SLEEP AND COGNITION AFTER ICU ADMISSION

By

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Abstract

As survival rates from critical illness improve, strategies to return patients to their pre-morbid cognitive and functional status are important research priorities. Upwards of 9 out of 10 ICU survivors will suffer some degree of cognitive impairment at hospital discharge and approximately half will have decrements that persist for years. While the mechanisms for this newly acquired brain injury are poorly understood, several risk factors have been identified. Unfortunately, it is unclear how to accurately predict long-term cognitive impairment. We undertook a multisite, prospective, longitudinal cohort study of sleep, electroencephalography and cognitive outcome in survivors of critical illness. Our hypotheses being that sleep and circadian disruption would negatively impact long-term cognitive impairment in survivors of critical illness, a relationship that may be modified by Apolipoprotein E genotype. Further, cortical electrophysiological activity may predict, and therefore serve as an intermediate endpoint, long-term cognitive outcomes. In our cohort, the quantity and quality of sleep remained poor on the ward after ICU but was not terribly dissimilar to that experienced by patients hospitalized for noncritical illness by literature review. A number of risk factors for poor sleep including admission diagnosis (sepsis, post-operative admission, higher severity of

illness). The other key finding of our cohort study was that rest-activity fragmentation was associated with worse cognitive impairment shortly after ICU discharge. This relationship, however, was lost at 6- and 12-months follow-up. Sleep and circadian variables studied did not seem to predict cognitive impairment at 6- or 12-months after ICU discharge. As the first multisite study to comprehensively examine the relationship between sleep, circadian function, and long-term cognitive impairment in survivors of critical illness, the single greatest limitation of this study is its internal validity as we experienced high losses to follow-up and unanticipated deaths. A larger study with more frequent covariate sampling might better elucidate the trajectory of recovery between sleep, circadian rhythm and long-term cognition.

Promising preliminary analyses of electroencephalography data would suggest that early poor cognitive performance after ICU discharge correlates with changes primarily seen in subcortical white matter. Further analyses of this data are ongoing.

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Contributions

Elizabeth Wilcox (author) solely prepared this thesis. All aspects of the body of this work including the planning, execution, analysis and writing of all original research and publications was performed in whole or in part by the author. The following contributions by other individuals are formally and inclusively acknowledged:

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CHAPTER 3 HYPOTHESES AND APPROACH

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List of Abbreviations

ICU – Intensive Care Unit
ARDS – Acute Respiratory Distress Syndrome
MMSE – Mini Mental Status Examination
TICS – Telephone Interview for Cognitive Status
CASI – Cognitive Abilities Screening Instrument
BNIS – Barrow Neurological Instrument Screening of Cognitive Function
MOCA – Montreal Cognitive Assessment
MCI – Mild Cognitive Impairment
APACHE –
APO – Apolipoprotein
OR – Odds Ratio
SD – Standard Deviation
IQR – Interquartile Range
BDI – Beck's Depression Inventory
PSG – Polysomnography
EEG – Electroencephalography
BIS – Bispectral Index
RCSQ – Richard Campbell Sleep Questionnaire
HRQOL – Health Related Quality of Life
ADL – Activities of Daily Living
IADL – Instrumental Activities of Daily Living
IQCODE – Informant Questionnaire on Cognitive Decline in Elderly
LOS – Length of Stay
PSQI – Pittsburgh Sleep Quality Index
RBANS – Repeatable Battery for the Assessment of Neuropsychological Status
CIND – Cognitive Impairment without Dementia
GEE – general estimating equations
SWS – Slow wave sleep
CAM – Confusion Assessment Method
REM – Rapid eye movement
iCORE – Toronto Intensive Care Observational Registry
TST – Total sleep time
SE – Sleep efficiency
IS – Interdaily stability
IV – Intradaily variability
TNF – Tumor necrosis factor
IL – Interleukin
WASO – Wake time after sleep
AD – Alzheimer's disease
TMT – Trail making test
GLM – General linear methods

Chapter 1 GENERAL INTRODUCTION

1.0 Preamble

Mortality from critical illness has decreased significantly over the past two decades and as a result the number of intensive care unit (ICU) survivors is increasing. These survivors frequently have newly acquired physical and cognitive impairments. Patients have made it clear that maintenance of cognitive function after critical illness is a leading priority (Fried et al. 2002). However, attempts to intervene in the post-critical illness period to improve cognitive outcomes of ICU survivors have met with limited success. To date, two randomized trials have evaluated prevention or treatment strategies to improve long-term cognitive outcomes after critical illness (Brummel et al. 2012; Jackson et al. 2012). Both were pilot studies testing the feasibility of combined physical and cognitive therapy interventions instituted in the ICU or at home after hospital discharge. The former found no evidence that early physical and cognitive therapy in the ICU affects long-term cognitive outcomes, whereas the latter suggested in-home therapy may reduce cognitive impairment. Neither trial was designed to provide more than feasibility data. As these strategies are both costly and resource intensive, an important knowledge gap is the ability to predict or identify those patients at high risk for long-term cognitive impairment, which may or may not be those survivors most likely to benefit from cognitive rehabilitation strategies. By exploring risk factors and markers for long-term cognitive impairment, we hope to better understand specific mechanisms of post-ICU brain injury so as to better inform the design of future interventional trials.

1.1 Thesis Organisation

This thesis is organized in a “multiple paper format” rather than a traditional “continuous design”. The chapters within contain mainly unaltered peer-reviewed content. This structure best reflects the sequential unfolding of results from this longitudinal cohort study and future projects resulting from this continuing work. Chapter 2 primarily serves to review the literature on cognitive outcomes and sleep after critical illness and is largely derived from a systematic review (Wilcox et al. 2013). The chapter that follows is the published protocol of our longitudinal cohort study (Wilcox et al. 2017). Chapters 4 (Wilcox et al. 2018) and 5 (Wilcox et al. 2019) present original research describing sleep on the wards after critical illness whereas

Chapter 6 (Wilcox et al. *Under review*) addressed the first two aims of our cohort investigating the influence of sleep and long-term cognitive outcome. Chapter 7 introduces preliminary data addressing our final aim of the study, investigating correlates between electroencephalography over time and long-term cognitive outcome. In addition, Chapter 7 briefly summarizes key findings, experienced challenges (Wilcox and Ely, 2019) and general conclusions of the thesis. In addition, ongoing and specific future directions are outlines in the discussion sections of Chapters of 4, 5 and 6 and are complemented by related general future thoughts in Chapter 7.

Chapter 2 LITERATURE REVIEW

This chapter is modified from the following:

Wilcox, ME et al. (2013). Cognitive dysfunction in ICU patients: risk factors, predictors, and rehabilitation interventions. Critical Care Medicine, 41(9):s81-98.

2.0 Abstract

In contrast to other clinical outcomes, long-term cognitive function in critical care survivors has not been deeply studied. In this narrative review, we summarize the existing literature on the prevalence, mechanisms, risk factors and prediction of cognitive impairment after surviving critical illness. Depending on the clinical subgroup, up to 100% of critical care survivors may suffer some degree of long-term cognitive impairment at hospital discharge and in approximately 50%, decrements in cognitive function will persist years later. While the mechanisms of acquiring this impairment are poorly understood, several risk factors have been identified. Unfortunately, no easy means of predicting long-term cognitive impairment exists. Despite this barrier, research is ongoing to test possible treatments for cognitive impairment. In particular, the potential role of exercise on cognitive recovery is an exciting area of exploration. Opportunities exist to incorporate physical and cognitive rehabilitation strategies across a spectrum of environments (in the ICU, on the hospital ward and at home, post-hospital discharge).

2.1 Introduction

Critical illness adversely affects short- and long-term cognitive function. Profound and persistent deficits in memory, attention/concentration and executive function negatively impact the functional status and health related quality of life (HRQOL) of survivors of critical illness. Recent investigations demonstrate that cognitive impairment is associated with psychological morbidity (anxiety and depression) and influences the ability to return to work (Herridge et al. 2003; Herridge et al. 2011; Hough and Herridge 2012; Rothenhausler et al. 2001; Hopkins and Brett 2005; Needham et al. 2013). This chapter provides a review of the prevalence of cognitive impairment in survivors of critical illness, describes risk factors associated with long-term cognitive function in these patients and finally, reports on studies for the prevention and rehabilitation.

2.2 Studies of Cognitive Impairment in Critical Illness

2.2.1 Methods

A literature search for all articles pertaining to critical illness and cognitive outcome was conducted using MEDLINE (1996 to January Week 4 2019) and EMBASE/EMBASE classic (1947 to 2019 Week 4) databases. Search terms included “critical illness”, “intensive care”, “ICU”, “dementia”, “cognition disorders”, “mild cognitive impairment”, “cognitive impairment”, “cognitive sequelae”, “neuropsychological impairment”, “dementia”, and “neurocognitive tests”. Specific inclusion criteria were applied; studies had to assess neurocognitive outcomes in a critically ill patient population and in so doing, have employed an objective measure of cognitive function.

2.2.2 Results

The search identified 1308 citations of potential relevance; six citations were identified through hand searches. After applying the inclusion criteria, 62 studies were considered in this review; abstracts that were published greater for more than 5 years and not published in full text at the time of the search were not included. Of these 62 studies, 14 studies reported cognitive outcomes in acute respiratory distress syndrome (ARDS) survivors, 4 studies in sepsis or septic

shock populations, 37 in mixed populations of medical and surgical ICU patients, and 7 studies were excluded as patient populations with moderate-severe traumatic brain injury or another primary neurological injury. The time to follow-up and the measures used in assessing cognitive function were highly variable. Further, a range of tools were used to determine if cognitive impairment.

2.3 Prevalence of Cognitive Impairment in ICU Survivors

In survivors of ARDS (n=1176; 14 studies; 11 distinct patient cohorts) the median time to follow-up was 12 months (range, 1-241 months). At hospital discharge, 70-100% of patients were determined to have cognitive impairment (Table 2.1). At 6- and 12-months follow-up, the prevalence of cognitive impairment was 34-79% and 25-78%, respectively. The domains of cognitive function most commonly affected were attention and concentration, memory, and executive function, though these domains were not assessed with equal depth or breadth across studies. In survivors of sepsis (n=1263; 4 studies), patients were followed-up at ICU discharge up until 8.3 years. Again, a range in domains of cognitive dysfunction was seen. Of note, there was an increase of 11% prevalence in moderate to severe cognitive impairment in patients surviving an ICU admission for sepsis. Thirty-seven studies (n=6388) have evaluated cognitive outcomes in general medical and surgical ICU patients. Again, there was a variable length of time to follow-up cognitive testing, with a median of 12 months (range, 2 weeks to 6 years). Cognitive impairment in varying domains was seen in 39-91% of patients at the time of hospital discharge, 17-57% at 3 to 6 months follow-up and 10-71% at 12 months. Again, multiple domains of cognitive function were affected including but not limited to attention, memory and executive function. Of note, rates of cognitive impairment were highest in patients who suffered traumatic brain injury, stroke or subarachnoid hemorrhage and required an ICU admission as compared to general medical or surgical ICU survivors.

2.4 Definitions of Cognitive Impairment after ICU

Comparison of cognitive impairment rates across studies is difficult as different batteries have been employed and widely divergent definitions of impairment used (Table 2.2). Four studies

report that memory complaint was obtained from self-report. Twenty-one studies used a screening test for general cognitive function; this was typically operationalized using the Mini Mental Status Examination (MMSE) score either alone or in combination with other measures including: a structured interview with the patient and informant, the Telephone Interview for Cognitive Status (TICS), the Cognitive Abilities Screening Instrument (CASI), the Barrow Neurological Instrument Screening of Cognitive Function (BNIS), the Montreal Cognitive Assessment (MOCA), or other. In 34 studies, formal neuropsychological testing was performed; numerous different tests were used to assess cognition. In addition to inconsistency in test selection, there was no consistency in impairment severity (e.g., 1 SD, 1.5 SDs or 2 SDs below the mean). Further, it was not always stated whether cut-off scores for impairment were adjusted for age, education or premorbid ability.

It is unclear as to how best practice is to be derived from the current state of the literature. A priority for clinical research would be to agree on a uniform set of criteria to operationalize cognitive impairment in this patient population. A suggestion would be, and what we have done, is to utilize the current Petersen and colleagues (2014) definition of mild cognitive impairment (MCI), an intermediate state between normal aging and dementia. MCI has become a focus for trials to prevent or delay progression to Alzheimer's disease; the expectation being that positive results with intervention are more likely to be achieved with earlier implementation. A similar goal pertains to our population of interest and therefore it is presumed that a similar definition for cognitive impairment may best identify the patients most likely to benefit from future intervention.

2.5 Reported Covariates in after ICU studies

Interestingly, but not surprisingly, there was variable reporting of important covariates (Table 2.2). The most commonly reported covariates were age and sex; level of education was reported in approximately half of studies (31/61, 51%). Severity of illness, duration of ICU or hospital stay, use of sedative agents, and incident delirium were also inconsistently reported.

2.6 Factors Associated with Cognitive Impairment

Studies to date have largely focused on describing cognitive outcomes in survivors of critical illness, with relatively few describing possible risk factors or mechanisms linking critical illness to subsequent impairment. The pathogenesis of cognitive impairment following critical illness is not fully understood but may represent an accelerated neurodegenerative process that develops in vulnerable hosts (e.g., older age, pre-existing cognitive dysfunction, genetic predisposition via Apolipoprotein E ε4, diminished cognitive reserve) or newly acquired brain injury due to insults associated with critical illness (e.g. hypoxemia, hypotension, anemia, fever, hyperglycemia, systemic inflammation, severe sepsis, pharmacologic agents, renal failure, and liver failure).

Histopathology and neuroimaging studies indicate specific patterns of brain injury associated with sepsis or ARDS (Janz et al. 2010; Hopkins, Gale, and Weaver 2006; Morandi et al. 2012; Gunther et al. 2012). A single small case series reported brain autopsy findings of patients whose critical illness was complicated by delirium reported that ischemic and hypoxemic hippocampal lesions were present in of 5 (71%) of 7 patients (Janz et al. 2010). Hopkins and colleagues, in an observational study of CT imaging in ARDS survivors, found that significant brain atrophy and ventricular enlargement was present when compared with matched control subjects (Hopkins, Gale, and Weaver 2006). Recently, Gunther and colleagues reported correlates between findings on brain imaging and neurocognitive testing (Gunther et al. 2012). In a cohort of medical and surgical ICU patients who were screened daily for delirium, patients who suffered a longer duration of delirium had greater overall brain atrophy and ventricular enlargement as well as smaller superior frontal lobes and hippocampal volumes 3 months following hospital discharge. At 1-year, these anatomical findings were associated with worse overall cognitive performance (in the case of overall brain atrophy) and worse executive functioning (in the case of superior frontal lobe atrophy) (Gunther et al. 2012). A second study, from the same cohort, reported that delirium duration was also associated with loss of white matter in the corpus callosum and internal capsule (representing disruptions of functional connectivity within the brain). These findings were present in survivors of critical illness at the

time of hospital discharge and persisted at 3-months follow-up. Changes on neuroimaging were associated with worse overall neurocognitive performance at 1-year follow-up (Morandi et al. 2012). Finally, left hippocampal volumes on MRI were markedly reduced in a cohort of patients with septic shock, compared to healthy controls, at 6 to 24 months follow-up (Semmler et al. 2013). The results of these preliminary histopathological and neuroimaging studies suggest that a variety of anatomic changes and disruption of functional connectivity are present among survivors of critical illness and that these changes may be responsible for the deficits seen on cognitive testing. The lack of baseline cognitive and neuroimaging data precludes definitive conclusions regarding strength of association of any causal associations, though it is increasingly clear that – in most cases – the cognitive impairment observed after critical illness is not simply a continuation of pre-existing deficits.

2.6.1 Patient-Associated Risk Factors

2.6.1.1 *Pre-existing Cognitive Impairment*

Although patients can develop cognitive impairment following critical illness *de novo* (Ehlenbach et al. 2010; Iwashyna et al. 2010), the role of pre-existing cognitive impairment as a risk for cognitive impairment following critical illness is unknown. Studies to date have enrolled younger cohorts of patients (e.g., where rates of pre-existing cognitive impairment are typically extremely low) or have excluded patients with severe dementia. One study, using data from the Mayo Clinical Study of Aging, reported the incidence of pre-existing cognitive impairment was higher (35%; n=136/387 patients) in patients admitted or transferred to the ICU, as compared to elderly patients admitted to hospital who didn't require ICU admission (18%; n=391/1733) (Teeters et al. 2011). Compared to patients without pre-existing cognitive impairment requiring ICU admission, patients with cognitive impairment were more likely to be older, male, and have a higher initial severity of illness score (APACHE III) (Teeters et al. 2011). These results suggest that pre-existing cognitive impairment is common among elderly patients admitted to ICUs. A study of patients with Alzheimer's disease who were hospitalized for an acute illness and developed delirium found a significant acceleration of cognitive decline over the course of next 5 years compared with patients who were never delirious (Gross et al. 2012).

These results suggest that among patients with pre-existing cognitive impairment, complications occurring during hospitalization may adversely affect cognitive trajectories following acute illness, perhaps due to the effects of decreased cognitive reserve. Whether these findings can be applied to patients with less severe forms of pre-existing cognitive impairment following critical illness requires further study.

2.6.1.2 *Apolipoprotein E ε4 (APOE ε4)*

Although there are no large studies of genetic susceptibility to cognitive impairment following critical illness, data suggest the APOE ε4 allele (a well-known genetic risk factor for Alzheimer disease) can have dramatic effects on the acute cognitive status of critically ill patients. In a study by Ely and colleagues, the APOE ε4 allele was associated with a seven-fold increase in the odds of a longer duration of delirium (OR 7.3; 95% CI, 1.8 - 30) (Ely et al. 2007). The presence of APOE ε4 was found to have a stronger association with duration of delirium than the covariates of age, severity of illness score (APACHE II), sepsis or benzodiazepine use (Ely et al. 2007). Although the duration of delirium is associated with worse cognitive performance after the ICU, the specific role of the APOE ε4 genotype in this association is unknown. Recent work in non-critically ill elderly patients by Pomara and colleagues found that benzodiazepine administration, a class of drugs commonly administered to ICU patients, in healthy elderly subjects (n=42) with the APOE ε4 allele was associated with more pronounced cognitive impairment and slower to recovery of cognitive functioning (Pomara et al. 2005; Pomara and Bruno 2011). Further, this association was found to be independent of deranged pharmacokinetics. Thus, the possibility arises that APOE ε4 may herald a more pronounced vulnerability to drug-related brain toxicity. The idea that certain genetic alleles may mediate and amplify the effects of specific drugs on the development of cognitive impairment has been relatively little studied. This concept however highlights a possible interaction between a susceptible host and an effect modifier through which worse cognitive impairment in survivors of critical illness might develop.

2.5.1.3 *Psychiatric Impairment (Pre-existing Depression)*

Few studies have explored the relationship between pre-existing psychiatric morbidity and long-term cognition following critical illness. Further, these studies used a variety of methods of varying rigor (e.g. prescription practices, chart review or surrogate reporting) to detect depression. The prevalence of baseline depression among these cohorts was 18%-28% (Jones et al. 2006; Weinert 2001; Kress et al. 2003). Unfortunately, none of these studies explored the association between pre-existing depression and long-term cognitive outcomes among survivors of critical illness. Nevertheless, depression is highly prevalent among survivors of critical illness, occurring in 10-58% of survivors of critical illness (Davydow et al. 2009; Adhikari et al. 2009; Adhikari et al. 2011; Weinert 2001). A recent systematic review examined 14 studies of depression in survivors of critical illness and found that one in three survivors of critical illness will suffer moderate to severe depressive symptoms, the exploration into the precise types of depression experienced by these individuals (e.g. Major Depressive Disorder vs. Dysthymia vs. Depressive Disorder not otherwise specified) has been minimal (Davydow et al. 2009). In a cross-sectional survey of 79 self-selected ARDS patients nearly half reported psychiatric morbidities and half of them had concomitant cognitive impairment (Mikkelsen et al. 2009). The most common deficiencies were in short-term memory and executive function. In another study, depressive symptoms (Beck Depression Inventory-II [BDI-II]) and memory complaints (Memory Assessment Clinics Self-rating scales-S) were shown to persist to 2 and 5 years follow-up (Adhikari et al. 2009; Adhikari et al. 2011). Median BDI-II scores were approximately 25% above age-adjusted population norms at 2 and 5 years. BDI-II scores can be influenced by physical complaints and the contributions to fatigue, lethargy, and sleepiness to elevated depression scores needs to be explored further. A higher BDI-II score at 2 years follow-up, longer duration of mechanical ventilation and delay in organ function recovery predicted worse BDI-II score at 5-year follow-up (Adhikari et al. 2009; Adhikari et al. 2011). In a prospective 2-year longitudinal study by Bienvenu and colleagues, pre-existing depressive symptoms were a risk factor for incident impaired physical function (Bienvenu et al. 2012). Thus, while the role of pre-existing depression on long-term cognitive outcomes is unclear, emerging data suggest that depression in the post-ICU period is associated with impaired

cognition and therefore may serve as a potentially treatable risk factor for cognitive impairment.

2.6.2 Clinical variables

2.6.2.1 *Hypoxia and Hypotension*

Data regarding the association between hypoxemia and hypotension and long-term cognitive outcomes in ICU survivors is mixed. In one of the first studies to assess cognitive impairment in survivors of ARDS (n=55), severity of hypoxemia was found to correlate with the degree of cognitive impairment; PaO_2 at enrolment was significantly associated with decrements in the General Memory Index ($p = 0.04$), Attention and Concentration Index ($p = 0.03$), and Delayed Recall Index ($p = 0.002$) (Hopkins et al. 1999). More recently, in a subset of patients from the FACTT factorial randomized trial pulmonary artery vs. central venous catheter-directed conservative vs. liberal fluid administration for patients with ARDS, cognitive impairment assessed at 2 months and 1 year after hospital discharge was common; 55% of survivors had cognitive impairment (decrements in memory, verbal fluency and executive function) at 1 year (Mikkelsen et al. 2012). Risk factors for long-term cognitive impairment included lower PaO_2 ($p = 0.02$), lower central venous pressure ($p = 0.04$) and enrollment in the conservative fluid-management strategy ($p = 0.004$) (Mikkelsen et al. 2012). Furthermore, these factors were also associated with worse executive function (Mikkelsen et al. 2012). The findings of this study are challenged by incomplete data and low enrollment of eligible patients, but are nonetheless intriguing, as they would suggest that both hypoxia and even relative hypotension could contribute to long-term cognitive impairment in ARDS survivors.

On the other hand, other studies of survivors of general critical illness have found no association between hypoxemia and cognitive impairment. In a report by Suchyta and colleagues (n=64), despite a high prevalence (64%) of patients with abnormalities on brain imaging (CT or MRI), there was no association with episodes of hypoxemia (Suchyta, Jephson, and Hopkins 2010). Furthermore, among patients admitted to a general trauma ICU (n=108), hypoxemia was not associated with incident delirium or cognitive impairment at 1 year

(Guillamondegui et al. 2011). Overall, these data suggest that the causal relationship between anoxia and short- or long-term cognitive impairment is unclear but could relate to the mechanism of brain injury. It is possible that hypoxia or hypotension are independent risk factors for cognitive impairment; their effects could be mediated directly or indirectly through a systemic inflammatory response inducing the activation of brain parenchymal cells and expression of proinflammatory cytokines and inflammatory mediators within the central nervous system (Khan et al. 2011; Hall, Shenkin, and Maclullich 2011).

2.6.2.2 *Dysglycemia*

Derangements in blood glucose are associated with cognitive impairment after critical illness. Hopkins and colleagues review of blood glucose control data among patients being treated for ARDS showed that after adjusting for covariates, patients with a highest blood glucose level (> 153.5 mg/dL) and those with greater fluctuations in blood glucose had three times the odds of being cognitive impaired at 1-year compared to patients who did not experience either glycemic condition (Hopkins et al. 2010). Hypoglycemia may also contribute; in a case-control study of 74 patients, surgical ICU patients who suffered at least one hypoglycemic event (< 40 mg/dL) demonstrated visual-spatial deficits at 1-year follow-up (Duning et al. 2010). Interestingly, hyperglycemia and fluctuations in blood glucose levels were also associated with deficits in visual-spatial skills.

2.6.2.3 *Delirium*

Delirium is an acute change in mental status that is characterized by inattention and a fluctuating course. It is highly prevalent in acutely ill patients, particularly among the critically ill where up to 80% of patients may develop it during their illness (Girard, Pandharipande, and Ely 2008; Pun and Boehm 2011; Morandi and Jackson 2011). Risk factors for delirium in the ICU are many; it is particularly common among elderly persons and those with pre-existing cognitive impairment (McNicoll et al. 2003; Inouye 2000; Inouye 2006; Barr et al. 2013). It is associated with longer lengths of stay, increased duration of mechanical ventilation and higher risk of death (Ely et al. 2001; Pisani et al. 2009; Ely et al. 2004). At 1-year follow-up, 71% of

survivors of general medial and cardiac ICUs that experience delirium in the ICU have cognitive impairment. After adjusting for age, education, pre-existing cognitive function, severity of illness, and exposure to sedative medications in the ICU, increasing duration of delirium is an independent predictor of worse cognitive impairment (Girard et al. 2010). The link between acute brain dysfunction (delirium) and chronic brain dysfunction (cognitive impairment) has been hypothesized to be mediated directly or indirectly through a systemic inflammatory response inducing the activation of brain parenchymal cells and expression of proinflammatory cytokines and inflammatory mediators within the central nervous system (Khan et al. 2011; Hall, Shenkin, and Maclullich 2011). This acute inflammatory response to critical illness then may prime microglia, activating them from a resting state. Activated microglia may then perpetuate a state of chronic neuroinflammation and neurotoxicity that may, in part, explain impaired long-term cognitive impairment (van Gool, van de Beek, and Eikelenboom 2010).

2.6.2.4 *Sleep Efficiency*

In general, sleep disorders appear to be associated with cognitive impairment. Data regarding sleep disorders following the ICU is only beginning to emerge (Kamdar, Needham, and Collop 2012). One large prospective multicenter cohort study (n=1625), reported no change in self-reported sleep quality in the year following critical illness, using a nonvalidated single instrument assessment (Orwelius et al. 2008). A second, small case series, reported sleep disruption and poor sleep efficiency as measured by polysomnography in five out of seven survivors of ARDS who did in fact report difficulties 6 months after hospital discharge (Lee et al. 2009). Neither study reported cognitive outcomes among these cohorts, and therefore the effects of poor sleep on long-term cognitive effects in survivors of critical illness is unknown. In populations of non-critically ill patients, however, a high index of sleep fragmentation (quantified by actigraphy) was associated with a nearly 1.5 fold increased risk of incident Alzheimer's disease after controlling for demographics, total daily rest time, chronic medical conditions, and the use of medications which commonly affect sleep in a prospective cohort study of community dwelling older adults, suggesting that long-term sleep disturbances can alter cognition (Lim et al. 2013). Further research is needed to determine the impact of poor

sleep efficiency both within the ICU and after ICU discharge on long-term cognitive function.

One of the biggest challenges of studying sleep in the ICU is how best to measure it. Sleep can be measured by a variety of objective and subjective techniques. The gold standard for the objective measurement of sleep is laboratory-based polysomnography (PSG). PSG is a multi-parametric test that monitors brain activity by electroencephalography (EEG), eye muscles (electrooculography), muscle activity or skeletal muscle activation (electromyography) and heart rhythm. It is the only method of sleep measurement capable of identifying individual sleep stages following the Rechtschaffen & Kales (R&K) rules; these stages are scored epoch-by-epoch in accordance with the American Association of Sleep Medicine criteria. The application of conventional classification criteria is challenging in the ICU as EEG patterns as alteration in cerebral metabolism, electrolyte disorders, intoxications, and medications influencing sleep pattern. Alternative or supplementary criteria for PSG scoring have been proposed by Drouot *et al.* (2012) separating EEG recordings into states of either pathological wakefulness or atypical sleep. Devised and validated on non-sedated patients in the ICU, this method of scoring predicted atypical sleep with a sensitivity of 100% and a specificity of 97% (Drouot et al. 2012).

As classical K&R sleep stages are discrete, they are unable to describe the continuum between wakefulness and sleep. Recently, an automated algorithm named odds ratio product (ORP) was developed that allows for continuous measure of sleep state ranging from full wakefulness (2.5) to deep sleep (0) (Younes et al. 2015). EEG is assessed by rating epochs based on the relative power spectrum of each frequency band (delta, theta, alpha-sigma and beta). In a validation dataset of outpatient PSG recordings, ORP <1 predicted sleep and ORP >2 wakefulness with 95% accuracy. Additionally, correlation (R^2 = 0.98) was high between the ORP and the probability of arousals and awakenings. Formal validation in a cohort of ICU patients has yet to be performed.

Bispectral index (BIS), an EEG-derived method for assessing the depth of sedation mainly used during general anesthesia in the operating room, has been proposed as an alternate measure of sleep assessment. Unfortunately, BIS is sensitive to technique and its interpretation is difficult.

Further, its use for sleep assessment is poorly documented. Spectral edge frequency (SEF) has been evaluated to assess sleep states as well as circadian rhythmicity (Gehlbach et al. 2012), but suffers from inconsistency in selecting which epochs to include. In addition, further studies are needed to determine its validity in an ICU population.

Actigraphy, which continuously measures an individual's movement using a wristwatch-like device on the wrist or ankle, is another alternative to PSG. The presence of movement indicates wakefulness, and its absence indicates sleep. This widely-used method has been validated in several populations for its measurement of total sleep time (TST) and sleep fragmentation (Lim et al. 2013). Actigraphy has been validated against biochemical markers of circadian rhythmicity (Lim et al. 2012). A recent systematic review of actigraphy in the ICU showed that actigraphy has been increasingly used as a measure of sleep. However, several limitations exist in its use as studies to date have been heterogeneous and lack data regarding actigraphy-based measures of sleep and patient outcomes (Table 2.3) (Schwab et al. 2018). Few studies have evaluated the use of actigraphy after ICU discharge. A study by Solverson and colleagues were unable to show a relationship between patients' subjective and objective sleep quality by questionnaire and actigraphy at 3-months follow-up (Solverson, Easton and Doig 2016) and is the only study to date that we are aware of assessing actigraphy as a long-term outcome measure of sleep.

The utilization of subjective measures of sleep assessment, such as patient or nurse questionnaires, is simple, easy, and relatively inexpensive compared to other objective measures of sleep. Patients may keep daily sleep diaries or a sleep log. The Richards-Campbell Sleep Questionnaire (RCSQ), the Sleep in the Intensive Care Unit Questionnaire, and the Verran and Snyder-Halpern (VHS) Sleep Scale have all been tested in ICU patient populations (Matthews et al. 2011). Incident delirium and the frequent use of sedatives limit the use of such instruments. Further, they typically report only on nighttime sleep whereas sleep in the ICU is distributed over a 24-hour period. Nursing assessment with the Echols Sleep Behaviour Observation Tool, Nurses' Observation Checklist and the RCSQ can be used to estimate sleep (Matthews et al. 2011). Nursing derived assessments however tend to overestimate TST and sleep efficiency but underestimate awakenings when compared to PSG. Subjective assessments

of sleep are variably reliable and provide no information on experienced sleep stages or circadian rhythmicity limiting their utility in assessing sleep outcomes the ICU.

2.7 Improving Cognitive Outcomes – Role of Improved Sleep

If unrecognized, poor sleep efficiency could contribute to cognitive impairment, possibly contributing to reductions in health-related quality of life (HRQOL) and fatigue precluding effective participation in physical rehabilitation of ICU survivors. Accordingly, Kamdar and colleagues recently introduced an ICU sleep-promotion quality improvement initiative to reduce incident delirium and cognitive impairment (Kamdar et al. 2013). This multifaceted intervention (nighttime: minimizing overhead pages, turning off patient electronic devices, dimming lights, and grouping care activities; daytime: natural light, promotion of wakefulness, encouraging mobilization, and minimization of caffeine prior to sleep) showed an insignificant increase in the overall rating on the RCSQ (primary outcome) but did significantly improvement daily noise ratings ($p = 0.001$), incidence of delirium/coma (OR: 0.46; 95% CI, 0.23-0.89; $p = 0.02$), and daily delirium/coma-free status (OR: 1.64; 95% confidence interval, 1.04-2.58; $p = 0.03$) (Kamdar et al. 2013). Further research is needed to determine the effect of poor sleep efficiency on cognitive outcomes and whether or not improved sleep lends to less cognitive impairment.

2.8 Known Barriers to Cognitive Testing

Little attention has been paid to determining barriers to assessing cognitive function. These include both social stigmatization and financial strain (i.e. disclosure in returning to work or application for health insurance) associated with age-inappropriate or accelerated cognitive impairment. High follow-up rates have successfully, and repeatedly, been achieved by a number of groups (Jackson et al. 2012; Jackson et al. 2010c; Hopkins et al. 2010; Hopkins et al. 2004; Hopkins et al. 2005; Bienvenu et al. 2012). Obstacles in testing and failure of retention strategies was nicely illustrated in the ARDS Cognitive Outcomes Study (ACOS) study (Mikkelsen et al. 2012) where of the 406 eligible patients, 18% declined participation (11% on initial approach; 6% after consent obtained) and another 145 patients (36%) were unable to be contacted. The inability to reach potential participants may have been a result of cognitive

impairment, change in contact information, or other. Further, 25% of enrolled patients were lost to follow-up on subsequent testing, and of those patients that did participate frustration was repeatedly expressed during testing despite reassurances of performance and requested to stop (n=8) (Mikkelsen et al. 2012). Inquiry into barriers to neurocognitive testing, or modifications of these tests to improve efficiency while retaining diagnostic properties, will require further investigation.

