived. Trait anxiety, on the other hand, corresponds to the person's tendency to become state anxious as part of their personality trait (22). Because critically ill patients are constantly exposed to a great variety of stressors while receiving intensive care treatment, state anxiety is highly prevalent in the ICU population, especially in those requiring mechanical ventilation (23). In Australia, for example, an investigation including 106 ICU patients found some level of anxiety in 85% of them (24). The level of anxiety reported was moderate to severe despite receiving sedation and/or analgesia (24).

In addition, it is known that anxiety during critical illness is either poorly assessed or not assessed at all because of the challenge implied in assessing a self-report
symptom in patients with inability to verbalise their feelings due to endotracheal intubation and mechanical ventilation. Thus, clinicians often identify state anxiety by observation of behavioral (e.g. restlessness) and physiological (e.g. tachycardia) manifestations (24, 25). Unfortunately, clinicians’ observations of these two components are unreliable indicators of state anxiety in ICU settings since common conditions such as delirium or pain share similar physiological and behavioural characteristics with this emotion which may lead to erroneous symptom interpretation (25). Moreover, it has been found that state anxiety may not always be accompanied by physiological changes (24, 26, 27).

Another factor that has made the assessment difficult is the lack of appropriate instruments to assess state anxiety in ICU patients. Only recently, specially designed tools for the assessment of this emotion in seriously ill patients have been available, although the use of these has not yet been included in routine clinical practice (24, 27-29). This study protocol proposes the development of a statistical model in order to acquire a better understanding about the relationship between state anxiety during the ICU stay and short and medium-term emotional outcomes in survivors of the ICU as well as the association between the levels of state anxiety and sedation/analgesia during the intensive care treatment.

Methods

Aims

This study aims to determine the association between state anxiety during the ICU stay and symptom of anxiety, depression and PTSD at three occasions in survivors
of the ICU; after ICU discharge but prior to hospital discharge and at the third and sixth months after ICU discharge. It also aims to examine the relationship between state anxiety and sedation/analgesia for ICU patients during the intensive care treatment.

**Design**

This research is a prospective longitudinal cohort study of ICU survivors. This observational design will allow studying state anxiety during the ICU stay as an intra-ICU risk factor for the subsequent development of adverse emotional outcomes during recovery. In addition, it will also allow follow up of the patients at three occasions to determine the short and medium-term effects of state anxiety on emotional recovery.

**Setting**

This study will be conducted in the adult ICU of a tertiary metropolitan hospital located in Brisbane, Queensland, Australia. This ICU has 25 beds, including general ICU patients and post-cardiac surgery patients. The nurse/patient ratio is 1:1 and in 2009/2010, there were approximately 2000 admissions to this ICU.

**Sample**

All adult patients (≥ 18 years of age) admitted to the ICU for ≥24 hours, who are able to: (1) communicate verbally or non-verbally; (2) understand English; and, (3) open their eyes spontaneously or in response to voice to respond to the Faces Anxiety Scale (FAS) will be invited to participate in this study.

**Sample size**

In this study, previous research exploring similar research question in the ICU population has been examined to determine the effect size reported and perform power
analysis a priori using G*Power 3.1.3 (30). The effect size reported in the literature testing correlations in the ICU context is often medium (1-3). Therefore, a medium effect size and a selected power of 80% with a significance of α=0.05 have been used to estimate the sample size for this study.

In addition, the variables that are significant at a 0.1 level will be entered into a multivariate regression analysis. The number of predictors that will be entered into this model is unknown at this stage, but based on the number of prior to critical illness, during intensive care treatment and after ICU discharge variables that will be controlled for; the number of predictors is expected to be seven. By convention, a moderate effect size for multiple regression is R²=0.13, therefore, using power of 80% and α=0.05, the number of participants needed is 104 (31, 32). Because longitudinal research in the ICU population often reports a number of patients lost to follow up, 170 patients will be assessed for state anxiety during their ICU stay to obtain a sample of about 104 patients prior to hospital discharge. We have estimated 70% completion of follow up prior to hospital discharge and an in-hospital mortality rate of 10%.

Recruitment process

All ICU patients will be screened daily by the principal investigator for potential enrolment, with liaison with the ICU Research Nurse to determine eligibility. Each participant will be approached at an appropriate time determined in consultation with the bedside ICU nurse. Patients’ assent will be required to include patients in this study during the ICU stay, and then when the patients are in the wards (after the ICU stay but prior to hospital discharge), written consent will be requested. This process has been approved by the relevant Human Research Ethics Committees.
Data collection

Data regarding prior to critical illness, during intensive care treatment and after ICU discharge variables will be collected in order to control for confounding variables when testing the association between state anxiety and adverse emotional outcomes. All the data needed for this study will be collected within nine months from the commencement of this study, at four occasions; (1) during the ICU stay, (2) after the ICU stay but prior to hospital discharge, (3) at the third and (4) sixth months after hospital discharge. During the patients’ ICU stay, the levels of state anxiety will be assessed according to a protocol, and clinical and demographic data will be collected from medical records. Data regarding adverse emotional outcomes and some confounding variables such as memories of the ICU, cognitive functioning, personality trait of optimism vs. pessimism, personality trait of anxiety, smoking and alcohol consumption and social support will be assessed using standardised questionnaires. These questionnaires will be administered after the ICU stay but prior to hospital discharge and at the third and sixth month after ICU discharge. The questionnaires will contain approximately 67 items, and will be given to the patient with a covering letter providing instructions for participants to complete the questionnaires within the next days at a time convenient to them, but without assistance from family members/friends. At the third and sixth months post ICU discharge, the same questionnaires, with the exception of personality trait of optimism vs. pessimism and personality trait of anxiety, will be posted to the participants’ address. An appointment for a phone interview will be scheduled so participants can read their answers to the researcher. Alternatively, a reply paid envelope will be provided. The researcher will contact the participant or next of kin to confirm that the participants are alive before posting all the questionnaires. 
Mortality during the ICU stay, at the third month and sixth month after ICU discharge will be recorded. Follow-up at the three occasions proposed in this study will enable the assessment of the impact of state anxiety during the ICU stay on medium and long-term emotional recovery and fluctuations of this relationship over time.

Variables

Prior to critical illness, during intensive care treatment and after ICU discharge variables, the relevant measure and the time point for assessment are summarised in tables 1 and 2. The assessment of state anxiety will be explained in more detail since this is the primary predictive variable of interest in this study.

State anxiety assessment tool

Self-reported levels of state anxiety during the ICU stay will be assessed by the Faces Anxiety Scale (FAS) (24). The FAS is a single-item instrument especially designed to measure state anxiety in ICU settings. It consists of a scale showing five faces representing five different levels of anxiety, ranging from no anxiety to extreme anxiety, scoring from one to five. The patient is asked how much anxiety is felt at the moment of assessment and the answer may by a verbal or a nonverbal response, i.e. they can point to the relevant face. The reported criterion validity of this tool was 0.64 (p<0.001) in mechanically ventilated patient (correlation between the self-report of anxiety on the FAS and clinical judgment of anxiety) (24). While its reliability has not been measured because of limitations in reliability methods for a single-item instrument (24, 33), the FAS is a practical tool to assess this emotion in critically ill patients.
State anxiety assessment protocol

After screening for eligible participants with the ICU research nurse, the researcher and the bedside nurse will discuss and plan the best time for the assessment. State anxiety will be assessed twice daily (morning 8-11am and evening 4-7pm). The time to perform this assessment is approximately one minute and does not involve any invasive procedure. After the bedside nurse agrees, the researcher will observe and record the airway status (tracheostomy, endotracheal tube), mechanical ventilation status (invasive, non-invasive, non-ventilation), delirium status (The Confusion Assessment Method for the ICU), oxygen saturation, pain score (Verbal Pain Scale and/or The Critical Care Pain Observation Tool) and main sedation administration method (continuous infusion, intermittent, daily sedative interruption). Then, the researcher will approach the patient and explain the procedure. The patient will be shown the Faces Anxiety Scale (FAS) with the following instructions:

These faces are showing different levels of anxiety.

This face shows no anxiety at all; this face shows a little bit more; a bit more (sweep finger along scale); right up to extreme anxiety.

Have a look at these faces and choose the one that shows how much anxiety you feel at the moment (34).

The level of state anxiety will be measured as a continuous variable (scale from 1 to 5 points), and then the value obtained will be categorised into, low (1-2) or moderate to severe anxiety (score 3-5) for analysis, consistent with instructions provided by the scale developer.
Adverse Emotional Outcomes

The adverse emotional outcomes assessed in this study include symptoms of anxiety, depression and PTSD measured at three occasions, after ICU discharge but before hospital discharge, at the third and sixth month after ICU discharge. These outcomes will be assessed by standardised self-report measures, widely used in ICU research.

Symptoms of anxiety and depression will be measured by the Hospital Anxiety Depression Scale (HADS) (35). This self-report questionnaire consists in 14 statements divided into two seven-statement subscales, one for depression and one for anxiety. Each statement has four possible alternatives (0-3) indicating the frequency of the feeling assessed. Only one alternative is chosen for each statement. Three scoring ranges for each subscale are possible: normal (0-7), borderline abnormal (8-10, suggesting possible psychological distress) and abnormal (11-21, suggesting probable psychological distress). Symptoms of anxiety and depression will be classified into the three categories of the HADS recommended in Zigmond&Snaith (1983). These categories are normal (score 0-7), possible case (score 8-10) and probably case (score 11-21). The HADS assesses symptoms of anxiety and depression in hospital settings, and it is commonly used as an instrument to measure these adverse emotional outcomes in critical care research (36-39).

Symptoms of post-traumatic stress disorder will be measured by the Post-Traumatic Stress Syndrome 10-Questions Inventory (PTSS-10) (40). This is a self-report two-part questionnaire (part A and part B) designed to screen for PTSD symptoms in survivors of critical illness. Part A consists in a statement about the patients’ memory of their ICU admission. Two alternatives (Yes/ No) are possible to
indicate the presence or absence of four traumatic memories. These memories are
memories of nightmares; severe anxiety or panic; severe pain; and, respiratory distress.
In part B, the presence and intensity of 10 PTSD symptoms are assessed. These
symptoms are sleeping disturbance, nightmares, depression, hyperalertness, emotional
numbing, irritability, labile mood, guilt, avoidance of activities prompting recall of the
traumatising event, and muscular tension. Each symptom can be rated from 1 (never) to
7 (always); therefore, a total score ranging from 10 to 70 points can be obtained.
Symptoms of PTSD will be classified according the recommended cut-off of 35 points
(scale from 10 to 70 points) into two categories, high probability of PTSD (total score
>35 points) and low probability of PTSD (<35 points) (40).

Planned analyses

The Statistical Package for the Social Sciences version 20.0 (SPSS IBM Corp. in
Armonk, NY) will be used to analyse the data. Once the data have been entered into
SPSS, all variables will be cleaned and checked for missing and invalid values.
Following data cleaning a 15% random sample of the database will be verified against
original questionnaires (this will be conducted for all data collection points).
Descriptions of categorical variables will be presented as numbers and percentages.
Continuous data will be presented as a mean (±SD) or median with interquartile range.
Appropriate statistical tests will be used to test bivariate relationships between the
dependent variables and the independent variables. Continuous/Interval variables will
be tested to confirm normality distribution before deciding on either parametric analysis
(independent t-test, one-way ANOVA, Pearson’s r) and/or non-parametric analysis
(Mann-Whitney U, Kruskal Wallis & Spearman’s). Chi-square tests will be performed
for categorical data. When considering the analysis of longitudinal data, appropriate
repeated measures analyses will be employed. Variables associated with p<0.10 on bivariate analysis will be included in the final models to identify which factors are independently associated with adverse emotional outcomes (symptoms of anxiety, depression and PTSD). A stepwise process will be used during the model building, where variables not reaching a significance level p<0.05 will be omitted. Modelling of longitudinal data will involve mixed effects analysis of emotional outcomes over time.

