ABSTRACT

Introduction There are little published data on the long-term psychological outcomes in intensive care unit (ICU) survivors and their family members in Australian ICUs. In addition, there is scant literature evaluating the effects of psychological morbidity in intensive care survivors on their family members. The aims of this study are to describe and compare the long-term psychological outcomes of intubated and non-intubated ICU survivors and their family members in an Australian ICU setting.

Methods and analysis This will be a prospective observational cohort study across four ICUs in Australia. The study aims to recruit 150 (75 intubated and 75 non-intubated) adult ICU survivors and 150 family members of the survivors from 2015 to 2018. Long-term psychological outcomes and effects on health-related quality of life (HRQoL) will be evaluated at 3 and 12 months follow-up using validated and published screening tools. The primary objective is to compare the prevalence of affective symptoms in intubated and non-intubated survivors of intensive care and their families and its effects on HRQoL. The secondary objective is to explore dyadic relations of psychological outcomes in patients and their family members.

Ethics and dissemination The study has been approved by the relevant human research ethics committees (HREC) of Australian Capital Territory (ACT) Health (ETH.11.14.315), New South Wales (HREC/16/HNE/64), South Australia (HREC/15/RAH/346). The results of this study will be published in a peer-reviewed medical journal and presented to the local intensive care community and other stakeholders.

Trial registration number ACTRN12615000880549; Pre-results.

INTRODUCTION

Over the last two decades, numerous long-term-outcome studies have shown that survivors of critical illnesses can suffer from a complex, myriad of health and socio-economic issues, long after discharge from hospital. Initial seminal studies on long-term outcomes in critical illnesses are based on survivors of Acute Respiratory Distress Syndrome (ARDS), a condition traditionally treated with invasive ventilation, sedation and muscle relaxants. Long-term outcomes of acute lung injury and ARDS survivors have been extensively studied, with emerging evidence of long-term follow-up outcomes in other categories of intensive care unit (ICU) survivors. The term ‘Post Intensive Care Syndrome’ was framed to describe new or worsening impairments in physical, cognitive or mental health status developing after an episode of critical illness and persisting beyond discharge.

Based on the above research, it has been established, beyond reasonable doubt, that a significant proportion of ICU survivors experience long-term psychological consequences, including post-traumatic stress disorder (PTSD),
anxiety and depression.16–20 The reported prevalence of adverse neuropsychiatric outcomes in intensive care survivors varies across studies. A recent systematic review of the literature from 2008 to 2012 suggests that up to 27% of ICU survivors suffer from PTSD.21 On the other hand, another recent study from the USA found that the prevalence of PTSD in ICU survivors was 16% at 3 months post ICU.22 A systematic review of the literature reveals that the reported prevalence of anxiety in ICU survivors ranges from 23% to 48% and 17% to 43% for depression.19 Another study shows an incidence of 31% for depressive symptoms, post ICU.22 Literature review suggests that the severity of illness as evidenced by the need for intubation, mechanical ventilation and sedation is an important risk factor for psychological stress in ICU survivors.23–26 However, there is very little literature on the incidence of psychological stress, post-ICU, in patients who do not need sedation, intubation or mechanical ventilation. Interventions to reduce PTSD in ICU survivors have excluded the less severe patient populations (not intubated and ventilated).27 It is possible the incidence of psychological symptoms in such a population is low, but this remains only a conjecture.

Published literature also suggests that a high proportion of family members of intensive care patients are left with varying psychological symptoms that can include anxiety, depression and PTSD.28–31 Some of the possible precipitating factors impacting the family’s psychological state include a concern for the nature of the patient’s critical illness, perception of inadequate communication in the ICU, lack of adequate understanding of the patient’s illness, concerns about the patient’s prognosis, surrogate decision making on end-of-life care and the prospect of providing continuing care to survivors.29 32 33

Family members and ICU survivors can essentially be considered a dyad and interactions between the dyads could have an influence on the physical and psychological health and health-related quality of life (HRQoL) outcomes of both.34 The emotional interdependence between ICU survivors and their spouses has been studied in a subset of adult sepsis and chronic critically-ill survivors.35 36

To date, there is little data from Australian ICUs about the prevalence of psychological stress in ICU survivors and their family members. Drawing comparisons between prevalence rates across the continents from studies predominantly originating in America and Europe may not be helpful due to the variation in critical care services.37 In addition, emotional interdependence of dyads of ICU survivors and their family members have not been previously studied in a diverse group of ICU survivors and family members.