2.9 Randomized Trials to Improve Cognitive Recovery

Research to prevent and rehabilitate survivors of critical illness is an important priority given that cognitive impairment prevents survivors from returning to work and older persons from returning home (Herridge et al. 2003; Herridge et al. 2011; Schweickert et al. 2009; Rothenhausler et al. 2001; Hoffmann and Tornatore 2009). The Returning to Everyday Tasks Using Rehabilitation Networks (RETURN) study randomized 21 medical and surgical ICU survivors to 12-weeks of either in-home combined cognitive and physical rehabilitation or usual care (characterized by sporadic rehabilitation) (Jackson et al. 2012). Despite nearly equivalent scores on a measure of executive functioning at baseline, at the end of the intervention patients in the intervention group demonstrated significantly better executive functioning and reported fewer disabilities in instrumental activities of daily living (Jackson et al. 2012). These encouraging results require further study in a larger patient population.

Two recent randomized controlled trials investigated the cognitive benefits of prevention and rehabilitation. First, a group of Chilean investigators evaluated the effect of early occupational therapy for delirium prevention in older (>60 years) ICU patients who have not been mechanically ventilated or have pre-existing cognitive impairment. Patients were randomized to receive either a nonpharmacologic delirium prevention program arm (early mobilization by physical therapist, reorientation protocol, correction of sensory impairment [e.g. provision of glasses and hearing aids], environmental management [e.g. clock, calendar, noise reduction, supervision by family to avoid restraints] or the early occupational therapy arm which adds multisensory stimulation (e.g. intense external stimulation), positioning (e.g. dorsa-flex splints),

cognitive stimulation (awareness, orientation, attention, memory, calculation, praxis), ADL training and upper limb motor stimulation with an occupational therapist twice daily. The outcome measures will include delirium incidence and duration, functional independence, grip strength and cognitive function at day 7 and hospital discharge. Occupational therapy was effective in decreasing duration and incidence of delirium in nonventilated elderly patients in the intensive care unit and improved functionality at discharge. Another US-based randomized trial in medical and surgical patients with respiratory failure or shock (Brummel et al. 2014) explored the effect of early physical and cognitive rehabilitation on short- and long-term cognitive outcomes. This trial had three randomized groups: (1) usual care, including daily awakening and breathing trials, (2) once-daily physical rehabilitation protocol, or (3) once daily rehabilitation protocol in-home cognitive rehabilitation for 12 weeks (orientation, digit span, memory and problem solving, reverse digit span, letters, numbers, puzzles and games). This pilot study demonstrated that early rehabilitation could be extended beyond physical therapy to include cognitive therapy, however further research would inform patient selection, intensity of treatment, and benefits of cognitive therapy in ICU patients.

2.10 Predicting Long-term Cognitive Impairment

Studies have so far been unable to identify patients at higher risk of cognitive impairment using brief cognitive screening tools. For example, in a study by Woon and colleagues, neither performance on the MMSE or MiniCog at the time of hospital discharge predicted cognitive impairment at 6-month follow-up (Woon, Dunn, and Hopkins 2012). Performance on more sensitive tests of cognitive impairment may have predictive value but these have not been employed in prediction-focused investigations to date. The lack of predictive ability restricts the ability of clinicians and researchers to adequately risk stratify patients to their individual rehabilitation needs.

2.11 Conclusions

Impaired cognitive functioning is common and persists after critical illness, and although improvement is seen with time, only a minority of critical care survivors return to their

cognitive baseline. The mechanisms of cognitive impairment remain incompletely understood. Interventional trials to improve cognitive outcomes for ICU survivors through prevention and rehabilitation are only now beginning. Further study to elucidate the causes and pathophysiology of this newly acquired chronic brain injury in different patient populations as well as strategies to return patients to their baseline cognitive status are important research priorities. For now, cognitive impairment in survivors of critical illness highlights opportunities to improve care possibly through risk reduction, in the ICU (e.g. timely resuscitation, sedation stewardship), on the hospital ward (e.g. assessment of sleep efficiency, mobilization) and after discharge in the post-hospital recovery period (e.g. ongoing cognitive or physical therapy, screening for psychological morbidity).

Table 2.1 Prevalence and domains of cognition impairment after ICU

a. ARDS studies

Study n	Age (yrs) Mean ± SD Time to FU	Prevalence of Cognitive Impairment (%)				Impaired Domain					
		Hospital discharge	6 months post-ICU discharge	12 months post-ICU discharge	≥1-year post ICU discharge	General cognitive impairment	Attention and concentration	Memory	Executive function	Mental processing speed	Visuospatial
Al-Saidi et al. 2003 87	44* 1.5 yrs				20			+			
Christie et al. 2006 79	43 ± 13 28 mos						+	+	+		
Hopkins et al. 1999 67	46 ± 16 1-yr	100		78			+	+			
Hopkins et al. 2004 66	46 ± 16 1-yr	70		46			+	+	+	+	
Hopkins et al. 2005 66	46 ± 16 1 and 2 yrs	70		46	47	+					
Hopkins et al. 2010 66	46 ± 16 1-yr			46	47						

Larson et al. 2007 66	45 ± 16 1 and 2 yrs	72		46	44						
Marquis et al. 2000 33	-- 1-yr		34	34	22	+	+	+	+	+	+
Mikkelsen et al. 2009 79	43 ± 13 1-241 mos			56*34% within 0-1 yrs	56*34% within 1-2 yrs			+	+		
Mikklesen et al. 2012 75	47 (IQR, 37-57) 1-yr			55				+	+	+	
Needham et al. 2013 174	47 (14) 6 and 12 mos		36	25			+	+	+	+	+
Pfoh et al. 2015 242	51 (16) 6 and 12 mos for ALTOS study; hospital discharge, 3 and 12 mos for ABC study[%]	90	38/79	25/71[%]		+					
Rothenhausler et al. 2001	42 ± 15						+				

46	Mean 6.4 yrs (1-12 yrs)										
Suchyta et al. 2004 30	51 ± 13 Mean 6.2 (2.1) yrs				*75% had moderate-severe CI if ARDS patient with sepsis		+	+	+	+	

b. Sepsis studies

Study **n**	**Age (yrs) Mean ± SD** **Time to FU**	**Prevalence of Cognitive Impairment**				**Impaired Domain**					
		Hospital discharge	**6 months post-ICU discharge**	**12 months post-ICU discharge**	**≥1-year post ICU discharge**	**General cognitive impairment**	**Attention and concentration**	**Memory**	**Executive function**	**Mental processing speed**	**Visuospatial**
Calsavara et al. 2018 33/16 evaluated at 1-yr	49 ±15 ICU discharge and 1 yr					+					*constructional apraxia didn't improve over time
Iwashyna et al. 2010 1194	77 Up to 8.3 yrs				(11% increase prevalence of moderate to severe CI)	+					
Pierrakos et al. 2017	69 ±15					+					

28	ICU discharge										
Semmler et al. 2013 25	56± 2 6-24 mos							+		+	

c. General ICU studies

Study **n**	**Age (yrs) Mean ± SD** **Time to FU**	**Prevalence of Cognitive Impairment**				**Impaired Domain**					
		Hospital discharge	**6 months post-ICU discharge**	**12 months post-ICU discharge**	**≥1-year post ICU discharge**	**General cognitive impairment**	**Attention and concentration**	**Memory**	**Executive function**	**Mental processing speed**	**Visuospatial**
Ambrosino et al. 2002 63/36 tested	68 ± 7 3- and 6-mos	39	17			+					
Baumbach et al. 2016 127	-- 3- and 6-mos		46								
Bruck et al. 2018 125	62 (42-73) 3 mos										*no association between the incidence of severe sepsis/septic shock or ICU delirium and later cognitive self-rated cognitive function

Chung et al. 2017 30	61 (IQR, 50–72) ICU discharge	43				+					
Davydow et al. 2013 150	49.0 ± 14.6 1 yr						+	+			*greater number of in-hospital acute stress symptoms was associated with significantly greater impairment in 12-month cognitive functioning
De Azevedo et al. 2017 413	57 (IQR, 46-72) 11 mos			49%; 29 – mild to moderate; 20 - severe							*in lower severity population of critically ill patients demonstrates that cognitive dysfunction is a frequent and severe long-term complication
De Rooij et al. 2008 164	81 ± 2 1-6 yrs				56 – mild to moderate 17 – severe	+					
Duggan et al. 2017 136	60 (IQR, 50-66)		26*3 mos						+		*executive dysfunction 3 months post-ICU was

	3- and 12-mos										independently associated with more depressive symptoms and worse mental HRQOL 12 months post-ICU
Duning et al. 2010 74	66±1 1-yr						+	+	+		
Ehlenbach et al. 2010 41	>65 3.7 yrs					+					
Ellger et al. 2009 38	-- 1-yr							+		+	
Girard et al. 2010 76/52	61 (IQR, 47-71) 3- and 12-mos		17 – mild to moderate 62 - severe	35 – mild to moderate 26 - severe		+					
Girard et al. 2018 586	61 (52–70) 3- and 12-mos					+					*longer duration of sedative-associated delirium predicted a worse RBANS global cognition score at 12 months
Hope et al. 2013	71 (IQR, 58–80)		64			+	+	+	+	+	

385	6-mos										
Hopkins et al. 2005 32	46 ± 16 6-mos	91	41			+					
Hughes et al. 2017 1046	63 (52-72) 3- and 12-mos		25*3mos	23		+			+		*surgery/anesthesia exposure (yes/no) was not associated with RBANS global cognition or Trails B executive function scores at 3 or 12 months (P > 0.2); higher baseline education level was associated with better global cognition at 3 and 12 months (P < 0.001), and longer in-hospital delirium duration was associated with worse global cognition (P < 0.02) and executive function (P < 0.01) at 3 and 12 months
Hughes et al. 2018 419	59 (48–69) 3- and 12-mos					+					*higher S100B was associated with worse global cognition at 3 and

											12 months (P = 0.008; P = 0.01)
Jackson et al. 2003 34	53±15 6-mos		32					+		+	+
Jackson et al. 2007 58	45 ± 14 1 to 2-yrs				57		+		+		
Jackson et al. 2009 80	65 (53-73) 3- and 12-mos			71		+					
Jackson et al. 2011 108	43 ± 17 12-mos			55		+					
Jones et al. 2006 30	54 (6-25) 2-mos							+			
Juan et al. 2018 50	61 (53-72) 6-mos		26				+	+	+	+	
Maley et al. 2016 409/43	59±15 Median 8 mos			56		+		+			
Mitchell et al. 2018	43-65		24						+	+	

148	3 and 6 mos										
Pandharipande et al. 2013 467	59 (IQR, 49-69) 3 and 12 mos		40 *3mos	34		+			+		
Sacanella et al. 2011 112	73 ± 6 1-yr			10		+					
Sakuramoto et al. 2015 79	ICU discharge	19				+					
Suchyta et al. 2010 64	58 $\pm$ 17 --	48				+		+	+		*
Sukantarat et al. 2005 51	60 (26-82) 3 and 9 mos		55*3 mos	27*9 mos		+			+		
Teeters et al. 2011 387	>70 yrs Q6mos					+ (17% absolute increase in CI)					*17% absolute increase in CI elderly admitted to ICU vs general hospitalization
Teebo et al. 2012 12	51 $\pm$ 13							+			

	2 weeks and 11 mos										
Tobar et al. 2009 8	66 (44-74) 3-mos		13			+					
Torgersen et al. 2011 477/55 (28 completed assessments)	52(14) 3 and 12 mos	64		10				+		+	
Wolters et al. 2017 363	60 (15) 12 mos					*multiple days of delirium associated with long-term CI					
Woon et al. 2012 53	55 $\pm$ 17 6 mos	51	57			+	+	+	+	+	
Zhao et al. 2015 332	-- ICU discharge and 3 mos	59						+			

d. Traumatic Brain Injury and other primary brain injury studies

Study	**Age (yrs)**	**Prevalence of Cognitive Impairment**	**Impaired Domain**

n	Mean ± SD Time to FU	Hospital discharge	6 months post-ICU discharge	12 months post-ICU discharge	≥1-year post ICU discharge	General cognitive impairment	Attention and concentration	Memory	Executive function	Mental processing speed	Visuospatial
De Oliveira Thais et al. 2014 234/46 evaluated at 3 yrs	34 ± 13 3 $\pm$ 1.8 yrs					+					
Godbolt et al. 2012 110	42 (24-52) 3-mos and 1-yr		57				+	+	+	+	+
Guillamondegui et al. 2011 108	42 ± 17 1-yr			61		+					
Lippert-Gruner et al. 2006 41	33 (16-64) 6 and 12 mos						+	+			*disorientation and inattention improved between 6- and 12-mos
Pasternak et al. 2008 878	52 ± 12 3 mos					+					
Schielke et al. 2005	64 ± 12				11 – mild	+					

27	1 and 2 yrs				26 – moderate to severe						
Vitaz et al. 2003 79/56 tested	34 $\pm$**17** Mean 28 mos (17-42)				49		+	+			

Table 2.2 Definitions used to report cognitive impairment after ICU

Study Dates	Study Design Population	Cognitive Test(	Definition of abnormality	Quality of outcome measured	Covariates reported in Table 1
Ambrosino et al. 2002 January 1996 – December 1998	Prospective; controlled; consecutive 63 COPD patients requiring MV; control group 34 stable COPD patient on LT oxygen therapy admitted to inpatient pulmonary rehabilitation program	Mini Mental Status Exam (MMSE)	MMSE < 24	2 (screening test)	Sex, age, BMI, PFTs, MIP/MEPs, PaCO2/PaO2
Baumbach et al. 2016 September 2014 – March 2015	Prospective cohort; self-selected by response to contact via mail 127 patients aged 18 to 85 years; mixed MSICU with minimum ICU LOS of 24 hrs	Functional Assessment of Cancer Therapy-Cognitive Function Adapted (FACT-$Cog_{adapted}$) Informant Questionnaire of Cognitive Decline in the Elderly (IQCODE)	Likert scale; no clear definition of CI	1 (self-reported)	Sex, age, education, employed (yes/no), APACHEII, hospital LOS, ICU LOS, days of MV, admission diagnosis
Bruck et al. 2018 January 2012 – February 2013	Prospective cohort; patients with sepsis who were part of the PRE-DELIRIC study who responded to questionnaire 125 patients; mixed MSICU with minimum ICU LOS of 24 hrs	Cognitive Failures Questionnaire (CFQ)	Total CFQ score > 25	2	Sex, age, history of cognitive impairment, alcohol use, drug use, diabetes, vascular disease, cardiac disease, APACHEII, type of ICU admission
Calsavara et al. 2018 --	Prospective cohort; severe sepsis or septic shock during ICU stay 33 patients; 16 patients at 1 year	Consortium to Establish Registry for Alzheimer's Disease (CERAD) battery	--	3 (Neuropsychological testing)	Sex, age, education, APACHEII, SOFA, ICU LOS, lab parameters (hemoglobin, Cr, lactate, CRP, glucose), site of infection, comorbidity index, IQCODE, cumulative doses of analgesia/sedatives/inotropes/pressors, steroid exposure, dialysis, days of MV

Christie et al. 2006 --	2 cross-sectional studies 1) 79 ARDS patients; internet ARDS support site 2) 34 ARDS patients discharged [in-person cognitive interviews]	Neurobehavioral Cognitive Status Exam (NCSE): Judgment Wechsler Memory Scale)WMS)-III: Digit Span; Letter-Number Sequencing; Logical Memory I/II; Similarities Controlled Oral Word Association Hayling Sentence Completion Test	2 test scores ≥1 SD or more below the population norm or a single test score ≥1.5 SDs below population norm	3	Sex, age, education, race, marital status, alcohol use, smoking status, comorbid conditions, prehospitalization function, prehospitalization cognition, prehospitalization depression
Chung et al. 2017 June 2014 – May 2015	Retrospective; consecutive 30 patients from MICU, CCU and SICU	Mini-Cog test	Recall of 0 items or recall of 1–2 items with an abnormal clock face	2	Sex, age, high school graduate (yes/no), type of ICU, reason for admission, GCS at admission, SOFA, days of MV, days delirious, ICU LOS
Davydow et al. 2013 September 2010 – August 2011	Prospective cohort; consecutive 150 nontrauma patients without cognitive impairment or dementia diagnosis who were admitted to an ICU for > 24 hrs; 120 patients completed FU	Telephone Interview for Cognitive Status modified ($TICS_m$) Mini International Neuropsychiatric Interview	--	2	Sex, age, education,
De Azevedo et al. 2017 March 2014 – February 2015	Prospective cohort; consecutive 413 adult patients mechanically ventilated	Digit span forward and backward Rey Auditory Verbal Learning Test (RAVLT) Clock-drawing test Verbal fluency test MMSE	Mild or moderate impairment if 2 test scores 1.5 SDs below the mean or test scores 2 SDs below the mean; severe CI if	3	Sex, age, education, APACHE IV, SOFA, days of MV, use of sedative agents, admission diagnosis, delirium (yes/no), ICU LOS

			≥3 test scores 1.5 SD below the mean		
De Oliveira et al. 2014 February 2001 – March 2009	Prospective cohort; consecutive 234 patients with severe TBI (GCS > or = 8); 46 were evaluated at 1 year	WMS-III Logical Memory First Recall; Logical Memory I/II; Visual Reproduction I/II/ III RVALT Total; Retention; Delayed Memory Wechsler Adult Intelligence Scale (WAIS)-III-Digit Span; Vocabulary; Similarities; Block Design; Letters Fluency; Category Fluency	--	3	Sex, age, education, hand dominance, glucose, CT head characteristics, SAH (yes/no), multisystem trauma (yes/no), type of trauma, GCS, pupils
De Rooij et al. 2008 January 1997 – December 2002	Retrospective; consecutive 164 patients >80 yrs; mixed MSICU who underwent elective surgery	IQCODE-SF Katz Activities of Daily Living(ADLs) EQ-5D	Score > 3.9 on IQCODE-SF severe CI; 3.1-3.8 mild-moderate CI	2	Sex, age, education, social status, cardiopulmonary resuscitation, GCS after 24 hrs, SAPS II, APACHE II, planned or unplanned admission, BMI, MV (%), ICU LOS
Duggan et al. 2017 --	Prospective; consecutive 826 patients mixed MSICU population for respiratory failure, cardiogenic shock, or septic shock	Behavior Rating Inventory of Executive Function–Adult (BRIEF-A) Trail Making Test B Beck's Depression Index (BDI)-II Short Form(SF)-36 ADLs Instrumental ADLs (IADLs)	BRIEF-A impairment defined as t-score ≥ 65; Trails B impairment is defined as t-score ≤ 35	3	Sex, age, race, marital status, employment status, baseline clinical status , pre-existing CI, history of depression, history of nondepressive mental illness, comorbidity index, admit diagnosis, ICU type, SOFA, days of MV, septic (yes/no), stroke in hospital (yes/no), ICU LOS, discharge destination
Dunning et al. 2010 January 2004 – December 2007	Case-control 74 patients 18-80 yrs of age; 37 patients had at least one hypoglycemic event during SICU admission	MMSE Boston Naming Test Nuernberg Gerontopsychological Inventory Digit symbol substitution Color word interference tasks	--	3 (compared to 2)	Matching criteria: sex, age, SAPS II, yr of ICU treatment; disease related criteria: type of OR, CP resuscitation, DM I or II, ICU LOS, mean am blood glucose, duration of sedation (<3 days, 3-7 days, 1-2

		WMS (revised) Regensburg Word Fluency Test Trail Making test Rey-Osterrieth Complex Figure RAVLT Recognition			weeks, > 2 weeks), PF ratio, CV failure (pressors, MV assist device), renal failure, hepatic failure, medications (steroids, immunosuppressants)
Ehlenbach et al. 2010 1994 – 1996 (2581 participants); 2000 – 2002 (additional 811 individuals)	Prospective; cohort Enrolled patients are evaluated q2yrs; 41 persons were hospitalized for critical illness	Cognitive Abilities Screening Instrument (CASI)	<86 prompted a full standardized clinical exam	2	Sex, age, race, education, CAD (yes/no), CV disease (yes/no), pulm dz (yes/no), D< (yes/no), renal dz, malignancy, follow-up time, study visits
Girard et al. 2010 October 2003 – March 2006	Nested in RCT; prospective 76 MICU patients	MMSE Digit span Trail Making tests A and B Digit Symbol Coding Rey-Osterrieth Complex Figure RVALT	2 cognitive test scores 1.5 SDs below the mean; one cognitive test score 2 SDs below the mean	3	Sex, age, education, APACHE II, admission diagnoses (sepsis, ARDS, MI/CHF, COPD/asthma, altered MS, hepatic or renal failure, malignancy, alcohol withdrawal, other), delirium in ICU (prevalence, duration), sedation exposure (benzos, opiates, propofol)
Girard et al. 2018 March 2007 - May 2010	Multicenter; prospective; cohort 586 patients managed in a medical or surgical ICU with respiratory failure, septic or cardiogenic shock, or both	RBANS MMSE Trail Making Test B IQCODE	--	3	Sex, age, race, education, short IQCODE, pre-existing CI, comorbidity index, admission diagnosis, APACHEII, SOFA, days of MV, dexamethasone/benzodiazepine/opioid/ propofol exposure, ICU LOS, hospital LOS, Framingham stroke risk profile, duration of severe sepsis, no. of 15 mins intervals with hypoxia

Godbolt et al. 2012 January 2010 – June 2011	Multicenter; prospective; cohort 110 patients with severe TBI	Barrow Neurological Institute Screening of Cognitive function	Total score < 2 SD below the mean	2	--
Guillamondegui et al. 2011 July 2006 – June 2007	Prospective; cohort 108 patients with moderate-severe TBI; patients with hypoxemic event (SaO2 < 85%) within first 48 hrs of admission	*Employment questions and battery of validated neuropsychological testing instruments*	2 test scores 1.5 SDs below the mean or 1 test score 2 SDs below the mean	3	Sex, age, ISS, ED GCS, ED pulse, ED SBP, transfusion, MV days, ICU LOS, SpO2 < 90% or 85% for > 5 mins; delirium (prevalence)
Hope et al. 2013 January 2003 - December 2007	Prospective; consecutive; cohort 385 adults admitted to a respiratory care unit for treatment of chronic critical illness; undergone elective tracheostomy for weaning	Validated telephone version of the Confusion Assessment Method (CAM)	Three possible values: dead, alive with brain dysfunction, and alive without brain dysfunction	2	Sex, age, race, cognitive impairment at baseline, residence prior to hospitalization, FIM at admission, IADLs at admission, admission diagnosis, type of ICU, ICU LOS, APACHE II, APS, comorbidity index
Hopkins et al. 1999 February 1994 – July 1988	Prospective; consecutive; cohort 67 ARDS survivors	WAIS-R WMS-R RAVLT Rey-Osterrieth Complex Figure Trail Making Tests A and B Verbal Fluency (verbal production)	2 test scores > 1.5 SD or 1 test score > 2 SD below the normative population mean	3	Sex, age, education, ICU LOS, duration MV
Hopkins et al. 2004 --	Prospective; consecutive; cohort 66 ARDS survivors	WAIS-R WMS-R RAVLT Rey-Osterrieth Complex Figure Trail Making Tests A and B Verbal Fluency (verbal production)	<80%, <85% or <90% (compared to normative data)	3	Sex, age, education, hospital LOS, ICU LOS, duration MV, APACHE II, mean MOF score, PF ratio, PaO2 at time of enrolment, mean PaO2, FiO2 at time of enrolment, days from ARDS onset to enrolment in 1 yr outcome study
Hopkins et al. 2005	Prospective; consecutive; cohort	WAIS-R WMS-R	2 or more test scores > 1.5 SDs	3	Sex, age, education, race, number of ARDS RFs, duration MV, ICU LOS,

February 1994 – December 1999	66 ARDS survivors (low vs. high tidal volume ventilation study)	RAVLT Rey-Osterrieth Complex Figure Trail Making Tests A and B Verbal Fluency (verbal production)	or 1 test score > 2 SDs below normative population mean		hospital LOS, at study enrolment (APACHE II, MOF score, PF ratio, FiO2, PaO2); total ICU stay (mean MOF score, mean PF ratio, Mean FiO2, mean PaO2)
Hopkins et al. 2005 --	Prospective; cohort 32 patients having received >5 days of MV	*Neuropsychological testing* --	≥2 test scores > 1.5 SDs or 1 test score > 2 SD below normative population mean	3	Sex, age, education, Charlson comorbidity index, number of ARDS RFs, duration MV, ICU LOS, hospital LOS, at study enrolment (APACHE II, MOF score, PF ratio, FiO2, PaO2); total ICU stay (mean MOF score, mean PF ratio, Mean FiO2, hrs oximetry SaO2 < 90%, hrs MBP < 60 mmHg, hrs MBP < 50 mmHg, days receiving either sedatives, narcotics or paralytics)
Hopkins et al. 2010 February 1994 – December 1999	Prospective; consecutive; cohort 66 ARDS survivors (low vs. high tidal volume ventilation study)	WAIS-R WMS-R RAVLT Rey-Osterrieth Complex Figure Trail Making Tests A and B Verbal Fluency (verbal production)	2 or more test scores > 1.5 SD or 1 test score > 2 SD below normative population mean using age, gender and education corrected t-scores	3	Sex, age, education, hospital LOS, DM I or II, total corticosteroid dose, at study enrolment (APACHE II, MOF score, PF ratio, FiO2, PaO2); total ICU stay (duration MV, ICU LOS, Mean FiO2, mean PaO2, hrs oximetry SaO2 < 90%, total insulin units/ICU hours, total potassium dose, mean blood glucose, lowest glucose, highest glucose)
Hughes et al. 2017 March 2007 - May 2010	Multicentre; prospective; cohort 1040 patients with major noncardiac surgery during hospital admission and with nonsurgical medical illness	RBANS Trail Making Test B	--	3	Sex, age, race, education, SES, IQCODE, clinical frailty score, functional activities questionnaire, comorbidity index, Framingham stroke risk profile, SOFA< APACHE II, sepsis in ICU, days of MV, ever delirious, coma, sedative or

					analgesia use, ICU LOS, hospital LOS
Hughes et al. 2018 --	Multicentre; prospective; cohort 419 adults admitted to a MICU or SICU with respiratory failure and/or shock	RBANS Trail Making Test B Katz ADLs Functional activities questionnaire	--	3	Sex, age, race, education, SES, IQCODE, clinical frailty score, functional activities questionnaire, comorbidity index, Framingham stroke risk profile, SOFA< APACHE II, sepsis in ICU, days of MV, ever delirious, coma, sedative or analgesia use, ICU LOS, hospital LOS
Iwashyna et al. 2010 1998 – 2006	Prospective; nonconsecutive; cohort Enrolled patients are evaluated q2yrs; survivors of severe sepsis	35-point scale; tests of memory, serial 7 subtractions, naming and orientation ADLs IADLs	--	2	Sex, age, education, race, LOS, required MV, required dialysis, used ICU, underwent major surgery, Charlson score, organ dysfunction score, acute conditions (CV dysfunction, neurologic dysfunction, hematologic dysfunction, hepatic dysfunction, renal/respiratory dysfunction), baseline cognitive impairment, baseline functional disability
Jackson et al. 2003 February 2000 – May 2001	Prospective; cohort; consecutive 34 patients; MICU and CICU; requiring MV	Modified Blessed Dementia Rating Scale (mBDRS) MMSE Digit Symbol Coding Thurstone Word Fluency Letter Number Sequencing Sequencing Verbal Paired Associates Digit Symbol Paired Recall Recall (Faces) Rey-Osterrieth Complex Figure	2 test scores > 2 SDs below the norm-referenced mean or 3 test scores $\geq$1.5 SD below norm-referenced mean	3	Sex, age, education, race, ADL, APACHE, Charlson, SOFA, Admission diagnosis

Jackson et al. 2007 January 2003 – December 2003	Prospective; nonconsecutive; cohort 58 trauma patients without ICH or focal neurologic deficits or moderate to severe TBI	Digit span Digit symbol FAS IQCODE-SF MMSE RAVLT Rey-Osterrieth Complex Figure Trail Making Tests A and B Katz ADLs	≥2 test scores > 1.5 SDs or 1 test score > 2 SDs below normative population	3 (compared to 2)	Sex, age, education, race, ISS, type of trauma, mental health history, employment status
Jackson et al. 2010 October 2003 – March 2006	Randomised controlled trial of SAT/SBT 80 patients requiring MV for > 72 hrs	Digit span Digit symbol IQCODE-SF MMSE RAVLT Rey-Osterrieth Complex Figure Trail Making Tests A and B Verbal Fluency test Katz ADLs	≥1.5 SDs below the mean on ≥2 of the nine cognitive tests or scored ≥2 SDs below the mean on ≥1 of the nine cognitive tests	3	Sex, age, APACHE II, SOFA, Admission diagnosis, pre-existing cognitive impairment, baseline ADL, baseline IADL, pre-enrolment sedative exposure, sedative exposure, lorazepam equivalents, fentanyl equivalents, propofol
Jackson et al. 2011 July 2006 – June 2007	Prospective; cohort 108 patients with moderate to severe trauma; no ICH	Digit span Digit symbol Verbal Fluency test (FAS) IQCODE-SF MMSE RAVLT Rey-Osterrieth Complex Figure Trail Making tests A and B	≥2 test scores > 1.5 SDs or 1 test score > 2 SDs below normative population	3	Sex, age, education, race, ISS, admission GCS, long-bone fracture, concussion, ICU LOS, hospital LOS, MV status, duration of MV, CAM+ days, type of trauma
Juan et al. 2018 July 2012 - May 2015	Prospective; cohort 50 survivors included from a prospective cohort of 138 patients admitted at the ICU for cardiopulmonary arrest	Naming subtest of the Lexis battery California Verbal Learning Test Doors and People test Digit span forward subtest of WAIS-IV	z score less than or equal to –1.65 SDs of the mean	3	Sex, age, cardiac etiology arrest, out of hospital cardiac arrest, time to return of spontaneous circulation, first shockable rhythm, therapeutic hypothermia (yes/no)

		Block tapping WMS-R Five-points test Digit-symbol subtest of the WAIS-IV Alert and Divided attention subtests of the Test battery Trail Making and Stroop tests from the GREFEX battery			
Jones et al. 2006 March 2003 – November 2004	Prospective; cohort 30 long-stay, MV patients	Cambridge Neuropsychological Test Automated Battery (CANTAB)	≤25 percentile compared with an age-, sex-matched control population	3	Sex, age, APACHE II, ICU LOS, diagnostic groups (peritonitis, pneumonia, asthma/COPD, sepsis, ARDS, trauma)
Larson et al. 2007 February 1994 – December 1999	Interventional trial; higher vs lower tidal volume ventilation strategy 66 ARDS survivors	WAIS-R (FSIQ; Vocabulary; Block Design) WMS-R (Attention Index; Verbal; RAVLT; Visual; Rey-Osterrieth Complex Figure) Trail Making Test B	≥2 test scores > 1.5 SDs or 1 test score > 2 SDs below normative population mean values using age, gender and education	3	Sex, age, hospital LOS, ICU LOS, duration of MV, APACHE II, Charlson Comorbidity index, mean MOF score, mean PaO2, mean FiO2, PF ratio, days receiving sedatives/narcotics/paralytics
Lippert-Gruner et al. 2006 --	Prospective; cohort 41 patients with severe TBI	Neurobehavioral Rating Scale	--	2	Sex, age
Maley et al. 2016	Prospective; mixed-methods investigation 43 survivors from two MICUs	Health Utilities Index - 3 cognitive questions Hospital Anxiety and Depression Scale (HADS)	--	1	Sex, age, race, marital status, no. of hospitalization in prior yr, comorbidity score, days of MV, sepsis LOS, shock LOS, ICU LOS,