**Ethical Considerations**

This study has been approved by the Hospital and Griffith University Human Research Ethics Committees. Verbal or nonverbal assent will be sought from each patient during the ICU stay prior to collection of data. Then, when the patients are in the wards, written informed consent will be sought from each patient. Patients, who do not give consent, will be asked permission to use the ICU based-data. If permission to use this information is not given, the data will be destroyed.

All data will be stored in locked facilities, with identifying and contact details stored separately to study data. Publications and presentations will be prepared in such a manner as to maintain the confidentiality and anonymity of all study participants. In this study, the general values and principles set out in the National Statement on Ethical Conduct in Human Research will be applied (41).

**Results and discussion**

The ICARe study is a single-center prospective longitudinal study that intends to address the issue of adverse emotional outcomes in survivors of the ICU. Whereas
previous studies have measured short, medium and long-term emotional outcomes and identified factors that may lead to the development of anxiety, depression and PTSD in ICU survivors, the impact of the amount of state anxiety that patients feel during the ICU stay on emotional recovery remains unclear.

To date, there is enough evidence to propose an existing relationship between state anxiety during the ICU stay and adverse emotional outcomes during recovery. Patients who present with moderate to severe levels of state anxiety during critical illness may be at a higher risk for developing symptoms of anxiety, depression and PTSD during recovery than those with low or no anxiety. This relationship may be through a direct link and/or an indirect link involving sedation. As the emotional component of state anxiety is poorly assessed during critical illness, state anxiety might not be detected in a timely manner and, therefore, remain unrelieved for long periods of time. This situation may have a direct impact on the development of adverse emotional outcomes in the longer term. On the other hand, if anxiety progresses to extreme levels and patients exhibit psychomotor agitation, the use of increased doses of sedative agents may be given. Thus, sedation could represent an indirect link to adverse emotional outcomes after the ICU experience.

The significance of this study can be considered from a number of viewpoints. The first aspect concerns ICU survivors and their families. For many patients, the presence of these emotional consequences can impact their quality of life, affecting for example, their family and social relationships; employment and economic status; and physical recovery.

The second aspect relates to health care professionals. State anxiety is widely acknowledged as a serious problem in ICU settings despite current ICU management.
However, the lack of evidence-based knowledge on the consequences that this emotion may have on the short, medium and long-term emotional recovery of patients, may lead clinicians to disregard the assessment and management of this emotion during ICU treatment. The ICARe study seeks to understand this association and inform clinicians about the short and medium-term effects of state anxiety on emotional recovery, so as to facilitate change in clinical practice and improve outcomes for ICU survivors.

The third aspect pertains to the efficient use of health care resources. Systematic reviews, with an international viewpoint, have estimated that approximately a quarter of the patients who survive the intensive care treatment develop emotional problems, which may endure for years (1-3). The emotional recovery of these patients involves health care resources, expenses that could be avoided by preventing these emotional consequences. Considering that annually millions of patients are admitted to ICUs around the world, this situation is, undoubtedly, an important public health issue. Ultimately, the findings of this study will generate new evidence to inform future research and clinical practice.

The strength of the ICARe study is that a comprehensive assessment of the most relevant prior to critical illness, during intensive care treatment and after ICU discharge factors described in the literature will be conducted. This strength will permit the development of a conceptual model where the significance of the relationships between risk factors and adverse emotional outcomes will be identified. In addition, the direction of these associations will be determined.

The ICARe study proposal has some constraints. State anxiety will be assessed after 24 hours of ICU admission, twice daily during the patients’ ICU stay. Therefore, it is possible that, despite frequent data collection, the ICARe study may not fully capture
the variations of the levels of anxiety within a 24 hour period. The levels of state anxiety may vary over time in a dynamic environment such as the ICU. Nevertheless, this emotion could only be assessed twice daily due to the burden associated with the data collection process. Although the design of the ICARe study includes a comprehensive collection of prior to critical illness, during intensive care treatment and after ICU discharge variables that will take into account confounding variables and bias, so that the effects of state anxiety on adverse emotional outcomes can be determined, some key risk factors for the development of these adverse emotional outcomes may still be unknown or unmeasured in this study.

**Conclusion**

The ICARe study is a prospective longitudinal study of survivors of ICU treatment six months after discharge. This study aims to provide new knowledge about the association between state anxiety during the ICU stay and the development of symptoms of anxiety, depression and PTSD during recovery. The strengths of the study include comprehensive measurement of prior to critical illness, during intensive care treatment and after ICU discharge risk factors for the development of relevant adverse emotional outcomes; an adequate sample size, determined by power analysis; and the development of a statistical model. This research has the potential to inform the development of interventions designed to improve the emotional outcomes of patients being admitted to intensive care units by describing factors that affect their recovery. Improved emotional recovery may result in reduced burden for patients, their families and the health care system.
Figure 1: Risk factors for the development of adverse emotional outcomes after the ICU experience

Pre-ICU factors
1. Female gender
2. Younger age
3. Low level of education
4. History of smoking
5. History of alcohol dependence
6. Mental health history
7. Personality trait of pessimism

Intra-ICU factors
1. Sedation
2. Length of respiratory support
3. Length of ICU stay
4. Neurobiological factors:
   • Hypoxaemia
   • Hypoglycaemia
   • Neuroendocrine dysregulation

Post-ICU factors
1. Memories of the ICU
2. Neurocognitive impairment
3. Lack of social support

Adverse emotional outcomes after the ICU experience
Table 1: study constructs, measures, number of items and data collection schedule

<table>
<thead>
<tr>
<th>Measure</th>
<th>Outcomes</th>
<th>ICU</th>
<th>After ICU, but prior to hospital discharge</th>
<th>rd. 3 mo.</th>
<th>th 6 mo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>HADS</td>
<td>Symptoms of anxiety</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>HADS</td>
<td>Symptoms of depression</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Part B of PTSS-10</td>
<td>Symptoms of PTSD</td>
<td>10</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Measure</strong></td>
<td><strong>Variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAS</td>
<td>State anxiety</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Part A PTSS-10</td>
<td>Memory</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>LOT-R</td>
<td>Trait pessimism</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STAI Form Y-2</td>
<td>Trait anxiety</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSPSS</td>
<td>Social support</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>MOS COG-R</td>
<td>Cognitive function</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>QF method</td>
<td>Smoking</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>GQF method</td>
<td>Alcohol consumption</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Patient demographics questionnaire</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level of education</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Mental health history</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-ICU medications (steroids, opioids, benzos, beta-blockers, anxiolytics)</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total No of Items</strong></td>
<td></td>
<td>1</td>
<td>67</td>
<td>48</td>
<td>48</td>
</tr>
</tbody>
</table>

HADS: Hospital Anxiety Depression Scale; PTSS-10: Post-Traumatic Stress Syndrome 10-Questions Inventory; PTSD: Post-traumatic Stress Disorder; FAS: Faces Anxiety Scale; LOT-R: Revised Life Orientation Test; STAI Form Y-2: State Trait-Anxiety Inventory Form Y-2; MSPSS: The Multidimensional Scale of Social Support; MOS COG-R: Medical Outcomes Study Cognitive Functioning Scale-Revised; QF method: Quantity Frequency method; GQF method: Graduated Quantity Frequency method; APACHE III: Acute Physiology and Chronic Health Evaluation III.
Table 2: clinical and demographic data, collected from medical records during the ICU stay

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender &amp; age</td>
<td></td>
</tr>
<tr>
<td>Airway status (tracheostomy, endotracheal intubation)</td>
<td></td>
</tr>
<tr>
<td>Hypoxaemia (oxygen saturation)</td>
<td></td>
</tr>
<tr>
<td>Diagnosis ICU admission</td>
<td></td>
</tr>
<tr>
<td>Severity of illness: Acute Physiology and Chronic Health Evaluation III (APACHE III)</td>
<td></td>
</tr>
<tr>
<td>Delirium</td>
<td></td>
</tr>
<tr>
<td>Length of mechanical ventilation, ICU &amp; hospital stay</td>
<td></td>
</tr>
<tr>
<td>MV status (invasive, non-invasive, non-ventilation)</td>
<td></td>
</tr>
<tr>
<td>Sedation administration method (continuous, intermittent, daily sedative interruption)</td>
<td></td>
</tr>
<tr>
<td>Duration of sedation &amp; total doses of sedatives, opioids, steroids and anxiolytics</td>
<td></td>
</tr>
</tbody>
</table>
References


impairment and consequently health-related quality of life in survivors of severe acute respiratory distress syndrome. *Critical Care* 2006;10(5):147.