The primary aim of this multicentre study is to determine and compare the prevalence of affective symptoms in intubated and non-intubated ICU survivors and family members by screening them for PTSD, anxiety, depression and HRQoL over a 12-month follow-up period. The secondary aims are to explore the dyadic relations of psychological outcomes in patients and their family members.

We anticipate that the Psychological Stress in Intensive Care survivors (PRICE) study will provide significant insight into the impact of affective symptoms on post-intensive-care survivors, especially the non-intubated groups and their family members as they have been previously excluded from studies. This will contribute to the existing body of knowledge, especially the interdependence between survivors and their family members.

**METHODS AND ANALYSIS**

**Study design**

PRICE is a multicentre, prospective, observational cohort study reviewing ICU survivors and their family members. The groups will be formed based on the following ICU admission characteristics: a) Intubated group: intubated ICU survivor and family member, b) Non-intubated group: non-intubated ICU survivor and family member.

**Setting**

The study will be conducted in four ICUs in Australia: The Canberra Hospital, Australian Capital Territory; Nepean Hospital and John Hunter Hospital, New South Wales and Royal Adelaide Hospital, South Australia. All the four ICUs are part of large public teaching hospitals. Local principal investigators, in conjunction with local research teams, will conduct the trial in their respective hospitals. It is estimated that the study will take 3 years (2015–2018) to complete recruitment and follow-up.

**Study population**

The study population will include adult (18 years and older) ICU survivors and their family members who have been discharged from the ICU during the study period. Detailed inclusion and exclusion criteria are as follows:

**ICU survivors**

**Inclusion criteria**

A. Intubated ICU survivor:
- Able to provide valid, informed consent after ICU discharge.
- Intubated and mechanically ventilated for more than 24 hours.
- Stayed in the ICU for more than 72 hours.

B. Non-intubated ICU survivor:
- Able to provide valid, informed consent after ICU discharge.
- Not intubated during current ICU stay.
- Received inotropic/vasopressor support and/or non-invasive ventilation during ICU stay.

**Exclusion criteria**

- Prior history of a psychiatric disorder/s in patient (psychotic disorders, chronic PTSD).
- Imminent death/palliative care patient (unlikely to be alive at follow-up at 3, 12 months).
- Suspected acute primary brain lesion that may result in global impairment of consciousness or cognition, such as traumatic brain injury, intracranial haemorrhage, stroke or hypoxic brain injury.
- Unable to give informed consent prior to hospital discharge.

**Family members**

**Inclusion criteria**

- Adult family members of ICU survivors.
- Companions of ICU survivors who have provided valid, informed consent.
- Aged 18 years and older.

**Exclusion criteria**

- Intubated ICU survivor.
- Non-intubated ICU survivor.
- Not a family member of ICU survivor.
- Unable to provide informed consent.

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- Unable to give informed consent prior to hospital discharge.
► Non-English speaking background.

**Family members**

**Inclusion criteria**

► Family member (spouse/partner/next of kin/lives with patient normally) of a consenting ICU patient with the above criteria.
► Age 18 years and older.

**Exclusion criteria**

► Refusal of consent from the associated ICU survivor (as detailed below).
► Unable to give informed consent prior to hospital discharge.
► Non-English speaking background.

Patients will be screened for eligibility by the research staff in the participating ICUs after discharge from the ICU. Research staff will approach medical and nursing teams in the hospital wards to seek their permission to approach the patients and also to confirm that the patients are not delirious and can provide appropriate consent. Absence of delirium will also be confirmed by reviewing the ward medical and nursing notes for the previous 24–48 hours before approaching the patients. Only patients with concerns about unresolved delirium in the hospital will be excluded.