January – May 2014		Connor-Davidson Resilience Scale Life-Space Questionnaire			hospital LOS, disposition destination
Marquis et al. 2000 --	Prospective; parallel controlled cohort 33 ARDS survivors; 24 critically ill controls	Trail Making Test B Symbol Digit Modalities test Test of Everyday Attention (Elevator Counting with Distraction)	--	3	--
Mikkelsen et al. 2009 --	Cross-sectional 79 self-reported ARDS survivors	NCSE (Orientation, Judgment) WMS-III (Digit Span, Letter – Number Sequencing, Logical Memory, Similarities) Hayling Sentence Completion Test Controlled Oral Word Association Test	≥2 test scores > 1 SD or 1 test score > 1.5 SDs below normative population	3	Sex, age, education, employment status, hospital LOS, precipitating factors (pneumonia, surgery, sepsis, trauma, other)
Mikkelsen et al. 2012 June 2000 – October 2005	Prospective; multicenter; cohort 75 ALI survivors	Neuropsychological test battery (45-60 minutes); *nil other specifics reported*	1 test score > 2 SDs below normative population	3	Sex, age, race, primary lung injury, coexisting conditions (none, DM, HIV/AIDS, cirrhosis, solid tumor, leukemia, lymphoma, immunosuppression), APACHE III, GCS, MAP, vasopressor use, PF ratio, conservative fluid strategy, PAC
Mitchell et al. 2016 November 2011 – December 2014	Prospective; cohort 148 adult surgical, medical and trauma patients enrolled; 88 tested at 3-months and 79 tested at 6-months	RBANS Trail Making Test Part B MMSE	Classified as severely impaired if they scored 1.5 SDs below the mean on ≥3 of the index scores or 2 SDs below the	3	Sex, age, education, admission diagnosis, APACHE II, APACHE III, ICU LOS, hospital LOS, Propofol/benzodiazepine/opioid dose, days of MV, delirium in ICU days

			mean on ≥2 of the index scores		
Needham et al. 2013 July 2008 – May 2012	Multicentre; prospective; cohort 174 patients	Controlled oral word association (COWA) Digit span Hayling sentence completion Logical memory I/II Similarities	<1.5 SDs on any of tests	3	Sex, age, race, high school education (yes/no), BMI, steroids (yes/no), living independently at home prior to admission (yes/no), employed (yes/no), SF-36, functional performance inventory score, comorbidity score, comorbidities at admission, critical illness characteristics (pneumonia, sepsis, baseline shock, baseline PF ratio, APACHE II, days of MV, hypoglycemia, steroids, insulin, benzodiazepines, NMBs, narcotics, ever coma, ever delirious, ICU LOS, hospital LOS)
Pandharipande et al. 2013 March 2007 – May 2010	Multicentre; prospective 467 adults admitted to a medical or surgical ICU with respiratory failure, cardiogenic shock, or septic shock	RBANS Trail Making Test B	1.5 and 2 SDs below the population means	3	Sex, age, race, ICU type, education, short IQCODE, comorbidity score, APACHE II, SOFA, admission diagnosis, days of MV, days delirious, coma (yes/no), hospital LOS, use of sedatives/analgesia in ICU
Pasternak et al. 2008 February 2000 – April 2003	Posthoc analysis of data from Intraoperative Hypothermia for Aneurysm Surgery Trial 878 patients with SAH; underwent aneurysm surgery	Benton Visual Retention test Controlled Oral Word Association Rey-Osterrieth Complex Figure Test Grooved Pegboard test Trail Making test Glasgow Outcome Score (GOS)	1 test score > 2 SDs below normative population	3	Blood glucose at aneurysm clipping, age, sex, race, BMI, preoperative hx (DM, HTN, smoking, time from SAH to induction), WFNS, Fisher grade, NIHSS, preoperative Rankin score, hydrocephalus on initial CT
Pfoh et al. 2015	Cross-sectional secondary analysis of data from two	MMSE COWA	MMSE conservative	2	Sex, age, education, employed, comorbidity score, psychiatric

July 2008 – May 2012	prospective studies of acute respiratory failure patients requiring mechanical ventilation in an ICU	Logical memory I/II Digit span total score, forward and backward	cut-off score of <24		condition, severity illness score, days of MV, ICU LOS, hospital LOS
Pierrakos et al. 2017 January 2013 - January 2014	Prospective; consecutive; cohort 28 patients with sepsis	MMSE IADLs	--	2	Sex, age, APACHE II, IADL, pCO_2, MAP, septic shock, days of MV, sedation, relapsing infection (yes/no), delirium (yes/no)
Rothenhausler et al. 2001 January 1985 – January 1995	Prospective; consecutive; cohort 46 ARDS survivors	Short Cognitive Performance test (SKT)	SKT total scores (profound cognitive impairment: 24-27; severe: 19-23, moderate: 14-18, mild: 9-13; subthreshold: 5-8)	2	Sex, age, RF for ARDS (trauma, sepsis, pneumonia, other)
Sacanella et al. 2011 --	Prospective; consecutive; Cohort 112 elderly patients electively admitted to MICU	MMSE IQCODE	MMSE < 24	2	Sex, age, APACHE II, SOFA, ICU LOS, cardiac dx, respiratory dx, severe sepsis, CV dx, other medical dx, % MV, % RRT, OMEGA score, Charlson index
Sakuramoto et al. 2015 July – December 2009	Prospective; consecutive; cohort 79 adults admitted to MICU or SICU	MMSE	MMSE < 24	2	Sex, age, comorbidity score, vision deficits, hearing deficits, mBDRS score, APACHE, SOFA, days of MV, ICU LOS, hospital LOS, admission diagnosis
Schielke et al. 2005	Prospective; consecutive; cohort	MMSE National Institutes of Health Stroke Scale	MMSE < 24	2	--

January 1999 – June 1999	27 patients treated for ischemic stroke requiring MV	Barthel Index modified Rankin Scale			
Semmler et al. 2013 January 2004 – August 2006	Two center; prospective; non-consecutive; cohort 25 survivors of sepsis; 19 non-septic ICU survivors	Neuro Cognitive Effects (NeuroCogFx) Trail Making tests A and B Auditory Verbal Learning Test Rey-Osterrieth Complex Figure Test	> 1.5 SD from z differences scores	3	Age, estimate premorbid verbal ability, APACHE II, SOFA, ICU LOS, duration MV, electrolyte levels (Na and K), PF ratio (max), creatinine (max), HCT (max), MAP < 70 mmHg, ARDS %, surgery (emergent or elective), admission diagnosis, comorbid medical disorders (cardiac, respiratory, live, DM, immunosuppressed, cancer, renal dx, CV dx, GI dx, multiple disorders), drugs (sedatives, analgesics, vasopressor, other drug)
Suchyta et al. 2004 --	Prospective; cohort 30 ARDS patients	--	≥2 test scores that were > 1 SD for mild, >1.5 SDs for moderate or ≥2 SDs for severe cognitive impairment	3	Sex, age, education, APACHE II, hospital LOS, PF ratio, RF for ARDS
Suchyta et al. 2010 July 2003 – June 2004	Prospective; non-consecutive; cohort 46 MSICU patients	--	--	--	Duration MV, ICU LOS, hospital LOS, APACHE II at ICU admission, % ARDS, admission diagnosis, co-morbid dx (cardiac, respiratory, liver, DM, immunosuppressed, cancer, renal dx, CV dx, GI dx, multiple disorders); hrs SpO2 < 90%, hrs MAP < 60 mmHg, sedatives (total dose ICU admission to scan) including

					lorazepam/fentanyl/morphine/midazolam/ propofol/hydromorphone, steroids
Sukantarat et al. 2005 April 2000 – March 2003	Prospective; consecutive; cohort 51 MSICU patients	Hayling Sentence Completion test Modified Six Element test Raven's Standard Progressive Matrices	Compared to percentiles of population norms	3	Sex, age, LOS, duration MV, APACHE II, TISS points
Teeters et al. 2011 2004 – 2008	Prospective; cohort 387 elderly patients admitted to ICU	Clinical Dementia Rating Scale FAQ Neurologic evaluation Neuropsychiatric testing	Expert consensus	3	Sex, age, APACHE III
Tembo et al. 2012 --	Qualitative 12 MSICU patients	Face-to-face interviews	Self-reported	2	--
Tobar et al. 2009 September 2008 – April 2009	Prospective; cohort 8 MICU patients	MMSE MOCA	MMSE < 21 (norm for Chile)	2	Sex, age, APACHE II, SOFA, delirium days, duration MV, hospital LOS
Torgersen et al. 2011 January 2008 – February 2009	Prospective; consecutive; cohort (parallel surgical cohort; not requiring ICU admission) 28 SICU patients; 24 surgical patients	CANTAB MMSE DMS (delayed matching to sample) Stocking of Cambridge Paired associate learning test SF-36	MMSE < 24 Z-score below -2 SD on 2 or below 1.5 SDs on 3 out of 10 results reported by CANTAB	3	Sex, age, ICU LOS, duration MV, SAPS II, mac SOFA score, Charlson comorbidity index
Vitaz et al. 2003 October 1995 – March 1998	Prospective; consecutive; cohort 56 patients with moderate TBI	Telephone interview; questions regarding ADLs and mental functioning	Self-report	1	Age, median 24-hr GCS, hospital LOS, ICU LOS, duration MV

Wolters et al. 2017 January 2011 – June 2013	Prospective; consecutive; cohort 363 adult patients in mixed MSICU for > 48 hrs	Cognitive Failures Questionnaire (CFQ)	--	1	Sex, age, comorbidity index, APACHE IV, SOFA, ICU LOS, admission type
Woon et al. 2012 August 2007 – December 2008	Prospective; consecutive; cohort 53 patients MSICU	MMSE Mini-Cog WASI (full-scale, verbal, performance) Trail Making tests A and B Hayling Sentence Completion Test WASI-R (digit symbol) WMS-III (logical memory) California Verbal Learning Test-II Rey-Osterrieth Complex Figure Test Finger Tapping test Controlled Oral Word Association test Wide-Range Assessment test-3 (reading) Golden Stroop test (inference trial)	MMSE < 24 MiniCog considered impaired if recalled no words, or recalled 1 or 2 words with an abnormal clock drawing score NP testing: ≥2 or test scores > 1.5 SDs or 1 test score that was > 2 SDs below population norms	3	Sex, age, education, ICU LOS, hospital LOS, duration MV, max FiO2, Min PaO2, APACHE II, ICU admission diagnosis
Zhao et al. 2017 January 2013 to September 2013	RCT 332 patients; 165 patients were included in the control group and 167 in the cognitive intervention group	Montreal Cognitive Assessment (MoCA)	< 26 was considered CI	2	Sex, age, education, ICU LOS, ICU type, comorbidity index, medications (steroids, analgesia, sedation)

ARDS: acute respiratory distress syndrome; ALI: acute lung injury; COPD: chronic obstructive pulmonary disease; LT: long-term; MV: mechanical ventilation; LOS: length of stay; ICU: intensive care unit; MSICU: medical-surgical ICU; CCU: coronary care unit; SICU: surgical ICU; CICU: cardiac ICU; FU: follow-up; TBI:

traumatic brain injury; GCS: Glasgow coma score; RCT: randomized controlled trial; SAT: spontaneous awakening trial; SBT: spontaneous breathing trial; ICH: intracerebral hemorrhage; SAH: subarachnoid hemorrhage

Table 2.3 Studies of sleep in ICU patient populations using actigraphy

Study Dates	Study Design	Population	Device placement Device; epoch setting	Sleep outcomes	Recording time TST	WASO Total awakenings	Sleep latency Sleep efficiency	Key findings
Beecroft et al. 2008 --	Prospective; case series; PSG, actigraphy and nurse assessment	12 medical-surgical patients; age 68 (13) yrs; 75% men; 67% tracheostomy	Wrist with least instrumentation Actiwatch Model AW-64; 30 sec	TST, SE, NA	8-12 hrs; median 7.26 (0.52) hrs PSG:3.10 (3.26) hrs Actigraphy: 4.4 (3.28) hrs	-- PSG: 40.0 (74.3) hrs Actigraphy: 48.5 (34.0) hrs	-- PSG: 41.9 (48.6) hrs Actigraphy: 61.3 (41.4) hrs	No correlation between actigraphy, nurse assessment and PSG measures of sleep
Bourne et al. 2008 --	Prospective; RCT; 10 mg melatonin (n=12) or placebo (n=12); BIS, actigraphy, nurse assessment and patient assessment (RCSQ)	24 mixed medical-surgical patients who underwent tracheostomy; age 64 (12) yrs; 46% men	Wrist Actiwatch; -- Bispectral index (BIS XP, Quattro sensor); 5 sec	SE	4 nights 3.5 hrs in intervention grp; 2.5 hrs in placebo	-- --	-- Intervention: 73 (95% CI, 53 – 93) Placebo: 75 (95% CI, 67 – 83)	No correlation between actigraphy and BIS measures of sleep
Chen et al. 2012 January – December 2009	RCT: valerian acupressure (n=41) or control (n=44)	85 medical ICU patients; age 71 (17) yrs; 76% men	Wrist or ankle ActiGraph GT1M	TNST, TWT, WF, SQS (SSS)	8 hrs x 2 nights Observation – Experimental: 2.9 (1.7) hrs Control: 2.7 (1.7) hrs Actigraphy –	-- Actigraphy – Experimental: 3.5 (4.5) Control: 5.3 (6.3)	-- --	Valerian acupressure increased sleep duration, decreases awake time, and decreases waking frequency

					Experimental: 7.5 (0.7) hrs Control: 7.2 (1.3) hrs			
Hamze et al. 2015 June – November 2011	Prospective; case series	12 ICU patients -nursing diagnosed as "disturbed sleep pattern" while in ICU; age 58 (11) yrs; 75% men	Wrist Actisleep	NA	24 hrs --	-- --	-- --	A mean of 44 interventions/patient days (1.8 interventions/patient/hr) was observed; 42% of interventions caused sleep disruption – 38% of disruptions occurred at night
Kroon et al. 2000 --	Prospective; case series; actigraphy, nurse assessment and patient assessment	13 CCU patients; age not reported; 0% men	Cannula free wrist --; 60 sec	TST, SL, NA, TWT	7 hrs 4.4 (1.2)	-- 1.9 (1.3)	0.4 (1.0) 74 (19)	In comparing actigraphy, nurse assessment and patient assessment no difference TST but significant difference in NA and SL
Mistraletti et al. 2009 --	Prospective; case series; Motor activity and its relationship to pain, sleep and agitation	13 medical-surgical ICU patients; 60 (16) yrs; 46% men	Wrist BioTrainer-Pro Activity monitor; 15 or 120 sec	Movement /hr	2-6 days --	-- --	-- --	Actigraphy measurements of movements per hr correlate with nurse-reported sleep
Ono et al. 2011 February 2006 – October 2006	RCT; bright light therapy (n=10) or standard care (n=12)	22 ICU patients post-esophagectomy; 2 were excluded as reintubated and 2 were unable to tolerate the brightness of the light; 64	Ankle Active-tracer (AC210); 120 sec	TST, circadian cycle	6 days Intervention: 7.3 (0.9) Control: 7.1 (1.4)	-- --	-- --	Compared to normal light, bright light therapy better entrains circadian sleep-wake rhythms and decreases nighttime activity

		(10) yrs; 81% men						
Raymond et al. 2004 January 2002 – March 2003	Prospective; case series; sleep and its relationship to pain and analgesic medication	16 ICU burn patients: 0% MV; 35 (9) yrs; 50% men	Wrist MicroMini Motionlogger Actigraph; 60 sec	TST, TWT, NA	12 days 8.3 (2.8)	5.5 (1.8) 3.4 (1.7)	-- --	Hospitalized burn patients experience low sleep duration with high sleep fragmentation
Redeker et al. 1996 --	Prospective; case series; activity patterns and recovery in women after CABG surgery	22 CABG patients; 64 (10); 0% men	Wrist MicroMini Motionlogger Actigraph; 60 sec	TST, NA, MSI, MWT	7 days 12.1 (4.6)	-- 16.6 (26.4)	-- --	Following CABG, women have sleep during the day and nighttime sleep is highly fragmented; improvement over time
Shilo et al. 1999 --	Prospective; case control study; regulation of sleep and secretion of melatonin regulation – ICU (n=14) as compared to ward patients (n=6)	14 ICU patients admitted for > 4 days; 61 (11); 43% men	Wrist Actigraph (Somnitor)	TST, number of sleep periods	72 hrs --	-- --	-- --	Compared to ward patients, ICU patients obtain less sleep with high fragmentation during day and night
Shilo et al. 2000 --	Prospective; case control study; melatonin vs placebo to improve sleep	8 patients admitted to a respiratory ICU (2 COPD patients; 6 patients with pneumonia);	Wrist Actigraph (Somnitor)	TST, NA	3 days ICU: 6.3 (1.1) Ward: 7.4 (2.1)	-- ICU: 1.4 (3.7) Ward: 1.8 (6.3)	-- --	Melatonin improves sleep duration and reduces sleep fragmentation in ICU patients

	quality; age and sex matched ward patient controls (3 COPD patients; 3 CHF patients)	50% MV: 62 (14) yrs; 38% men						
Takaesu et al. 2015	Prospective; cohort; consecutive patients emergently admitted to the CCU	23 patients admitted to the CCU and 19 age-matched controls; actigraphy and melatonin secretion; age not stated; 68% men	Wrist --	TST, SL, WASO, SE	24 hr 5.6 (1.2)	1.0 (0.7) --	0.9 (1.2) 70 (14)	Melatonin secretion is lower and measured sleep indices worse in CCU patients as compared to healthy controls
Van der Kooi et al. 2013	Prospective; cohort; PSG compared to actigraphy in patients admitted after cardiothoracic surgery	7 patients admitted to the CT-SICU; actigraphy and melatonin secretion; 65 yrs; 86% men	Wrist Actiwatch; 30 sec	TST, SE, NA, WASO	16 hr --	-- --	-- --	--

Chapter 3 HYPOTHESES AND APPROACH

This chapter is modified from the following:

Wilcox et al. (2017) A study protocol for an observational cohort investigating COGnitive outcomes and WELLness in survivors of critical illness: the COGWELL study. BMJ Open,7(7): e015600. doi: 10.1136/bmjopen-2016-015600.

3.0 Abstract

Up to 9 out of 10 ICU survivors will suffer some degree of cognitive impairment at hospital discharge and approximately half will have decrements that persist for years. While the mechanisms for this newly acquired brain injury are poorly understood. The purpose of this study is to describe the prevalence of sleep abnormalities and their association with cognitive impairment, examine a well-known genetic risk factor for dementia (APOE $\varepsilon 4$) that may allow for genetic risk stratification of ICU survivors at greatest risk of cognitive impairment, and determine if EEG is an independent predictor of long-term cognitive impairment, and possibly a candidate intermediate end point for future clinical trials. This is a multisite, prospective, observational cohort study. The setting for this trial will be medical and surgical intensive care units of five large tertiary care referral centres. The participants will be adult patients admitted to a study ICU and invasively ventilated for ≥3 days who survive to hospital discharge. Participants will undergo follow-up within 7 days of ICU discharge, 6-months, and 1-year. At each time point patients will have an EEG, blood work (biomarkers; gene studies), sleep study (actigraphy), complete a number of questionnaires, as well as undergo neuropsychological testing. The primary outcome of this study will be long-term cognitive function at 12-months follow-up as measured by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and Trails Making Test B. The study has received the following approvals: University Health Network Research Ethics Committee (13-6425-BE), Sunnybrook Health Centre Research Ethics Committee (365-2013), Mount Sinai Research Ethics Committee (14-0194-E), and St. Michael's Hospital Research Ethics Committee (14-295). Results will be made available to critical care survivors, their caregivers, the funders, the critical care societies, and other researchers. This study is registered with ClinicalTrials.gov (NCT02086877).

3.1 Introduction

Cognitive outcomes have been evaluated in various ICU patient populations; mixed critically ill patients who required prolonged mechanical ventilation (Hopkins, Jackson, and Wallace 2005; Ambrosino et al. 2002), survivors of sepsis and septic shock (Iwashyna et al. 2010; Semmler et al. 2013) and medical patients who underwent elective surgery (Torgersen et al. 2011). Impaired cognition was seen in several domains at varying time periods. Cognitive impairment was seen in 39-91% of patients at hospital discharge, 13-79% at 3 to 6 months follow-up and 20-71% at 1 year (Wilcox et al. 2013). Little is known regarding the interactions between identifiable risk factors (host factors and acute events in the ICU and after ICU discharge), and cognitive function after critical illness. Moreover, there are few objective tools with which to risk stratify patients with regard to persistent cognitive dysfunction. Identifying objective risk factors and risk markers are first steps towards developing and effectively targeting interventions to prevent post-ICU cognitive impairment.

3.2 Current Knowledge

3.2.1 Sleep Disorders

There is considerable evidence linking sleep disordered breathing and poor sleep quality with cognitive impairment in a variety of patient populations (Lim et al. 2013; Lim et al. 2012; Lim and Saper 2011; Blackwell et al. 2011; Gozal et al. 2007). Cognitive domains particularly associated with sleep disruption include working memory, semantic memory, processing speed, and visuospatial abilities (Lim et al. 2012). Experimental studies support a number of potential neurobiological mechanisms including accumulation of beta amyloid pathology (Kang et al. 2009; Ju et al. 2013), abnormalities of tau (Lim et al. 2013), synaptic abnormalities (Bushey, Tononi, and Cirelli 2011), changes in hippocampal long term potentiation (Arrigoni et al. 2009), impaired hippocampal neurogenesis (Mueller, Mear, and Mistlberger 2011; Guzman-Marin et al. 2005), and gene expression changes (Cirelli, Faraguna, and Tononi 2006). The appeal of

sleep and circadian dysfunction as potential mechanisms mediating post-ICU cognitive impairment is that effective interventions exist to improve sleep and circadian function.

Few studies have rigorously evaluated the prevalence of sleep disruption after critical illness, and its potential role in potentiating cognitive impairment. A prospective multicenter cohort study (n=1625), reported no change in self-reported sleep quality in the year following critical illness using a non-validated single instrument assessment (Orwelius et al. 2008). However, subjective reports of sleep quality can be confounded by poor recall and misperception. A second small case series reported sleep disruption and poor sleep efficiency as measured by polysomnography in five out of seven survivors of ARDS each of whom reported sleep difficulties 6 months after hospital discharge (Lee et al. 2009). Neither study reported cognitive outcomes. A study demonstrating the prevalence of sleep abnormalities after critical illness and their longitudinal association with cognitive impairment would yield potential targets for therapy and novel endpoints for ICU based studies.

3.2.2 Genomics

The Apolipoprotein E (*APOE*) ε4 allele is a well-established and common genetic risk factor for Alzheimer disease (Corder et al. 1993; Poirier et al. 1993; Saunders et al. 1993), and is also a risk factor for cognitive impairment in a number of medical conditions including sleep apnea (O'Hara et al. 2005; Gozal et al. 2007; Cosentino et al. 2008) and following repeated head trauma (Jordan et al. 1997). Recently, in a longitudinal cohort of 737 community dwelling older adults without dementia, the *APOE* ε4 allele was shown to accentuate the impact of sleep fragmentation on the risk of incident Alzheimer's disease in older persons, an effect that was mediated by the accumulation of tau pathology (Lim et al. 2013; Hou et al. 2012). In individuals with high sleep fragmentation, the presence of at least one *APOE* ε4 allele (*APOE* ε4 +/- or +/+) was associated with a three times faster rate of cognitive decline as compared to individuals not carrying an APOE ε4 allele (*APOE* ε4 -/-) (Lim et al. 2013).

This study may identify *APOE* genotype as a biological marker of susceptibility to cognitive impairment and the disruptive effects on sleep following ICU discharge. If this is true, then *APOE* ε4 positive individuals may represent a subpopulation of critical illness survivors who may benefit form particularly close cognitive monitoring and early intervention to improve sleep and circadian function.

3.2.3 Neurophysiology

Studies have so far been unable to identify patients at higher risk of long-term cognitive impairment using screening tools at hospital discharge. For example, in a study by Woon and colleagues, neither the Folstein Mini Mental Status Examination (MMSE) or MiniCog performance at hospital discharge predicted cognitive impairment at 6-month follow-up (Woon, Dunn, and Hopkins 2012). Performance on more sensitive tests of cognitive impairment may have predictive value, but these have not been evaluated. This lack of predictive ability restricts the capacity of clinicians and researchers to adequately risk stratify patients with regard to the likelihood of cognitive impairment.

One candidate predictor for cognitive impairment is quantitative EEG. Serial quantitative EEG has been used to diagnose delirium in older patients (n=25) with and without underlying dementia on an inpatient geriatric psychiatry service (Jacobson et al. 1993). Not only did quantitative EEG (amount of slow wave activity in theta and delta frequencies) prove sensitive, as compared to the clinical exam, for the diagnosis of delirium across a range of underlying etiologies (medication intoxication, hypoxia, and electrolyte disturbances, etc.), it also measured severity of delirium. In the ICU, quantitative EEG has also been found to be a sensitive predictor of mortality in patients with severe sepsis, with well-defined categories (numerical and qualitative variables: no encephalopathic changes, mild encephalopathy and severe encephalopathy) of progressively slower EEG waveforms associated with an increased risk of death, with the highest risk associated with burst suppression (Young et al. 1994; Young et al. 1992).

Similar findings were found in a prospective observational study in medical ICU patients, where burst suppression was found to be an independent predictor of death at 6 months (Watson et al. 2008). Finally, a recent case series of sepsis survivors showed EEG to be a possible candidate predictor of cognitive impairment. Deficits in verbal learning and memory were associated with low-frequency activity on routine EEG at 6 to 24 months following hospital discharge (indicative of nonspecific brain dysfunction) (Semmler et al. 2013). This study is supportive of our study hypothesis but is insufficient to answer the question of whether EEG could be used as a predictive tool in studying cognitive function after critical illness as it was limited by small sample size (n=25) and inadequate control of time, as follow-up was not standardized (single data collection point per patient; range of 6-24 months) (Semmler et al. 2013).

Although it is likely an imperfect tool, EEG may be able to provide prognostic information. If quantitative EEG is linked with long-term cognitive outcomes, it may serve as a good intermediate endpoint in therapeutic trials assessing interventions to decrease the risk of post-ICU cognitive impairment.

3.3 Study Aims

3.3.1 Research Hypothesis and Aims

We hypothesize that critical illness will be associated with decrements in sleep and circadian function, quantifiable by actigraphy, that are in turn associated with worse cognitive performance in ICU survivors at 6 and 12 months after hospital discharge. Second, APOE genotype will be a risk factor for cognitive impairment following a number of brain insults (e.g. intermittent hypoxia, sleep disruption) and may modify the effect of sleep fragmentation on cognition in ICU survivors. APOE genotype may help predict the trajectory of recovery from critical illness, specifically with respect to cognitive impairment. Finally, we hypothesize that survivors of critical illness with cognitive dysfunction will have a greater proportion of low frequency vs. high frequency cortical electrophysiological activity compared to survivors without cognitive

dysfunction. EEG will be a predictor of long-term cognitive impairment and therefore could serve as a surrogate endpoint for clinical trials.

To test our first hypothesis, we will determine the impact of sleep and circadian disruption on long-term cognitive impairment in survivors of critical illness. Further, we will determine the relationship between the APOE genotype, sleep disruption and cognitive impairment in a cohort of survivors of critical illness. This is an exploratory aim to examine for direct associations between *APOE* genotype and cognitive function, as well as for gene and environment interaction (e.g. *APOE* and sleep fragmentation interaction) effects on cognitive function. Lastly, we will determine the relationship between rhythmic cortical electrophysiological activity, measured by serial quantitative EEG, and long-term cognitive outcomes in a cohort of patients who have survived critical illness and are clinically stable prior to hospital discharge.

3.4 METHODS

3.4.1 Study Protocol

This is a multisite, prospective, observational cohort study involving five teaching hospitals (Toronto Western Hospital, Toronto General Hospital, St. Michael's Hospital, Mount Sinai Hospital, and Sunnybrook Health Sciences Centre) at the University of Toronto. Study patients will enter the cohort after they have been mechanically ventilated for at least 3 days, after they meet inclusion/exclusion criteria (see Table 1), and they have survived to ICU discharge. Trained research personnel obtained informed consent from the patient or their next of kin. Patients left the cohort one year after discharge from ICU or at the time of death.

At the time of enrollment, we recorded the following data: baseline demographic, admission diagnosis and dates, severity of illness (APACHEII); burden of comorbid illness; pre-existing cognitive impairment by Informant Questionnaire on Cognitive

Decline in the Elderly Short Form (IQCODE-SF); intensive care unit (ICU) and hospital length of stay (LOS).

Study personnel blinded to study hypothesis will prospectively collect data on important confounders such as hemodynamic and ventilator parameters, glycemic control and the presence or absence of delirium on a daily basis. At the time of study enrollment, information collected on each patient will include the following: APACHE II/III disease category, patient demographics, dates of hospital and ICU admission, initial date of mechanical ventilation, admission diagnosis, history of comorbid disease(s) present at the time of ICU admission and pre-existing dementia by the IQCODE-SF. During the course of each patient's stay in the ICU data will be collected on: APACHE II/III score, mean partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2), central venous pressure, mean arterial pressure and blood glucose, daily mean Riker's sedation agitation score, Confusion Assessment Method in the ICU (CAM-ICU) status and average daily doses of the following medications: benzodiazepines, propofol, narcotics, and dexmedetomidine. All patients underwent standardized follow-up prior to hospital discharge, and at 6- and 12-months. Outcome variables collected at each time point are shown in Figure 1. Study participants were identified with a study number only. No identifying information was transferred outside of the participating hospital site.

3.4.2 Measurement of Exposures and Confounders

3.4.2.1 *Actigraphy*

Actigraphy is the continuous measurement of an individual's movement using a wristwatch-like device (Actiwatch Spectrum, Phillips Respironics, Bend, OR) and is an objective method of quantifying sleep and circadian rhythms. It has been validated against polysomnography for the measurement of total sleep time and sleep fragmentation (Weiss et al. 2010; Lim et al. 2013) and validated against biochemical markers for the assessment of circadian rhythmicity (Lim et al. 2012). Patients will have an actigraph placed on their nondominant wrist days within 1 week of ICU discharge.

Recordings will continue while on the inpatient ward; however, we anticipate that the number of days of actigraphic data recorded in hospital will likely vary depending on severity of illness and trajectory of recovery. If patients are discharged home or to a rehabilitation facility prior to attaining 10 days of actigraphic data, the patient will be asked to continue the recording and return the actigraph to the study centre by pre-paid courier. Patients will be asked to return to follow-up clinic at 6- and 12-months where actigraphs will be again worn for 10 days as an outpatient.

All actigraph data will be analyzed using MATLAB (Mathworks, Natick, MA). Markers of sleep and circadian function include: (1) circadian timing (average time of the activity acrophase [midpoint of 8 consecutive hours] of each 24 hours of greatest activity), (2) sleep duration (determined by the Cole-Kripke algorithm), (3) sleep fragmentation (quantified by P_{RA}) (Lim et al. 2013; Lim et al. 2012; Lim et al. 2011), and (4) regularity of circadian rhythmicity (determined using the chi-square periodogram) (Sokolove and Bushell 1978).

3.4.2.2 *Richards-Campbell Sleep Questionnaire (RCSQ)*

This is a five-item, visual analogue scale designed to assess the perception of sleep in critically ill patients (Richards, O'Sullivan, and Phillips 2000). The scale evaluates perceptions of depth of sleep, sleep onset latency, number of awakenings, time spent awake, and overall sleep quality. Patients will be asked to complete the questionnaire as they reflect on their last night's stay in the ICU prior to ward discharge.

3.4.2.3 *Pittsburgh Sleep Quality Index*

The Pittsburgh Sleep Quality Index (PSQI) is a self-rated questionnaire, assessing sleep quality over a 1-month time interval. Nineteen individual items generate seven "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of scores for these seven components yields one global score; a

global PSQI score greater than 5 yielded a diagnostic sensitivity of 89.6% and specificity of 86.5% in distinguishing good and poor sleep quality (Buysse et al. 1989). Patients will be asked to complete the questionnaire first, while in hospital, to identify any pre-existing sleep disorders (reporting on their sleep the month prior to hospitalization) and then again at 6- and 12-months, reporting perceived reasons for impaired sleep, if any, the month prior to each follow-up appointment.

3.4.2.4 *Apolipoprotein E4*

The APOE coding single-nucleotide polymorphism sites rs7412 and rs429358 will be determined using the Invitrogen Snapshot assay at The Centre for Applied Genomics at The Hospital for Sick Children Hospital (Toronto, ON; www.tcag.ca). Blood samples (5-10 ml) will be drawn prior to discharge in a lavender top ethylenediaminetetraacetic acid tube. Blood will be stored at -20°C prior to being shipped for testing at The Hospital for Sick Children Hospital.

3.4.2.5 *Electroencephalography*

Within 7 days after ICU discharge, approximately 30 minutes of EEG activity was digitally acquired (XLTEK, Oakville, ON) with electrodes placed according to the international 10–20 system with additional surface sphenoidal electrodes. In outpatient follow-up, at 6- and 12-months, 30 minutes of EEG activity was also recorded. Data sampling occurred at a rate of 256 Hz. Power spectra will be calculated for consecutive 4-s windows for each electrode contact, and absolute spectral band power for conventional EEG frequency bands (δ: 0.5–4 Hz; θ: 4–8 Hz; α: 8–13 Hz; β: 13–20 Hz; γ: 20–40 Hz) will be averaged across different windows. Given that global changes are expected, the band power values will be averaged over all electrode contacts. Similar measures have been previously used to characterize Alzheimer's disease and depression and, in the former, were correlated with clinical measures of severity of dementia (Hinrikus et al. 2010; Helkala et al. 1991; Soininen et al. 1989).

3.4.2.6 *Beck's Depression Inventory (BDI-II)*

This instrument screens for depression using criteria consistent with the Diagnostic and Statistical Manual of Mental Disorders- Fourth Edition. Higher scores (range, 0-63) indicate more depressive symptoms. Based on testing in psychiatric outpatients, depression symptom severity is classified as minimal (score, 0-13), mild (score, 14-19), moderate (score, 20-28), and severe (score, 29-63) (Richter et al. 1998). The BDI-II was performed after each neuropsychological assessment as depression could confound our primary outcome, cognition. Recently, the BRAIN-ICU study, a prospective cohort of mixed medical, surgical and cardiac patients, reported that regardless of age, executive dysfunction was independently associated with subsequent worse severity of depressive symptoms and worse mental health related quality of life (Duggan et al. 2017).