## Appendix 4: Anxiety during critical illness – Model Building

### Trait anxiety model building

<table>
<thead>
<tr>
<th>Count</th>
<th>Variables</th>
<th>R</th>
<th>R²</th>
<th>R adjusted</th>
<th>Comments/Diagnostics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Trait optimism</td>
<td>0.641</td>
<td>0.411</td>
<td>0.406</td>
<td>Residuals fine</td>
</tr>
<tr>
<td>2</td>
<td>Trait optimism, (add) State anxiety</td>
<td>0.681</td>
<td>0.464</td>
<td>0.455</td>
<td>Residuals fine, no collinearity issues</td>
</tr>
<tr>
<td>3</td>
<td>Trait optimism, State anxiety, (add Evidence of mental health treatment)</td>
<td>0.703</td>
<td>0.464</td>
<td>0.466</td>
<td>Residuals fine, no collinearity issues</td>
</tr>
<tr>
<td>4</td>
<td>Trait optimism, State anxiety, Evidence of mental health treatment, (add Smoking)</td>
<td>0.708</td>
<td>0.501</td>
<td>0.484</td>
<td>Smoking not significant (Beta=0.085, p=0.228). Smoking removed</td>
</tr>
<tr>
<td>5</td>
<td>Trait optimism, State anxiety, Evidence of mental health treatment, (add Age)</td>
<td>0.728</td>
<td>0.530</td>
<td>0.513</td>
<td>Residuals fine, no collinearity issues</td>
</tr>
<tr>
<td>6</td>
<td>Trait optimism, State anxiety, Evidence of mental health treatment, Age, (add Marital status)</td>
<td>0.730</td>
<td>0.532</td>
<td>0.512</td>
<td>Marital status not significant (Beta=0.058, p=0.440). Marital status removed.</td>
</tr>
<tr>
<td>7</td>
<td>Trait optimism, State anxiety, Evidence of mental health treatment, Age, (add Pain)</td>
<td>0.728</td>
<td>0.530</td>
<td>0.510</td>
<td>Pain not significant (Beta=0.028, p=0.679). Pain removed.</td>
</tr>
<tr>
<td>8</td>
<td>Trait optimism, State anxiety, Evidence of mental health treatment, Age, (add Total dose of fentanyl)</td>
<td>0.732</td>
<td>0.535</td>
<td>0.515</td>
<td>Total dose of fentanyl not significant (Beta=0.077, p=0.253). Total does of fentanyl removed.</td>
</tr>
<tr>
<td>9</td>
<td>Trait optimism, State anxiety, Evidence of mental health treatment, Age, (add Hours of fentanyl infusion)</td>
<td>0.729</td>
<td>0.531</td>
<td>0.510</td>
<td>Hours of fentanyl infusion not significant (Beta=0.005, p=0.605). Hours of fentanyl infusion removed.</td>
</tr>
<tr>
<td></td>
<td>Trait optimism, State anxiety, Evidence of mental health treatment, Age, (add Length of hospital stay)</td>
<td>0.731</td>
<td>0.534</td>
<td>0.513</td>
<td>Length of hospital stay not significant (Beta=0.066, p=0.311). Length of hospital stay removed.</td>
</tr>
<tr>
<td>---</td>
<td>--------------------------------------------------------------------------------------------------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>11</td>
<td>Trait optimism, State anxiety, Evidence of mental health treatment, Age, (add Total dose of midazolam)</td>
<td>0.728</td>
<td>0.530</td>
<td>0.509</td>
<td>Total dose of midazolam not significant (Beta=0.021, p=0.756) removed.</td>
</tr>
<tr>
<td>12</td>
<td>Trait optimism, State anxiety, Evidence of mental health treatment, Age, (add Hours of propofol infusion)</td>
<td>0.728</td>
<td>0.530</td>
<td>0.509</td>
<td>Hours of propofol infusion not significant (Beta=0.003, p=0.95) removed.</td>
</tr>
<tr>
<td>13</td>
<td>Trait optimism, State anxiety, Evidence of mental health treatment, Age, (add Total dose of morphine)</td>
<td>0.731</td>
<td>0.535</td>
<td>0.514</td>
<td>Total dose of morphine not significant (Beta=-0.074, p=0.263) removed.</td>
</tr>
<tr>
<td>14</td>
<td>Trait optimism, State anxiety, Evidence of mental health treatment, Age, (add Total dose of propofol)</td>
<td>0.728</td>
<td>0.530</td>
<td>0.509</td>
<td>Total dose of propofol not significant (Beta=0.003, p=0.971) removed.</td>
</tr>
<tr>
<td>15</td>
<td>Trait optimism, State anxiety, Evidence of mental health treatment, Age, (add Total dose oxycodone)</td>
<td>0.729</td>
<td>0.532</td>
<td>0.511</td>
<td>Total dose oxycodone not significant (Beta=0.050, p=0.458) removed.</td>
</tr>
</tbody>
</table>
### Multiple Linear Regression: Factors associated with trait anxiety in ICU patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Unstandardised Coefficients</th>
<th>Standardised Coefficients</th>
<th>Sig.</th>
<th>95.0% Confidence Interval for B</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Constant)</td>
<td>62.369</td>
<td>4.209</td>
<td>0.000</td>
<td>54.030</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70.707</td>
</tr>
<tr>
<td>Trait optimism</td>
<td>-1.549</td>
<td>0.181</td>
<td>0.000</td>
<td>-1.908</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-0.563</td>
<td></td>
<td>-1.190</td>
</tr>
<tr>
<td>State anxiety</td>
<td>2.235</td>
<td>0.728</td>
<td>0.003</td>
<td>0.792</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.204</td>
<td></td>
<td>3.678</td>
</tr>
<tr>
<td>Evidence of mental health treatment</td>
<td>4.186</td>
<td>1.586</td>
<td>0.009</td>
<td>1.043</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.175</td>
<td></td>
<td>7.329</td>
</tr>
<tr>
<td>Age</td>
<td>-0.142</td>
<td>0.049</td>
<td>0.004</td>
<td>-0.238</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-0.188</td>
<td></td>
<td>-0.045</td>
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</table>
### State anxiety model building

<table>
<thead>
<tr>
<th>Count</th>
<th>Variables</th>
<th>R</th>
<th>R2</th>
<th>R adjusted</th>
<th>Comments/Diagnostics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Trait anxiety</td>
<td>0.333</td>
<td>0.111</td>
<td>0.103</td>
<td>Residuals fine</td>
</tr>
<tr>
<td>2</td>
<td>Trait anxiety, (add) evidence of mental health treatment</td>
<td>0.352</td>
<td>0.124</td>
<td>0.109</td>
<td>Evidence of mental health treatment not significant ($\text{Beta}=0.121, \ p=0.190$) removed.</td>
</tr>
<tr>
<td>3</td>
<td>Trait anxiety, Pain</td>
<td>0.376</td>
<td>0.142</td>
<td>0.127</td>
<td>Residuals fine, no collinearity issues</td>
</tr>
<tr>
<td>4</td>
<td>Trait anxiety, Pain, Trait optimism</td>
<td></td>
<td></td>
<td></td>
<td>Trait optimism not significant ($\text{Beta}=0.083, \ p=0.462$), removed</td>
</tr>
</tbody>
</table>

### Multiple Linear Regression: Factors associated with state anxiety in ICU patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Unstandardised Coefficients</th>
<th>Standardised Coefficients</th>
<th>Sig.</th>
<th>95.0% Confidence Interval for B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Constant)</td>
<td>1.204</td>
<td>0.317</td>
<td>0.000</td>
<td>0.577</td>
</tr>
<tr>
<td>Trait anxiety</td>
<td>0.027</td>
<td>0.294</td>
<td>0.001</td>
<td>0.011</td>
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<tr>
<td>Pain</td>
<td>0.095</td>
<td>0.180</td>
<td>0.043</td>
<td>0.003</td>
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</table>
## Appendix 5: Symptoms of anxiety over six months after ICU discharge – Model Building

<table>
<thead>
<tr>
<th>Model</th>
<th>Observations</th>
<th>Variables</th>
<th>AIC</th>
<th>BIC</th>
<th>Comments/Diagnostics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>310</td>
<td>Cognition</td>
<td>1609.809</td>
<td>1635.965</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>310</td>
<td>Cognition (add Depression)</td>
<td>1494.13</td>
<td>1520.286</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>309</td>
<td>Cognition, Depression (add Memories of anxiety)</td>
<td>1478.988</td>
<td>1508.855</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>309</td>
<td>Cognition, Depression, Memories of anxiety (add Memories of pain)</td>
<td>1476.595</td>
<td>1510.195</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>308</td>
<td>Cognition, Depression, Memories of anxiety, Memories of pain (add Optimism)</td>
<td>1465.7</td>
<td>1503.001</td>
<td>Model 5 best AIC/BIC, all variables still significant (checked residuals and vifs)</td>
</tr>
<tr>
<td>6</td>
<td>284</td>
<td>Cognition, Depression, Memories of anxiety, Memories of pain, Optimism (add PTSS at 3months)</td>
<td>1358.684</td>
<td>1398.823</td>
<td>Does improve AIC/BIC however PTSS at 3 months not significant.</td>
</tr>
<tr>
<td>7</td>
<td>267</td>
<td>Cognition, Depression, Memories of anxiety, Memories of pain, Optimism (add PTSS at 6months) (remove PTSS at 3months)</td>
<td>1253.997</td>
<td>1293.457</td>
<td>AIC/BIC improved. PTSS at 6 months significant. Memories of pain no longer significant, remove.</td>
</tr>
<tr>
<td>8</td>
<td>267</td>
<td>Cognition, Depression, Memories of anxiety, Optimism, PTSS at 6months (add Social support at 6months) (remove Memories of pain)</td>
<td>1256.23</td>
<td>1295.689</td>
<td>AIC/BIC shows no improvement. Social Support at 3 months not significant.</td>
</tr>
<tr>
<td>9</td>
<td>267</td>
<td>Cognition, Depression, Memories of anxiety, Optimism, PTSS at 6months (add State anxiety) (remove Social support at 6months)</td>
<td>1253.592</td>
<td>1293.052</td>
<td>State anxiety and Optimism no longer significant, take out State anxiety as it is the least significant and re-run</td>
</tr>
<tr>
<td>10</td>
<td>267</td>
<td>Cognition, Depression, Memories of anxiety, Optimism, PTSS at 6months (remove State anxiety)</td>
<td>1254.624</td>
<td>1290.496</td>
<td>Optimism is not significant &amp; does not improve the AIC/BIC.</td>
</tr>
<tr>
<td>11</td>
<td>264</td>
<td>Cognition, Depression, Memories of anxiety, PTSS at 6months (Add trait anxiety) (remove</td>
<td>1237.99</td>
<td>1273.75</td>
<td>Addition of Trait anxiety is significant, improves the AIC/BIC.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>264</td>
<td>Cognition, Depression, Memories of anxiety, PTSS at 6months, Trait anxiety (Add Pain)</td>
<td>1239.966</td>
<td>1279.301</td>
<td><em>Addition of Pain is not significant and it does not improve the AIC/BIC.</em></td>
</tr>
<tr>
<td>13</td>
<td>264</td>
<td>Cognition, Depression, Memories of anxiety, PTSS at 6months, Trait anxiety (add Marital Status) (remove Pain)</td>
<td>1235.812</td>
<td>1282.299</td>
<td><em>Addition of marital status only significant for widow compared with married/defacto. Try another marital status variable. Will Leave Marital Status for now.</em></td>
</tr>
<tr>
<td>14</td>
<td>263</td>
<td>Cognition, Depression, Memories of anxiety, PTSS at 6months, Trait anxiety (add Alcohol consumption) (remove Marital Status)</td>
<td>1233.944</td>
<td>1273.237</td>
<td><em>Alcohol consumption significant and AIC/BIC improved.</em></td>
</tr>
<tr>
<td>15</td>
<td>263</td>
<td>Cognition, Depression, Memories of anxiety, PTSS at 6months, Trait anxiety, Alcohol consumption (add Evidence of mental health treatment)</td>
<td>1231.914</td>
<td>1274.78</td>
<td><em>Evidence of mental health treatment significant and improvement in AIC. Alcohol consumption no longer significant.</em></td>
</tr>
<tr>
<td>16</td>
<td>264</td>
<td>Cognition, Depression, Memories of anxiety, PTSS at 6months, Trait anxiety, Evidence of mental health treatment (remove alcohol)</td>
<td>1235.529</td>
<td>1274.865</td>
<td><em>Slight increase in AIC/BIC from Model 16.</em></td>
</tr>
<tr>
<td>17</td>
<td>264</td>
<td>Cognition, Depression, Memories of anxiety, PTSS at 6months, Trait anxiety, Evidence of mental health treatment (add Memories of nightmares)</td>
<td>1235.835</td>
<td>1278.746</td>
<td><em>Memories of nightmares not significant, and there is no improvement in AIC/BIC.</em></td>
</tr>
<tr>
<td>18</td>
<td>264</td>
<td>Cognition, Depression, memories of anxiety, PTSS at 6months, Trait anxiety, Evidence of mental health treatment (add Oxycodone total dose) (remove Memories of nightmares)</td>
<td>1237.105</td>
<td>1280.016</td>
<td><em>Oxycodone total dose not significant, and there is no improvement in AIC/BIC.</em></td>
</tr>
<tr>
<td>19</td>
<td>264</td>
<td>Cognition, Depression, Memories of anxiety, PTSS at 6months, Trait anxiety, Evidence of mental health treatment (add Fentanyl total dose) (remove Oxycodone total dose)</td>
<td>1237.521</td>
<td>1280.432</td>
<td><em>Fentanyl total dose not significant, and there is no improvement in AIC/BIC.</em></td>
</tr>
<tr>
<td>Page</td>
<td>Column1</td>
<td>Column2</td>
<td>Column3</td>
<td>Column4</td>
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</tr>
<tr>
<td>20</td>
<td>264</td>
<td>Cognition, Depression, Memories of anxiety, PTSS at 6months, Trait anxiety, Evidence of mental health treatment (add Memories of difficulty breathing) (remove Fentanyl total dose)</td>
<td>1237.506</td>
<td>1280.417</td>
<td>Memories of difficulty breathing not significant, no improvement in AIC/BIC.</td>
</tr>
<tr>
<td>21</td>
<td>264</td>
<td>Cognition, Depression, Memories of anxiety, PTSS at 6months, Trait anxiety, Evidence of mental health treatment (add First anxiety assessment) (remove Memories of difficulty breathing)</td>
<td>1236.419</td>
<td>1279.331</td>
<td>First anxiety assessment not significant, minimal improvement in AIC/BIC.</td>
</tr>
<tr>
<td>22</td>
<td>260</td>
<td>Cognition, Depression, Memories of anxiety, PTSS at 6months, Trait anxiety, Evidence of mental health treatment (Add Social support) (remove first anxiety assessment)</td>
<td>1219.08</td>
<td>1261.808</td>
<td>Social support not significant, minimal improvement in AIC/BIC.</td>
</tr>
<tr>
<td>23</td>
<td>264</td>
<td>Cognition, Depression, Memories of anxiety, PTSS at 6months, Trait anxiety, Evidence of mental health treatment (Add Pre-ICU opioids) (remove Social support)</td>
<td>1236.523</td>
<td>1279.435</td>
<td>Pre-ICU opioids not significant, no improvement in AIC/BIC.</td>
</tr>
<tr>
<td>24</td>
<td>264</td>
<td>Cognition, Depression, Memories of anxiety, PTSS at 6months, Trait anxiety, Evidence of mental health treatment (add Age) (remove pre-ICU opioids)</td>
<td>1237.51</td>
<td>1280.421</td>
<td>Age is not significant, no improvement in AIC/BIC.</td>
</tr>
<tr>
<td>25</td>
<td>263</td>
<td>Cognition, Depression, Memories of anxiety, PTSS at 6months, Trait anxiety, Evidence of mental health treatment (add Employment status) (remove Age)</td>
<td>1237.186</td>
<td>1294.34</td>
<td>Employment status is not significant, no improvement in AIC/BIC.</td>
</tr>
<tr>
<td>26</td>
<td>264</td>
<td>Cognition, Depression, Memories of anxiety, PTSS at 6months, Trait anxiety, Evidence of mental health treatment (add Intra-ICU benzos) (remove Employment status)</td>
<td>1237.528</td>
<td>1280.439</td>
<td>Intra-ICU benzos is not significant, no improvement in AIC/BIC</td>
</tr>
<tr>
<td>27</td>
<td>264</td>
<td>Cognition, Depression, Memories of anxiety,</td>
<td>1235.494</td>
<td>1278.406</td>
<td>Hours of propofol infusion is not</td>
</tr>
<tr>
<td>No.</td>
<td>Value</td>
<td>Description</td>
<td></td>
<td></td>
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<tr>
<td>28</td>
<td>1236.233</td>
<td>Cognition, Depression, Memories of anxiety, PTSS at 6months, Trait anxiety, Evidence of mental health treatment (add Hours of propofol infusion) (remove Intra-ICU benzos)</td>
<td></td>
<td></td>
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<tr>
<td>29</td>
<td>1237.295</td>
<td>Cognition, Depression, Memories of anxiety, PTSS at 6months, Trait anxiety, Evidence of mental health treatment (add Propofol total dose) (remove Hours of propofol infusion)</td>
<td></td>
<td></td>
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<tr>
<td>30</td>
<td>1236.508</td>
<td>Cognition, Depression, Memories of anxiety, PTSS at 6months, Trait anxiety, Evidence of mental health treatment (add Hours of fentanyl infusion) (remove Propofol total dose)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>1237.442</td>
<td>Cognition, Depression, Memories of anxiety, PTSS at 6months, Trait anxiety, Evidence of mental health treatment (add Paracetamol total dose) (remove Hours of fentanyl infusion)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>1236.826</td>
<td>Cognition, Depression, Memories of anxiety, PTSS at 6months, Trait anxiety, Evidence of mental health treatment (add Hours of invasive mechanical ventilation) (remove Paracetamol total dose)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>1237.529</td>
<td>Cognition, Depression, Memories of anxiety, PTSS at 6months, Trait anxiety, Evidence of mental health treatment (add Hours of non-invasive mechanical ventilation) (remove Hours of invasive mechanical ventilation)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Significant, minimal improvement in AIC/BIC