Hospital records for patients will be checked for next of kin details and this will be confirmed from the patient. Patients and family members will be explained about the study and provided with the appropriate study information sheet (online supplementary appendix 1 and 2). Opportunities will be given for follow-up questions prior to seeking study consent. The consent form (online supplementary appendix 3 and 4) will have an option for the participants to only participate in a postal follow-up survey. Consenting patients included in the study will have follow-up assessments, even if the family member declines to participate. Consenting family members will not be recruited if the patient declines to participate, as it will not be possible to gather patient demographic data without patient consent. Those enrolled will also be encouraged to contact the principal researcher at any time if they need further clarification on any aspects of the study.

**Follow-up**

The initial (baseline) assessments with consenting patients and families will be conducted in-hospital after ICU discharge using validated screening tools as described below. Patient and family member contact details (name, mailing address, contact numbers) will be collected to enable contact for the 3 and 12 months’ assessments. If a participant is lost to follow-up at 3 months, they will continue to be included in the study until the next follow-up at 12 months. Participant follow-up will include postal and phone follow-ups. Hospital databases will be screened to obtain information to confirm their discharge from hospital and any recorded death of the patients before attempting to contact the participants. In the event of a recorded patient death, no attempt will be made to contact participating families in an attempt to avoid distress. If hospital records indicate that the patient continues to be a hospital in-patient or has been readmitted to hospital during the designated follow-up time period, researchers will meet with him/her personally to check his/her well-being and deliver the assessment tools. Participants will be considered lost to follow-up if neither 3 or 12-month follow-up data is available. If the patient or the family member revoke consent, they will be withdrawn from the study and neither the patient nor the family member will be approached about the study again.

**Figure 1**

Assessment tools and follow-up intervals. DASS-21, Depression and Anxiety Stress Scales-21; EQ-5D-5L, 5-level Health-Related Quality of Life tool (EuroQol group); IES-R, Impact of Event Scale-Revised; PTSS-14, Post-Traumatic Stress Syndrome-14 intensive care screening tool.

**Screening tools**

Post-Traumatic Stress Syndrome-14 (PTSS-14) is a 14-item screening tool to identify patients at risk of suffering PTSD in ICUs.38 39 PTSS-14, although not a diagnostic tool, is a self-reporting screening tool; each item is rated 1 (never) to 7 (always) with a total score ranging from 14 to 98 (online supplementary appendix 5).

Impact of Event Scale–Revised (IES-R), has 22 questions to better capture the DSM-IV criteria for PTSD10 11 (online supplementary appendix 6). The tool, though not diagnostic for PTSD, is an appropriate instrument to measure the subjective response to a specific traumatic event, especially in the response sets of intrusion (intrusive thoughts, nightmares, intrusive feelings and imagery, dissociative-like re-experiencing), avoidance (numbing of responsiveness, avoidance of feelings, situations and ideas), and hyperarousal (anger, irritability, hypervigilance, difficulty concentrating, heightened startle).

Depression and Anxiety Stress Scales-21 (DASS-21) is a screening tool for identifying, differentiating and
assessing depression, anxiety, and stress. DASS-21 consists of 7 items per scale. DASS allows a way to measure the severity of a patient’s core symptoms related to depression, anxiety and stress (online supplementary appendix 7). In addition, DASS has Australian normed values for drawing comparisons with.

All the above screening tools are short self-administered scales, each taking about 3 to 5 min to administer and will not overtire patients who could still be weak. Importantly, these screening tools are used to assess symptoms of affective disorders and do not replace a clinician-administered diagnostic interview, which needs significant time and professional expertise to complete.

The prevalence of PTSD symptoms will be obtained by using the PTSS-14 for ICU survivors and IES-R for the family members. To screen for anxiety and depressive disorders, DASS-21 tool will be administered to survivors and their family members. In addition to the above tools at 3 and 12 months follow-up, the ICU patient survivors and family members will be assessed for their HRQoL using the EQ-5D-5L questionnaire (https://euroqol.org/wp-content/uploads/2016/10/Sample_UK___English_EQ-5D-5L_Paper_Self_complete_v1.0__ID_24700.pdf).