3.4.2.7 *The Informant Questionnaire on Cognitive Decline in the Elderly Short Form (IQCODE-SF)*

The IQCODE-SF is a brief questionnaire that uses information provided by an informant (typically a close relative) to assess a person's change in cognitive functioning over the preceding ten years. The questionnaire is often used as a screening test to detect dementia. The standard method used to generate the test score is to take the average rating across 16 situations. A person who has no cognitive decline will have an average score of 3, while scores of greater than 3 indicate that some decline has occurred (Jorm 2004).

3.4.3 Measurement of Outcomes

3.4.3.1 *Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)*

The RBANS is a comprehensive and validated neuropsychometric battery for the evaluation of global cognition, including individual domains of immediate and delayed memory, attention, visuospatial construction, and language (Randolph et al. 1998). The population age-adjusted mean (± SD) for the RBANS global cognition score and for the individual domains is 100 ± 15 (on a scale ranging from 40 to 160, with lower scores

indicating worse performance). The RBANS has been validated in diverse patient populations including those with mild cognitive impairment, moderate to severe traumatic brain injuries, vascular dementias, and Alzheimer's Disease (Duff et al. 2010; Duff et al. 2008; McKay et al. 2007; Hobson et al.2010).

3.4.3.2 *Trailing Making Tests A and B*

Executive function (specifically, cognitive flexibility) will be tested using the Trail Making tests A and B (Reitan and Wolfson 1985).

3.4.3.3 *Telephone Interview for Cognitive Status (TICS)*

The TICS instrument will be used as a secondary means to assess cognitive outcome prior to hospital discharge, as well as at 6- and 12-month follow-up. It is made of 11 test items: 10 word immediate and delayed recall tests of memory, a serial 7s subtraction test of working memory, counting backwards to assess attention and processing speed, an object naming test to assess language, and recall of the date and US president (or Canadian prime minister) to assess orientation (Knopman et al. 2010). Composite scores using all the items create a measure of cognitive functioning, which can range from 0 to 35. It takes approximately 10 minutes to administer and score. T-scores are based on normative data from 6,726 persons (Knopman et al. 2010). In an effort to minimize loss to follow-up when in depth neuropsychological testing can't be performed due to patient time pressures, we will try to administer this less burdensome instrument. The TICS tool has been extensively validated; it was the cognitive assessment tool used in the Health and Retirement Study (HRS) to make national estimates of dementia and cognitive impairment without dementia (CIND) in the US (n=30,000) (Plassman et al. 2007). Its performance was determined against a detailed neuropsychological and clinical assessment in a smaller subsample. The overall levels of dementia and of CIND estimated using TICS was similar to those directly estimated from the neuropsychological study. The TICS was found however to be less sensitive at

discriminating between normal cognitive function and mild cognitive impairment (Crimmins et al. 2011).

3.4.4 Statistical Analysis Plan

Assessing the epidemiology of long-term cognitive impairment will focus on prevalence, severity and natural history. Prevalence will be determined based on binary assessment of patient having or not having clinically significant cognitive impairment, defined as test scores 1 standard deviations (SD) below the population mean on the RBANS global cognition score. We will screen the covariates using the univariate association between the outcome and level of education, RCSQ and PSQI scores, BDI-II, hospital LOS, and days of mechanical ventilation and selecting those with $p<0.2$. Logistic regression analysis models will be used to determine the association between sleep fragmentation and cognitive impairment at 1-year while adjusting for the variables selected. We will enter into the model only those covariates that are not multicollinear based on the variance inflation factor criterion. Given that we predict we will have approximately 30 events at the 1-year follow-up, this will give us at least 5 events per variable (Vittinghoff and McCulloch 2007).

Generalized estimating equations (GEE) models, to take into account the correlation between the 3 measurements per subject, will be used to determine the association of EEG and the effect of time on cognitive impairment. We will test the association between APOE $\varepsilon 4$ (+/- or +/+) versus APOE $\varepsilon 4$ (-/-) and cognitive impairment using χ^2 test. The degree of association between APOE and sleep efficiency will be determined using Spearman's correlation; this information will be used to inform future trials.

We calculated our sample size based on logistic regression analysis with outcome cognitive impairment at 12 months. We used a proportion of 30% cognitive impairment at 1-year in this patient population. We do not know a priori the association between our sleep efficiency variable and the other covariates so we will use a range of R-

squared (R-squared obtained by regressing the sleep efficiency variable on the other covariates) from low to moderate (0.1 to 0.5). With a sample size of approximately 110, we have 80% power with α=0.05 for R-squared=0.5 to detect an absolute increase in percentage of cognitive impairment of 20% (from 30% to 50%) for a decrease in sleep efficiency value with one standard deviation from the mean or an increase of 15% (from 30 to 45%) for a R-squared=0.2. With 110 patients, approximately 20% in the APOE ε4(+/- or +/+) group, a χ^2 test at α=0.05 will be able to detect a 37.5% difference (25% in the APOE ε4[-/-] group and 62.5% in the APOE ε4[+/- or +/+] group) in the cognitive impairment group with about 92% power or about 80% power to detect a difference of 31% (25% in the APOE ε4[-/-] group versus 56% in the APOE ε4[+/- or +/+] group).

A total of approximately 150 patients will be consented to participate. This estimate is based on a calculated 1-year mortality rate of 15% in patients discharged from critical care units and a conservative loss to follow-up rate of 15%.

3.4.5 Anticipated Methodological Issues

Our longitudinal study design, in which parallel covariates are reliably and repeatedly measured over time, will allow us to look at changes over time in the same patient, defining the temporal sequence of changes, and providing stronger evidence for causality than could be obtained from a cross-sectional design. Although our genomic association theory is an exploratory aim, it is based on strong scientific reasoning from other patient populations and if our hypothesis is true, would provide an easy way of identifying susceptible individuals who may benefit the most from interventions to decrease the risk of cognitive impairment.

The primary limitation of this study is loss to follow-up and missing data points that would challenge the internal validity of reported results from COGWELL. Efforts to minimize loss to follow-up will include respecting the time commitment of patients, formal tracking procedures of patients enrolled including acquiring of multiple contacts

for arranging follow-up, strong interpersonal skills of study personnel, and flexible hours for testing (Tansey et al. 2007).

3.5 Consort and Follow-up Procedure in the Main Cohort

Enrollment in this study began at the University Health Network in December of 2013; the last patient (n=150) was enrolled in June 2017 with 1-year follow-up having completed in June 2018. Eighteen patients died while in ICU, 3 died between ICU discharge and the 7-day follow-up and 113 were included in the 1-year longitudinal cohort. The proportion of patients alive and eligible for follow-up at each visit was 90% (n=102/113) at 7 days, 82% (n=69/84) at 6 months, and 95% (n=39/41) at one year respectively. At each time point the denominator includes only patients who were alive and not withdrawn, defined as missing all outpatient visits. Thirteen percent of patients received at least one off-site visit during the 1-year of follow-up and 75% of those were home visits.

ICU survivors had a mean age of 57 years and 44% were female. For those reporting education and work status, the majority of patients had some secondary or post-secondary education, and most were engaged in part- or full-time work. The majority lived at home and independently prior to their critical illness. The median APACHE III was 57 (IQR, 43-75). The median duration of mechanical ventilation for patients discharged alive from ICU was 7 days (5 - 13) and ICU LOS was 13 days (IQR, 7-21). Fifty eight percent of patients reported a comorbidity; the most common comorbidities were respiratory disease (29.4%), cardiovascular disease (19.6%), and diabetes (14.7%). The most common admitting diagnostic categories were pneumonia (10.3%), other respiratory condition (37.1 %), and sepsis/shock.

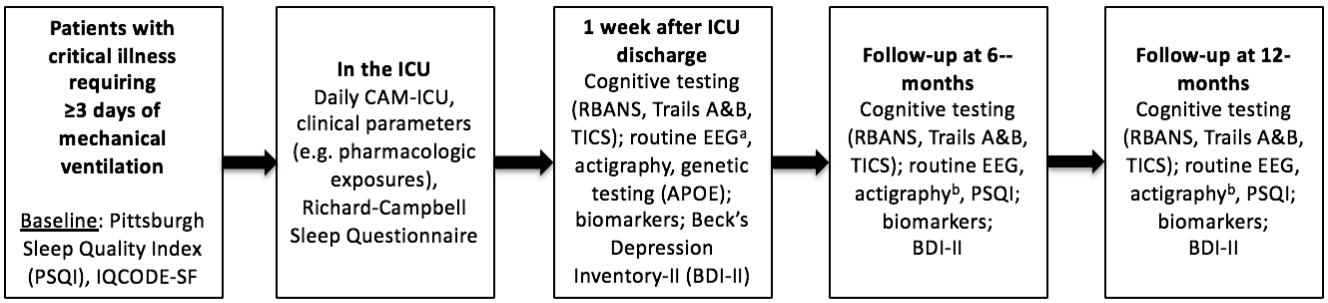
Table 3.1 Inclusion and exclusion criteria

Inclusion criteria	• ≥16 years of age • Admission to study ICU for invasive mechanical ventilation (≥ 3 days)
Exclusion criteria	• Advanced cognitive impairment or unable to follow simple commands before their acute illness (e.g. end-stage Alzheimer's disease) • Primary neurological injury (e.g. anoxic injury, stroke or traumatic brain injury) • Anticipated death within 3 months of discharge (e.g. palliative) • Uncontrolled psychiatric illness at hospital admission • Not fluent in English • Unlikely to adhere with follow-up (e.g. no fixed address) • Residence greater than 300 kms from referral centre

Table 3.2 Enrollment number by site

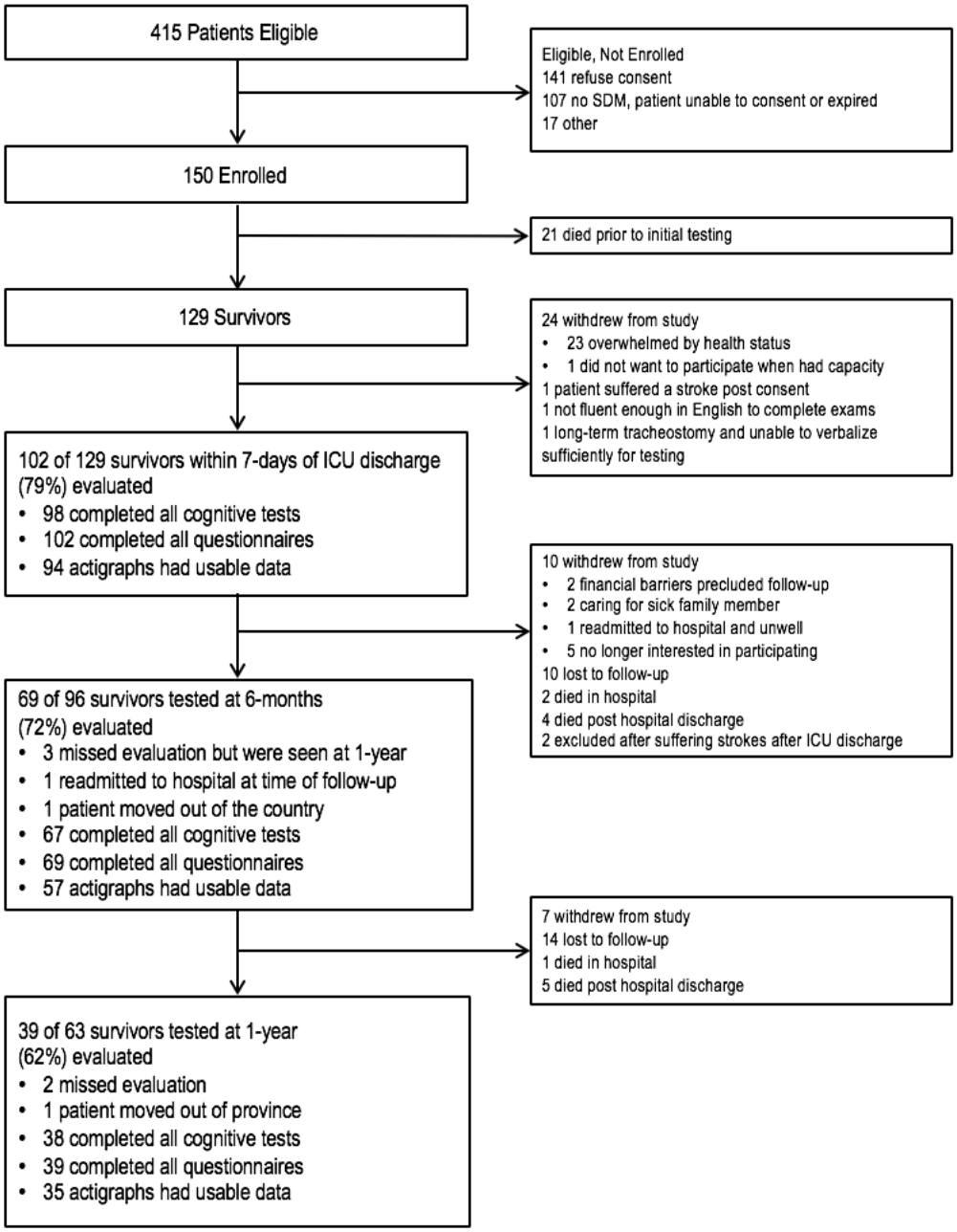
Site	No. of patients
Toronto General Hospital	110
Toronto Western Hospital	24
Mount Sinai Hospital	6
St. Michael's Hospital	5
Sunnybrook Health Sciences Centre	5

Figure 3.1 Flow diagram of the COGnitive Outcome and WELLness in survivors of critical illness (COGWELL) study



[a] 30-mins of routine EEG activity except for 20 patients had 12-16 hours of overnight recording.
[b] 10 days of home actigraphy.

Figure 3.2 CONSORT diagram. Screening and details of the 1-year follow-up cohort the proportion of patients unable to attend a visit



Chapter 4 POLYSOMNOGRAPHIC SLEEP ON THE WARDS AFTER ICU DISCHARGE

This chapter is modified from the following:

Wilcox, ME et al. (2018). Sleep on the ward in intensive care unit survivors: a case series of polysomnography. Intern Med J, 48(7): 795-802.

4.0 Abstract

Background: Few studies have investigated sleep in patients after intensive care despite the possibility that inadequate sleep might further complicate an acute illness impeding recovery.

Aims: Our objectives were to assess the quality and quantity of a patients' sleep on the ward by polysomnography (PSG) within a week of intensive care unit (ICU) discharge and to explore the prevalence of key in-ICU risk factors for persistent sleep fragmentation.

Methods: We enrolled twenty patients after they have been mechanically ventilated for at least 3 days and survived to ICU discharge. We included all patients over the age of 16 years and excluded patients with advanced cognitive impairment or unable to follow simple commands before their acute illness, primary admission diagnosis of neurological injury, uncontrolled psychiatric illness, or not fluent in English.

Results: Twenty patients underwent an overnight PSG recording on day 7 after ICU discharge (SD, 1 day). ICU survivors provided 292.8 hours of PSG recording time with median recording times of 16.8 hours (Interquartile range [IQR], 15.0 to 17.2 hours). The median total sleep time per patient was 5.3 hours (IQR, 2.6 to 6.3 hours). In a multivariable regression model, postoperative admission diagnosis ($p = 0.04$) and patient report of poor ICU sleep ($p = 0.001$) were associated with less slow wave (restorative) sleep on the wards after ICU discharge.

Conclusions: Patient reported poor sleep while in the ICU and a post-operative admission diagnosis may identify a high-risk subgroup of patients that may derive greater benefit from interventions to improve sleep hygiene.

4.1 Introduction

Intensive care unit (ICU) survivors are a vulnerable patient population given both their in-ICU exposures predisposing them to impaired sleep but also their need for rehabilitation given their acquired functional morbidity. In a single centre study (n=12) following patients across their inpatient stay, polysomnography (PSG) recordings were performed both in the ICU and on the ward following a myocardial infarction (Broughton and Baron 1978). A marked disturbance of nocturnal sleep was seen in all patients while present in the ICU, as compared to the ward (Broughton and Baron 1978). Interestingly, an abrupt change of sleep patterns was not seen on patient transfer, suggesting that poor sleep in the ICU was not solely a result of the ICU environment itself (Broughton and Baron 1978). In a study of tracheostomized patients (n=22) transferred to a step-down unit after ICU discharge, three patients (14%) had reduced percentage of stage 3 slow wave sleep (SWS) (Fanfulla et al. 2011). Sleep amount and quality did not differ between patients breathing spontaneously as compared to those on mechanical ventilation (Fanfulla et al. 2011), suggesting that mechanical ventilation or devices associated with ICU care are not the main contributors to poor sleep in the ICU. In a prospective study of elderly patients admitted for acute cardiac, respiratory or renal disease (n=10), actigraphy was used to assess rest-activity rhythms and showed that circadian rhythms were severely altered during the initial period of hospitalization (Vinzio et al. 2003). Progressive improvement in circadian rhythmicity was associated with clinical improvement in health (Vinzio et al. 2003).

A number of PSG studies have been done in the ICU (Freedman et al. 2001; Freedman, Kotzer, and Schwab 1999; Nicolas et al. 2008; Elliott et al. 2013) but none have looked at whether or not sleep abnormalities persist after a patient is discharged from the ICU. Surviving the ICU, patients are within a window of their trajectory where they are physically, mentally and cognitively frail and the role of sleep may play an important role in their recovery. As few studies have evaluated sleep on the ward after an ICU stay, our primary aim was to describe the quality and quantity of patients' sleep on the ward

within a week following ICU discharge using PSG. Further, given that sleep disturbances in ICU survivors discharged to the medical/surgical wards might be an important determinant of capacity to engage in physical and occupational rehabilitation, our secondary aims were to explore key predictors of impaired sleep in the ICU as this may identify a high-risk group suited for ward-based sleep hygiene interventions.

4.2 Methods

4.2.1 Study Setting and Sample

This was a single site study of two medical/surgical ICUs at the University Health Network (Toronto Western Hospital and Toronto General Hospital). Patients were included if aged ≥16 years and admitted to a study ICU for ≥3 days of invasive mechanical ventilation. Exclusion criteria included a history of sleep disorders (e.g. obstructive sleep apnea), advanced cognitive impairment or inability to follow simple commands before their acute illness, admission for a primary neurological injury (e.g. anoxic injury, stroke or traumatic brain injury), anticipated death within 3 months of discharge (e.g. palliative), uncontrolled psychiatric illness at hospital admission, and lack of fluency in English. Research Ethics Committee approvals were obtained from the University Health Network (13-6425-BE). Data were collected from December 2013 to December 2014. Screening for study eligibility was performed on weekdays only.

4.2.2 Data Collection

Demographic and clinical data were collected from the patient's record. The Acute Physiology and Chronic Health Evaluation (APACHE) II severity of illness score on admission were calculated to assess severity of illness. On enrolment, patients were asked to rate their sleep quality over a 1-month time interval preceding their hospital admission using the Pittsburgh Sleep Quality Index (PSQI). The PSQI is a self-rated questionnaire assessing nineteen individual items to generate seven "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction (Buysse et al.

1989). If patients were delirious, then a close friend or family member provided collateral information on the pre-ICU sleep habits. The sum of scores for these seven components yields one global score; a global PSQI score greater than 5 yielded a diagnostic sensitivity of 89.6% and specificity of 86.5% in distinguishing good and poor sleep quality. On the day of ICU discharge, patients were asked to rate their last night's sleep in the ICU using the Richard-Campbell Sleep Questionnaire (RCSQ). The RCSQ is a five-item, visual analogue scale designed to assess the perception of sleep in critically ill patients. The scale evaluates perceptions of depth of sleep, sleep onset latency, number of awakenings, time spent awake, and an overall sleep quality score (Kamdar et al. 2012).

4.2.3 EEG Acquisition

Accredited technologists recorded 12-18 hours of continuous scalp electroencephalogram (EEG) (XLTEK, Oakville, ON) on all patients once within 5-10 days of ICU discharge. Electrodes were placed according to the international 10–20 system with additional surface sphenoidal electrodes. Data was sampled at 256 Hz. As all patients were on a medical or surgical ward, none were comatose and recordings started in the late afternoon. Patients were free to move about their room but the majority of their care (e.g. physiotherapy) had already been performed. When an intervention was required (e.g. computerized tomography scan) this was documented by the ward nurse and these epochs were not included in the analysis. PSG epochs, each 30 seconds in duration, were scored manually by a registered PSG technologist and overseen by a board-certified sleep physician (Andrew Lim). Sleep was staged by 2007 American Association of Sleep Medicine criteria (http://www.aasmnet.org/).

4.2.4 Statistical Analysis

Continuous variables are described using medians and interquartile ranges (IQRs) and/or means and standard deviations; categorical variables are described using frequencies and proportions. Amounts of time spent in each sleep stage are described in

terms of minutes and in percentages of total sleep time scored. Given limitations in number of PSG recording performed the mean percentage (11%) was used to divide into either greater or lesser SWS; patients were categorized into two groups based on the percentage of SWS seen during their overnight recording (i.e. all studies with a percentage of SWS greater than the mean were categorized as greater SWS). The proportion of time spent in SWS, gender, pre-existing sleep problems, reported in ICU sleep disturbance, admitting diagnosis, ICU length of stay (LOS), APACHE II score, duration of mechanical ventilation, days delirious in the ICU, hours of continuous analgesia or sedation and environmental factors at time of PSG recording (number of patients beds, frequency of vitals) were compared using Fisher's Exact Test or the Wilcoxon Rank Sum test. Linear regression was used to determine the association of measured covariates and sleep efficiency as determined by PSG and then actigraphy. Given the small sample size our analyses were limited to a series of univariate analyses. Differences were considered significant at p-value ≤ 0.05. All analyses were performed using Stata11 software (StataCorp LP, College Station, Texas, USA) (Daniel 1983).

4.3 Results

4.3.1 Sample Characteristics

Informed consent was obtained from a total of 20 patients; however 2 patients did not have useable PSG data: one requested removal of PSG after recording began due to discomfort and a corrupt file prevented another from being analyzed. Patient baseline demographic data are illustrated in Table 4.1. Median age was 56 years (IQR, 37 to 60 years), patients were ill with a median enrollment APACHE II score of 18 (IQR, 15 to 22), duration of mechanical ventilation was 12 days (IQR, 7 to 17 days) and 8 (44%) were postoperative surgical patients. All patients survived to hospital discharge.

4.3.2 Description of PSG Studies

The 18 patients studied provided 292.8 hours of recording time with a median duration of PSG recording time per patient of 16.8 hours (IQR, 15.0 to 17.2 hours; Figure 4.1 and

Table 4.2). The median total sleep time per patient was 5.3 hours (IQR, 2.6 to 6.3 hours). Patients were awake for 110.9 hours of the recording time. The majority of sleep was made up of stages 1 (71 hours) and 2 (51 minutes), median percent of time in stages 1 and 2: 22.5% (IQR, 12.2 to 33.9%) and 50.9% (IQR, 33.3 to 63.0%), respectively. Patients had a median time in SWS of 2 minutes (IQR, 0 to 1.1 hours) and SWS accounted for 11.0 hours of total recording time. REM accounted for 34 minutes (standard deviation [SD], 42 minutes) per patient of total sleep time; median 23 minutes per patient (IQR, 0 to 51 minutes); and REM was seen in 10 hours and 8 minutes of total recordings of all 18 patients.

4.3.3 Factors associated with sleep quality

Patients remained in the ICU for a median of 15 days (IQR, 9 to 19 days). Sleep studies were performed within 7 days of discharge. The majority of patients (n=14; 78%) were in either one- (n=8; 44%) or two- (n=6; 33%) patient rooms at the time of their recording. On average, patients had their vitals taken 4 times (SD, 5 times) over the course of their recording. Patients with greater percentage of SWS during their recording had shorter ICU length of stay on average (10.9 days as compared to 17.7 days; rank sum: 2.04; p-value = 0.04). Although not reaching statistical significance, patients with greater percentage of SWS had shorter durations of mechanical ventilation (9.0 days as compared to 14.7 days; p-value = 0.09; Table 4.3). There was no significant association between number of beds in the room at the time of the recording and percentage of SWS, however among patients with higher percentage of SWS vitals were checked more often (p-values: 0.63 and 0.09, respectively).

The mean duration of continuous intravenous administration of sedatives and/or analgesics was 101.3 hours (SD, 123.4 hours; range, 0 to 418 hours). The mean number of days that a patient was delirious, as measured by the Confusion Assessment Method for the ICU (CAM-ICU), while in the ICU was 3 (SD, 3 days). At the time of the PSG recording, 7 patients (39%) were taking a medication (e.g. sedative-hypnotics) for sleep;

of these, 5 of the 7 patients (70%) were on a medication for sleep at home prior to admission. No significant correlations were seen between number of days delirious in the ICU or number of hours of continuous intravenous administration of sedatives and/or analgesics and percentage of SWS. Further, no correlation was seen between medications used for sleep prior to admission and percentage of SWS.

We first looked at univariate associations between greater percentage of SWS within 7 days of ICU discharge and age, gender, self-reported pre-existing sleep problems, use of medications for sleep prior to admission, patient reported poor sleep in the ICU, admission diagnosis, ICU length of stay, APACHE II score, duration of mechanical ventilation, number of days delirious in the ICU, duration of continuous intravenous administration of sedatives and/or analgesics, and environmental factors at the time of the PSG recording (e.g. number of beds in room). Variables with a p-value < 0.2 in this series of analyses included self-reported pre-existing sleep problems ($p = 0.13$), patient reported poor sleep in the ICU ($p < 0.001$), post-operative admission diagnosis ($p = 0.02$), and ICU length of stay ($p = 0.05$). We started with all variables in the multiple regression models and then used backward selection method; in the final model only a postoperative admission diagnosis ($p=0.04$) and patient reports in ICU poor sleep ($p = 0.001$) were left.

4.4 Discussion

This study provides a current characterization of the quality and quantity of sleep in ICU survivors within 7 days of discharge to the medical or surgical ward. In this study, sleep quality remained poor in approximately two-thirds (61%) of ICU survivors with a number of patients experiencing little or no SWS and/or REM independent of environmental factors such as the frequency of vitals or number of beds in the room. The median total sleep time was similar to that experienced among adult medical inpatients (Yoder et al. 2012), albeit shorter than that reported for the average total sleep time per night of healthy, community dwelling adult Canadians (men: 8 hours and women 8.2 hours)

(Gilmour et al. 2013). This current study shows that in some patients, but not all, sleep quality is good as they transition through ward care, possibly because their acuity of their illness subsides or environmental factors such as increased noise, nursing intensity, pain, and/or ambient light exposure changes. It is remains to be determined however as to which survivors will have persistent sleep disorders out and subsequent to hospital discharge, a finding that may contributing to experienced long-term morbidity, such as depression and cognitive impairment.

Few studies have rigorously evaluated the prevalence of sleep disruption after critical illness. A recent systematic review by Altman and colleagues reported on 22 studies examining sleep after hospital discharge in survivors of critical illness (Altman, Knauert, and Pisani 2017). Sleep disturbances were common and despite improving over time, up to two-thirds (61%) of patients still reported poor sleep at 6 months follow-up (Altman, Knauert, and Pisani 2017). Analysis of risk factors for sleep disturbances were conflicting, however persistent sleep disturbances were frequently associated with post discharge psychological comorbidities and impaired quality of life. Unfortunately, none of these studies reported on repeat sleep studies or cognitive outcomes. Interestingly, in a prospective cohort of ICU survivors (n=55) severity of illness was a predictor of reduced sleep duration and increased sleep disruption after hospital discharge (Solverson, Easton, and Doig 2016). In this study, over 60% of patients reported poor sleep quality and an associated reduced HRQOL at 3 months follow-up (Solverson, Easton, and Doig 2016).

Attempts to date at elucidating mechanisms of sleep derangements in the critically ill have been anchored in intervention-based studies performed in the ICU environment (Poongkunran et al. 2015). A number of studies have assessed how the mode of mechanical ventilation was associated with sleep quality (Alexopoulou et al. 2013; Bosma et al. 2007; Cordoba-Izquierdo et al. 2013; Roche-Campo et al. 2013; Parthasarathy and Tobin 2002). Timed mode of ventilation was better than spontaneous

mode of ventilation in improving sleep quality and quantity. Non-mechanical ventilation-based therapies such as melatonin (Bourne, Mills, and Minelli 2008) or music therapy (Su et al. 2013) also improved sleep. These studies however were small and inadequately powered to measure important patient-outcomes such as delirium, hospital length of stay or even mortality. In community-dwelling participants, increased sleep fragmentation due to chronic insomnia has been independently associated with all-cause and cardiopulmonary mortality (Parthasarathy et al. 2015). Some of the mechanistic basis for such an association may be mediated by systemic inflammation. This is consistent with controlled experiments in healthy volunteers that reveal an elevation in pro-inflammatory mediators following sleep loss (Grandner et al. 2013). Different biological phenotypes have described within delirious patient populations of critically ill patients, categorized as “inflamed” and “non-inflamed” subgroups, with differential cytokine profiles (van den Boogaard et al. 2011). These biological findings may explain the emergence of differential clinical phenotypes for delirium, those found to be rapidly reversing as compared to persistently delirious patients (Patel et al. 2014). The relationship between poor sleep in the ICU and delirium has yet to be explained. Interestingly, sleep fragmentation in older adults has been shown to be associated with incident Alzheimer’s disease. In this study of more than 700 older persons without dementia, increased sleep fragmentation was associated with a 1.5 fold increased risk of subsequent development of Alzheimer’s disease (Lim and Saper 2011). Further, Lim and colleagues showed that the Apolipoprotein E4 allele, a known risk factor for delirium in the ICU (Ely et al. 2007), accentuated the impact of sleep fragmentation on the risk of incident Alzheimer’s disease. This effect is mediated by the accumulation of tau pathology (Lim et al. 2013). Further work is needed in this emerging area of research. A study demonstrating the prevalence of sleep abnormalities after critical illness and their longitudinal association with other post-ICU morbidities such as cognitive impairment or mood disorders could potentially yield potential targets for therapy and novel endpoints for ICU based studies.

Strengths of this study are that despite the challenge of using PSG we were able to obtain usable data assessing sleep on the wards prior to hospital discharge during an important time in their recovery trajectory as more rigorous physical rehabilitation is likely occurring in these patients; it attempts to study both in ICU exposures that might impact sleep after critical illness as well as environmental factors at time of testing; and lastly, it is less likely to be limited in interpretation of PSG given the relative 'remoteness' of sedation exposure that would influence in ICU conventional Rechtschaffen & Kales analysis (e.g. benzodiazepine increasing EEG spindle activity). The main limitation of this study is its small sample size and therefore limited power. The limited sample size speaks to the logistic complexity of performing post-ICU follow-up on wards in this case flexibility in the availability of EEG technologists and PSG monitoring equipment. Further, the population was heterogeneous with both medical and surgical patients being enrolled.

4.5 Conclusions

Further studies are needed to determine the relationship between in ICU risk factors for poor sleep and persistent sleep fragmentation. Longer ICU length of stay, greater durations of mechanical ventilator days, and more frequent vital signs may identify at subgroup at higher risk of poor sleep and therefore may warrant greater attention to interventions to improve sleep hygiene. The relationship between systemic inflammation, delirium and poor sleep requires further investigation in a larger patient population.

Table 4.1 Patient baseline characteristics - polysomnography

Patient	Ag	Gender	APACHE II score	Reason for Admission	Days of MV	ICU LOS	Days delirious in ICU	Hours of continuous sedation	RCSQ at ICU discharge	Sedative medications at time of study	Day after ICU discharge study performed	% total sleep time in SWS	% total sleep time in REM
1	34	W	8	Pneumonia	28	29	6	156 (fentanyl)	0	None	6	0	0.6
2	58	W	16	Pneumonia	7	8	0	58 (midazolam, fentanyl/morphine)	0	Zopiclone	9	42.9	0
3	64	M	24	Postoperative	7	9	0	138 (propofol, *intermittent* fentanyl/morphine)	32	None	6	29.6	4.2
4	37	M	22	Postoperative	13	15	1	139 (propofol, midazolam, fentanyl)	80	None	9	42.3	12.4
5	63	M	26	Sepsis	20	23	9	43 (midazolam, morphine)	68	Quetiapine	6	0	0
6	27	M	18	Postoperative	12	14	0	8 (propofol, midazolam, fentanyl)	22	None	7	17.7	6.2
7	59	W	19	Pneumonia	9	15	4	26 (propofol, *intermittent* morphine)	21	None	9	0	8.8

8	39	W	21	Decreased LOC	24	28	0	-	59	None	6	0	0
9	59	M	26	Postoperative	13	15	1	-	23	None	8	0	20.5
10	70	M	16	Postoperative	14	17	0	-	62	None	8	0	11.3
11	37	M	17	ARDS	18	24	5	418 (propofol)	70	Zopiclone	7	5.2	37.2
12	35	W	16	Stroke	10	11	3	108 (propofol)	41	Zopiclone	5	24.8	0
13	67	M	18	Sepsis	4	6	3	52 (propofol)	13	None	7	0	17.5
14	55	M	22	Trauma	17	19	2	351 (propofol)	3	Zopiclone, Clonazepam	9	0	18.2
15	42	W	14	Postoperative	11	14	7	251 (propofol, fentanyl)	26	Quetiapine	6	31.1	6.0
16	33	W	11	Sepsis	5	6	4	102 (midazolam, *intermittent* morphine)	79	None	7	3.6	12.2
17	57	M	10	Postoperative	3	5	3	14 (propofol)	76	None	8	3	0
18	60	W	15	Postoperative	10	13	0	115 (midazolam, fentanyl)	50	Clonazepam	6	0	19.8
19*	53	M	-	Respiratory arrest/OD	3	3	1	40 (propofol)	4	-	-	-	-
20*	56	W	-	Postoperative	22	27	3	454 (propofol, midazolam, fentanyl)	42	Zopiclone	-	-	-
Median	56	**-**	18	-	12	15	3	55	36	**-**	7	1.5	7.5

IQR 25th	37	-	15	-	7	9	0	8	17	-	6	0	0
IQR 75th	60	-	22	-	17	19	4	138	65	-	9	24.8	17.5
Percent	-	44	-	-	-	-	-	-	-	33	-	-	-
Mean (SD)	-	-	-	-	-	-	-	101 (123)	38 (28)	-	7 (1)	11 (16)	9.7 (10)

*Not included in median, IQR, proportion or mean as no overnight PSG recording. Patients 6 and 7 had chronic renal failure and were receiving dialysis three times a week; patient 9 had newly acquired acute renal failure while in the ICU and still required dialysis on a routine basis during the time of his PSG study.