Propofol total dose is not significant, min improvement in AIC/BIC

Hours of fentanyl infusion is not significant, no improvement in AIC/BIC

Paracetamol total dose is not significant, no improvement in AIC/BIC

Hours of invasive mechanical ventilation is not significant, no improvement in AIC/BIC

Hours of non-invasive mechanical ventilation is not significant, no improvement in AIC/BIC

Length of ICU stay is not significant, no improvement in AIC
<table>
<thead>
<tr>
<th></th>
<th></th>
<th>mental health treatment (add Length of ICU stay) (remove Hours of non-invasive mechanical ventilation)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>264</td>
<td>Cognition, Depression, Memories of anxiety, PTSS at 6months, Trait anxiety, Evidence of mental health treatment (add Hours of midazolam infusion) (remove Length of ICU stay)</td>
<td>1234.589</td>
<td>1277.5</td>
</tr>
</tbody>
</table>

*Hours of midazolam infusion is not significant, no improvement in AIC/BIC.*

| 35 | 263 | Cognition, Depression, Memories of anxiety, PTSS at 6months, Trait anxiety, Evidence of mental health treatment (add smoking) (remove Hours of midazolam infusion) | 1230.82 | 1273.686 |

*Smoking is not significant, no improvement in AIC/BIC*

| 36 | 264 | Cognition, Depression, Memories of anxiety, PTSS at 6months, Trait anxiety, Evidence of mental health treatment (remove Smoking) | 1234.692 | 1272.027 |

*All significant, slight increase in AIC but drop in BIC.*

| 37 | 264 | Cognition, Depression, Memories of anxiety, PTSS at 6months, Trait anxiety, Evidence of mental health treatment (add Marital status) | 1234.207 | 1284.27 |

*Marital status not significant. AIC/BIC no improvement.*

AIC: Akaike Information Criteria; BIC: Bayesian Information Criterion; PTSS: Post-traumatic Stress Symptoms; ICU: Intensive Care Unit; vifs: Variance Inflation factors.
### Linear Mixed Model: Factors associated with symptoms of anxiety over six months after ICU discharge (n=120)

<table>
<thead>
<tr>
<th>Factors</th>
<th>Coefficient (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>2.90 (0.77, 5.01)</td>
<td>0.007</td>
</tr>
<tr>
<td>Time 2 (3 months)</td>
<td>-0.83 (-1.49, -0.16)</td>
<td>0.015</td>
</tr>
<tr>
<td>Time 3 (6 months)</td>
<td>-0.55 (-1.21, 0.10)</td>
<td>0.100</td>
</tr>
<tr>
<td>Cognitive functioning (per 10 units) (score range 0-100)</td>
<td>-0.41 (-0.64, -0.19)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Symptoms of depression (per unit) (score range 0-21)</td>
<td>0.37 (0.27, 0.48)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Trait anxiety (per 10 units) (score range 20-80)</td>
<td>0.63 (0.20, 1.06)</td>
<td>0.004</td>
</tr>
<tr>
<td>Post-traumatic stress symptoms at 6mo (per 10 units) (score range 10-70)</td>
<td>0.63 (0.30, 0.97)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Memories of experiencing anxiety during ICU stay
- No                                                                     Reference
- Yes                                                                    0.84 (0.17, 1.51)  0.014

Evidence of mental health treatment prior to ICU admission
- No                                                                     Reference
- Yes                                                                    -0.92 (-1.8, -0.09) 0.029

Akaike Information Criterion for base model=1612, n=310; Akaike Information Criterion for best model=1235, n=264
### Appendix 6: Symptoms of depression over six months after ICU discharge – Model Building

