Long-term cognitive impairment and delirium in intensive care: a prospective cohort study

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Conflicts of Interest: Professor Marion Mitchell and Professor Leanne Aitken are both Life Members of ACCCN. Professor David Shum is currently the Dean of Research (Health) at Griffith University. Ms Jenny Murfield and Mr Gabor Mihala have no conflict of interest to declare.

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ABSTRACT

Background: Whilst there is a growing body of research exploring the effect of delirium in intensive care unit (ICU) patients, the relationship between patient delirium and long-term cognitive impairment has not been investigated in settings where low rates of delirium have been reported.

Objectives: To assess the association between the incidence of delirium, duration of mechanical ventilation and long term cognitive impairment in general ICU patients.

Methods: Prospective cohort study conducted in a tertiary level ICU in Queensland, Australia. Adult medical and surgical ICU patients receiving ≥12 hours' mechanical ventilation were assessed for delirium on at least one day. Cognitive impairment was assessed at three and/or six-months using the: Repeatable Battery for the Assessment of Neuropsychological Status (RBANS); Trail Making Test (TMT) Part A and B; and Mini-Mental State Examination (MMSE).

Results: Of 148 enrollees, 91 (61%) completed assessment at three and/or six months. Incidence of delirium was 19%, with 41% cognitively impaired at three months and 24% remaining impaired at six months. Delirium was associated with impaired cognition at six-months: mean TMT Part A scores (information processing speed) were 7.86 seconds longer than those with no delirium (p=0.03), and mean TMT Part B scores (executive functioning) 24.0 seconds longer (p=0.04).

Conclusions: ICU delirium was positively associated with impaired information processing speed and executive functioning at six-months post-discharge for this cohort. Testing for cognitive impairment with RBANS and TMT should be considered due to its greater sensitivity in comparison to the MMSE.

Introduction

Delirium is a common neuropsychiatric syndrome that, although occurring in a range of healthcare settings, is particularly prevalent in hospitalized intensive care unit (ICU) patients. However, the incidence of ICU delirium varies widely worldwide – 23 to 84% in North America; [1-4] 15% to 39% in Europe; [5, 6] 63% in Asia [6]; and 12% to 45% in Australia.[6, 7] Reasons for these disparities include differences in the severity of illness of ICU patients between countries,[3] methodological differences in research, the fluctuating nature of delirium and the inability of clinicians to detect delirium.[8] Models of care differ in relation to sedation and mobilization practices which affect rates of delirium in ICU patients.[1]

Delirium in the ICU patient has been associated with various risk factors including patient age;[6] excessive alcohol consumption;[6] psychoactive medications including benzodiazepines and opioids;[9] mechanical ventilation;[10] coma; infection; metabolic acidosis and severity of illness.[6] Adverse patient outcomes, both during hospitalization and in the longer-term, post-discharge are also reported.[11-18] These include prolonged mechanical ventilation;[15] increased ICU and hospital length of stay (LOS);[15] increased risk of in-hospital falls;[16] increased risk of post-traumatic stress symptoms;[12] reduced quality of life post-discharge;[11] increased risk of newly acquired functional disability in activities of daily living post-discharge;[2] and increased

mortality rates. [11] In addition, patients are also at an increased risk of cognitive impairments months to years after ICU.[19] Whilst improvements in cognitive function typically occur in the first year post ICU discharge,[20] between a quarter and half of ICU survivors report persistent impairment at one,[3, 4] two,[21] and six years.[22] Both longer duration of delirium[4, 5] and, more recently, greater severity of delirium,[23] have been identified as risk factors of cognitive impairment. Analgesics and sedative medications have also been posited as possible mechanisms through which both delirium and cognitive impairment develops, [19] although findings to date remain mixed.[4, 24]

Whilst there is a growing body of research exploring the effect of delirium in ICU patients, the relationship between patient delirium and cognitive impairment has limited reports of investigation in settings where low rates of delirium have been reported.[6, 11, 17, 18] Consequently, the current study sought to explore the association between the incidence of delirium, duration of mechanical ventilation and patients' cognition at three and six-months post ICU discharge. To aid international comparison, the study design was based on that conducted in the USA by Girard et al,[3] which was the first prospective cohort study to identify delirium as a predictor of long-term cognitive impairment at three and 12-months post-discharge All risk factors, covariates and outcomes were determined *a priori* and based on Girard et al's work.[3] However, limitations of Girard et al's study included the exclusion of surgical patients, and the study being nested within a sedation and weaning protocol clinical trial[3] which may have had some inadvertent impact on the results.

Methods

Study Design, Sample, and Setting

This prospective cohort study was conducted in the ICU at a tertiary referral teaching hospital in Australia. The 750-bed hospital has a 25-bed ICU with approximately 2,200 adult surgical, medical and trauma patients admitted yearly.