** ICU: intensive care unit; LOS: length of stay; MV: mechanical ventilation; APACHE: Acute Physiology and Chronic Health Evaluation; OD: overdose; IQR: interquartile range; ARDS: acute respiratory distress syndrome; LOC: level of consciousness

Table 4.2 Sleep outcomes – PSG-derived data, sleep time and stages

Outcomes	**(n=18)**
Duration of PSG recording median (IQR), hours	16.8 (15.0 to 17.2)
Total Sleep Time, median (IQR), hours	5.3 (2.6 to 6.3)
Stage 1 Sleep, median (IQR), hours	1.0 (0.6 to 1.4)
Stage 1 Sleep, mean (SD), %	29.8 (24.1)
Stage 2 Sleep, median (IQR), hours	2.4 (1.2 to 4.0)
Stage 2 Sleep, mean (SD), %	49.4 (19.5)
Slow Wave Sleep, median (IQR), hours	0.1 (0 to 1.1)
Slow Wave Sleep, mean (SD), %	11.1 (15.8)
Rapid Eye Movement, median (IQR), hours	0.6 (0 to 0.9)
Rapid Eye Movement, mean (SD), %	9.7 (10.1)
Arousals, median (IQR), No. per hour	23 (15 to 48)
Sleep onset latency, median (IQR), hours	1.6 (0.9 to 4.9)
Rapid Eye Movement latency, median (IQR), hours	1.4 (0 to 6.9)

PSG: Polysomnography; IQR: Interquartile range; SD: Standard deviation; No.: Number

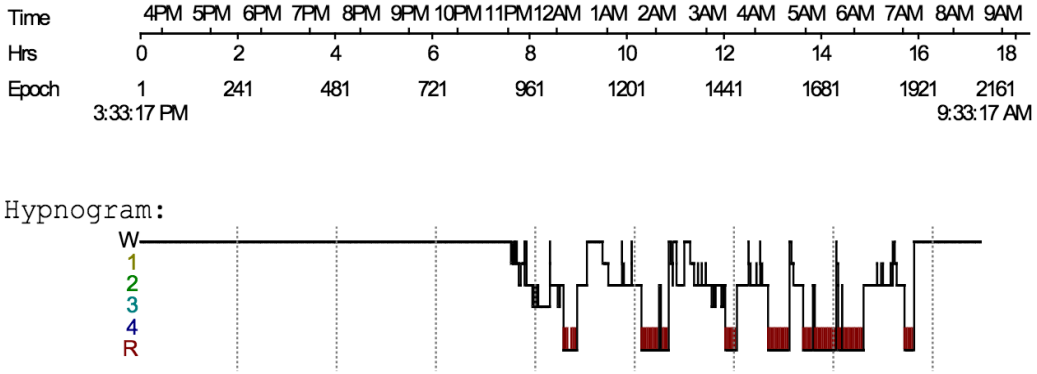
Table 4.3 Univariate Association of Time Spent in SWS Stage and Self-Reported Pre-existing Sleep Disorder, Severity of Illness, Days Delirious and ICU Length of Stay

Characteristic	**Higher percentage of SWS sleep**		**p-value**
	No (n=11)	Yes (n=7)	
	n (%)	n (%)	
Gender (Woman)	6 (45)	3 (43)	0.91
Preexisting sleep problems	3 (27)	0 (0)	0.13
APOE ε4 genotype	2 (18)	2 (29)	0.27
Drugs for sleep prior to admission	2 (18)	3 (43)	0.26
In ICU sleep disturbance	1 (9)	6 (86)	0.001
Pneumonia	4 (36)	1 (14)	0.31
Sepsis	2 (18)	0 (0)	0.23
Post-operative	2 (18)	5 (71)	0.02
	Mean (SD)	Mean (SD)	
Age	52.36 (13.85)	45.71 (13.95)	0.32
No. hours of sleep per night prior to hospitalization	6.73 (1.79)	7.57 (1.62)	0.11
ICU length of stay	17.73 (7.84)	10.86 (3.72)	0.04
APACHE II score	18.09 (5.63)	17.14 (4.74)	0.62
No. days of mechanical ventilation	14.73 (7.56)	9.00 (3.51)	0.09
No. days delirious in ICU	3.09 (2.88)	2.00 (2.58)	0.54
No. hours of continuous IV sedation and/or analgesia	100.64 (146.76)	102.29 (85.07)	0.30
No. of beds in room at time of PSG	2.00 (1.34)	2.00 (1.00)	0.63
Absolute No. of times vitals checked during PSG	3.18 (4.73)	4.29 (5.25)	0.09

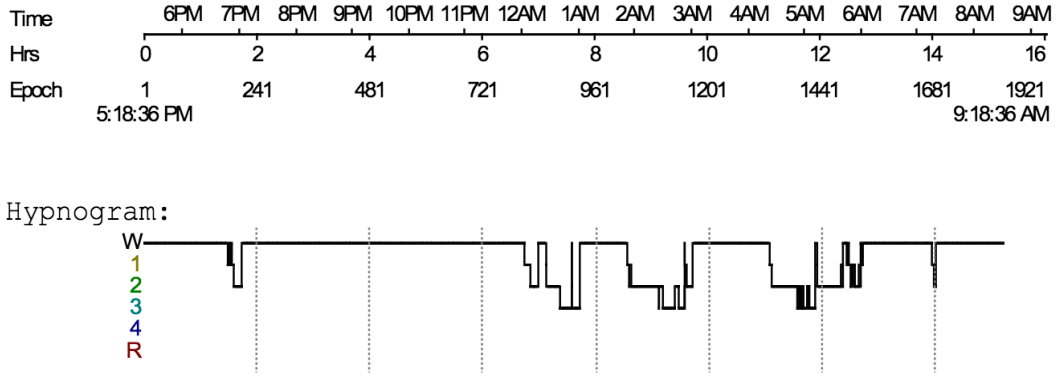
PSG: Polysomnography; No.: Number; ICU: Intensive Care Unit; REM: Rapid Eye Movement

Figure 4.1 Representative histograms of a night's sleep illustrating a range in sleep quality and quantity of sleep stages after ICU ([W] wakefulness; [1] stage 1; [2] stage 2; [3 and 4] Slow Wave Sleep [SWS]; and [R] rapid eye movement [REM]).

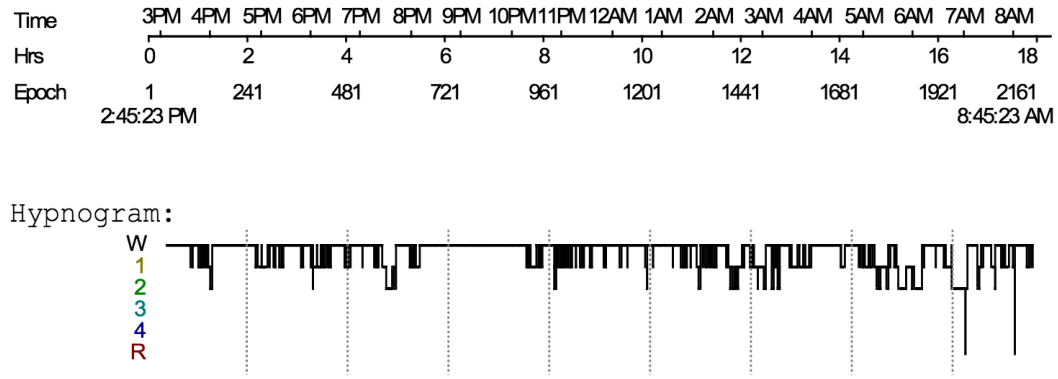
A. Normal appearing sleep – presence of SWS and REM.



B. Somewhat normal appearing sleep – presence of SWS; absence of REM.



C. Abnormal sleep – absence of SWS or REM.



Chapter 5 ACTIGRAPHIC MEASURE OF SLEEP ON THE WARDS AFTER ICU DISCHARGE

This chapter is modified from the following:

Wilcox, ME et al. (2019). Actigraphic measures of sleep on the wards after ICU discharge. Journal of Critical Care. 54: 163-69.

5.0 Abstract

Background: There is evidence that patients' sleep in the intensive care unit (ICU) during critical illness is severely disrupted.

Aims: The purpose of this study was to use an objective measure to evaluate sleep quality on the ward after ICU discharge in survivors of critical illness.

Methods: This was a prospective cohort study of 94 patients admitted to a multidisciplinary ICU between December 2013 and June 2017. Adult patients received ≥3 days of mechanical ventilation. Sleep quality was measured using multi-night sleep actigraphy. Baseline sleep quality (i.e. sleep prior to hospitalization) was evaluated using the Pittsburgh Sleep Quality Index.

Results: A total of 65% of patients had poor sleep quality measured with the PSQI. The average (SD) sleep time and sleep efficiency was 6.03 hrs (3.70 hrs) and 44% (27%), respectively. An admission diagnosis of sepsis was associated with shorter total sleep time (TST; $p = 0.03$) and reduced sleep efficiency (SE; $p = 0.04$) as were severity of illness and duration of sedative exposure ($p = 0.12$ and 0.03; $p = 0.09$ and <0.01; respectively for TST and SE). Weak correlations were seen between pro-inflammatory biomarkers and sleep quality.

Conclusions: This study highlights the important role that future interventions might have in patients at high-risk of sleep disorders after critical illness.

5.1 Introduction

There has been increasing interest in sleep after critical illness and its essential role in the recovery from acute illness. There is evidence that patients' sleep in the intensive care unit (ICU) during critical illness is severely disrupted. Studies have used polysomnography (PSG) and found that critically ill patients have significantly decreased total sleep time (TST), decreased rapid eye movement sleep, more arousals, and increased sleep fragmentation (Pisani et al. 2015; Parthasarathy and Tobin 2004; Elliott et al. 2013; Freedman, Kotzer, and Schwab 1999; Watson et al. 2013; van der Kooi et al. 2013; Roche-Campo et al. 2013; Andrejak et al. 2013; Kondili et al. 2012; Trompeo et al. 2011). The etiology of poor sleep quality in ICU is thought to be multifactorial and associated with severity of illness, increased noise, nursing interventions, pain, ambient light and sedation (Altman et al. 2018; Ding et al. 2017; Kamdar et al. 2016; Dube et al. 2008; Patel et al. 2014). Interventional studies to improve in ICU sleep quality have met limited success.

Evidence suggests that disrupted sleep is associated with both poor health (Medic, Wille, and Hemels 2017; Barbar et al. 2000; Kutner et al. 1994) and worse health-related quality of life (HRQOL) (Orwelius et al. 2008; Ohayon and Vecchierini 2005). Few studies have assessed sleep quality in survivors of critical illness after ICU discharge. Further, prior studies have not shown a relationship between ICU factors such as length of stay (LOS), severity of illness or duration of mechanical ventilation and out of hospital sleep quality (Orwelius et al. 2008; Parsons et al. 2012). Recently, a case series of PSG studies performed on the ward after ICU showed that a post-operative admission diagnosis and patient report of poor sleep while in the ICU might predict a high-risk subgroup of patients for long-term sleep disruption (Wilcox et al. 2018). This study was limited by its sample size of 20 patients. Only one study to date has used PSG in seven patients to objectively assess sleep quality six or more months following critical illness; all participants had persistent sleep abnormalities (Lee et al. 2009). At three months post-hospital discharge poor sleep quality, as measured by the Pittsburgh Sleep Quality Index (PSQI) in 45 ICU survivors, was associated with anxiety, reduced mobility and reduced HRQOL (Solverson, Easton, and Doig 2016). A small number of studies have used questionnaires to show survivors

of critical illness may be at increased risk of poor sleep quality (Granja et al. 2005; Parsons et al. 2012; Lee et al. 2009; McKinley et al. 2012; Orwelius et al. 2008), however sleep questionnaires have been variably chosen, and inconsistently validated. With these concerns noted, up to 50% of patients have reported poor sleep quality from six to 12 months post ICU discharge (McKinley et al. 2012; Orwelius et al. 2008; Parsons et al. 2012).

The goal of our study was to assess the quality of sleep of survivors of critical illness necessitating mechanical ventilation within a week of ICU discharge through assessment of multi-night sleep by actigraphy. Additionally, we examined if sleep on the hospital ward after ICU discharge was associated with risk factors during their ICU stay or an exacerbation of pre-existing sleep difficulties with the goal of identifying high risk populations for targeted interventions before sleep disruptions become fixed.

5.2 Methods

5.2.1 Study Setting and Sample

This was a multisite study to investigate sleep quality after ICU discharge. The complete protocol for the COGnitive outcomes and WELLness (COGWELL) study was approved by all participating sites research ethics boards and written informed consent from all participants or a representative obtained prior to testing (Wilcox et al. 2017).

Study patients entered the cohort after they have been mechanically ventilated for at least three days. We chose a minimum duration of mechanical ventilation in an attempt to have a sicker cohort of patients, as compared to no need for mechanical ventilation or patients extubated promptly or within hours of ICU arrival; assuming that these patients would have a greater likelihood of exposure to in ICU risk factors for poor sleep. The exclusion criteria were age below 18 years, advanced cognitive impairment or unable to follow simple commands before their acute illness (e.g., end-stage Alzheimer's disease), primary neurological injury (e.g., anoxic injury, stroke or traumatic brain injury), anticipated death within three months of discharge (e.g. palliative), uncontrolled psychiatric illness at hospital admission, not fluent in

English, unlikely to adhere with follow-up (e.g., no fixed address) or a residence greater than 300 kms from the referral centre.

4.2.2 Data Collection

Demographic and clinical data were collected from the patient's record by trained data collectors for the Toronto Intensive Care Observational Registry (iCORE). The dataset includes definition standards for reason for mechanical ventilation and diagnosis at ICU admission. The Acute Physiology and Chronic Health Evaluation (APACHE) III severity of illness score on admission was calculated to assess severity of illness. The Pittsburgh Sleep Quality Index (PSQI) was administered first in a format that asked participants to answer questions regarding their sleep "before their recent hospitalization." This was intended to reflect their premorbid sleep patterns in the community prior to their acute hospitalization. The PSQI is a self-rated questionnaire assessing nineteen individual items to generate seven "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction (Buysse et al. 1989). The sum of scores for these seven components yields one global score; a global PSQI score greater than 5 yielded a diagnostic sensitivity of 89.6% and specificity of 86.5% in distinguishing good and poor sleep quality (Buysse et al. 1989). If patients were delirious, then a partner, if available, provided collateral information on pre-ICU sleep habits. The sum of scores for these seven components yields one global score; a global PSQI score greater than 5 yielded a diagnostic sensitivity of 89.6% and specificity of 86.5% in distinguishing good and poor sleep quality. On the day of ICU discharge, patients were asked to rate their last night's sleep in the ICU using the Richard-Campbell Sleep Questionnaire (RCSQ). The RCSQ is a five-item, visual analogue scale designed to assess the perception of sleep in critically ill patients. The scale evaluates perceptions of depth of sleep, sleep onset latency, number of awakenings, time spent awake, and an overall sleep quality score (Kamdar et al. 2012). The participant places a mark along a 100-mm line, indicating a score for each category and scored by taking the average of the 5 marking, where 1 mm equates to one point. Scores range from 0 (lowest possible score) to 100 (best possible score). The total RCSQ score has been validated against PSG (Ancoli-Israel

et al. 2003). The CAM-ICU was used as an assessment tool for delirium in all ICUs participating in the study (Ely et al. 2001). While in the ICU, the tool was administered by the bedside nurse every 12 hours and possibly more frequently if clinically indicated.

5.2.3 Actigraph Recordings

The actigraph used in this study was the Actiwatch Plus (Spectrum, Phillips Respironics, Bend, Oregon, USA). The Actiwatch is a waterproof wrist-watch-like accelerometer based on an internal cantilevered piezoelectric bilayer attached to an inertial mass. It measures changes in acceleration primarily in an axis parallel to the face of the device, although it has some sensitivity to movements in other axes. This signal is subject to hardware analog filtering with a pass-band between 0.5-3.0 Hz and then amplified and digitally sampled at 32 Hz. The resulting signal is then rectified, integrated across 15 seconds, and rounded to the nearest integer to create an integrated "count" for each 15-sec period – referred to hereafter as one "epoch" – which is recorded to the on-board memory. Counts for each epoch are positive integers ranging from 0 to a maximum of 2000-3000 depending on the record. Research assistants attached the actigraph to the nondominant wrist of each subject and instructed to leave it on for a maximum of 10 days. We specifically chose to take measurements after ICU discharge as subjects on the ward or at a rehabilitation facility were unlikely to be in restraints limiting the accuracy of measurements.

All actigraph data was downloaded to a PC and analyzed using MATLAB (Mathworks, Natick, MA). Actigraphic charts provided a global view of the rest and activity time as well as missing data (actigraph not worn or malfunctioning). Markers of sleep and circadian function included: Total sleep time (TST) measured as the mean 24-hour sleep time limited to sleep intervals as determined by actigraphy software as well as ignoring sleep intervals as determined by actigraphy software. Sleep efficiency (SE) was calculated as the mean percentage of periods classified as "rest" by the Actiware software that were actually spent sleeping. The interdaily stability (IS) describes the 24-hour rhythmic component in evaluating the "invariability" between days. The IS varies between 0 (gaussian noise) and 1 (perfect stability). It quantifies

the strength of coupling of rhythm to environmental synchronizers. The intradaily variability (IV), a marker of the fragmentation of the rest-activity record, was calculated by conventional approaches across multiple sampling intervals. For a perfect sine wave, the IS value is 0 and is 2 for a gaussian noise (IV may be higher than 2 is an ultradian component exists). M10 is the 10 hours with maximal activity and L5 is the five hours with the least measured activity. Relative amplitude (P_{RA}), calculated from M10 and L5, is a measure of the difference between M10 and L5, normalized to overall activity. Higher values of P_{RA} and L5 indicated more fragmented sleep.

5.2.4 Biomarkers

At the time of actigraph application, blood samples were drawn in ethylenediaminetetraacetic acid and citrate tubes. Samples were centrifuged at 1700 x 2 g at 4ºC for 10 minutes at which time plasma was collected and frozen in cryogenic tubes at -80ºC. Plasma was assayed for both pro-inflammatory and anti-inflammatory mediators (e.g. Interleukin[IL]-6 and IL-10) using a Luminex mediator panel with Multiplexing immunoassays instrument (Luminex technology, Austin, USA). All assays will be performed in duplicate and the average levels used in analyses.

5.2.5 Statistical analysis

Normality of data distributions were evaluated for the study. Using k-means clustering, patients were partitioned into 2 groups with each observation belonging to the cluster with the nearest mean. TST, SE, P_{RA}, gender, pre-existing sleep problem, reported in-ICU sleep disturbance, admitting diagnosis, ICU length of stay (LOS), APACHE III score, duration of mechanical ventilation, days delirious in the ICU, and days of continuous intravenous sedation were compared using Fisher's Exact Test or the Wilcoxon Rank Sum test. Linear regression was used to determine the association of measured covariates and TST as determined by actigraphy as well as SE. Differences were considered significant at p-values of ≤ 0.05. Univariate associations between sleep variables and selected pro- and anti-inflammatory markers were also determined. All analyses were performed using Stata11 software (StataCorp LP, College Station, Texas, USA) (Daniel 1983).

5.3 Results

5.3.1 Sample characteristics

Informed consent was obtained from a total of 150 patients; 18 patients died prior to ICU discharge; 1 patient died between ICU discharge and 7-day follow-up; 10 patients withdrew consent; 19 actigraphs experienced a technical failure and therefore no data was recovered; 1 actigraph recording was able to generate data for all measures of SE except TST. Patient baseline demographic data (n=94) are illustrated in Table 1. Median age was 57 years (interquartile range [IQR], 47 – 66 years); illness severity was measured by the APACHE III and was a median of 60 (IQR, 45 – 76); duration of mechanical ventilation was a median of 7 days (IQR, 5 – 13 days); and ICU LOS was a median of 13 days (IQR, 7-21 days). Thirty-three patients (35%) were admitted post-operatively, 13 patients (18%) had a primary diagnosis of pneumonia and 10 (10%) were admitted for sepsis or septic shock.

5.3.2 Description of actigraphy studies

Patients wore their actigraphs on average for 3.9 days (SD, 2.5 days); the minimum number of days recorded was 2 days with a maximum of 9.5 days (Table S1). In total 429 days of data were analyzed. Within 7 days of ICU discharge, for the days recorded, the TST as measured as the mean 24-hour sleep time limited to sleep intervals as determined by actigraph software was 6.79 hours (IQR, 3.23 to 8.57 hours). SE was 54% (IQR, 19 to 64%) and IS was a median of 0.49 (IQR, 0.38 to 0.67). Measures of sleep fragmentation, both P_{RA} (tendency to maintain sustained rest) and L5 (amount of activity in the 5 least active hours of each day) were a median of 0.05 (IQR, 0.04 to 0.06) and 1393 (IQR, 598 to 2932), respectively. M10 (10 hours with maximal activity) had a median activity count of 6574 (IQR, 3554 to 11500).

5.3.3 Factors associated with sleep quality

Sixty-six (65%) of patients had pre-existing sleep disturbances prior to hospitalization. The mean score on the PSQI for the quality of patient sleep the month prior to admission was 2.61 (SD, 2.52). Forty-three (42%) patients were taking medications for sleep prior to admission. The mean duration of continuous sedation received in the ICU was 5.87 days (SD, 6.69 days); there were varying durations of various sedatives and analgesics prescribed. No significant

correlations were seen between pre-existing sleep problems or medication use for sleep prior to admission and measured sleep variables within 7 days of ICU discharge. Further, patient report of in ICU sleep disruption was not associated with sleep disruption on the medical or surgical ward. Although the number of days delirious in ICU was not associated with measured sleep variables, the number of days of continuous sedation or analgesia received in the ICU was associated with SE. Incident delirium while in the ICU was independent of TST or SE (p=0.43 and 0.38, respectively).

We first looked at univariate associations between partitioned clusters based on means for each sleep variable (k_{means}: high and low) and age, gender, pre-existing sleep disruption, medication use for sleep prior to admission, admission diagnosis, reported average number of hours of sleep per night prior to admission, ICU LOS, APACHE III score, number of days of mechanical ventilation, duration of continuous intravenous administration of sedatives and/or analgesics and self-reported in ICU sleep on the evening prior to ICU discharge. Variables with a p-value <0.2 in this series of analyses included an admission diagnosis of sepsis (p = 0.03), APACHE III score (p = 0.12), and number of days of continuous sedation and/or analgesic (p = 0.09). We started with all variables in the multiple regression model and then used the backward selection method; in the final model, only a sepsis diagnosis at admission (p = 0.02 and 0.01) for TST and SE, respectively, remained.

5.3.4 Biomarkers after ICU and sleep quality

Only weak correlations were seen between pro-inflammatory biomarkers (TNF-α, IL-17a and IL-6) as measured in the serum at the time of actigraph study initiation and measures of sleep (TST, SE and L5; Table 4). In patients with the admission diagnosis of sepsis moderate negative correlations were seen between TST (rho = -0.58, p=0.10), SE (rho = -0.57, p = 0.11) and TNFα, whereas a strong positive correlation was seen between IS (rho = 0.71, p=0.03) and IL-1ß.

5.4 Discussion

This study adds to the existing literature regarding sleep on the hospital ward following ICU discharge, using actigraphy to facilitate multi-night measure. The total sleep time was 6.8 hours per 24-hour period (41% of patients less than 6 hours per 24-hour period) with SE below population expected values. If we compare to the reported hours of sleep prior to hospitalization (PSQI, mean 8.1 hours) our patients experience reductions in total sleep time after critical illness of at least an hour; although, actigraphy may have overestimated TST participants' sleep (Kapella et al. 2017; Kushida et al. 2001; Maglione et al. 2013; Sivertsen et al. 2006; Taibi, Landis, and Vitiello 2013). This is compared to healthy subjects, where sleep has been described using both PSG and actigraphy to average sleep times exceeding 7.0 hours, sleep efficiency greater than 85%, and sleep latency less than 15 minutes (Ustinov and Lichstein 2013; Rowe et al. 2008; Walsleben et al. 2004). Interestingly, our findings are similar to those reported by Delaney and colleagues, where in a cross-sectional study of medical and surgical patients admitted to the wards, a mean reduction in hospital sleep of 1.8 hours was seen compared to home (Delaney et al. 2018). In our study, sepsis seems to be associated with poor sleep with correlations consistent with a persistent inflammatory response possibly influencing sleep quality. Circadian rhythm disturbances persist in some but not all patients after an ICU admission; patients with higher sedation exposure seem to be at increased risk.

This study is a characterization of sleep within 7 days after ICU discharge when survivors are in a period of physical and neuropsychological recovery. Studies in institutional settings (e.g. nursing homes, acute care hospitals) suggest that sleep problems are associated with functional impairment, social isolation, and poor health (Alessi et al. 2008; Alessi et al. 2005). Redeker and colleagues found that both increased sleep efficiency and better self-reported sleep time predicted improved physical function and emotional well-being after cardiac surgery (Redeker et al. 1996). Further, in a related study these investigators showed that more normal sleep-wake cycle (measured by wrist actigraphy) resulted in decreased hospital length of stay and improved physical function at the time of discharge (Redeker et al. 1994). In this vulnerable period of rehabilitation post-ICU, the development of poor sleep may be particularly important

as once established abnormal sleep/wake might negatively impact motivation, fatigue levels, and willingness to participate. This may in turn impact functional and cognitive recovery, common comorbidities experienced by survivors of critical illness (Herridge et al. 2003; Herridge et al. 2011; Needham et al. 2013; Hopkins and Brett 2005). In a study of older patients undergoing rehabilitation after acute illness, excess daytime sleepiness was associated with less functional recovery up to 3 months following hospital admission (Alessi et al. 2008). Similar persistence of mild to severe sleep disturbances have been documented in traumatic brain injury (Duclos et al. 2016; Nakase-Richardson et al. 2013), burn (Raymond, Ancoli-Israel, and Choiniere 2004; Raymond et al. 2001; Rose et al. 2001), and trauma populations (Swann et al. 2018) at the time of admission to a rehabilitation facility as well as for months following. Whereas patients who reached acceptable sleep-wake cycle consolidation were more likely to have lower disability at discharge (Duclos et al. 2014; Duclos et al. 2016).

One possible target for intervening to improve a patient's sleep-wake cycle might be in regulation of the immune system. A number of cytokines have been hypothesized to influence sleep regulation, including sleep promotion and inhibition (Blalock 1989; Kapsimalis et al. 2005; Benca et al. 1992; Irwin 2002). IL-6 may be a somnogenic proinflammatory cytokine, and exogenous administration in healthy subjects leads to decreased REM sleep and decreased slow wave sleep (SWS) (Spath-Schwalbe et al. 1998). A negative correlation of IL-6 with SWS has been described, with a reduction of IL-6 levels during the night of recovery sleep following its deprivation (Vgontzas et al. 2007). Loss of sleep during part of the night may exacerbate immunological alterations described in subjects under environmental or psychological stress (Benca et al. 1992; Irwin 2002). Given that the diagnosis of sepsis was associated with sleep disruption, we specifically looked for associations with select cytokines within this subgroup. A moderate positive correlation between both total sleep time and sleep efficiency was seen with TNFα, whereas a strong negative correlation was seen between interdaily stability and IL-1ß. The small number of patients admitted with a diagnosis of sepsis makes it difficult to ascertain what influence circulating cytokine levels might have on the sleep-wake cycle. The complexity of critical illness makes this challenging physiology to study, as cytokines storm in sepsis making

these measurements very noisy and correlations challenging. Given that this study was primarily designed to study the influence of sleep after critical illness, a study to better understand of the interaction between sleep and neurohumoral regulation could be important step in improving the recovery of ICU survivors.

This is the first study as far, as we are aware, to study sleep on the ward using actigraphy after ICU discharge, by studying short-term sleep quality in survivors we may identify which patients are at highest risk for persistent poor sleep quality (i.e. sepsis diagnosis, high severity of illness). Identifying high-risk subgroups for sleep disruption may allow for early intervention in the post-ICU discharge period. We can infer that an intervention targeting sleep, inflammation, or immune response could plausibly have an effect on the other two processes. This assumption is supported by beneficial effects that 6 months of moderate exercise training has on sleep quality and cytokine profile of older individuals (Santos et al. 2012). After training, participants showed decreased REM latency, decreased levels of IL-6 and TNF-α, and increased levels IL-10. Critical illness survivors may benefit from screening for sleep disorders and undergo further testing for diagnosis, as the treatment of sleep disorders including insomnia and obstructive sleep apnea are known to improve HRQOL (Ishak et al. 2012; Serrano Merino et al. 2018). The main limitation of our study however is that it is correlational or cross-sectional in nature, limiting the ability to make causal inferences about the relationship between sleep and health. In addition, our study lacked a comparative reference group of non-ICU hospitalized patients. Lastly, further information regarding environmental (e.g. noise levels, luminance, number of bedded bays) as well as pharmacological exposures (e.g. nocturnal sleep aids such as melatonin or imovane) at the time of actigraphy recordings would have added to the richness of our dataset.

5.5 Conclusions

Reduced sleep quality following critical illness is common. We found higher severity of illness, longer duration of sedative exposure and an admission diagnosis of sepsis to be associated with worse sleep, and possibly identify a high-risk group of patients for sleep disruption after critical

illness. This cohort study highlights the important role that future interventions might have in the recovery of patients after critical illness. Further research is required to study objective sleep in large numbers of critical illness survivors, specifically those with and with-out sepsis, and examine interventions that may improve both the sleep and overall recovery of these patients.