<table>
<thead>
<tr>
<th>Model</th>
<th>Observations</th>
<th>Variables</th>
<th>AIC</th>
<th>BIC</th>
<th>Comments/Diagnostics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>311</td>
<td>Cognition</td>
<td>1630.866</td>
<td>1653.305</td>
<td>n/a</td>
</tr>
<tr>
<td>2</td>
<td>311</td>
<td>Cognition (and Mental health history)</td>
<td>1626.037</td>
<td>1652.215</td>
<td>Mental health history significant improves the AIC/BIC.</td>
</tr>
<tr>
<td>3</td>
<td>310</td>
<td>Cognition, Mental health history (and Anxiety)</td>
<td>1505.885</td>
<td>1535.777</td>
<td>Anxiety significant improves the AIC/BIC.</td>
</tr>
<tr>
<td>4</td>
<td>309</td>
<td>Cognition, Mental health history, Anxiety (and Memories of pain)</td>
<td>1501.205</td>
<td>1534.805</td>
<td>AIC/BIC improved. Memories of pain not significant, remove.</td>
</tr>
<tr>
<td>5</td>
<td>309</td>
<td>Cognition, Mental health history, Anxiety (add Optimism) (remove Memories of pain)</td>
<td>1489.134</td>
<td>1522.734</td>
<td>Optimism is significant &amp; improved AIC/BIC.</td>
</tr>
<tr>
<td>6</td>
<td>285</td>
<td>Cognition, Mental health history, Anxiety, Optimism (add PTSS at 3 months)</td>
<td>1368.214</td>
<td>1404.739</td>
<td>PTSS at 3 month is significant &amp; improves AIC/BIC.</td>
</tr>
<tr>
<td>7</td>
<td>260</td>
<td>Cognition, Mental health history, Anxiety, Optimism, PTSS at 3 months (add PTSS at 6 months)</td>
<td>1251.328</td>
<td>1290.495</td>
<td>PTSS at 6 month is NOT significant, though it does improve AIC/BIC.</td>
</tr>
<tr>
<td>8</td>
<td>282</td>
<td>Cognition, Mental health history, Anxiety, Optimism, PTSS at 3 months (add Social support at 3 months) (remove PTSS at 6 months)</td>
<td>1352.8</td>
<td>1392.861</td>
<td>Social support at 3 months is significant.</td>
</tr>
<tr>
<td>9</td>
<td>260</td>
<td>Cognition, Mental health history, Anxiety, Optimism, PTSS at 3 months, Social support at 3 months (add Social support at 6 months)</td>
<td>1245.842</td>
<td>1288.57</td>
<td>Social support at 6 months not significant. Social support at 3 months and Optimism also no longer significant. Take out Social support at 6 months.</td>
</tr>
<tr>
<td>10</td>
<td>282</td>
<td>Cognition, Mental health history, Anxiety, Optimism, PTSS at 3 months, Social support at 3 months (add Trait anxiety) (remove Social support at 6 months)</td>
<td>1350.968</td>
<td>1394.671</td>
<td>Trait anxiety is significant. Optimism (0.251), Social support (0.116), Mental health history (0.113) no longer significant. Take out Optimism and re-run.</td>
</tr>
<tr>
<td>11</td>
<td>282</td>
<td>Cognition, Mental health history, Anxiety, PTSS at 3 months, Social support at 3 months, Trait anxiety (remove Optimism)</td>
<td>1350.275</td>
<td>1390.336</td>
<td>Social support (0.072) &amp; Mental health history (0.162) still no longer significant. Take out Mental health history and re-run.</td>
</tr>
<tr>
<td>Page</td>
<td>Text</td>
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</tr>
<tr>
<td>12</td>
<td>282</td>
<td>Cognition, Anxiety, PTSS at 3 months, Social support at 3 months, Trait anxiety (remove Mental health history)</td>
<td>1350.207</td>
<td>1386.626</td>
<td>All significant, better AIC/BIC than models 10 &amp; 11.</td>
</tr>
<tr>
<td>13</td>
<td>282</td>
<td>Cognition, Anxiety, PTSS at 3 months, Social support at 3 months, Trait anxiety (add Marital status)</td>
<td>1353.777</td>
<td>1401.122</td>
<td>Marital status not significant, remove.</td>
</tr>
<tr>
<td>14</td>
<td>282</td>
<td>Cognition, Anxiety, PTSS at 3 months, Social support at 3 months, Trait anxiety (add Pre-ICU benzos) (remove Marital status)</td>
<td>1345.341</td>
<td>1385.402</td>
<td>Pre-ICU benzos significant. Social support at 3 months (0.173) &amp; PTSS at 3 months (0.089) no longer significant. Remove Social support at 3 months and re-run.</td>
</tr>
<tr>
<td>15</td>
<td>285</td>
<td>Cognition, Anxiety, PTSS at 3 months, Trait anxiety, Pre-ICU benzos (remove Social support at 3 months)</td>
<td>1358.594</td>
<td>1395.119</td>
<td>PTSS at 3 months no longer significant (remove and re-run).</td>
</tr>
<tr>
<td>16</td>
<td>306</td>
<td>Cognition, Anxiety, Trait anxiety, Pre-ICU benzos (remove PTSS at 3 months)</td>
<td>1466.919</td>
<td>1500.431</td>
<td>All variables significant, check residuals and vifs.</td>
</tr>
<tr>
<td>17</td>
<td>306</td>
<td>Cognition, Anxiety, Trait anxiety, Pre-ICU benzos (add State anxiety)</td>
<td>1468.835</td>
<td>1506.071</td>
<td>State anxiety not significant, remove.</td>
</tr>
<tr>
<td>18</td>
<td>306</td>
<td>Cognition, Anxiety, Trait anxiety, Pre-ICU benzos (add Pain) (remove State anxiety)</td>
<td>1468.064</td>
<td>1505.3</td>
<td>Pain not significant, remove.</td>
</tr>
<tr>
<td>19</td>
<td>306</td>
<td>Cognition, Anxiety, Trait anxiety, Pre-ICU benzos (add Oxycodone total dose) (remove Pain)</td>
<td>1467.561</td>
<td>1504.796</td>
<td>Oxycodone total dose not significant, remove.</td>
</tr>
<tr>
<td>20</td>
<td>306</td>
<td>Cognition, Anxiety, Trait anxiety, Pre-ICU benzos (add Fentanyl total dose) (remove Oxycodone total dose)</td>
<td>1468.409</td>
<td>1505.644</td>
<td>Fentanyl total dose not significant, remove.</td>
</tr>
<tr>
<td>21</td>
<td>305</td>
<td>Cognition, Anxiety, Trait anxiety, Pre-ICU benzos (add Alcohol consumption) (remove Fentanyl total dose)</td>
<td>1464.789</td>
<td>1501.992</td>
<td>Alcohol consumption not significant, remove.</td>
</tr>
<tr>
<td>22</td>
<td>305</td>
<td>Cognition, Anxiety, Trait anxiety, Pre-ICU benzos (add Smoking) (remove Alcohol consumption)</td>
<td>1461.359</td>
<td>1498.562</td>
<td>Smoking significant. Check residuals and vifs.</td>
</tr>
<tr>
<td>23</td>
<td>304</td>
<td>Cognition, Anxiety, Trait anxiety, Pre-ICU</td>
<td>1459.51</td>
<td>1500.397</td>
<td>Memories of difficulty breathing not</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>24</td>
<td>305</td>
<td>Cognition, Anxiety, Trait anxiety, Pre-ICU benzos, Smoking (add Memories of difficulty breathing)</td>
<td>1463.156</td>
<td>1504.079</td>
<td>Intra-ICU benzos not significant, remove.</td>
</tr>
<tr>
<td>25</td>
<td>305</td>
<td>Cognition, Anxiety, Trait anxiety, Pre-ICU benzos, Smoking (add Paracetamol total dose) (remove Intra-ICU benzos)</td>
<td>1462.192</td>
<td>1503.115</td>
<td>Paracetamol total dose not significant, remove.</td>
</tr>
<tr>
<td>26</td>
<td>305</td>
<td>Cognition, Anxiety, Trait anxiety, Pre-ICU benzos, Smoking (add Diagnostic category) (remove Paracetamol total dose)</td>
<td>1455.545</td>
<td>1503.909</td>
<td>Last diagnostic group is significant – keep aside and put into the final model.</td>
</tr>
<tr>
<td>27</td>
<td>305</td>
<td>Cognition, Anxiety, Trait anxiety, Pre-ICU benzos, Smoking (add Employment status) (remove Diagnostic category)</td>
<td>1463.288</td>
<td>1519.093</td>
<td>Employment status not significant, remove.</td>
</tr>
<tr>
<td>28</td>
<td>304</td>
<td>Cognition, Anxiety, Trait anxiety, Pre-ICU benzos, Smoking (add Memories of anxiety) (remove Employment status)</td>
<td>1456.636</td>
<td>1497.523</td>
<td>Memories of anxiety not significant, remove.</td>
</tr>
<tr>
<td>29</td>
<td>305</td>
<td>Cognition, Anxiety, Trait anxiety, Pre-ICU benzos, Smoking (add First anxiety assessment) (remove Memories of anxiety)</td>
<td>1462.518</td>
<td>1503.441</td>
<td>First anxiety assessment not significant, remove.</td>
</tr>
<tr>
<td>30</td>
<td>305</td>
<td>Cognition, Anxiety, Trait anxiety, Pre-ICU benzos, Smoking (add Educational level) (remove First anxiety assessment)</td>
<td>1464.269</td>
<td>1512.633</td>
<td>Education level not significant, remove.</td>
</tr>
<tr>
<td>31</td>
<td>305</td>
<td>Cognition, Anxiety, Trait anxiety, Pre-ICU benzos, Smoking (add Airway status) (remove Educational level)</td>
<td>1462.418</td>
<td>1503.342</td>
<td>Airway status not significant, remove.</td>
</tr>
<tr>
<td>32</td>
<td>305</td>
<td>Cognition, Anxiety, Trait anxiety, Pre-ICU benzos, Smoking (add Hours of invasive mechanical ventilation) (remove Airway status)</td>
<td>1463.292</td>
<td>1504.216</td>
<td>Hours of mechanical ventilation not significant, remove.</td>
</tr>
<tr>
<td>33</td>
<td>305</td>
<td>Cognition, Anxiety, Trait anxiety, Pre-ICU benzos, Smoking (add Hours of Fentanyl infusion) (remove hours of invasive mechanical ventilation)</td>
<td>1463.138</td>
<td>1504.061</td>
<td>Hours of fentanyl infusion not significant, remove.</td>
</tr>
<tr>
<td>Page</td>
<td>Line</td>
<td>Text</td>
<td>AIC</td>
<td>BIC</td>
<td>Interpretation</td>
</tr>
<tr>
<td>------</td>
<td>------</td>
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<td>----------------</td>
</tr>
<tr>
<td>34</td>
<td>305</td>
<td>Cognition, Anxiety, Trait anxiety, Pre-ICU benzos, Smoking (add Midazolam total dose) (remove Hours of fentanyl infusion)</td>
<td>1463.167</td>
<td>1504.09</td>
<td>Midazolam total dose not significant, remove.</td>
</tr>
<tr>
<td>35</td>
<td>304</td>
<td>Cognition, Anxiety, Trait anxiety, Pre-ICU benzos, Smoking (add Memories of nightmares) (remove Midazolam total dose)</td>
<td>1458.313</td>
<td>1499.201</td>
<td>Memories of nightmares not significant, remove.</td>
</tr>
<tr>
<td>36</td>
<td>305</td>
<td>Cognition, Anxiety, Trait anxiety, Pre-ICU benzos, Smoking (add Pre-ICU opioids) (remove Memories of nightmares)</td>
<td>1462.48</td>
<td>1503.404</td>
<td>Pre-ICU opioids not significant, remove.</td>
</tr>
<tr>
<td>37</td>
<td>305</td>
<td>Cognition, Anxiety, Trait anxiety, Pre-ICU benzos, Smoking (add Length of ICU stay) (remove Pre-ICU opioids)</td>
<td>1463.346</td>
<td>1504.27</td>
<td>Length of ICU stay not significant, remove.</td>
</tr>
<tr>
<td>38</td>
<td>305</td>
<td>Cognition, Anxiety, Trait anxiety, Pre-ICU benzos, Smoking (remove Length of ICU stay)</td>
<td>1461.359</td>
<td>1498.562</td>
<td>Smoking no longer significant, remove.</td>
</tr>
<tr>
<td>39</td>
<td>306</td>
<td>Cognition, Anxiety, Trait anxiety, Pre-ICU benzos, (remove Smoking)</td>
<td>1466.919</td>
<td>1500.431</td>
<td>All significant, check residual and vifs.</td>
</tr>
<tr>
<td>40</td>
<td>306</td>
<td>Cognition, Anxiety, Trait anxiety, Pre-ICU benzos, (add Diagnostic group)</td>
<td>1458.505</td>
<td>1499.465</td>
<td>Last diagnostic group significant from surgical.</td>
</tr>
<tr>
<td>41</td>
<td>264</td>
<td>Cognition, Anxiety, Trait anxiety, Diagnostic group, (add Evidence of mental health treatment)</td>
<td>1358.176</td>
<td>1395.119</td>
<td></td>
</tr>
</tbody>
</table>

AIC: Akaike Information Criteria; BIC: Bayesian Information Criterion; PTSS: Post-traumatic Stress Symptoms; ICU: Intensive Care Unit; n/a: not applicable
### Linear Mixed Model: Factors associated with symptoms of depression over six months after ICU discharge (n=120)

<table>
<thead>
<tr>
<th>Factors</th>
<th>Coefficient (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>1.13 (-1.11, 3.38)</td>
<td>0.323</td>
</tr>
<tr>
<td>Time 2 (3 months)</td>
<td>-0.49 (-1.15, 0.16)</td>
<td>0.145</td>
</tr>
<tr>
<td>Time 3 (6 months)</td>
<td>-0.30 (-0.99, 0.37)</td>
<td>0.373</td>
</tr>
<tr>
<td>Cognitive functioning (per 10 units) (score range 0-100)</td>
<td>-0.46 (-0.68, -0.23)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Symptoms of anxiety (per unit) (score range 0-21)</td>
<td>0.43 (0.33, 0.54)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Trait anxiety (per 10 units) (score range 20-80)</td>
<td>0.75 (0.34, 1.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Post-traumatic stress symptoms at 3mo (per 10 units) (score range 10-70)</td>
<td>0.54 (0.18, 0.89)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