The lead investigator has obtained permission to use the questionnaires for the study via e-mail correspondence with Dr Emma Twigg (PTSS-14), Prof Daniel Weiss (IES-R) and the EuRoQol Research Foundation (EQ-5D-5L), while the DASS-21 tool is freely available.

### Managing participant distress

In general terms, the investigators will deal with participant distress using the LAST approach:

- **L**isten to concerns.
- Acknowledge participant’s distress.
- **A**ssist them by first apologising for raising the matter with them and then provide information about seeking appropriate counselling.
- **S**tart by thanking the participants for their involvement in the study to date.

In the case of distress in study participants at the time of the telephone survey, trained ICU research staff will enact the above protocol and the study investigators will attempt to make contact with the participant within 72 hours to ensure their well-being. At this time the distressed participants will be advised to see their General Practitioner, to have the investigators organise this contact for them, if they so wish.

Study participants will not immediately be excluded from the study at this stage as they may feel that they will benefit from the increased oversight provided by the study. However, they will be asked directly if they still want to continue in the study. In the case of a refusal to continue with the study, the participants will be excluded from any further contact by the ICU research staff.

### Data collection

#### Screening log

A screening log will be maintained to identify reasons for non-recruitment and withdrawal of consent.

#### Baseline data

Once consent is obtained, retrospective chart data will be collected as follows:

- Demographic data at the time of ICU admission [age, sex, Acute Physiology And Chronic Health Evaluation (APACHE) II Score, APACHE III Diagnosis, type of ICU admission [trauma/emergency surgical/medical]].
- Duration and type of mechanical ventilation in ICU (invasive/non-invasive).
- Types of sedative drugs used during ICU stay, especially use of benzodiazepines and dexmedetomidine.
- Record of routine sedation scores used in the participating ICU (if any).
- Record of delirium assessment by Confusion Assessment Method for the ICU scale or any other validated tool (if available) during their ICU stay.
- Review of new onset antipsychotic medications administered in the ICU (haloperidol, olanzapine, risperidone, quetiapine).
- Cumulative fluid balance during ICU stay.
- Length of ICU stay.
- Length of hospital stay.
- Discharge destination from ICU and hospital (home/rehabilitation hospital/nursing home).

#### Data management and statistical analysis plan

The confidentiality of the participant data will be maintained unless disclosure is required by law. Participants will not be identified by name, and confidentiality of the information derived from medical records will be preserved. All data, including paper-based Contact Report Form will be stored securely. The electronic database will be maintained in a password-protected computer maintained on secure government servers.

#### Power

The primary aim of the study is to characterise the long-term psychological outcomes (affective symptoms) in Australian intensive care survivors and family members. The study investigators performed a power calculation to compare the difference in prevalence between the intubated and non-intubated group. A sample size of 62 patients in the intubated group and 62 in the non-intubated group will provide 80% power to detect a statistically significant difference between the two groups, with an underlying prevalence of post-ICU affective symptom estimate of 30% and 10% in the intubated and non-intubated populations, respectively, using X² tests at a significance level of 5%. The estimate rate for the populations was based on literature review as described below. Based on literature, a potential attrition rate of 20% will be used for the 3 and 12-month follow-up and hence, the study.
will plan to recruit 150 participants (75 patients and 75 family members) in each of the groups. Sample size calculations were performed using Stata V. 12.1.

The prevalence of affective symptoms in ICU survivors varies widely between studies based on the screening assessment tools. An assumed prevalence of 30% in the study group was based on a broad literature review. The review by Davydow et al across several studies revealed a median point prevalence of substantial questionnaire-ascertained substantial PTSD symptoms of 22%. In another review by Davydow et al, the median point prevalence of substantial PTSD symptoms in ARDS was 28%. In a recent review, Myrhen et al showed that a significant proportion of the patients (26.9%) had severe PTSD-related symptoms. The incidence of depressive symptoms in ICU survivors has also been noted to be between 28%–30%.