Table 5.1 Patient baseline characteristics - actigraphy

Characteristic (n=97)	
Age – yr	
Median (IQR)	57 (47-66)
Male sex – no. (%)	54 (56)
Patients with any comorbidity	92 (95)
No. of comorbidities – no. (%)	
Chronic kidney disease or dialysis	4 (4.1)
Hepatic failure or cirrhosis	6 (6.2)
Immune suppression or AIDS	8 (8.2)
Diabetes	13 (13.4)
Cardiovascular disease	20 (20.6)
Respiratory disease	28 (28.9)
Oncologic diagnosis	2 (1.1)
Other	11 (11.9)
APACHE III score	
Median (IQR)	57 (41-73)
Reason for admission – no. (%)*	
Respiratory failure	61 (62.9)
Pneumonia	11 (13.9)
Other respiratory condition (e.g. transplant)	36 (37.1)
Sepsis/Shock	10 (10.3)
GI bleed/GI inflammatory disorder	5 (5.2)
Respiratory/cardiac arrest	5 (5.1)
Lung neoplasm/pulmonary emboli	3 (3.1)
Vascular disease/Peripheral artery bypass	3 (3.1)
Trauma	2 (2.1)
COPD	2 (2.1)
Liver transplant/rejection	2 (2.1)
Drug overdose	2 (2.1)
Metabolic disease	1 (1.0)

Meningitis	1 (1.0)
Orthopedic condition	1 (1.0)
Other	19 (19.6)
ICU LOS – days	
Median (IQR)	13 (7-25)
Duration of MV – days	
Median (IQR)	7 (5-13)
Days delirious	
Median (IQR)	0 (0-3)
Days continuous sedation – days	
Propofol – median, IQR	2, 1-5
Midazolam – median, IQR	0, 0-2
Fentanyl – median, IQR	3, 1-7
Morphine – median, IQR	0, 0-0
Dexmedetomidine – median, IQR	0, 0-0
Sleep medications prior to hospital admission – no. (%)	41 (43.6)
Pittsburgh Sleep Quality Index	
Median (IQR)	7 (4, 11)
RCSQ at ICU discharge	
Median (IQR)	33.5 (13.3, 61.0)
BDI-II at 7days ICU – no. (%)**	
Normal mood (0-10)	41 (49.4)
Mild mood disturbance to borderline clinical depression (11-20)	31 (37.4)
Moderate to severe depression (>21)	11 (13.3)

*Missing in 2 patients; **Missing in 14 patients

Table 5.2 Sleep outcomes – Actigraphy-derived data, sleep time, sleep fragmentation, and circadian rhythm

Characteristic (n)	7 days post-ICU discharge	
	Median	IQR
Total sleep time in hours* (TST)	6.79	3.23, 8.57
TST high (70)	7.99	6.09, 9.07
TST low (23)	0	0, 1.54
Sleep efficiency in percentage (SE)	54	19, 64
SE high (63)	61	54, 68
SE low (31)	6	0, 19
Probability of movement per unit of time (P_{RA})	0.05	0.04, 0.06
P_{RA} high (11)	0.11	0.09, 0.12
P_{RA} low (83)	0.04	0.03, 0.05
Activity count during 5 hours with least activity (L5)	1393	598, 2932
L5 high (39)	3193	2416, 4401
L5 low (55)	738	361, 1195
Interdaily stability (IS)	0.49	0.38, 0.67
IS high (42)	0.68	0.61, 0.84
IS low (52)	0.41	0.33, 0.47
Intradaily variability across multiple sampling intervals (IV)	1.15	0.95, 1.45
IV high (50)	1.44	1.27, 1.71
IV low (44)	0.93	0.75, 1.02

*TST missing for one patient for the 7 days post-ICU data

Table 5.3 Univariate association between differentially grouped sleep variables and baseline patient characteristics as well as in ICU risk factors

	Total Sleep Time (TST)			Sleep Efficiency (SE)			Relative Amplitude (P_{RA})		
	High (n=70)	Low (n=23)	p-value	High (n=62)	Low (n=31)	p-value	High (n=83)	Low (n=11)	p-value
	N (%)	N (%)		N (%)	N (%)		N (%)	N (%)	
Gender (woman)	30 (43)	11 (48)	0.68	28 (44)	14 (45)	0.95	44 (53)	3 (27)	0.22
Pre-existing sleep problems	43 (64)	10 (56)	0.50	40 (65)	14 (58)	0.60	49 (65)	5 (46)	0.20
Drugs for sleep prior to admission	27 (40)	9 (45)	0.46	24 (39)	12	0.34	30 (40)	6 (55)	0.36
Pneumonia	11 (19)	2 (11)	0.41	7 (14)	6 (25)	0.24	12 (19)	1 (10)	0.50
Sepsis	5 (9)	5 (29)	0.03	4 (8)	6 (26)	0.04	8 (13)	2 (20)	0.53
Post-operative diagnosis	28 (50)	5 (29)	0.41	26 (50)	9 (38)	0.24	29 (45)	6 (60)	0.39
	Mean (SD)			Mean (SD)			Mean (SD)		
No. hours of sleep per night prior to hospitalization	6.93 (1.80)	6.89 (2.03)	0.86	6.77 (1.89)	7.27 (1.66)	0.17	6.88 (1.77)	7.09 (2.30)	0.66
BDI-II	11.4 (8.31)	10.6 (5.96)	0.96	11.0 (7.73)	11.6 (8.15)	0.80	11.0 (7.74)	12.0 (8.38)	0.87
ICU length of stay	17.1 (13.5)	19.1 (18.9)	0.88	17.5 (14.2)	17.2 (14.7)	0.62	15.7 (11.2)	30.2 (25.2)	0.07
APACHE III	59 (22.4)	69 (21.3)	0.12	58.2 (23.3)	67.7 (18.1)	0.03	61.2 (22.9)	61.6 (18.8)	0.93
No. days of mechanical ventilation	10.9 (10.7)	14.4 (14.1)	0.56	11.5 (11.0)	12.0 (12.9)	0.50	10.7 (9.92)	19.4 (19.4)	0.08
No. days delirious in ICU	1.39 (2.24)	2.13 (4.07)	0.70	1.40 (2.26)	1.94 (3.64)	0.67	1.42 (2.33)	2.72 (5.08)	0.42

No. days of continuous iv sedation or analgesia	5.34 (4.66)	4.52 (6.12)	0.09	5.75 (4.74)	3.74 (5.43)	0.003	5.11 (5.14)	4.91 (4.39)	0.91
In ICU sleep disturbance	42.2 (29.5)	47.7 (54.8)	0.77	43.0 (28.9)	42.5 (50.8)	0.34	42.4 (36.9)	46.2 (32.6)	0.59

ICU: intensive care unit; BDI-II: Beck's Depression Inventory-II; No.: number; iv: intravenous

Table 5.4 Univariate association between sleep variables as compared to average amount of same variable and selected pro- and anti-inflammatory serum biomarkers

n=87	IL1β-1	IL-2	IL-4	IL-8	IL17a	TNFα	IFNγ	IL-10	VEGF	GCSF	IL-6
Mean (SD) pg/ml	5.25 (12.5)	5.23 (14.2)	27.3 (70.1)	69.3 (195.3)	13.3 (29.8)	38.4 (33.0)	35.2 (57.6)	69.6 (119.2)	472.6 (498.6)	151.6 (242.5)	42.9 (57.0)
Total Sleep Time											
Rho	-0.02	0.06	-0.01	-0.15	0.07	-0.22	0.07	-0.01	-0.09	-0.09	-0.17
p-value	0.87	0.58	0.92	0.17	0.54	0.04	0.54	0.90	0.41	0.38	0.12
Sleep Efficiency											
Rho	-0.05	0.01	0.02	-0.18	0.09	-0.23	0.04	-0.11	-0.07	-0.10	-0.21
p-value	0.66	0.98	0.85	0.09	0.39	0.03	0.69	0.33	0.51	0.35	0.05
Probability of movement per unit of time (P_{RA})											
Rho	0.02	0.09	0.07	0.01	0.08	-0.02	-0.06	0.02	-0.02	0.07	0.06
p-value	0.84	0.40	0.51	0.99	0.46	0.83	0.57	0.88	0.85	0.52	0.59
5 hours with least activity (L5)											
Rho	0.01	0.02	0.13	-0.29	-0.08	-0.36	-0.19	-0.13	-0.19	-0.12	-0.26
p-value	0.98	0.84	0.24	0.01	0.44	<0.001	0.08	0.22	0.08	0.28	0.01
10 hours with maximal activity (M10)											
Rho											
p-value											
Interdaily stability (IS)											
Rho	0.04	0.14	0.04	-0.02	0.09	0.02	0.01	-0.16	-0.10	-0.06	-0.01
p-value	0.72	0.21	0.70	0.83	0.40	0.87	0.98	0.14	0.35	0.61	0.98
Intradaily variability across multiple sampling intervals (IV)											
Rho	-0.05	-0.13	0.06	0.18	-0.01	0.24	0.05	0.18	0.17	0.11	0.21
p-value	0.67	0.25	0.57	0.09	0.96	0.03	0.67	0.10	0.13	0.29	0.05

5.6 Supplemental Material

We examined the relationship between actigraphic and polysomnographic metrics of sleep fragmentation in 20 individuals who underwent simultaneous diagnostic studies. Subjects were recruited from consecutive patients undergoing diagnostic polysomnography on a medical or surgical ward at the University Health Network in Toronto, Canada. Clinical, actigraphic, and polysomnographic characteristics of the subjects are shown in Table S.1. Actigraphy was recorded using the Actiwatch Plus (Spectrum, Phillips Respironics, Bend, Oregon, USA) as described in the main text. The actigraphs were placed on subjects' non-dominant wrists at the commencement of overnight polysomnography. A median of 5 hours (IQR, 4-7 hours) of recording per subject were obtained. P_{RA} was then calculated for each subject as described in the main text. PSG was performed and scored in 30-second epochs accordance with American Academy of Sleep Medicine guidelines (Kushida et al. 2005). Arousal index (AI), sleep efficiency (SE), and wake time after sleep onset (WASO) were calculated using standard methods (Iber et al. 2007). These 3 PSG indices were compared to actigraphic measure (P_{RA}) by calculating bivariate Pearson correlation coefficients.

Actigraphic measures of P_{RA} were weakly correlated with PSG measures of SE and WASO (rho=0.14 [p=0.59] and -0.13 [p=0.61], respectively). There was a moderate correlation between the two measures for AI (rho=0.38; p=0.13). The unadjusted sensitivity of actigraphy as a measure of total sleep time was calculated at 92% with an unadjusted specificity of 45%. With regards to the feasibility of using an actigraph as a portable outcome measure, individuals were adherent with wearing the device approximately 40% of the time.

Table S.1 Feasibility of an actigraph as a portable outcome measure in survivors of mechanical ventilation

	7 days post-ICU discharge
Mean # days (SD)	3.9 (2.5)
Minimum # days	2.0
Maximum # days	9.51
Total # days	429
% adherence	46

Table S.2 Clinical, Actigraphic, and Polysomnograhic Characteristics of Study Subjects (n=20)

Characteristics		**Median (IQR)**
Clinical Characteristics	Age - yrs	56 (37, 60)
	Female - %	9 (45%)
Actigraph Characteristics	Days of recording	5 (4,7)
	Rest Fragmentation P_{RA}	0.042 (0.033,0.051)
Polysomnographic Characteristics	Hours of recording	16.8 (15,17.1)
	Arousal Index – per hr	22.5 (15,48)
	Sleep Efficiency - %	31 (17,43)
	Wake Time after Sleep Onset - mins	392 (260,673)

Figure S.1 Association between actigraphic and polysomnographic metrics of sleep fragmentation (n=17)

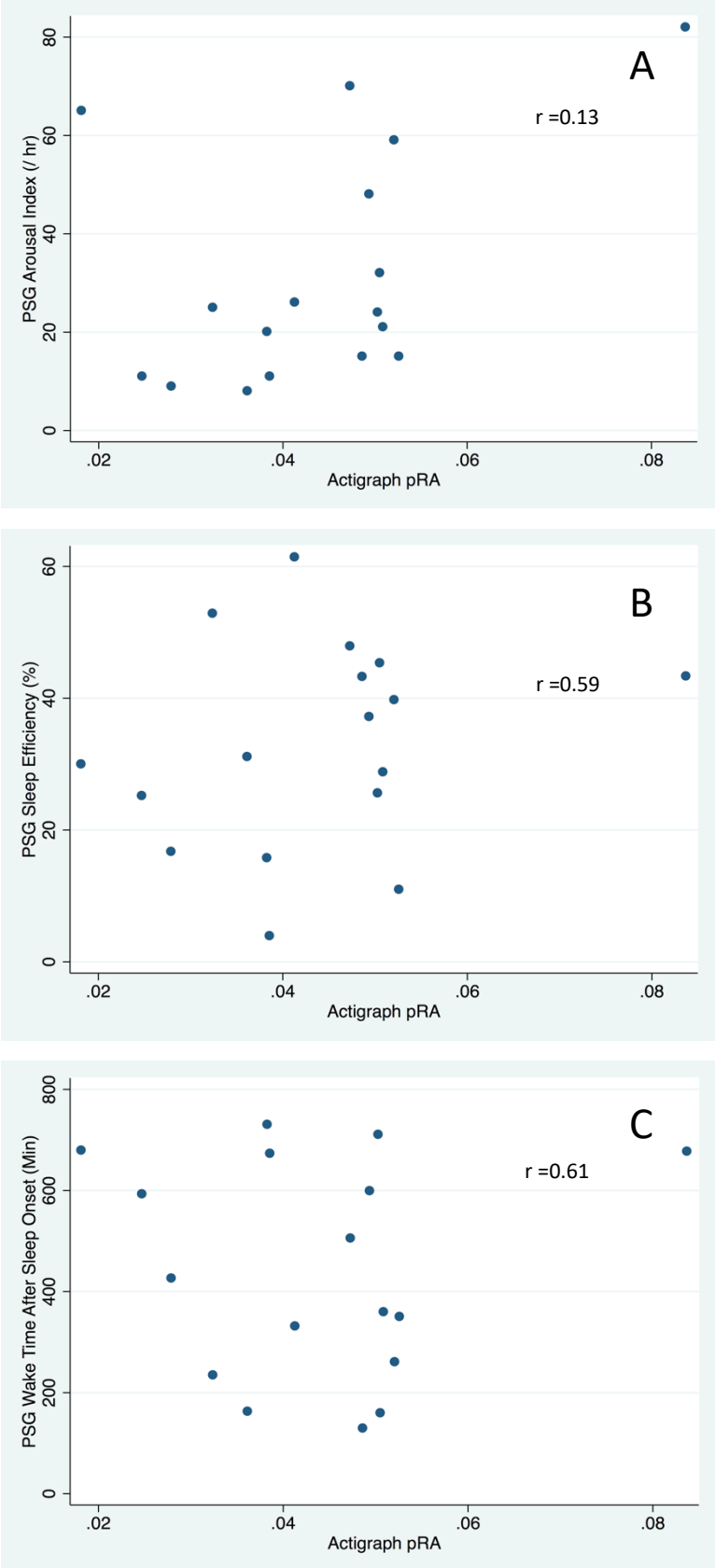


Table S.3 Actigraphy as a measure of total sleep time had a sensitivity of 92% and a specificity of 45% as compared to the gold standard of polysomnography

	+ asleep	- awake	
+ asleep	9116	9506	18622
- awake	828	7932	8760
	9944	17438	

*Missing 1199

Sensitivity would reflect the ability of the actigraphy to detect sleep when the PSG had also scored sleep; specificity, the ability of the actigraphy to detect wakefulness when the PSG did the same; and accuracy, the ability of the actigraphy to detect both sleep and wakefulness compared to PSG. The sensitivity and specificity that we found was similar to that in other clinical settings and populations using actigraphy outside of the ICU (Beecroft et al. 2008; Paquet, Kawinska, and Carrier 2007; Jean-Louis et al. 2001; Jean-Louis et al. 2000; Blackwell et al. 2005; Merilahti et al. 2007; Lotjonen et al. 2003). We found the use of actigraphy to be moderately practical and reliable as patients wore their actigraph approximately half of the 10 days requested. This study demonstrated that continuous actigraphy may be a feasible means that is more adept at monitoring changes in sleep with different interventional trials.

Chapter 6 SLEEP ALTERATIONS AND THE RISK OF COGNITIVE IMPAIRMENT AFTER CRITICAL ILLNESS

This chapter is modified from the following:

Wilcox, ME et al. *(submitted and under review).* Sleep Alterations and the Risk of Cognitive Impairment after Critical Illness.

6.0 Abstract

Background: Survivors of critical illness can experience both cognitive dysfunction and sleep alterations.

Aim: As sleep disorders have been linked with cognitive impairment in various patient populations, and that the apolipoprotein E (APOE) genotype can modulate cognition, we set out to determine if there was an association between sleep, cognition and APOE status in intensive care unit (ICU) survivors.

Methods: We enrolled 150 patients from five centres who had been mechanically ventilated for at least 3 days; 102 patients survived to ICU discharge. Actigraphic measures of sleep and cognitive testing using the RBANS and Trail-Making tests were undertaken at 7 days, 6- and 12-months after ICU discharge. APOE single nucleotide polymorphisms were assessed for each patient.

Results: Sleep fragmentation but not total sleep time (TST) or interdaily stability (measure of circadian rhythmicity) was associated with worse cognitive impairment at 7 days of ICU discharge. No actigraphy variable for sleep at 7 days post-ICU discharge predicted cognitive impairment or persistent sleep abnormalities at 6- and 12- months of follow-up. Possessing the APOE ε4 allele was not significantly associated with sleep alterations and its presence did not modify the risk of cognitive impairment at long-term follow-up.

Conclusions: Sleep fragmentation was associated with worse cognitive performance in hospital, but not at later time intervals. The APOE ε4 allele did not identify a high-risk group for cognitive impairment after ICU discharge. Further research is needed to better delineate the relationship between sleep fragmentation and cognition.

6.1 Introduction

Sleep disturbance is a risk factor for cognitive dysfunction (Lim et al. 2013; Lim and Saper 2011; Blackwell et al. 2011). Cognitive domains particularly associated with sleep fragmentation include working memory, semantic memory, processing speed, and visuospatial abilities (Lim et al. 2012). Experimental studies support a number of potential neurobiological mechanisms including accumulation of beta amyloid pathology (Kang et al. 2009; Ju et al. 2013), abnormalities of tau (Lim et al. 2013), synaptic abnormalities (Bushey, Tononi, and Cirelli 2011), changes in hippocampal long term potentiation (Arrigoni et al. 2009), impaired hippocampal neurogenesis (Mueller, Mear, and Mistlberger 2011; Guzman-Marin et al. 2005), and gene expression changes (Cirelli, Faraguna, and Tononi 2006). In addition, it is well documented that circadian rhythm disturbance is associated with an increased risk of developing Alzheimer's disease (AD). One study that measured circadian rhythm by actigraphy showed that decreased amplitude of the sleep-wake cycles and delayed acrophase increased the odds of developing dementia in a community-based population (Lim et al. 2011). Sleep fragmentation has also been shown to increase the risk of incident AD in community dwelling, cognitively normal elderly (Lim et al. 2013). Moreover, sleep consolidation has been reported to decrease the incidence of AD in community dwelling elderly (Lim et al. 2012).

The Apolipoprotein E (APOE) ε4 allele is a well-established and common genetic risk factor for AD (Poirier et al. 1993), and is also a risk factor for cognitive impairment in a number of medical conditions including sleep apnea (O'Hara et al. 2005; Gozal et al. 2007; Cosentino et al. 2008) and repeated head trauma (Jordan et al. 1997). Recently, in a longitudinal cohort of 737 community dwelling older adults without dementia, the APOE ε4 allele was shown to accentuate the impact of sleep fragmentation on the risk of incident Alzheimer's disease, an effect that was mediated by the accumulation of tau pathology (Lim et al. 2013; Hou et al. 2012; Lim et al. 2012). In individuals with high sleep fragmentation, the presence of at least one APOE ε4 allele (APOE ε4 +/- or +/+) was associated with a three times faster rate of cognitive decline as compared to individuals not carrying an APOE ε4 allele (APOE ε4 -/-) (Lim et al. 2013; Lim et al. 2012).

Given the considerable evidence linking poor sleep quality with cognitive impairment in a variety of patient populations (Lim et al. 2013; Lim et al. 2012; Lim and Saper 2011), we set out to determine whether early sleep alteration and circadian disruption was associated with long-term cognitive impairment in intensive care unit (ICU) survivors. Further, we examined the relationship between APOE genotype, sleep alteration and cognitive impairment in a cohort of survivors of critical illness.

6.2 Methods

6.2.1 Subjects

This was a multisite study of five academic adult medical/surgical ICUs. Outcome measures included cognitive performance assessed 7 days (+/- 48 hours), 6-months, and one year following discharge from the ICU. The COGnitive outcomes and WELLness (COGWELL) study protocol was approved by the University Health Network Research Ethics Committee (13-6425-BE), Sunnybrook Health Centre Research Ethics Committee (365-2013), Mount Sinai Research Ethics Committee (14-0194-E), and St. Michael's Hospital Research Ethics Committee (14-295) (Wilcox et al. 2017). Written informed consent from all participants or a representative was obtained prior to testing.

Study patients entered the cohort after they had been mechanically ventilated for at least 3 days. The exclusion criteria were age younger than 18 years, significant cognitive impairment limiting a patient's ability for independent living (determined by either chart review or patient/family member report prior to consent), primary neurological injury (e.g., stroke), known sleep disorder (e.g. obstructive sleep apnea), anticipated death within 3 months of discharge (e.g. palliative), mental illness as the reason for hospitalization (e.g. untreated depression or anxiety leading to an admission for self-harm), non-fluency in English, and unlikely adherence with follow-up (e.g. no access to communication means for follow-up) or residence greater than 300 kilometers from the referral center.

6.2.2 Actigraph Recordings

The actigraph used in this study was the Actiwatch Plus (Spectrum, Phillips Respironics, Bend, Oregon, USA); it was attached to each patient's non-dominant wrist approximately 7 days after ICU discharge and again at 6- and 12-months. Participants were asked to wear an actigraph for 10 days. The Actiwatch Plus is a waterproof wrist-watch-like microelectromechanical system-based accelerometer sampling at 32Hz; the resulting signal is then rectified, integrated across 15 seconds, and rounded to the nearest integer to create an integrated "count" for each 15-sec period – referred to hereafter as one "epoch" – which is recorded to the on-board memory. Counts for each epoch are positive integers ranging from 0 to a maximum of 2000-3000 depending on the record.

Markers of sleep and circadian function included: (1) circadian timing (average time of the activity acrophase (midpoint of 8 consecutive hours) of each 24 hours of greatest activity), (2) sleep duration (determined by the Cole-Kripke algorithm as adapted to the Actiwatch in the Actiware software package [Phillips-Respironics, Bend, OR] using the "medium" setting), (3) sleep fragmentation (quantified by a measure of transitioning from a state of rest to a state of activity: P_{RA}) (Lim et al. 2013; Lim et al. 2012; Lim et al. 2011), and (4) regularity of circadian rhythmicity (determined using the chi-square periodogram) (Sokolove and Bushell 1978). Total sleep time (TST) was calculated as the mean time spent in epochs classified as sleep during periods classified as rest by the Actiware software per 24-hour period. Sleep efficiency (SE) was calculated as the mean percentage of periods classified as "rest" by the Actiware software that were actually spent sleeping.

6.2.3 Apolipoprotein E (APOE) status

The APOE coding single-nucleotide polymorphism sites rs7412 and rs429358 were determined using the Invitrogen Snapshot assay at The Centre for Applied Genomics at The Hospital for Sick Children Hospital (Toronto, ON; www.tcag.ca). Blood samples (5-10 ml) were drawn prior to discharge and stored at -20°C prior to being shipped for testing.

6.2.4 Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

The RBANS is a brief but comprehensive and validated test battery for the evaluation of cognition (Randolph et al. 1998). The population age-adjusted mean (± SD) for the RBANS global cognition score and for individual domains is 100 ± 15 (on a scale ranging from 40 to 160, with lower scores indicating worse performance). Prevalence was determined based on binary assessment of patient having or not having clinically significant cognitive impairment, based on the standard definitions of impairment as test scores 1.5 standard deviations (SDs; mean RBANS score < 78) below the population mean on at least 2 domains or 2 SDs below the population mean on any one domain. Cognitive change (either improvement or decrement) was defined as a difference of at least 0.5 SD ($\geq$ 7 points) on the RBANS global score between the first and second assessment or second and final assessment (Jackson 2018). As per Jackson et al. (2018), individuals whose RBANS scores were within 6 points of their previous assessment were characterized as having no change.

6.2.5 Trailing Making Tests A and B

Psychomotor speed and divided attention were assessed using the Trail Making Test (TMT) forms A and B. The TMT form A evaluates visuoperceptual abilities, TMT form B reflects primarily working memory and secondarily task-switching ability, while B minus A provides a relatively accurate index of executive control (Sanchez-Cubillo et al. 2009).

6.2.6 Estimated Premorbid Cognitive Impairment

Premorbid cognitive impairment was estimated based on the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (Jorm 2004). The questionnaire was applied to proxy informants during the patient's hospital stay evaluating their memory for the last ten years.

6.2.7 Confusion Assessment Method – ICU (CAM-ICU)

The CAM-ICU was used as an assessment tool for delirium in the ICU (Ely et al. 2001). While a patient is in the ICU, the tool was administered by the bedside nurse every 12 hours and possibly more frequently if clinically indicated.

6.2.8 Statistical Analyses

All analyses were performed using Stata11 software (StataCorp LP, College Station, Texas, USA). Normality of data distributions were evaluated for the study. Student T, Mann-Whitney U, Chi-squared tests were used for data analysis when appropriate. Performance on the RBANS at different time points were compared using paired Student's t-tests. Differences were considered significant at p-value ≤ 0.05. Generalized linear equations models were used to determine the association between different estimate measures of sleep and circadian rhythmicity captured by actigraphy, and cognitive impairment as assessed by the RBANS, controlling for possible confounders, and testing for an interaction with the APOE genotype. No adjustment for the p-values was made for multiple comparisons.

6.3 Results

6.3.1 Clinical and Actigraphic Characteristics of Participants

Two hundred ninety-one patients were approached and 150 were recruited, for an enrollment rate of 51%. One hundred and two were evaluated within 7 days (+/- 48 hours) of ICU discharge; the clinical characteristics of these participants are described in in Table 1. Median age was 57 years (interquartile range [IQR], 47 – 66 years); 45 (44%) were women; the vast majority of participants (n=96) had completed high school with 56 (55%) having completed varying degrees of post-secondary education; no patients exhibited symptoms of pre-existing cognitive impairment with an average IQCODE score of 3.1 (SD, 0.2); 20 (22%) patients were determined to have one or both APOE ε4 allele(s); 59 (58%) of patients had existing comorbid conditions, most commonly cardiovascular disease, respiratory conditions or diabetes. With regards to in ICU characteristics, illness severity was measured by the APACHE III and was a median of 60 (IQR, 45 – 80); duration of mechanical ventilation was a median of 7 days (IQR, 5 – 13 days); and ICU LOS was a median of 13 days (IQR, 7-21 days).

Actigraphs were worn on average for 4.6 days (range, 1-9 days; median 5 days; 429 days in total recorded from 94 patients), 4.7 days (range, 1-8 days; median 5 days; 265 days in total recorded from 57 patients) and 4.7 days (range 2-8 days; median 5 days; 156 days in total recorded from

35 patients) starting at 7 days of ICU discharge, 6- and 12-months follow-up, respectively; recordings that were shorter than 10 days were usually continuous. Seven days after ICU discharge, mean TST as measured as the mean 24-hour sleep time limited to sleep intervals as estimated by actigraph software was 6.1 hours (SD, 3.7 hours; Table 2). At 6- and 12-months follow-up the mean TST recording increased to 8.0 hours (SD, 1.7 hours) and 8.4 hours (SD, 2.1 hours), respectively. Sleep efficiency improved from a mean of 44% to more than 65% at both 6- and 12-months follow-up. The mean value of sleep fragmentation measured as rest-activity fragmentation was stable over time: P_{RA} 0.047 (range 0.035 – 0.057) at 7 days of ICU discharge, 0.053 (0.042 – 0.066) at 6-months follow-up and 0.049 (0.038 – 0.063) at 1-year. Interdaily stability was consistent across time points with a mean of 0.6 (SD, 0.22), 0.6 (SD, 0.17) and 0.6 (SD, 0.16) at 7 days post ICU discharge, 6- and 12-months follow-up, respectively.

6.3.2 Cognitive Performance

At 7 days of ICU discharge 58% (57/98) were classified as having cognitive impairment. The mean scores for each RBANS domain are presented in Table 6.3. In comparison to normative data, patients underperformed on both the short-term and delayed memory at 7 days of ICU discharge. As expected, there was a significant increase in the score of all subtests at long-term follow-up with the majority of gain seen by 6-months (increase in the mean RBANS summary score of 11.8 points; 95% CI 14.8 to 8.9; $p<0.001$; Figures 6.1, 6.2 and 6.3). The proportion of patients who demonstrated improvement, no change or a decrement in their performance on the RBANS global score between 7-day follow-up and 6 months was 68% (42/62), 23% (14/62) and 10% (6/62), respectively. Patients demonstrating improvement, no change or a decrement between 6-months and 12-months follow-up: 13% (5/39), 64% (25/39) and 23% (9/39), respectively.

Shortly after ICU discharge, a considerable number of patients could not complete the TMT before the maximum of five minutes traditionally allotted or quit from frustration before completion. Again, over time a significant reduction in the average test time for both the TMT

forms A and B was seen (Table 6.4); only one patient surviving to one year required greater than the normative standards for completion of the TMT form B.

Differences in mean global cognitive performance on the RBANS between APOE4 allele present and absent participants over time is illustrated in Figure 6.4. The mean global score of APOE ε4 +/- or +/+ as compared to APOE ε4 -/- patients was consistently lower across all time points, but this difference was not statistically significant. For example, within 7 days of ICU discharge APOE ε4 +/- or +/+ scored 76.4 (SD, 12.7) whereas APOE ε4 -/- patients scored 80.7 (SD, 14.5; p-value = 0.23). Similar trends were seen with the TMT forms A and B; mean time to complete the TMT A at 7 days of ICU discharge was 63.4 seconds (SD, 46.3 seconds) and 55.7 seconds (SD, 33.7 seconds) in the APOE ε4 +/- or +/+ and APOE ε4 -/- groups, respectively (p-value = 0.38). For the TMT B, APOE ε4 +/- or +/+ and APOE ε4 -/- patients completed within 176.6 seconds (SD, 116.5 seconds) and 129.9 seconds (SD, 70.3 seconds), respectively (p-value = 0.24).

6.3.3 Sleep Fragmentation and Cognitive Impairment

Composite global cognitive performance as a function of TST, P_{RA} and IS was explored by linear mixed models adjusted for education and severity of illness (Table 6.5). Increased sleep fragmentation was associated with worse cognitive performance at 7 days of ICU discharge (p = 0.02). None of the other sleep variables were significantly associated with cognitive performance at any timepoint. Sleep variables at 7 days of ICU discharge did not correlate with future cognitive performance (i.e., RBANS total score at 6- or 12-months). Higher levels of education were associated with better cognitive performance across all time points.

6.4 Discussion

The main finding of our study is that rest-activity fragmentation was associated with worse cognitive impairment shortly after ICU discharge. This relationship, however, was lost at 6- and 12-months follow-up. TST and IS were not associated with global cognitive performance at any of the time points studied. Sleep variables studied (TST, P_{RA} and IS) did not predict cognitive impairment at 6- or 12-months after ICU discharge. APOE ε4 allele genotype was not

significantly correlated with cognitive function. In a series of linear mixed effect models, no statistically significant interaction was seen with TST, P_{RA} or IS and the presence of the APOE ε4 allele on cognitive impairment at any time point. We demonstrated that poor sleep consolidation may contribute to worse cognitive performance proximal to ICU discharge, but that its influence is not seen at 6- or 12- months follow-up. Strategies to improve sleep in the ICU have become the focus of many recent initiatives and may improve the quality of a patient's stay and reduce short-term complications such as delirium (Kamdar et al. 2016; Kamdar, Needham, and Collop 2012; Thomas et al. 2012).

Unlike in AD in which the association between sleep alteration and cognitive impairment is due to changes in brain biology (i.e., accumulation of beta amyloid), poor sleep in hospital and resultant impaired cognition is likely the result of environmental factors (e.g., noise, vital signs) and/or patients related factors such as age and severity of illness. The transient nature of ICU-based therapies (e.g., ventilation, analgesia and sedation exposure) may not lead to any pathobiological change in sleep or circadian rhythm. Our results with regards to long-term cognitive outcomes are similar to those by Calsavara et al (2018) in which patients who survived sepsis underperformed on both the Mini Mental Status Examination and constructional praxis at 24 hours after ICU discharge but regained cognitive performance at 1-year follow-up (Calsavara et al. 2018). The role of inflammation on cognition has been demonstrated in experimental studies and there is increasing evidence of this phenomenon in humans (Hennessy et al. 2017; Skelly et al. 2018). Our study was underpowered to look specifically at subgroups of a general ICU patient population, specifically sepsis. The mechanisms by which cytokines affect cognition are as yet fully elucidated. How systemic inflammation may lead to changes in behaviors persisting for a few days to weeks, and whether or not a neuroinflammatory process persists leading to long-term cognitive impairment has yet to be confirmed.

On the other hand, it may be possible that better sleep does in fact predict cognitive recovery and that our negative finding was due to our specific patient population. Specifically, level of education may have influenced performance on the RBANS. As our cohort was highly-

educated, exhibiting cognitive reserve (Fratiglioni and Wang 2007), the RBANS may not have been sensitive enough to detect a decrement in a subject's baseline performance (i.e., a patient experience significant long-term cognitive impairment from baseline but still performing above population norm). It is also possible that more frequent sleep quality assessment (e.g., every month after ICU) might have better delineated a relationship between sleep and cognition, as we hypothesize that improved cognition is indeed a lagging variable behind better sleep consolidation following hospitalization. In previous community-based studies successfully linking sleep fragmentation and changes in cognition, significantly larger populations were needed to pick up modest effects (Lim et al. 2013; Lim et al. 2012; Lim and Saper 2011).

Our results showed a trend for worse cognitive performance in patients who possessed the APOE ε4 allele. Given the wealth of data linking APOE to cognitive outcomes (Ely et al. 2007; Davidson, Cusimano, and Bendena 2015; Guaita et al. 2015; Quintino-Santos et al. 2015), this trend may have reached statistical significance had our sample size been larger. At 6- months follow-up, only 9 surviving subjects possessed the APOE ε4 allele, which by one year was further reduced to just 4 subjects. APOE plays a biologically relevant immunomodulatory role in the setting of infection and acute injury (Laskowitz et al. 2000; Lynch et al. 2003; de Bont et al. 1999). The APOE ε4 isoform is less effective at suppressing central nervous system inflammation compared with APOE ε2 and APOE ε3, possibly leading to both acute and long-term cognitive impairment in models of sepsis (Lynch et al. 2003). Having a larger sample of survivors with the APO4 allele may have better assessed whether sleep potentiated this effect.

This is the first multisite study to comprehensively examine the relationship between sleep, circadian function, and long-term cognitive impairment in survivors of critical illness. Our longitudinal study design was meant to afford the opportunity to look at changes over time in the same patient, defining the temporal sequence of changes, and providing stronger evidence for causality. The single greatest limitation of this study is its internal validity as we experienced high losses to follow-up and unanticipated deaths; this is unfortunately a common limitation in long-term follow-up studies of ICU patient populations (Jackson et al. 2010b). A larger study

with more frequent covariate sampling might better elucidate the trajectory of recovery between sleep, circadian rhythm and long-term cognition.

6.5 Conclusions

Sleep fragmentation was associated with worse cognitive impairment at 7 days of ICU discharge; sleep fragmentation and cognition at 6- and 12-months follow-up did not reach statistical significance within the small sample size studied. The well-known genetic risk factor for dementia (APOE $\varepsilon 4$) did not identify a group of patients at greater risk of cognitive impairment as compared to individuals who did not possess the allele.