#### Reason for ICU admission
- Medical: Reference
- Surgical (Including cardiac surgery): -0.39 (-1.21, 0.41) p=0.337
- Trauma: 1.72 (0.58, 2.85) p=0.003

**Akaike Information Criterion for base model=1612, n=310; Akaike Information Criterion for best model= 1358, n=264**
## Appendix 7: Post-traumatic Stress Symptoms over six months after ICU discharge—Model Building

<table>
<thead>
<tr>
<th>Model</th>
<th>Observations</th>
<th>Variables</th>
<th>AIC</th>
<th>BIC</th>
<th>Comments/Diagnostics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>187</td>
<td>Cognition</td>
<td>1425.44</td>
<td>1441.595</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>187</td>
<td>Cognition (add Depression)</td>
<td>1413.564</td>
<td>1432.951</td>
<td>Depression is significant and improves AIC/BIC.</td>
</tr>
<tr>
<td>3</td>
<td>187</td>
<td>Cognition, Depression (add Anxiety)</td>
<td>1411.114</td>
<td>1433.731</td>
<td>Anxiety is significant and improves AIC/BIC. Cognition no longer significant (0.082).</td>
</tr>
<tr>
<td>4</td>
<td>187</td>
<td>Depression, Anxiety (remove Cognition)</td>
<td>1412.1</td>
<td>1431.486</td>
<td>Residuals good. No issues with vifs. All significant.</td>
</tr>
<tr>
<td>5</td>
<td>187</td>
<td>Depression, Anxiety (add Optimism)</td>
<td>1411.366</td>
<td>1433.984</td>
<td>Residuals good. No issues with vifs. Optimism not significant (0.095), remove.</td>
</tr>
<tr>
<td>6</td>
<td>186</td>
<td>Depression, Anxiety (remove Optimism) (add Trait anxiety)</td>
<td>1400.336</td>
<td>1422.917</td>
<td>Residuals good. Remove Depression - less significant, also moderate-high correlation with Anxiety (0.6648).</td>
</tr>
<tr>
<td>7</td>
<td>186</td>
<td>Anxiety, Trait anxiety (remove Depression)</td>
<td>1400.444</td>
<td>1419.799</td>
<td>Residuals good. No issues with vifs.</td>
</tr>
<tr>
<td>8</td>
<td>186</td>
<td>Anxiety, Trait anxiety (add Mental health history)</td>
<td>1396.065</td>
<td>1418.646</td>
<td>Residuals good. No issues with vifs. Mental health history significant (0.010).</td>
</tr>
<tr>
<td>9</td>
<td>186</td>
<td>Anxiety, Trait anxiety, Mental health history (add Memories of anxiety)</td>
<td>1397.043</td>
<td>1422.849</td>
<td>Residuals good. No issues with vifs. Memories of anxiety not significant (0.310).</td>
</tr>
<tr>
<td>10</td>
<td>186</td>
<td>Anxiety, Trait anxiety, Mental health history (remove Memories of anxiety) (add Age)</td>
<td>1393.399</td>
<td>1419.205</td>
<td>Residuals good. No issues with vifs. Age significant (0.029).</td>
</tr>
<tr>
<td>11</td>
<td>186</td>
<td>Anxiety, Trait anxiety, Mental health history, Age (add Pain)</td>
<td>1392.808</td>
<td>1421.839</td>
<td>Residuals good. No issues with vifs. Pain not significant (0.106).</td>
</tr>
<tr>
<td>12</td>
<td>186</td>
<td>Anxiety, Trait anxiety, Mental health history, Age (remove Pain) (add Pre-ICU benzos)</td>
<td>1393.267</td>
<td>1422.299</td>
<td>Residuals good. No issues with vifs. Pre-ICU benzos not significant (0.141).</td>
</tr>
<tr>
<td>13</td>
<td>186</td>
<td>Anxiety, Trait anxiety, Mental health history, Age (remove Pre-ICU benzos) (add Oxycodone)</td>
<td>1395.014</td>
<td>1424.046</td>
<td>Residuals good. No issues with vifs. Oxycodone total dose not significant</td>
</tr>
<tr>
<td></td>
<td>Total dose)</td>
<td>Anxiety, Trait anxiety, Mental health history, Age (remove Oxycodone total dose) (add Hours of ketamine infusion)</td>
<td>1394.88</td>
<td>1423.911</td>
<td>Residuals good. No issues with vifs. Hours of ketamine infusion not significant (0.471).</td>
</tr>
<tr>
<td>---</td>
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<td>---------------------------------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>14</td>
<td>186</td>
<td>Anxiety, Trait anxiety, Mental health history, Age (remove Hours of ketamine infusion) (add Fentanyl total dose)</td>
<td>1395.089</td>
<td>1424.121</td>
<td>Residuals good. No issues with vifs. Fentanyl total dose not significant (0.578).</td>
</tr>
<tr>
<td>15</td>
<td>186</td>
<td>Anxiety, Trait anxiety, Mental health history, Age (remove Fentanyl total dose) (add Diagnostic category)</td>
<td>1396.541</td>
<td>1432.025</td>
<td>Residuals good. No issues with vifs. Diagnostic category not significant.</td>
</tr>
<tr>
<td>16</td>
<td>186</td>
<td>Anxiety, Trait anxiety, Mental health history, Age (remove Diagnostic category) (add Non-invasive mechanical ventilation dichotomous)</td>
<td>1394.073</td>
<td>1423.104</td>
<td>Residuals good. No issues with vifs. Non-invasive mechanical ventilation dichotomous not significant (0.248).</td>
</tr>
<tr>
<td>17</td>
<td>186</td>
<td>Anxiety, Trait anxiety, Mental health history, Age (remove Non-invasive mechanical ventilation dichotomous) (add Hours of non-invasive mechanical ventilation)</td>
<td>1394.482</td>
<td>1423.514</td>
<td>Residuals good. No issues with vifs. Hours of non-invasive mechanical ventilation not significant (0.337).</td>
</tr>
<tr>
<td>18</td>
<td>186</td>
<td>Anxiety, Trait anxiety, Mental health history, Age (remove Hours of non-invasive mechanical ventilation) (add Level of education)</td>
<td>1398.981</td>
<td>1434.464</td>
<td>Residuals good. No issues with vifs. Level of education not significant.</td>
</tr>
<tr>
<td>19</td>
<td>186</td>
<td>Anxiety, Trait anxiety, Mental health history, Age (remove Level of education) (add Social support at 3months)</td>
<td>1382.034</td>
<td>1410.969</td>
<td>Residuals good. No issues with vifs. Social support at 3months not significant (0.969).</td>
</tr>
<tr>
<td>20</td>
<td>186</td>
<td>Anxiety, Trait anxiety, Mental health history, Age (remove Social support at 3months) (add Ketamine total dose)</td>
<td>1394.904</td>
<td>1423.935</td>
<td>Residuals good. No issues with vifs. Ketamine total dose not significant (0.481).</td>
</tr>
<tr>
<td>21</td>
<td>186</td>
<td>Anxiety, Trait anxiety, Mental health history, Age (remove Ketamine total dose) (add Paracetamol total dose)</td>
<td>1395.395</td>
<td>1424.427</td>
<td>Residuals good. No issues with vifs. Paracetamol total dose not significant (0.953).</td>
</tr>
<tr>
<td>22</td>
<td>186</td>
<td>Anxiety, Trait anxiety, Mental health history, Age (remove Paracetamol total dose) (add Marital status)</td>
<td>1399.131</td>
<td>1434.614</td>
<td>Residuals good. No issues with vifs. Marital status not significant.</td>
</tr>
<tr>
<td>23</td>
<td>186</td>
<td>Anxiety, Trait anxiety, Mental health history, Age (remove Marital status) (add Hours of invasive mechanical ventilation)</td>
<td>1395.373</td>
<td>1424.405</td>
<td>Residuals good. No issues with vifs. Hours of invasive mechanical ventilation not significant (0.535).</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>25</td>
<td>186</td>
<td>Anxiety, Trait anxiety, Mental health history, Age (remove Hours of invasive mechanical ventilation) (add State anxiety)</td>
<td>1394.597</td>
<td>1423.629</td>
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<tr>
<td></td>
<td></td>
<td>Residuals good. No issues with vifs. State anxiety not significant (0.369).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>186</td>
<td>Anxiety, Trait anxiety, Mental health history, Age (remove State anxiety) (add Memories of difficulty breathing)</td>
<td>1395.354</td>
<td>1424.386</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Residuals good. No issues with vifs. Memories of difficulty breathing not significant (0.833).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>186</td>
<td>Anxiety, Trait anxiety, Mental health history, Age (remove Memories of difficulty breathing) (add Length of ICU stay)</td>
<td>1395.372</td>
<td>1424.403</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Residuals good. No issues with vifs. Length of ICU stay not significant (0.869).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>186</td>
<td>Anxiety, Trait anxiety, Mental health history, Age (remove Length of ICU stay) (add First anxiety assessment)</td>
<td>1395.135</td>
<td>1424.167</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Residuals good. No issues with vifs. First anxiety assessment not significant (0.607).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>186</td>
<td>Anxiety, Trait anxiety, Mental health history, Age (remove First anxiety assessment) (add Hours of fentanyl infusion)</td>
<td>1395.313</td>
<td>1424.345</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Residuals good. No issues with vifs. Hours of fentanyl infusion not significant (0.769).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>186</td>
<td>Anxiety, Trait anxiety, Mental health history, Age (remove Hours of fentanyl infusion) (add Memories of pain)</td>
<td>1395.175</td>
<td>1424.206</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Residuals good. No issues with vifs. Memories of pain not significant (0.635).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>186</td>
<td>Anxiety, Trait anxiety, Mental health history, Age (remove Memories of pain) (add Propofol total dose)</td>
<td>1395.37</td>
<td>1424.402</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Residuals good. No issues with vifs. Propofol total dose not significant (0.865).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>186</td>
<td>Anxiety, Trait anxiety, Mental health history, Age (remove Propofol total dose)</td>
<td>1393.399</td>
<td>1419.205</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Residuals good. No issues with vifs.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AIC: Akaike Information Criteria; BIC: Bayesian Information Criterion; vifs: Variance Inflation factors.
<table>
<thead>
<tr>
<th>Factors</th>
<th>Mean [95% CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>17.4 (7.0, 27.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Time (6 months)</td>
<td>2.0 (-0.5, 4.5)</td>
<td>0.112</td>
</tr>
<tr>
<td>Symptoms of Anxiety (per unit) (score range 0-21)</td>
<td>0.6 (0.2, 1.1)</td>
<td>0.005</td>
</tr>
<tr>
<td>Trait anxiety (per 10 units) (score range 20-80)</td>
<td>2.2 (0.3, 4.1)</td>
<td>0.023</td>
</tr>
<tr>
<td>Age (per 10 units) (age range 18-84)</td>
<td>-1.4 (-2.6, -0.2)</td>
<td>0.024</td>
</tr>
<tr>
<td>Evidence of mental health treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5.2 (1.5, 8.9)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Akaike Information Criterion/Bayesian Information Criterion for model = 1394/1423
Appendix 8: Participant information and consent form

Princess Alexandra Hospital

Ipswich Rd, Woolloongabba, QLD, 4102
Ph (07) 3176 2111

Participant Information and Consent Form
Version 2, dated 10 August 2012

Relationship between state anxiety during the ICU stay and adverse emotional outcomes during recovery

Principal Researcher: Ms Maria Isabel Castillo Escobar, Griffith University
Senior Researchers: Prof Leanne Aitken, Professor of Critical Care Nursing, Princess Alexandra Hospital and Griffith University
Prof Marie Cooke, Professor at Griffith University

This Participant Information and Consent Form is four pages long. Please make sure you have all the pages.