The prevalence of psychological/emotional stress varies in the family members of ICU survivors. The incidence of anxiety, PTSD and depression among family members of ICU survivors is high at the time of the ICU admission of their loved ones, but this decreases post discharge, and is variably quoted between 20% and 40% in various studies. There is no specific literature related to psychological outcomes in non-intubated ICU patients. Australian population prevalence rates for PTSD are approximately 5% and 10% for anxiety and depression, respectively. Hence, a composite estimate of 10% was used for the non-intubated group.

Statistical analysis plan
Patient demographic and baseline characteristics in the two patient cohorts will be summarised using means, SD, medians, and 25%–75% quartiles for continuous measures and frequencies and percentages for categorical measures. ICU patient survivor outcomes (PTSS-14 and DASS-21) at baseline and at 3 and 12-month follow-ups will be compared between the groups using a mixed model analysis. A time by group interaction will be tested. Means and standard errors for PTSS-14 and DASS-21 scores for each time period and risk group will be presented and compared. ICU patient family member outcomes using IES-R and DASS-21 will be analysed similarly. The EQ-5D-5L evaluates HRQoL using 5-point intensity rating scales ranging from ‘none’ to ‘severe’, with high scores indicating severe issues in the domain. Once the total score has been summed, an algorithm will be used to convert the score, consistent with the approach used by the scale authors. Index scores will then be compared with a UK dataset, as advised and confirmed by e-mail correspondence with the EQ-5D-5L Research Foundation. For the purposes of the primary outcome, missing data would be ignored.

Associations in the prevalence of affective disorders between patients and their family members will be explored using a modification of an actor-partner-interdependence model. In particular, the plan is to model the probability of affective disorders among patients and family members at 3 and 12 months using a multilevel generalised mixed model, using a nested variance structure with family unit as a random effect, and family member nested within family unit. Covariates of interest will include the affective disorder status of patient/family members at the preceding time, as well as patient characteristics for example, intubation status.

All analysis will be two-tailed, and p-value <0.05 will be considered statistically significant. All analyses will be performed using SPSS V. 22.

Patient and public involvement
The PRICE study protocol was reviewed by the local human research ethics committees (HREC), which routinely have community and consumer representatives. Protocol review by HREC involved community views and feedbacks, which contributed to the final study protocol. Patients were not involved in the recruitment and conduct of the study. Where requested, results will be disseminated to the study participants in the form of a published manuscript.

ETHICS AND DISSEMINATION
This study will be performed in accordance with the ethical principles of the Declaration of Helsinki and National Health and Medical Research Council National Statement on Ethical Conduct in Research Involving Humans (March 2007). The principal investigator will ensure adherence to these guidelines. Amendments to the study protocol will be submitted for ethical approval. The results of this study will be published in a peer-reviewed medical journal and presented to the local intensive care community and other stakeholders.

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Acknowledgements Helen Rodgers for advice with ethics and assistance with creating the PRICE database. Miranda Hardie and Alexis Poole for their assistance with local ethics and site governance.

Contributors SR is the chief investigator of the multicenter study, PRICE.SR, RB, IM wrote the first draft of the manuscript.SR, RB, FVH, TN, KS, AR, IM all contributed to the study design.SR, IM were co-applicants on the ACT Health Private Practice Fund grant.KS, SR were co-applicants on the Maurice Sando Foundation Sponsorship Scheme. All authors have critically evaluated and approved the manuscript.

Funding This work was supported by the ACT Health Private Practice Fund and Maurice Sando Foundation Sponsorship Scheme 2015 by a local competitive grant process.
Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study has been approved by the relevant human research ethics committees (HREC) of Australian Capital Territory (ACT) Health (ETH.11.14.315), New South Wales (HREC/16/NHH/64), South Australia (HREC/15/RAH/346). Individual hospitals will obtain approval from their local site-specific governance committees.

Provenance and peer review Not commissioned; externally peer reviewed.

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