Table 6.1 Clinical and demographic characteristics of patients included in study (n=102). Data presented as mean ± SD, N (%) or median (IQR)

Characteristic	Surviving Patients (n=102)	Patients who died or withdrew (n=48)
Age – yr		
Median	57	57
IQR	47-66	46-64
Male sex – no. (%)	57 (56)	24 (50)
Level of Education – no. (%)*		
Less than grade 12	6 (6)	--
High School	34 (35)	
College or University	51 (53)	
Postgraduate studies	5 (5)	
Patients with any comorbidity	59 (58)	37 (79)
No. of comorbidities – no. (%)		
Chronic kidney disease or dialysis	5 (4.9)	6 (12.8)
Hepatic failure or cirrhosis	6 (5.9)	4 (8.5)
Immune suppression or AIDS	10 (9.8)	6 (12.8)
Diabetes	15 (14.7)	8 (17)
Cardiovascular disease	20 (19.6)	7 (14.9)
Respiratory disease	30 (29.4)	21 (44.7)
Oncologic diagnosis	2 (2)	3 (6.4)
APACHEIII score		
Median	57	75
IQR	43-75	50-87
Reason for admission – no. (%)		
Pneumonia	10 (10.3)**	9 (18.8)***
Other respiratory condition (e.g. transplant)	36 (37.1)	20 (43.5)
Sepsis/Shock	10 (10.3)	3 (6.5)
Other medical diseases (e.g. CHF)	8 (8.3)	6 (13)

Trauma	2 (2.1)	0 (0)
COPD	2 (2.1)	1 (2.2)
Liver transplant/rejection	2 (2.1)	4 (8.7)
Respiratory/cardiac arrest	5 (5.1)	1 (2.2)
Orthopedic condition	1 (1.0)	1 (2.2)
Neuromuscular disease	0 (0)	1 (2.2)
Drug overdose	2 (2.1)	0 (0)
GI bleed/GI inflammatory disorder	5 (5.2)	0 (0)
Lung neoplasm/pulmonary emboli	3 (3.1)	0 (0)
Vascular disease/Peripheral artery bypass	3 (3.1)	0 (0)
Metabolic disease	1 (1.0)	0 (0)
Meningitis	1 (1.0)	0 (0)
ICU LOS – days		
Median	13	16
IQR	7-21	9-33
Duration of MV – days		
Median	7	10.5
IQR	5-13	5-21
Days delirious		
Median	0	0
IQR	0-3	0-3.5
Days continuous sedation – days		
Propofol – median, IQR	2, 1-5	2.5, 1-6
Midazolam – median, IQR	0, 0-2	0, 0-2
Fentanyl – median, IQR	3, 1-7	4.5, 1-10.5
Morphine – median, IQR	0, 0-0	0, 0-0
Dexmedetomidine – median, IQR	0, 0-0	0, 0-0
IQCODE- SF – median, IQR	3, 3-3.1	--
– mean (SD)	3.1 (0.43)	
ApoE ε4 status – no. (%)****		
ApoE ε4 -/-	73 (78.5)	--

ApoE ε4 -/+ or +/+	20 (21.5)	
BDI-II at 7days ICU – no. (%)****		
Normal mood (0-10)	41 (49.4)	--
Mild mood disturbance to borderline clinical depression (11-20)	31 (37.4)	
Moderate to severe depression (>21)	11 (13.3)	

*Level of education missing for 7 patients; **Missing in 5 patients; ***Missing in 2 patients; ****Missing in 9 patients

Table 6.2 Sleep outcomes – Actigraphy-derived data, sleep time, sleep fragmentation, and circadian rhythm over time

Characteristic	Within 7 days (+/- 48 hours) of ICU discharge (n=94)		6 months follow-up (n=57)		12 months follow-up (n=35)	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Total Sleep Time (TST)*	6.1 (3.7)	6.8 (3.2-8.6)	8.0 (1.7)	7.8 (6.8-9.0)	8.4 (2.1)	8.0 (7.1-9.0)
Sleep Efficiency as a percentage (SE)	44 (27)	54 (19-64)	68 (11)	70 (64-76)	71 (10)	69 (65-78)
Activity count during 10 hours with maximal activity (M10)	141,718 (104,024)	117,909 (58,889-208,322)	299,916 (119,978)	294,824 (222,436-387,595)	344,618 (154,212)	334,905 (216,714-457,997)
Activity count during 5 hours with least activity (L5)	14.8 (3.5)	15.1 (12.3-17.1)	11.8 (2.2)	11.7 (10.4-12.9)	11.7 (2.3)	11.9 (9.9-13.8)
Probability of movement per unit of time (P_{RA})	0.052 (0.027)	0.047 (0.035-0.057)	0.056 (0.020)	0.053 (0.042-0.066)	0.054 (0.022)	0.049 (0.038-0.063)
Interdaily stability (IS)	0.55 (0.22)	0.49 (0.38-0.67)	0.62 (0.17)	0.64 (0.51-0.70)	0.59 (0.16)	0.62 (0.46-0.72)
Intradaily variability across multiple sampling intervals (IV)**	1.21 (0.38)	1.15 (0.95-1.45)	1.03 (0.21)	0.99 (0.91-1.16)	0.92 (0.17)	0.93 (0.84-1.03)

*Missing for one patient for the 7 days post-ICU data (technical failure of device); **missing for 1 patient at 12 months follow-up data

Table 6.3 Mean score obtained on RBANS subtests 7 days after discharge from ICU, 6- and 12-months follow-up. The means were compared with expected cut-off for mild cognitive impairment as defined by the literature (> 1.5 SD below the age-adjusted mean) at each evaluation. One-sample t-Test, one-tailed probability P (Hypothesized sample mean > mean [77.5]). N = number, M = mean, SD = standard deviation.

	7 days after discharge					6 months follow-up					12 months follow-up				
	n	M	SD	t	p	n	M	SD	t	p	n	M	SD	t	p
Short term memory	98	80.4	17.9	1.59	0.06	62	90.1	17.3	5.71	<0.001	39	89.4	21.2	3.49	<0.001
Attention	98	85.3	17.6	4.36	<0.001	62	101.6	18.5	10.3	<0.001	39	103.9	17.4	9.48	<0.001
Visuospatial	98	87.89	13.1	7.84	<0.001	62	93.8	10.9	11.8	<0.001	39	97.1	16.7	7.32	<0.001
Language	98	84.2	20.7	3.22	<0.001	62	95.2	16.2	8.6	<0.001	39	92.3	12.8	7.24	<0.001
Delayed memory	98	79.6	19.1	1.09	0.14	62	92.9	18.0	6.7	<0.001	39	94.4	15.6	6.76	<0.001
RBANS total	98	79.6	14.2	1.45	0.07	62	93.0	15.2	8.02	<0.001	39	94.0	15.4	6.71	<0.001

Figure 6.1 RBANS global cognition score over time in survivors of critical illness requiring mechanical ventilation. The box-and-whisker plots show the age-adjusted global cognition scores on RBANS with a population age-adjusted mean (± SD) of 100 (± 15); lower scores indicate worse cognition. The dashed line indicates the age-adjusted population mean (100) for healthy adults, and the blue band indicates standard deviation (15).

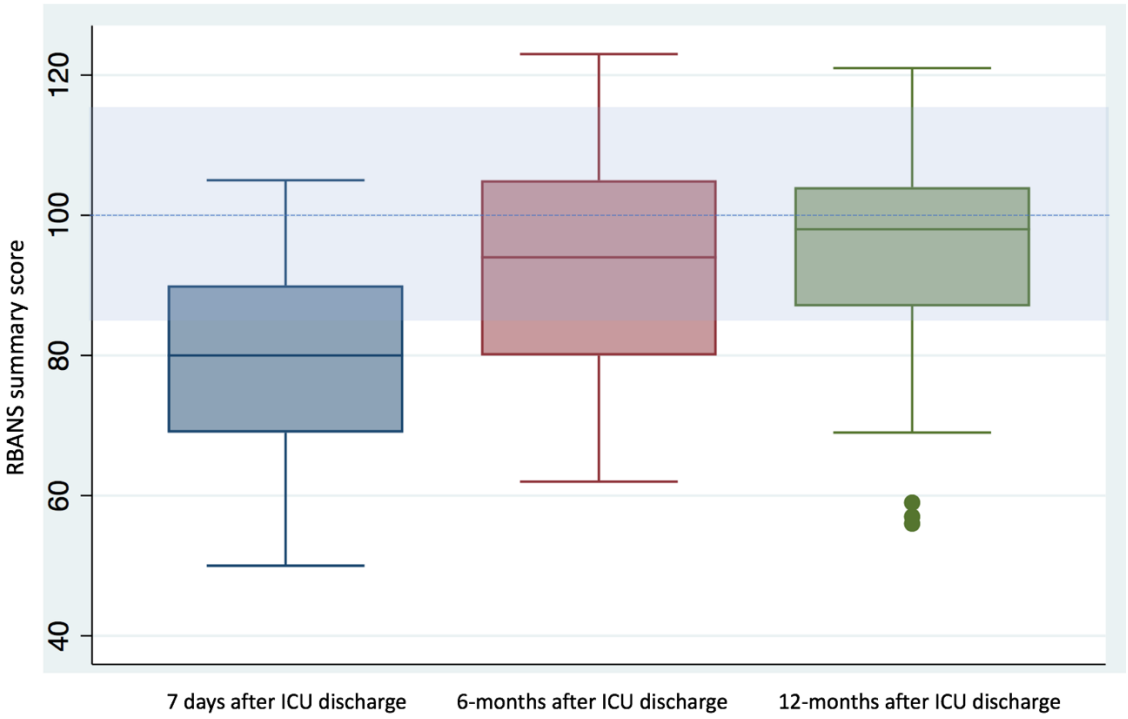


Table 6.4 Performance of patients on Trial Making Test Form A and B

	7 days after discharge	6 months follow-up	12 months follow-up
Trail Making Test A			
Patients who required more than 64 seconds to complete the test, no. (%)	27 (19)	11 (18)	4 (10)
Time to complete trails (seconds)	47 (36, 71)	39 (29,50)	29 (25, 39)
Trail Making Test B			
Patients who required more than 190 seconds to complete the test, no. (%)	16 (18)	2 (3)*	1 (3)**
Time to complete trails (seconds)	123 (88, 174)	78 (55, 111)	65 (51,81)

*2 patients unable to complete testing; ** 1 patient unable to complete testing

Table 6.5 GLM of selected variables and RBANS total score at 7 days after ICU discharge, 6- and 12-months

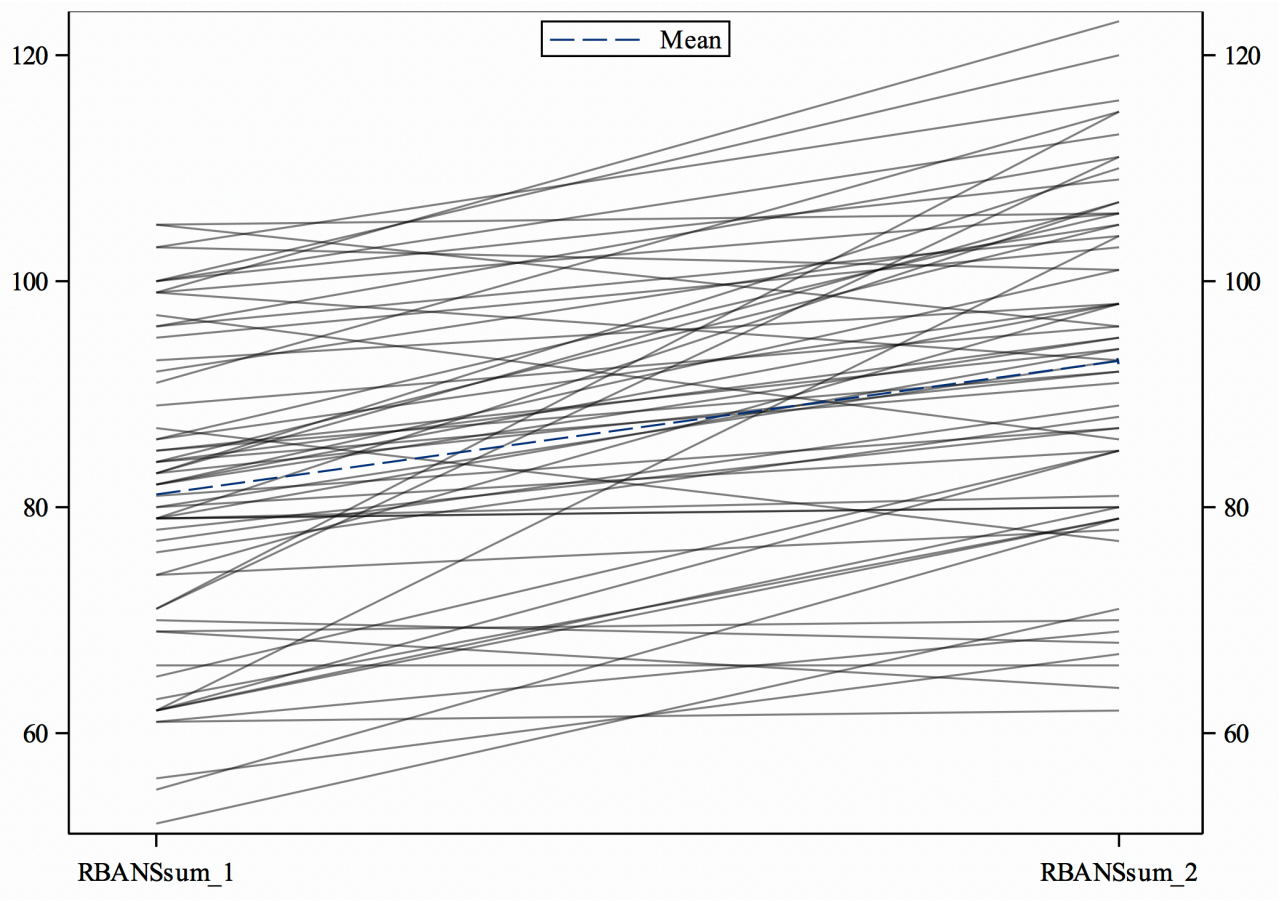
	7 days after ICU discharge					6 months following ICU discharge					12 months following ICU discharge				
	β	SE (β)	z	p-value	95% CI	β	SE (β)	z	p-value	95% CI	β	SE (β)	z	p-value	95% CI
Intercept	78.4	5.21	15.1	<0.001	68.1, 88.8	90.8	9.88	9.28	<0.001	70.9, 110.6	108.9	8.95	12.2	<0.001	90.6, 127.2
TST	0.7	0.41	1.71	0.09	-0.12, 1.53	0.89	1.17	0.76	0.45	-1.45, 3.24	-1.55	1.11	-1.39	0.17	-3.82, 0.72
APACHE III	-0.14	0.06	-2.20	**0.03**	-0.27, -0.01	-0.19	0.09	-2.25	**0.03**	-0.37, -0.02	-0.11	0.10	-1.17	0.25	-0.31, 0.08
Level of education	8.55	2.98	2.87	**0.01**	2.61, 14.5	9.8	4.19	2.33	**0.02**	1.33, 18.2	10.3	4.43	2.32	**0.03**	1.25, 19.3

	7 days after ICU discharge					6 months following ICU discharge					12 months following ICU discharge				
	β	SE (β)	z	p-value	95% CI	β	SE (β)	z	p-value	95% CI	β	SE (β)	z	p-value	95% CI
Intercept	79.5	6.17	12.9	<0.001	67.2, 91.8	88.0	10.0	8.76	<0.001	67.8, 108.1	88.4	9.85	8.98	<0.001	68.3, 108.5
IS	0.68	0.80	0.85	0.40	-0.91, 2.27	1.32	1.23	1.08	0.29	-1.14, 3.79	1.79	1.32	1.36	0.18	-0.89, 4.48
APACHE III	-0.14	0.07	-2.10	**0.04**	-0.27, -0.01	-0.17	0.08	-2.05	0.05	-0.34, -0.003	-0.16	0.09	-1.82	0.08	-0.34, 0.02
Level of education	7.51	3.18	2.37	**0.02**	1.19, 13.8	10.37	4.08	2.54	0.01	2.18, 18.6	9.73	4.44	2.19	**0.04**	0.68, 18.8

	7 days after ICU discharge					6 months following ICU discharge					12 months following ICU discharge				
	β	SE (β)	z	p-value	95% CI	β	SE (β)	z	p-value	95% CI	β	SE (β)	z	p-value	95% CI
Intercept	90.5	5.24	17.3	<0.001	80.0, 100.9	101.2	8.56	11.8	<0.001	84.0, 118.4	104.8	8.83	11.9	<0.001	86.8, 122.8
P_{RA}	-1.31	0.55	-2.38	**0.02**	-2.41, -0.21	-0.72	1.13	-0.64	0.52	-2.99, 1.54	-0.85	1.02	-0.82	0.42	-2.94, 1.25
APACHE III	-0.14	0.06	-2.26	**0.03**	-0.21, 0.07	-0.18	0.09	-2.17	**0.03**	-0.36, -0.01	-0.19	0.09	-2.01	**0.05**	-0.04, 0.002
Level of education	7.42	2.95	2.51	**0.01**	1.54, 13.3	10.2	4.11	2.48	**0.02**	1.94, 18.5	10.3	4.53	2.27	**0.03**	1.03, 19.5

Figure 6.2 RBANS total score over time

a. Change in RBANS total score from 7 days after ICU discharge to 6 months (n=62)



b. Change in RBANS total score from 6- to 12-months follow-up (n=39)

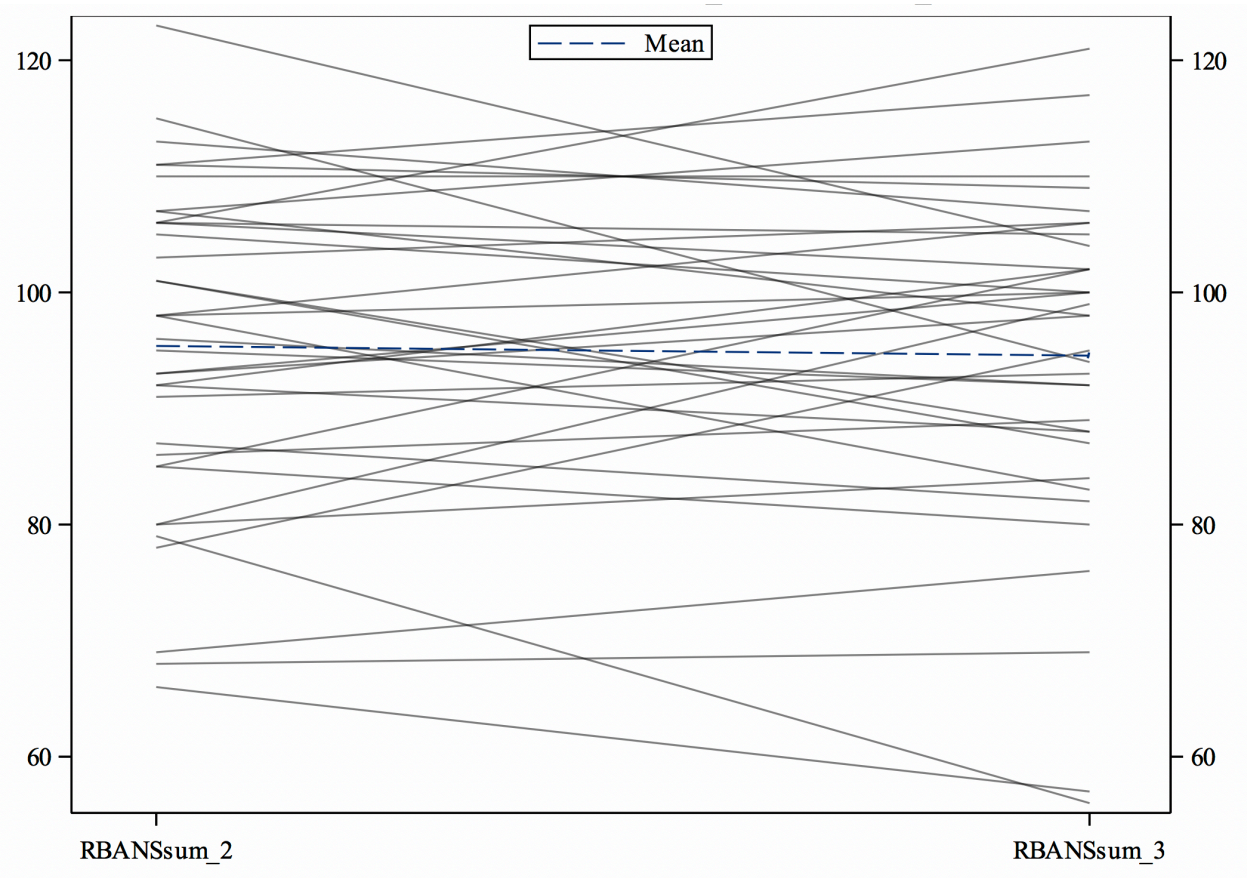
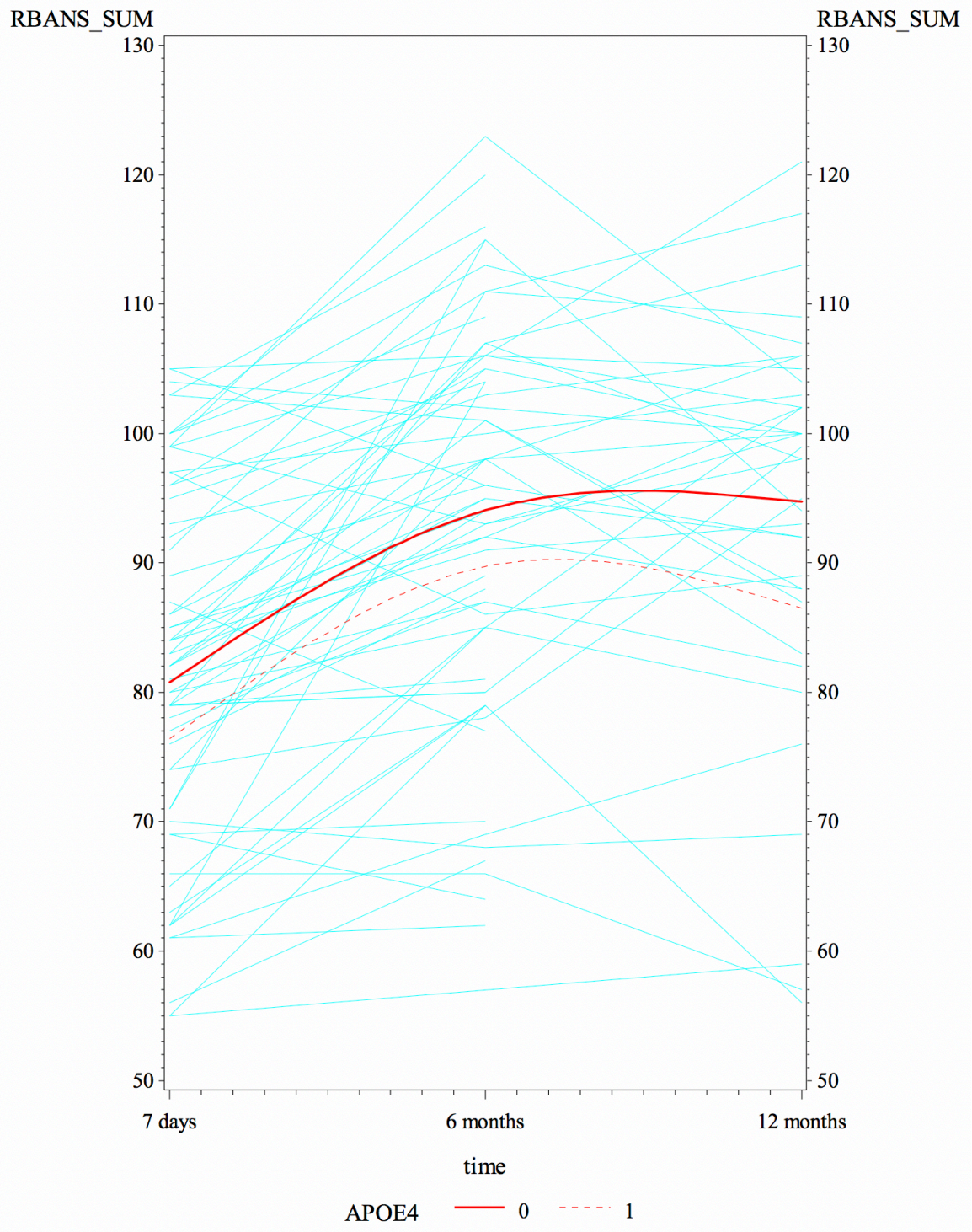


Figure 6.3 Change in RBANS total score over time grouped by APOE status



Chapter 7 CONCLUDING SUMMARY, GENERAL DISCUSSION, AND FUTURE DIRECTIONS

This chapter is modified from the following:

M. Elizabeth Wilcox and E. Wesley Ely. (2019). Challenges in Conducting Long-term Outcomes Studies in Critical Care. Current Opinion in Critical Care. 25(5): 472-88.

7.1 Concluding Summary

The "multiple paper format" of this thesis permits specific discussion sections for each chapter that contained new data (see sections 3.4, 4.4, and 5.4). In the hopes of reducing redundancy, these brief final unifying thoughts are limited to how our findings have contributed to the existing literature, what we foresee will be areas of future investigation, and the practical lessons we learned conducting this longitudinal cohort study.

7.2 Contributions made to the existing literature and future directions

Sleep is poor for patients suffering an acute illness requiring hospitalization. In our cohort, the quantity and quality of sleep remained poor on the ward after ICU but was not terribly dissimilar to that experienced by patients hospitalized for noncritical illness. A number of risk factors for poor sleep were identified, including admission diagnosis (sepsis, post-operative admission). As it seems that poor sleep and its association with poor cognition was primarily frontloaded in a patient's trajectory, our interests have turned towards better understanding the relationship between sepsis and how the inflammatory response possibly influences sleep quality and circadian rhythm.

ICUs are experiencing an epidemic of patients with acute brain dysfunction (i.e. delirium). Delirium develops in up to 80% of patients during their acute critical illness and is associated with increased lengths of stay, duration of mechanical ventilation and risk of death. A disturbed sleep-wake rhythm occurs commonly during delirium, but it is unclear whether this abnormality is a cause or early sign of delirium, or both. It is also unknown how such dysregulation might be influenced by critical inflammatory conditions, or infection, or in turn affect the innate response to infection. To determine if such an association exists, we have undertaken a project investigating the prevalence of circadian abnormalities in critically ill patients diagnosed with sepsis, the *"24: Circadian Rhythm, Sleep and Delirium in the ICU"* study. Circadian rhythm will be objectively quantified by actigraphy, urinary melatonin and temperature profiling. Sleep will be objectively quantified by EEG using the odds ratio product (Younes et al. 2015). We will leverage actigraphic, genomic, proteomic, and clinical data from three existing cohorts –

COGWELL, the Ontario Health Study (OHS), and Melatonin for Prevention of Delirium in Critically Ill Patients (MELLOW-1). The results from this study may better risk stratify patients allowing for personalized cognitive and sleep rehabilitation strategies.

The other key finding of our study was that rest-activity fragmentation was associated with worse cognitive impairment shortly after ICU discharge. This relationship, however, was lost at 6- and 12-months follow-up. Further sleep and circadian variables did not seem to predict cognitive impairment at 6- or 12-months after ICU discharge. Given that poor sleep did not seem to predict cognitive impairment after critical illness, we focus our attention to one of the final aims of COGWELL investigating EEG as a potential intermediate end point of long-term cognitive performance. EEG has been used with some success as a prognostic tool with a number of studies showing some utility of neurophysiology in monitoring brain function and predicting outcome. No quantitative scoring system has been universally adopted, as studies have enrolled very heterogeneous patient populations. The most convincing evidence for quantitative EEG predicting short- and long-term prognosis comes from the stroke literature. At one-year, functional outcome after stroke in one series was predicted correctly by clinical criteria 60% of the time whereas the addition of EEG data improved the predictive value to 85% (for both raw and quantitative EEG) (Cillessen et al. 1994). The acute delta change index correlates with 30-day NIH stroke score (NIHSS) as accurately as initial mean transit time on MRI and better than initial diffusion weighted imaging volume (emphasizing the link between quantitative parameters and blood flow) (Finnigan et al. 2004). Further, the delta/alpha ratio and the relative alpha percentage also correlate with the 30-day NIHSS (Finnigan et al. 2007). Accurately predicting outcome after ICU would enable clinicians to anticipate consequences, thereby focusing treatment and rehabilitation and potentially improving long-term outcome.

As outline in Chapter 3, an EEG was performed within hours of each cognitive evaluation. The International 10-20 System for electrode placement was used. Recording times were approximately 30 minutes and attempts were made to have all recordings performed in the morning as possible given the subject's schedule. EEGs were read in a blinded manner by Richard Wennberg and classified according to a self-designed grading system to grossly identify

cortical, subcortical white matter and subcortical grey matter abnormalities (see Table 7.1). As part of a preliminary analysis, EEGs were divided into 2 groups based on the presence of any EEG abnormality as compared to normal. The Wilcoxon test was then used to examine differences in RBANS total scores at 7 days after ICU discharge between the two groups. Ninety-eight patients from the main cohort underwent an EEG recording within 7 days of ICU discharge. For 5 recordings the files were corrupt and therefore could not be analyzed. 25/93 (27%) recordings were normal; 20/93 (21%) were scored as being mildly abnormal; 30/93 (32%) were scored as moderately abnormal; and 18/93 (20%) were grossly abnormal. The most frequent abnormalities were non-epileptiform and seen in the subcortical white matter. For the patients with a normal EEG, the mean RBANS total score was 85.0 (SD, 10.6; n=32) whereas the mean score for those with an abnormal EEG was 77.8 (SD, 14.9; n=61). This difference was found to be statistically significant (p=0.03).

The above analysis linking EEG abnormalities to cognitive impairment suggests that a true relationship between the two exists. The data, however, are preliminary and should be considered exploratory. Nonetheless, there would appear to be a sufficient signal that deeper study into how EEG changes might affect cognition is warranted. To that end, we have completed the scoring of EEG performed at 6- and 12-months and analyses of patient performance over time is underway. Furthermore, given the promising nature of these preliminary analyses we have undertaken a more formal quantitative EEG analysis as outlined in Chapter 3.

Building on our interest in both the predictive value of EEG and delirium in the ICU, we recently received funding to study phase synchrony and spatiotemporal variability of EEG and its association with delirium in post cardiovascular surgery patients (The SOS study). Similar to the evaluation of heart variability (Lerma et al. 2008; Moorman et al. 2011), electroencephalography (EEG) is another noninvasively acquired physiological signal whose variability can be quantified. Previous studies have shown that fluctuating patterns of variability indicate a wide range of states of neuronal interactions, or configurations of connections, in both healthy and pathological states (Garcia Dominguez et al. 2013; Nayak et al. 2017;

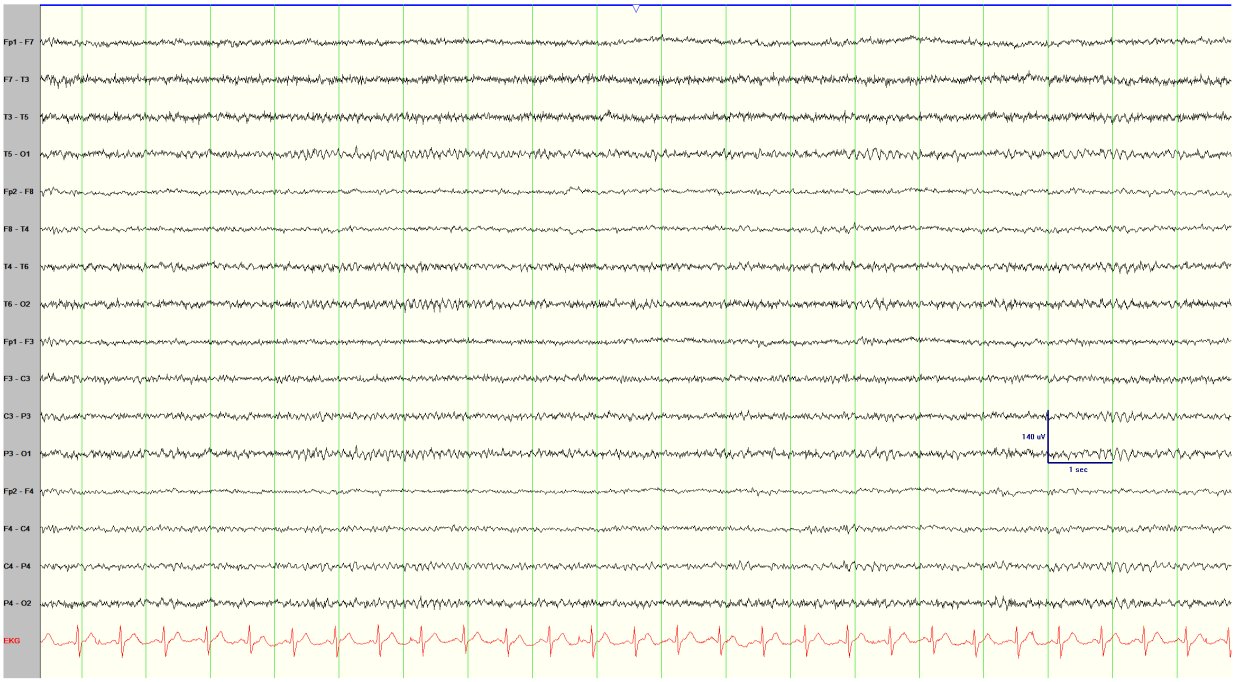
Nenadovic et al. 2008; Nenadovic et al. 2014; Perez Velazquez et al. 2007; Shields et al. 2007). EEG phase synchrony analysis is a relatively new concept but being increasingly used to evaluate neurophysiological data. Recently, variability in EEG phase synchrony and spatio-temporal variability was reviewed in 84 children emerging from coma after traumatic brain injury (TBI), cardiac arrest or stroke (Nenadovic et al. 2014). Despite an absence of signs of improvement on visual inspection of the EEG recording, changes in phase synchrony and variability indices were able to differentiate between good and poor neurological outcome (Nenadovic et al. 2014). Similar findings were seen in a study of adults with TBI (Shields et al. 2007).