1. Your Consent

We wish to invite you to take part in this research project. This Participant Information contains detailed information about the research project. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project before you decide whether or not to take part in it.

Please read this Participant Information carefully. Feel free to ask questions about any information in the document. You may also wish to discuss the project with a relative or friend - feel free to do this.

Once you understand about the project and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form, you indicate that you understand the information and that you give your consent to participate in the research project. You will be given a copy of the Participant Information and Consent Form to keep as a record.
2. Purpose and Background

Emotional problems are common after critical illness and they may negatively affect individuals’ quality of life, the health care system and society in general.

This study hopes to identify risk factors during the intensive care treatment that may lead to the development of these adverse emotional outcomes.

3. Procedures

If you agree to participate, you will be asked to complete questionnaires that will take about 25 minutes to complete. You will be asked to complete these questionnaires before your hospital discharge, and at 3 months and 6 months from the date of your discharge from the ICU. The questionnaires will contain questions about your health, how you feel, employment details and any support you receive from family or friends. The 3 and 6 months questionnaires will be posted to you and you will be asked to complete them without assistance from family or friends at your convenience. We will phone you to obtain your results to the questionnaire or alternatively to make arrangements for you to post the questionnaire back to us (a reply paid envelope will be provided).

We will also ask for contact details of two next of kin or friends who do not reside at the same address as you.

In addition, we will seek information that describes your experiences assessed during the ICU stay and subsequent care from your ICU medical records.

4. Possible Benefits and Risks

You may not benefit directly from participation in this study, but it is hoped that identification of risk factors that may lead to the development of emotional problem during recovery will help to improve the intensive care treatment of the ICU patients in the future. Any improvements in the system of intensive care have the potential to reduce emotional problems, improve recovery and reduce costs for survivors of the ICU.

There is a possibility that you may experience some distress during completion of these questionnaires. If this is the case you should advise the interviewer about your feelings. You may choose to not answer a question or to stop the interview at any time. If you feel distress the interviewer will offer guidance in how you might obtain counselling if you would like it.

5. Privacy, Confidentiality and Disclosure of Information

The questionnaires will be completed confidentially. Any information obtained in connection with this project will remain confidential. It will only be disclosed with your permission, except as required by law.
In any publication, information will be provided in such a way that you cannot be identified. Only summarised data will be made publicly available to maintain confidentiality. Information you provide for this study will be retained for a minimum of 5 years. After this time, all data will be destroyed.

6. Further Information and Ethical Approval
If you require further information or have any problems concerning this project you can contact Ms Maria Isabel Castillo (telephone 07 3176 7256).

The Human Research Ethics Committees of the Princess Alexandra Hospital and Griffith University have approved this study. Should you have any questions or concerns about the ethical conduct of this study please contact the Secretariat of the Human Research Ethics Committee (07 3176 5856) at the Princess Alexandra Hospital.

7. Participation is Voluntary
Participation in any research project is voluntary. If you do not wish to take part you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage. Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with the Princess Alexandra Hospital. If you decide to withdraw from this project, please notify a member of the research team before you withdraw.
Relationship between state anxiety during the ICU stay and adverse emotional outcomes during recovery (ICARe study)

Participant Information and Consent Form
Version 2, dated 10 August 2012

Principal Researcher: Ms Maria Isabel Castillo Escobar, Griffith University
Senior Researchers: Prof Leanne Aitken, Professor of Critical Care Nursing, Princess Alexandra Hospital and Griffith University
Prof Marie Cooke, Professor at Griffith University

I have read and understand the Participant Information, Version 2, dated 10 August 2012.
I freely agree to participate in this project according to the conditions in the Participant Information.
I will be given a copy of the Participant Information and Consent Form to keep.
The researcher has agreed not to reveal my identity and personal details if information about this project is published or presented in any public form.

Participant’s Name (printed) ……………………………………………………………
Signature Date

Name of Witness to Participant’s Signature (printed) …………………………………
Signature Date

Researcher’s Name (printed) ……………………………………………………………
Signature Date
Relationship between state anxiety during the ICU stay and adverse emotional outcomes during recovery

Revocation Of Consent Form
Version 1, dated 25 March 2012

Principal Researcher: Ms Maria Isabel Castillo Escobar, Griffith University
Senior Researchers: Prof Leanne Aitken, Professor of Critical Care Nursing, Princess Alexandra Hospital and Griffith University
Prof Marie Cooke, Professor at Griffith University

I hereby wish to WITHDRAW my consent to participate in the research proposal described above and understand that such withdrawal WILL NOT jeopardise any treatment or my relationship with Princess Alexandra Hospital.

Participant’s Name (printed) ……………………………………………………………

Signature                                      Date
Appendix 9: Ethics approval letters

15 May 2012

Ms Maria Isabel Castillo Escobar
34/287 Wickham Terrace
Spring Hill QLD 4000

Dear Ms Castillo Escobar,

**HREC Reference number: HREC/12/OPAH/173**

**Project Title:** Relationship between state anxiety during the ICU stay and adverse emotional outcomes during recovery.

Thank you for submitting the above research protocol to the Metro South Health Human Research Ethics Committee for ethical and scientific review. This protocol was first considered by the Human Research Ethics Committee (HREC) at the meeting held on 01 May 2012.

I am pleased to advise that the HREC has granted approval of this research protocol.

You are reminded that this letter constitutes ethical approval only. You must not commence this research protocol at a site until separate authorisation from the District CEO or Delegate of that site has been obtained.

A copy of this approval must be submitted to the District Research Governance Officer/Delegate of the relevant institution with a completed Site Specific Assessment (SSA) Form for authorisation from the CEO or Delegate to conduct this research at the Princess Alexandra Hospital.

The documents reviewed and approved include:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application Protocol</td>
<td>1</td>
<td>28 March 2012</td>
</tr>
<tr>
<td>Patient Information Sheet/Consent Form</td>
<td>1</td>
<td>25 March 2012</td>
</tr>
<tr>
<td>Script and Assent Form</td>
<td>1</td>
<td>25 March 2012</td>
</tr>
<tr>
<td>Patient Information Sheet/Consent Form: Family Member</td>
<td>1</td>
<td>25 March 2012</td>
</tr>
<tr>
<td>Permission to Use Information Form</td>
<td>1</td>
<td>25 March 2012</td>
</tr>
<tr>
<td>Response to Request for Further Information</td>
<td>1</td>
<td>08 May 2012</td>
</tr>
</tbody>
</table>

Please note the following conditions of approval:

1. The Coordinating Principal Investigator will immediately report anything which might warrant review of ethical approval of the protocol in the specified format, including unforeseen events that might affect continued ethical acceptability of the protocol. Serious Adverse Events must be notified to the HREC as soon as possible. In addition the Investigator must provide a summary of the adverse events, in the specified format, including a comment as to suspected causality and whether changes are required to the Patient Information and Consent Form. In the case of Serious Adverse Events occurring at the local site, a full report is required from the Coordinating Principal Investigator, including duration of treatment and outcome of the event.
2. Amendments to the research protocol which may affect the ongoing ethical acceptability of a protocol must be submitted to the HREC for review. Major amendments should be reflected in a revised online NEAF (accompanied by all relevant updated documentation and a cover letter from the principal investigator, providing a brief description of the changes, the rationale for the changes, and their implications for the ongoing conduct of the study). Hard copies of the revised NEAF, the cover letter and all relevant updated documents, with tracked changes, must also be submitted to the HREC office as per standard HREC SOP. (Further advice on submitting amendments is available at http://www.health.qld.gov.au/ohmr/documents/researcher_userguide.pdf http://www.health.qld.gov.au/pahospital/research/amendments.asp)

3. Amendments to the research protocol which only affect the ongoing site acceptability of the protocol are not required to be submitted to the HREC for review. These amendments requests should be submitted directly to the Research Governance Office.

4. Proposed amendments to the research protocol which may affect both the ethical acceptability and site suitability of the protocol must be submitted firstly to the HREC for review and, once HREC approval has been granted, then submitted to the Research Governance Office.

5. Amendments which do not affect either the ethical acceptability or site acceptability of the protocol (e.g. typographical errors) should be submitted electronically (track changes) and in hard copy (final clean copy) to the Research Ethics Manager. These should include a cover letter from the Coordinating Principal Investigator or Study Co-ordinator providing a brief description of the changes and the rationale for the changes, and accompanied by all relevant updated documents with tracked changes.

6. The HREC will be notified, giving reasons, if the protocol is discontinued at a site before the expected date of completion.

7. The Coordinating Principal Investigator will provide an annual report to the HREC and at completion of the study in the specified format.

This HREC approval is valid for 3 years from the date of this letter.

8. If you require an extension for your study, please submit a request for an extension in writing outlining the reasons. Note: One of the criteria for granting an extension is the compliance with the approval’s conditions including submission of progress reports.

9. Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes (WHO / ICMJE 2008 definition) should be registered, including early phase and late phase clinical trials (phases I-III) in patients or healthy volunteers (WHO Recommendation / ICMJE policy). If in doubt, registration is recommended. All studies must be registered prior to the study’s inception, i.e. prospectively.

http://www.anzctr.org.au/

Should you have any queries about the HREC’s consideration of your protocol please contact the Ethics Secretariat on 07 3176 7672.

Please note that the Metro South HREC is constituted and operates in accordance with the National Health and Medical Research Council’s (NHMRC) National Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007) and the CPMP/ICH Note for Guidance on Good Clinical Practice. Attached is the HREC Composition with specialty and affiliation with the Hospital (Attachment 1).

The HREC Terms of Reference, Standard Operating Procedures, membership and standard forms are available from the following websites:
Once authorisation to conduct the research has been granted, please complete the Commencement Form (Attached) and return to the Metro South Human Research Ethics Committee.

The Metro South HREC wishes you every success in your research.

Yours sincerely,

Associate Professor Maher Gandhi
Chair
Metro South Health Service District
Human Research Ethics Committee (EC00167)
Centres for Health Research
Princess Alexandra Hospital

C.c. Ms Bonnie Macfarlane
Dear Mrs Castillo

I write further to your application for ethical clearance for your project PR: Relationship between state anxiety during the ICU stay and adverse emotional outcomes during recovery" (GU Ref No: NRS/35/12/HREC). This project has been considered by Human expedited review 1.

The Chair resolved to grant this project conditional ethical clearance, subject to you resolving the following matters:

As per the expectations articulated in the National Statement on Ethical Conduct in Human Research (2007) and Booklet 8 of the Griffith University Research Ethics Manual, because of the prior review by another HREC, this research has been subject to a special administrative review.

The use of an alternative contact point for concerns or complaints about the ethical conduct of this research is accepted. Please provide an assurance that the Manager, Research Ethics will be promptly notified if any concerns or complaints are received about the ethical conduct of this research.

The contact person signing the s17 declaration (available from the forms page of the Griffith University Human Research Ethics web site or upon request from the Office for Research).

This decision was made on 03-Aug-12. Your response to these matters will be considered by Office for Research.

The ethical clearance for this protocol runs from 03-Aug-12 to 15-May-13.

Please forward your response to Dr Gary Allen, Manager, Research Ethics, Office for Research, as per the details below.