The magnitude of synchrony and fluctuations in synchronization over time and space are thought to reflect the brain's performance in information processing (Guevara Erra et al. 2016; Guevara Erra et al. 2017). More recently, a 40 patient cohort of healthy adults assessed the long-range phase synchronization during awake and various sleep stages (Nayak et al. 2017). The findings support the hypothesis that oscillations during states of vigilance (awake and sleep stages) are highly orchestrated with complex interaction between thalamoneocortical networks and are regulated by brainstem modulatory systems (Nayak et al. 2017). EEG phase synchrony and variability has had limited investigation during transition from coma to wakefulness in response to sedation and analgesia. Studying changes in phase synchrony and variability during and after sedative-induced coma is an exciting opportunity to better understand EEG changes during transitions in states of arousal. It is expected that consciousness should be higher in entropy and greater in complexity in the number of configurations of pairwise connections as compared to sedative-induced coma. If sufficiently sensitive, it may be possible to identify states of lower entropy and fewer configurations when patient are aroused but with altered sensorium (e.g. delirium).

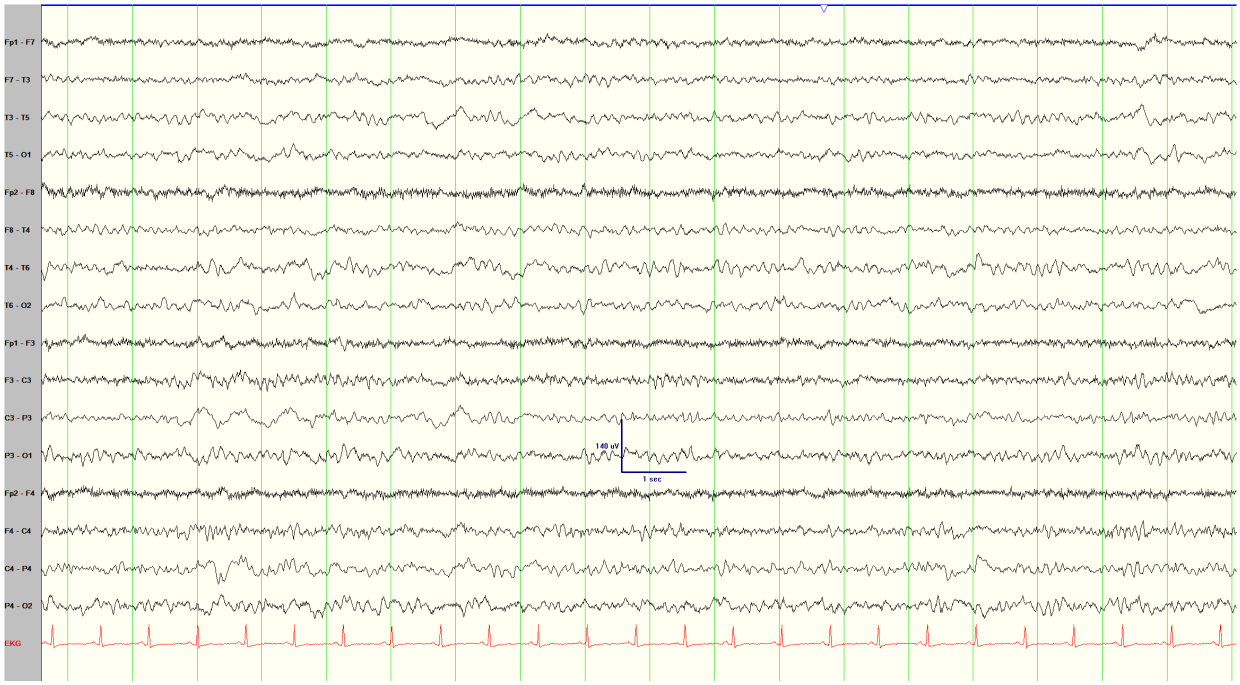
Table 7.1 Preliminary scoring guide for EEG recordings - Non-epileptiform activity

	Score
Cortical	
None	0
Theta	1
Theta and Delta	2
Delta	3
Discontinuous Theta-Delta	4
Burst Suppression	5
Asymmetrical	2
Subcortical white matter (focal/regional)	
None	0
Theta	1
Theta and Delta	2
Delta	3
Continuous Theta-Delta	4
Multifocal – 2 foci	1
Multifocal – > 2 foci	2
Subcortical grey matter (paroxysmal/rhythmic/generalized)	
None	0
Theta	1
Theta and Delta	2
Delta	3
Continuous Theta-Delta	4

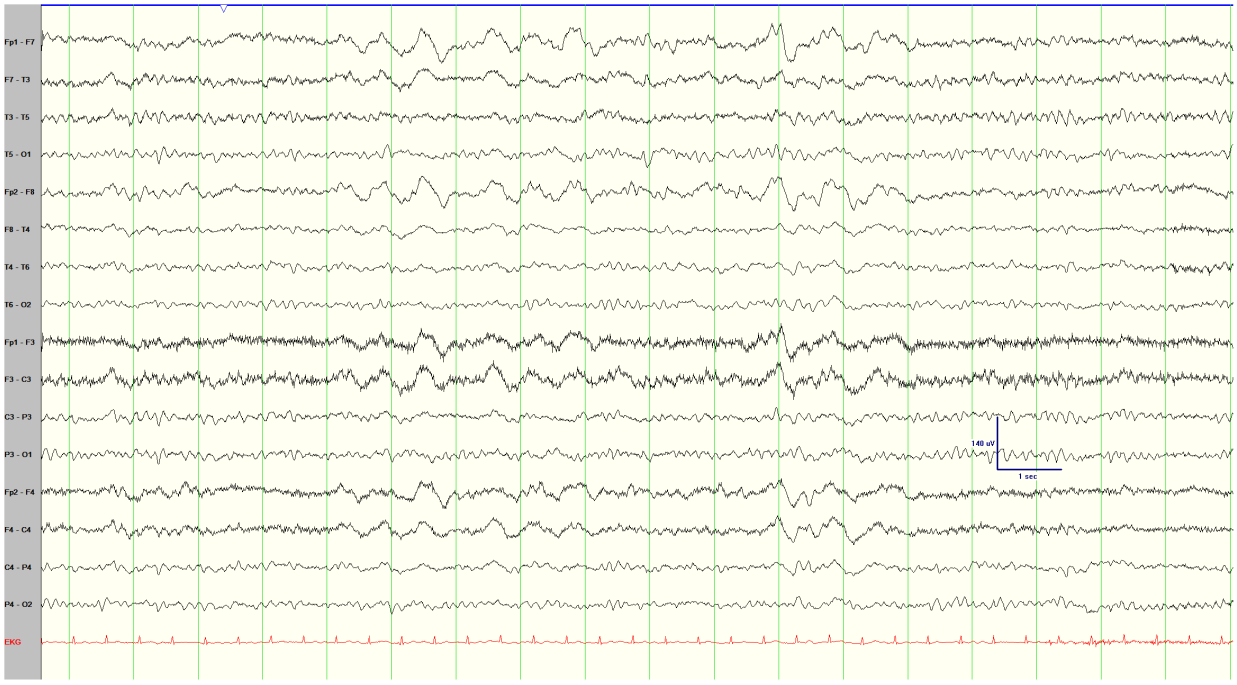
Figure 7.1 Examples of EEGs from survivors of critical illness scored by Richard Wennberg as per Table 7.1



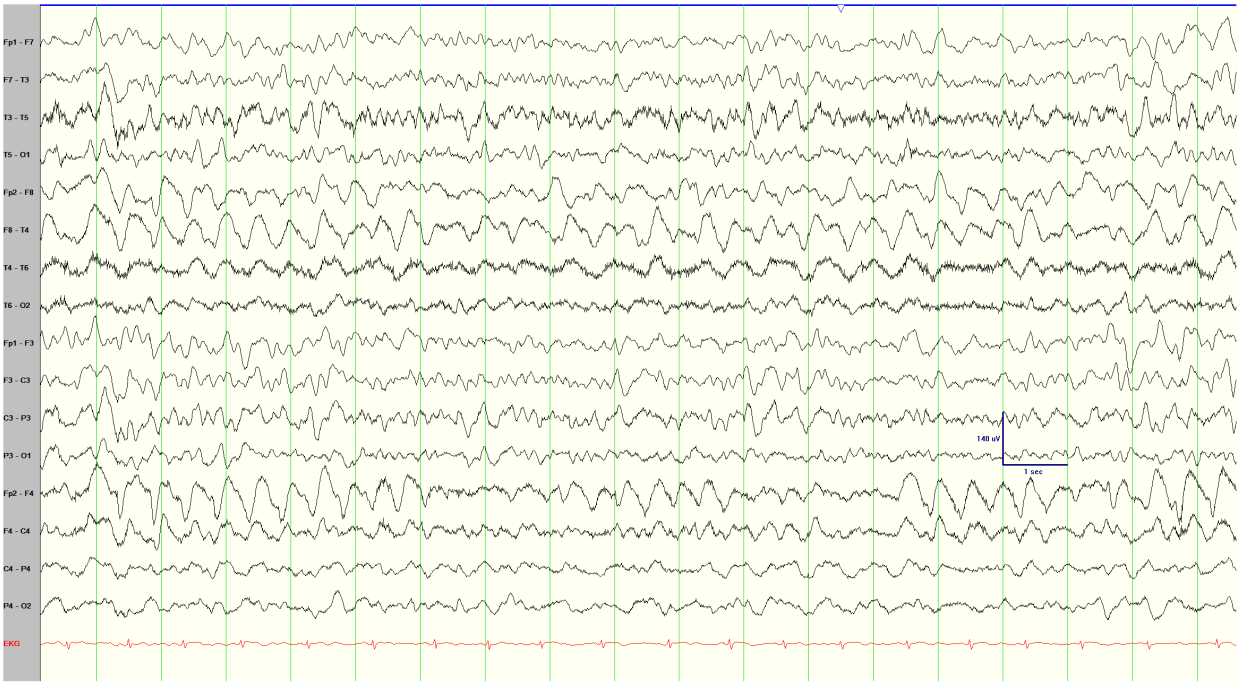
Normal EEG



Abnormal background theta (cortical)
Abnormal multifocal intermittent theta/delta (subcortical white matter)



Abnormal background theta (cortical)
Abnormal generalized paroxysmal bilaterally synchronous delta (subcortical grey matter)



Abnormal asymmetrical background theta (cortical)
Abnormal multifocal theta/delta (subcortical white matter)
Abnormal generalized bilaterally synchronous delta (subcortical grey matter)

7.3 Lessons learned from running a longitudinal cohort study

Study recruitment for the first year was very challenging as it was mandated by the group at UHN to have sequential co-enrollment for follow-up studies; patients were first consented for TOWARDS RECOVER and then offered the opportunity to participate in COGWELL. Of the patients enrolled over the first year of the study opening, the inclusion requirement of a minimum of 7 days of mechanical ventilation led to the recruitment of many patients with profound weakness. It could then take months of repeated visits before the patient had the strength to hold a pen or pencil to perform the RBANS and Trails test. As a result of this, the inclusion criteria were changed from $\geq$7 to $\geq$3 days of mechanical ventilation after patient number 14. In addition, for a number of patients (33%) testing occurred over a number of visits secondary to testing fatigue. In the odd case, in fact, the RBANS was completed over two sessions with the test being completed on the first day to include delayed memory and then the remainder of the domains completed on the following day. Testing on the ward proved to be challenging. While all efforts were made to have an interrupted session (e.g. moving to a quiet conference room), this was not possible in all cases.

The high rates of death were unanticipated. Numbers were conservatively calculated based on enrollment at the same centres in the TOWARDS RECOVER study. The rates of study withdrawal were somewhat more predictable given the challenges noted in previous studies of follow-up of cognition after critical illness (personal communication; Mary Pat McAndrews from the Toronto Outcomes study). Only 20 patients had an overnight EEG recording as this also proved to be very challenging in practice. Patients found it uncomfortable (e.g. hot) and in fact one patient refused to have a routine EEG recording at 6- and 12-months as they recalled the discomfort from the initial sampling. Manpower problems also proved challenging as EEG technicians were able to attach the patients but unavailable to disconnect and clean the electrodes in the morning. As a result, the protocol was amended such that patients only underwent a routine recording at all future time points.

Lastly, with regards to challenges with data collection, 5 patients did not return their actigraphs either due to having moved to another country or prolonged travel. A few of these samplings were permanently lost as a result of battery malfunction. One actigraph has yet to be returned as the patient was lost to further follow-up. Actigraphs were worn on average for 3.9 days (range, 1-9 days; 429 days in total recorded from 94 patients), 4.1 days (range, 1-8 days; 265 days in total recorded from 57 patients) and 4.3 days (range 2-8 days; 156 days in total recorded from 35 patients) starting at 7 days of ICU discharge, 6- and 12-months follow-up, respectively. In retrospect, collecting qualitative data on reasons for low adherence to wearing the actigraph would have been informative regarding feasibility of portable outcome measures.

Manpower problems with the expansion and restructuring of the UHN epilepsy monitoring unit limited the availability of EEG technicians during daytime hours. As a result, a deal had to be brokered for off-hours stipends for inpatient EEG services. A small pool of technicians was committed to off-hour work, and thus weekends and holidays were especially challenging to schedule sessions. The unpredictable nature of ICU discharge led to a small number of patients either missing their EEG at 7 days follow-up or its performance being delayed (e.g. on day 10 after ICU discharge). We were fortunate to have had access to a portable EEG machine for the first 2 years of the study. This allowed us to perform either home visits or visits to rehabilitation facilities if patients were discharged from hospital before their 7 days follow-up testing could be completed. Unfortunately, the portable EEG machine had a software malfunction after having performed a home visit for 7 days follow-up on patient 45. After this time, it was impossible to perform portable studies as there were no funds to replace the equipment.

7.3.1 Mortality and long-term follow-up

Survivors of critical illness have poor long-term survival. In a recent large cohort of ICU survivors from 21 ICUS in France and Belgium, 1-year mortality was 21% (Gayat et al. 2018). The need for mechanical ventilation portends a worse long-term prognosis, with an epidemiological study of over 35,000 Medicare patients having survived ICU admission demonstrating that mechanical ventilation was associated with a 58% risk of death at 3 years (Wunsch et al. 2010). The need for greater in-ICU resource intensity has been shown to necessitate greater resource utilisation

after discharge leading to greater likelihood of readmission (Hill et al. 2016); as high as 84% of ICU survivors return to the emergency department with 65% requiring hospital readmission. The majority of rehospitalizations occur within the first year following discharge, a time period during which long-term follow-up in ICU survivorship trials is concentrated (Hill et al. 2016). Beyond one year, 25% of ICU survivors are readmitted to the ICU during the 5 years following index hospitalization. Age and pre-existing chronic illnesses are the greatest influences on predicted risk of death, with overall 1-year survival for patients over the age of 80 years being reported as low as 42% (Andersen et al. 2015). Depending on the patient population (e.g. admitting diagnosis of sepsis or older age) as well as the duration of follow-up (i.e. with longer duration a greater number of subjects are likely to die before end of study) special consideration should be taken into the calculation of sample size to ensure there will be an adequate number of subjects to assess at long-term follow-up. Achieving and maintaining adequate numbers of subjects is of increasing importance as the state of research shifts from primarily descriptive reviews of mortality and functional outcomes towards attempting to ascertain causal inference.

7.3.2 Loss to follow-up

Low follow-up rates are an important limitation in the interpretation of long-term ICU outcomes studies, especially because the patients lost to follow-up likely have important cognitive and/or physical deficits leading to their lack of retention. Researchers continue to debate the minimum participant retention rate acceptable to preserve study validity. The social science literature suggests a minimum rate of 70-80% (Desmond et al. 1995); no such guidelines exist for studies of ICU survivorship. It seems, however, that in both longitudinal cohorts and randomized controlled trials with long-term follow-up, investigators are achieving on average rates of 70-80%. For example, Herridge and colleagues in the Towards RECOVER study (n=391) evaluated 90% of subjects in hospital, and then 71%, 74% and 83% of eligible ICU survivors at 3-, 6- and 12-months respectively (Herridge et al. 2016). These follow-up rates were achieved by a well-experienced team with expertise in retention strategies for long-term follow-up. Comparing follow-up in the BRAIN-ICU (Pandharipande et al. 2013) and COGWELL (Wilcox et al.

2017) studies, one may get an idea of the size of team required to achieve such numbers (Figure 7.2). In the BRAIN-ICU study (Pandharipande et al. 2013) at 1-year follow-up, a large team of over 10 dedicated research personnel were able to achieve follow-up rates of 94%. In contrast, a single researcher and part-time research assistant in the COGWELL study achieved follow-up rates of only 73% (62% evaluated).

It is common to underestimate the number of study personnel required to ensure adequate follow-up and to misjudge the financial expense needed from external funding for such ventures. Strategies suggested for subject retention include using a systematic method for patient contact, scheduling, and cohort retention monitoring (e.g. obtaining multiple contacts for each participant, including two contacts not residing with the participant); minimizing participant burden through characteristics and procedures of follow-up study clinics (e.g. offering flexible clinic appointments); and specifically training and managing study personnel (e.g. assigning one primary physician to each participant or hiring culturally sensitive staff with strong interpersonal skills) (Robinson et al. 2015; Teague et al. 2018). Effective incorporation of these measures requires time, dedication, and training. Most importantly, adequate follow-up requires a large budget for adequate staffing and to allow staff the time to pursue resource-intense endeavors that limit study attrition (Davies et al. 2016).

Expanding on the need to further understand and develop strategies to maximize subject retention, future strategies might include off-site or home visits, either in person or via available technologies. Waters and colleagues recently analyzed patient-related factors for requiring off-site or home visits in follow-up of subjects participating in either the Toronto 5-year ARDS outcomes study and RECOVER program (Waters et al. 2019). Patients with the most significant functional dependency and medical complexity were more likely to require an off-site or home visit for follow-up (Waters et al. 2019). Further study of the need for off-site or home visits may provide not only an opportunity to limit study attrition rates but might identify and therefore allow investigators to address issues that might prevent study follow-up, and possibly even readmission or death.

Although the current evidence supports the effectiveness of transitional care models in reducing hospital readmissions, the component of transitional care delivery from which patients are most likely to benefit has yet to be determined (Hansen et al. 2011). In a randomized controlled trial of elderly patients discharged from hospital, visits from an advanced practice nurse during the first four weeks after hospital discharge significantly delayed the time to first readmission and reduced the total number of multiple readmissions (Naylor et al. 1999). In a pair of studies of patients with chronic congestive heart failure, those patients who received home visits within 7 to 14 days after discharge had fewer unplanned readmissions and longer survival (Stewart and Horowitz 2002). In a retrospective cohort of Medicaid recipients requiring complex care for their chronic conditions, home visits reduced the likelihood of a 30-day readmission by almost half, as compared to less intensive forms of nurse-led transitional care support (Jackson et al. 2016). Higher risk patients seemed to experience the greatest benefit in terms of number of inpatient admissions and total cost of care 6 months following discharge (Jackson et al. 2016). Outside of home visits, thinking of other solutions to meet the needs of follow-up subjects may need to be more creative. For example, a research study "car service" may facilitate in-person appointments. For an ICU survivor who lived 27 kilometres from the follow-up clinic and lacked the confidence in her own motor dexterity and response time to drive on the highway, our study team drove out to pick her up so that she could undergo a full cognitive evaluation and an electroencephalography study. By her second follow-up, her motor dexterity improved, as had her confidence. As a result she was enthusiastic to report that she was able to transport herself to clinic for her 12-months follow-up visit. Further study of the needs of patients unable to attend in-person follow-up is desperately needed to investigate the benefit of such a laborious endeavor for researchers and to minimize the inherent bias introduced by high rates of loss to follow-up.

7.3.3 Missing data points

Subjects who are not necessarily lost to follow-up but have missing data from incomplete study visits also contribute to decreased precision and statistical power, thus introducing selection

bias. Many ICU survivors have poor baseline health and health related quality of life, and often face new or worse physical, psychological and cognitive morbidity after hospitalization (Needham et al. 2012). These impairments may present difficulties for subjects to participate in longitudinal studies as follow-up assessments tend to be lengthy and involve multiple neuropsychological and physical surveys as well as performance-based tests (Jackson et al. 2010; Jackson et al. 2014; Needham et al. 2006; Needham et al. 2013a; Needham, et al. 2013b; Needham et al. 2017). As an example, to perform the minimum acceptable Core Outcome Measurement Set, comprising 42 questions, the estimated completion time is 12 minutes. Including the optional Montreal Cognitive Assessment instrument with the Short Form-36 raises the total number of questions to 91 and requires an estimated 26 minutes (Needham et al. 2017). These times of course do not take into account initial time spent speaking with the subject, and possibly a family member or friend, about how things have been going since hospital discharge or the reassurance needed to complete the assessments if significant functional, cognitive or mood impairments exist.

A real-world illustration of how morbidities experienced by this patient population may influence subject performance is shown in Figure 7.3. Although a minimum outcome dataset is an important initiative to help guide measurement selection, it may also be seen as a challenge in and of itself in this type of research. As investigators we need to maintain a degree of adaptability to meet the needs of our patients, while they are trying to provide us with the answers to ICU survivorship. We need to remain sensitive to the individual trajectories of disability and ensure that we don't contribute to the frustrations that our patients face during recovery. Sensitivity to the needs of our patients should always supersede the need for a complete dataset.

A greater understanding of the barriers to complete data collection during follow-up visits may assist investigators anticipate and tailor their follow-up efforts. These factors are just starting to be elucidated. Recently, Heins and colleagues evaluated risk factors for missed assessments over a 6 to 24 months follow-up period in survivors of acute respiratory distress syndrome;

number of dependencies in activities of daily living at hospital discharge was associated with higher odds of missed assessments at the initial visit of 3 months follow-up (Heins et al. 2018). Variables associated with higher odds of missed assessments at subsequent visits were two or more dependencies of instrumental activities of daily living at hospital discharge and having missed assessments at the prior follow-up (Heins et al. 2018). Just like adaptive trial design for mortality outcomes can reduce missing assessments, longitudinal clinical research studies may benefit from modifying parameters of follow-up based on subject performance. For example, if a subject has significant functional impairment at 3-months, future outcome measures might be modified such that those most important to the study are evaluated first; this then becomes the dataset carried through for that subject until the end of the trial.

7.3.4 Outcome measure selection across studies

Heterogeneity in the outcomes and measurement instruments used in ICU survivor studies has created a major barrier in synthesizing results. In a recent review by Turnbull et al., more than 300 original research publications on ICU survivors' outcomes after hospital discharge since 2000 had highly variable time to follow-up and measures (Turnbull et al. 2017). A further scoping review found that 250 unique measurement instruments were used between 1970 and 2013 to assess ICU survivors after hospital discharge (Needham et al. 2017). As of May 2019, there are 16 projects registered with the Core Outcome Measures in Effectiveness Trials (COMET) Initiative (http://www.comet-initiative.org/).

Other than establishing a core set of outcomes and measurement instruments, work must also focus on standardizing definitions of clinically important difference. As an example of the difficulty in defining a clinically important difference, we can draw on our own experience in studying cognitive outcomes. Our attempt to compare rates of cognitive impairment across studies proved difficult as different batteries have been employed and widely divergent definitions of impairment used (See Chapter 2 Table 2.2). We found no consistency in the definitions used for impairment (e.g. 1 SD, 1.5 SDs or 2 SDs below the normative mean).

Further, there was inconsistent reporting of whether cut-off scores for impairment were adjusted for age, education or premorbid ability.

7.3.5 Reporting of key covariates

Interestingly, but not surprisingly, there is variable reporting of important covariates in studies of ICU survivors after hospital discharge. Again, using the example of long-term cognitive impairment, the most commonly reported covariates were age and sex in follow-up of ICU survivors; level of education was reported in only half of the studies (31/61; 51%). Severity of illness, duration of ICU or hospital stay, use of sedative agents, and incident delirium were also inconsistently reported. In order to inform a comprehensive understanding of outcomes after ICU, more uniform reporting of key covariates is necessary to synthesize the results of different cohorts. Such an understanding is essential for researchers and clinicians to advance research and enhance future care of ICU survivors.

7.3.6 Family and friends of ICU survivors

Physical, cognitive, emotional and social problems are common among ICU survivors. These wide-ranging issues are also seen frequently in family members and friends (Cameron et al. 2016). While many of these problems are new, unmasked, or exacerbated by acute illness, in-hospital events may also strip away compensatory strategies that had helped patients or their caregivers cope in the past. Social relationships have a two-way influence on health and well-being; social isolation in many disease processes is known to exacerbate conditions and predict mortality (Boothroyd and Fisher 2010). Conversely, social relationships are also known to have a protective impact on health, especially in disease processes such as cancer and depression (Cameron et al. 2007; Stansfeld et al. 1997). Therefore, understanding the emotional and social needs of not only our patients, but also their caregivers, will help improve our understanding of ICU survivorship. Given the key role of family members and friends in the lives of our patients, future research should include further understanding the relationship between survivors and their caregivers, including their respective social networks (McPeake et al. 2019), to determine how acquired co-morbidities may be managed and mitigated.

Figure 7.2 Consort diagrams of two studies a. BRAIN-ICU study (Pandharipande et al. 2013) and b. COGWELL study (Wilcox et al. 2017) of long-term cognitive follow-up of varying numbers of both participants and study personnel. All efforts should be made to limit study attrition from loss to follow-up to minimize bias, enhance generalizability as well as study validity. Strategies to mitigate loss to follow-up are heavily dependent on numbers of study personnel, dedicated time to allocate to retention strategies, and adequate funding to enact such aggressive strategies.

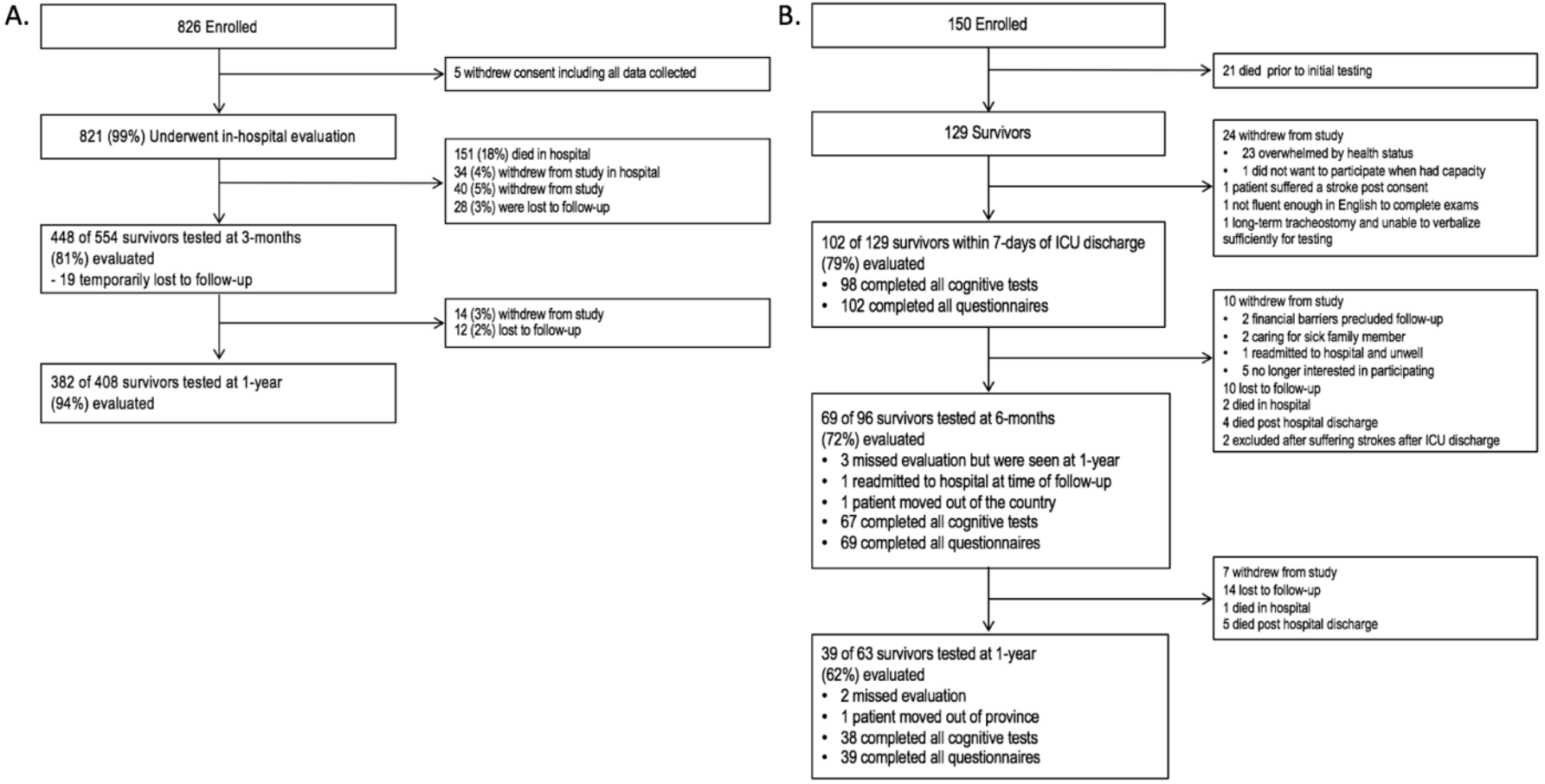
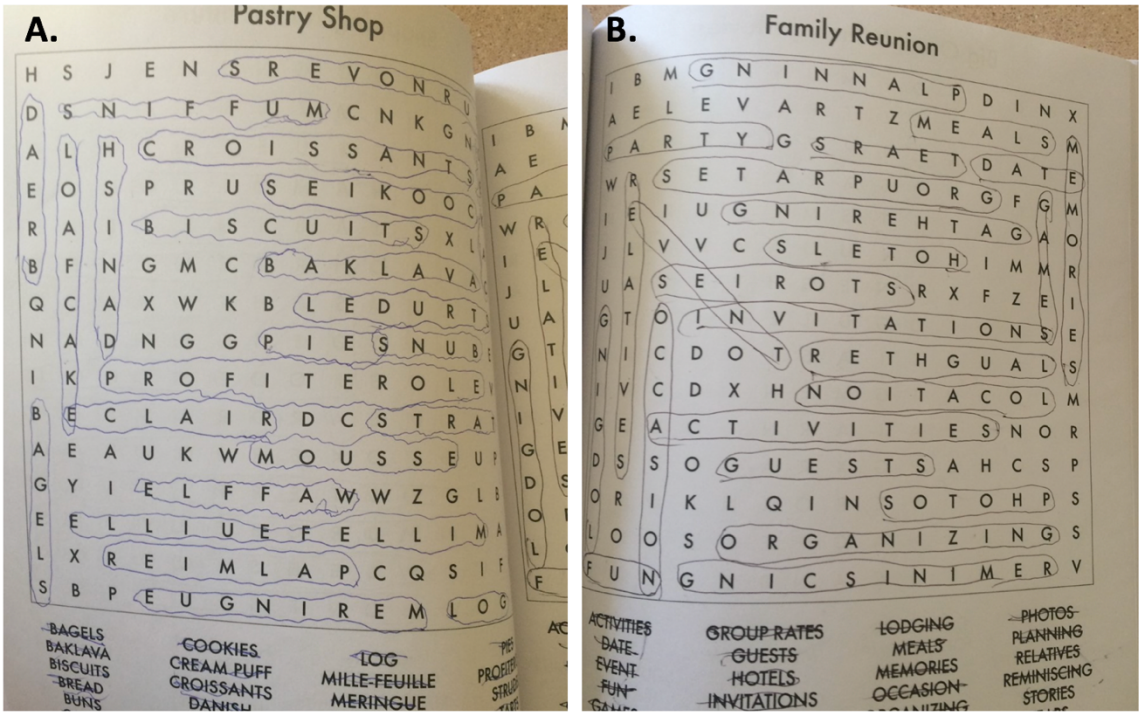


Figure 7.3 Fifty-six-year-old university educated woman status post lung transplant. After hospital discharge, she reported difficulties with concentration and found reading to be overwhelming. She started to do word searches in the hopes that it would mediate some of her experienced symptoms. Shown on the left is a puzzle completed around her 6-months follow-up appointment; as can be seen her fine motor dexterity had not returned to her baseline at that time. Outside of this finding, her cognitive testing was within normal limits. Shown on the right is a puzzle she again completed but this time proximate to her 1-year follow-up. At this time, she not only subjectively felt that her concentration had improved but also her confidence in her daily activities, both of which seemed to lag behind her functional recovery.



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