Please refer to the attached sheet for the standard conditions of ethical clearance at Griffith University, as well as responses to questions commonly posed by researchers.

It would be appreciated if you could give your urgent attention to the issues raised by the Committee so that we can finalise the ethical clearance for your protocol promptly.

Regards
CC:

At this time all researchers are reminded that the Griffith University Code for the Responsible Conduct of Research provides guidance to researchers in areas such as conflict of interest, authorship, storage of data, & the training of research students. You can find further information, resources and a link to the University’s Code by visiting http://www62.gu.edu.au/policylibrary.nsf/xupdatemonth/e7852d226231d2b44a25750c0062f457?opendocument

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GRiffith University Human Research Ethics Committee

Aug-2012

Dear Mrs Castillo

I write further to the additional information provided in relation to the conditional approval granted to your application for ethical clearance for your project "PR: Relationship between state anxiety during the ICU stay and adverse emotional outcomes during recovery" (GU Ref No: NRS/35/12/HREC).

This is to confirm receipt of the remaining required information, assurances or amendments to this protocol.

Consequently, I reconfirm my earlier advice that you are authorised to immediately commence this research on this basis.

The standard conditions of approval attached to our previous correspondence about this protocol continue to apply.
At this time all researchers are reminded that the Griffith University Code for the Responsible Conduct of Research provides guidance to researchers in areas such as conflict of interest, authorship, storage of data, & the training of research students. You can find further information, resources and a link to the University's Code by visiting http://www62.gu.edu.au/policylibrary.nsf/xupdatemonth/e7852d226231d2b44a25750c0062f457?opendocument PRIVILEGED, PRIVATE AND CONFIDENTIAL
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Appendix 10: Australian College of Critical Care Nurses

Novice Researcher Grant

Ms Maria Castillo

27 October 2012

Dear Maria,

RECIPIENT OF THE PRIZE FOR THE ACCCN NOVICE RESEARCHER GRANT

Congratulations to you and your colleagues on being judged the winners of the prize for the ACCCN Novice Researcher Grant at the ANZICS/ACCCN Intensive Care ASM Adelaide 2012.

The award amount is $7,500.

Should you have any queries, please contact Mr John Jannese on 03 9896 4100.

Kind regards,

Prof Paul Fulbrook
ACCCN President
Appendix 11: Intensive Care Foundation Research Grant

Intensive Care Foundation
...we save lives

Research Grant Awarded to

Maria Isabel Castillo Escobar (Chief Investigator)
Princess Alexandra Hospital

ICU anxiety and emotional recovery

A$ 11,100
October 27, 2012

Prof. Jeffrey Ljoman
Co-Chair Scientific Review Committee

A/Prof. Yahya Shehabi
Chairman

Prof. Sharon McKinley
Co-Chair Scientific Review Committee
Appendix 12: Hospital Anxiety and Depression Scale (HADS)

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Appendix 13: Post-traumatic Stress Symptoms 10-Question Inventory (PTSS-10)

PTSS-10 Intensive Care Screen

This form should not take longer than about 5 minutes to complete. The form has two sections, Part A and Part B.

PART A

This consists of four statements about your memory of the time you spent on the Intensive Care Unit. Read each statement. If a statement is FALSE, tick the NO box. If the statement is TRUE, tick the YES box. Please answer ALL four questions. Tick only ONE box for each statement. If you make a mistake, simply cross out the wrong answer and tick the correct box.

PART B

This consists of 10 statements about how you have been feeling in the past few days. You need to decide HOW OFTEN you have been feeling this way in the past few days.

If you have NOT EVER felt or experienced what the statement says in the past few days, circle 1 (never).

If you have been feeling or experiencing it ALL THE TIME, circle 7 (always).

Otherwise, circle one of the numbers in between that best describes how much you have been feeling or experiencing what the statement says in the past few days.

Please circle only one number for each statement. If you make a mistake, simply cross it out and circle the correct number. PLEASE be sure to choose a number for ALL 10 statements.

A. When I think back to the time of my severe illness and the time I spent in the ICU, I remember:

<table>
<thead>
<tr>
<th>Statement</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nightmares</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe Anxiety or Panic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe Pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Troubles to breath, feelings of suffocation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No</td>
<td>Yes</td>
<td></td>
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</tr>
</tbody>
</table>
B. Presently (this means in the past few days) I suffer from:

1. **sleep problems**
   - never: 2, 3, 4, 5, 6, 7
   - always: 1

2. **nightmares**
   - never: 2, 3, 4, 5, 6, 7
   - always: 1

3. **depression, I feel defeated/downtrodden**
   - never: 2, 3, 4, 5, 6, 7
   - always: 1

4. **jumpsiness, I am easily frightened by sudden sounds or sudden movements**
   - never: 2, 3, 4, 5, 6, 7
   - always: 1

5. **the need to withdraw from others**
   - never: 2, 3, 4, 5, 6, 7
   - always: 1

6. **irritability, that is, I am easily agitated/annoyed and angry**
   - never: 2, 3, 4, 5, 6, 7
   - always: 1

7. **frequent mood swings**
   - never: 2, 3, 4, 5, 6, 7
   - always: 1

8. **a bad conscience, blame myself, have guilt feelings**
   - never: 2, 3, 4, 5, 6, 7
   - always: 1

9. **fear of places and situations, which remind me of the Intensive Care Unit**
   - never: 2, 3, 4, 5, 6, 7
   - always: 1

10. **muscular tension**
    - never: 2, 3, 4, 5, 6, 7
    - always: 1

---

Appendix 14: Trait component of the State and Trait Anxiety Inventory (STAI)

Unable to reproduce in full due to copyright law

Appendix 15: Faces Anxiety Scale

Appendix 16: MOS 6-Item Cognitive Functioning Scale

Unable to reproduce due to copyright law

Appendix 17: Multidimensional Scale of Perceived Social Support

Multidimensional Scale of Perceived Social Support (Zimet, Dahlem, Zimet & Farley, 1988)

Instructions: We are interested in how you feel about the following statements. Read each statement carefully. Indicate how you feel about each statement.

Circle the “1” if you Very Strongly Disagree
Circle the “2” if you Strongly Disagree
Circle the “3” if you Mildly Disagree
Circle the “4” if you are Neutral
Circle the “5” if you Mildly Agree
Circle the “6” if you Strongly Agree
Circle the “7” if you Very Strongly Agree

1. There is a special person who is around when I am in need. 1 2 3 4 5 6 7 SO
2. There is a special person with whom I can share my joys and sorrows. 1 2 3 4 5 6 7 SO
3. My family really tries to help me. 1 2 3 4 5 6 7 Fam
4. I get the emotional help and support I need from my family. 1 2 3 4 5 6 7 Fam
5. I have a special person who is a real source of comfort to me. 1 2 3 4 5 6 7 SO
6. My friends really try to help me. 1 2 3 4 5 6 7 Fri
7. I can count on my friends when things go wrong. 1 2 3 4 5 6 7 Fri
8. I can talk about my problems with my family. 1 2 3 4 5 6 7 Fam
9. I have friends with whom I can share my joys and sorrows. 1 2 3 4 5 6 7 Fri
10. There is a special person in my life who cares about my feelings. 1 2 3 4 5 6 7 SO
11. My family is willing to help me make decisions. 1 2 3 4 5 6 7 Fam
12. I can talk about my problems with my friends. 1 2 3 4 5 6 7 Fri

The items tended to divide into factor groups relating to the source of the social support, namely family (Fam), friends (Fri) or significant other (SO).

Appendix 18: Patient Demographics Questionnaire

Please answer the following questions about yourself by underlying the answer that corresponds to you:

1. **Marital status:**
   - Married
   - Never married
   - De facto
   - Separated
   - Divorced
   - Widowed

2. **Highest level of education completed:**
   - Primary school
   - Secondary school (Grades 8, 9, 10)
   - Secondary school (Grades 11, 12)
   - Vocational/Apprenticeship/Trade Certificate
   - Associate Diploma/Diploma
   - Undergraduate Degree
   - Postgraduate Degree
   - Other (please list) __________

3. **Employment status before the ICU admission:**
   - In paid Full time work
   - In paid Part time work
   - In paid Casual work
   - If in paid work, how many hours per week do you usually work? ______
   - Retired
   - Student
   - On Disability Benefit
   - Unemployed
   - Other (Please specify) __________
4. Have you ever visited a general practitioner (GP) or a mental health professional for symptoms of psychological distress or emotional problems?

Yes        No

5. Please record how often in the last 12 months you have smoked (please underline).

Daily       Weekly       Less than weekly       Ex-smoker       Never-smoker

6. How many cigarettes (manufactured or roll-your own) did you used to smoke per day previous to the ICU stay? ____________

7. Where you taking any of the following medications before the ICU admission (12 months)?

   Corticosteroids replacement therapy (Hydrocortisone, prednisone, prednisolone)
   Other, please list ________________  Yes        No

   Opioids (e.g. morphine, MSContin, OxyContin, fentanyl, methadone)
   Other, please list ________________  Yes        No

   Benzodiazepines, anxiolytics, antidepressant (e.g. diazepam, alprazolam, oxazepam)
   Other, please list ________________  Yes        No

   Beta-blockers (e.g. propranolol, metoprolol)
   Other, please list ________________  Yes        No
## Appendix 19: ICU data flow sheet

<table>
<thead>
<tr>
<th>Patient's Name</th>
<th>Hospital Admit Date</th>
<th>ICU Admit Date</th>
<th>ICU D/C Date</th>
<th>Hospital D/C Date</th>
<th>LOICUS ___days</th>
<th>LOHS ___days</th>
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<tbody>
<tr>
<td>URN</td>
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<table>
<thead>
<tr>
<th>Consented Y / N</th>
<th>Age</th>
<th>DOB</th>
<th>Gender</th>
<th>Marital status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y / N</td>
<td></td>
<td></td>
<td>F / M</td>
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### Anxiety Assessments

<table>
<thead>
<tr>
<th>Date</th>
<th>Anxiety AM</th>
<th>Comments</th>
<th>Anxiety PM</th>
<th>Comments</th>
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316
## Appendix 20: Medications data collection instrument

<table>
<thead>
<tr>
<th>Total doses of benzos, opioids, analgesics, anxiolytics, corticoids, and beta-blockers in milligrams (mg)</th>
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<tbody>
<tr>
<td>Medication / Date</td>
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<tr>
<td>Scheduled (mg)</td>
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<tr>
<td>One-time &amp; stat (mg)</td>
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<td></td>
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<tr>
<td>PRN (mg)</td>
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<td></td>
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<tr>
<td>Continuous (mg)</td>
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</table>
Appendix 21: Mechanical ventilation data collection instrument

<table>
<thead>
<tr>
<th>Date</th>
<th>Invasive MV (hrs)</th>
<th>Non-invasive MV (hrs)</th>
<th>Fentanyl (hrs)</th>
<th>Midazolam (hrs)</th>
<th>Propofol (hrs)</th>
<th>Morphine (hrs)</th>
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MV: Mechanical Ventilation; hrs: hours.
*Any sedative or analgesic given as continuous infusion

320
## Appendix 22: Follow up data flow sheet

<table>
<thead>
<tr>
<th>URN</th>
<th>Study No</th>
<th>Name</th>
<th>Consent date</th>
<th>Surveys back date</th>
<th>2\textsuperscript{nd} follow up date</th>
<th>Comments</th>
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