ICU nurses with advanced knowledge and previous training in all aspects of research including screening, data collection and data entry worked as research nurses for the project. They screened ICU patients daily for inclusion, with those aged ≥18 years and mechanically ventilated for ≥12 hours eligible. Patients were excluded if they: were not receiving active ICU treatment as determined in discussion with the ICU consultant (i.e., palliative care); were unable to communicate in English; were likely to be inaccessible in-person (i.e., geographically) for follow-up; had a pre-existing neurological deficit that prevented independent living; [3] or had a traumatic brain injury with a Glasgow Coma Scale[24] score <14.

Ethical approval for the study was granted by the relevant Human Research Ethics Committees (HREC/11/QPAH/230; NRS 34/11/HREC). Ethical principles stated in the Declaration of Helsinki and the National Statement on Ethical Conduct in Research Involving Humans were adhered to. Patient's next of kin provided written informed consent at study enrolment, with subsequent written consent obtained from the patient prior to discharge and confirmed before subsequent assessments.

Risk Factors, Covariates, and Outcomes

Risk Factors: The primary predictor was the number of delirium days the patient experienced in the ICU. Duration of delirium was defined as the number of days, to a maximum of 28, participants were assessed as positive using the Confusion Assessment Method for the ICU (CAM-ICU)(25) at least once each day. Participants assessed as having a Richmond Agitation-Sedation Scale (RASS) [26] score of -4 or -5

(i.e. deeply sedated) were not assessed for delirium in line with instructions for use of the CAM-ICU. [25] Both the RASS and CAM-ICU are routinely used in the study ICU.

A secondary predictor variable was the duration of mechanical ventilation (defined as the time from endotracheal intubation to successful extubation and unassisted ventilation). In keeping with Girard et al,[3] duration of mechanical ventilation was included to explore the possibility that it was a predictor of cognitive impairment. [12, 27]

Covariates: Covariates included: age; sex; highest level of education; admission diagnosis; severity of illness (Acute Physiology and Chronic Health Evaluation II and III scores [APACHE II & III])[28, 29]; ICU LOS; hospital LOS; total doses administered in ICU of propofol, benzodiazepines (milligram [mg] of lorazepam equivalent using the following conversion formulas: 1 mg of lorazepam equals: 0.5mg of alprazolam; 5mg of diazepam; 2.5mg of midazolam; 15mg of oxazepam; and 15mg of temazepam [personal email correspondence with Girard TD, 11th September 2014]), and opioids (mg of fentanyl equivalent using the following conversion formulas: 1 mg of fentanyl equals 70mg of methadone; 66.7mg of morphine; 10mg of oxycodone; and 0.83mg of remifentanyl).

Outcomes: The primary outcome was participants' cognitive status at three and six-months post ICU discharge. Cognitive assessment was conducted by trained psychologists blinded to the details of each participant's critical illness and number of delirium days. Assessment was undertaken face-to-face at the participant's home, the hospital, or the university's Psychology Clinic. Three validated measures were used to assess participant's cognition:

1) The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[30] profiles cognitive impairment across five domains that are each

comprised of sub-tests that provide raw scores, adjusted for age, to give a standardized index score for domain and an overall score (mean 100; *SD*=15). Lower scores indicate worse cognitive functioning. RBANS has demonstrated reliability and validity in various contexts and countries,[30, 31] and Australian normative data are available. [31] In this study, participant's scores were categorized as: no cognitive impairment; mild-moderate cognitive impairment; severe cognitive impairment based on their standardized index scores using the procedures found in Girard et al's study.[3] That is, participants were classified as mildly to moderately impaired if they scored 1.5 *SD* below the mean on two of the index scores or 2 *SD* below the mean on one of the index scores. They were classified as severely impaired if they scored 1.5 *SD* below the mean on three or more of the index scores or 2 *SD* below the mean on two or more of the index scores. Participants who scored higher than 1.5 *SD* of the means on four or five of the index scores were classified as having no impairment.

2) Trail Making Test (TMT)[32] is comprised of two parts, both of which are timed tests and focus on sequential responses. Part A measures information processing speed, whilst Part B provides an index of executive functioning. The two parts are scored and reported separately. The participant's performance metric is the time taken to complete the tests. TMT has been used in a variety of settings, and Australian normative data is available.[33] In this study, a TMT_Part A completion time of ≥40 seconds indicated impaired information processing speed, and a TMT_Part B completion time of ≥92 seconds indicated impaired executive functioning.[32]

3) The Mini-Mental State Examination (MMSE)([34]) is a commonly used global cognitive assessment in older adults and can be used to measure cognitive changes over time. Scores range from 0-30, with lower scores indicative of greater cognitive impairment. In this study, a score of ≤26 indicated cognitive impairment, with scores

of 27-30 indicating normal cognitive functioning. A higher than usual cutoff of 26 was adopted because MMSE scores have been found to be related to years of education and lower cutoff scores may incorrectly misclassify someone who is cognitively impaired, but able to compensate for performance because of higher educational level. A higher cutoff is considered appropriate for screening purpose when sensitivity should be emphasized over specificity.[35]

Data Analysis

To explore whether duration of delirium or days of mechanical ventilation predicted long-term cognitive impairment at three and six-months post-discharge, a series of linear regressions were undertaken for the three outcome measures (RBANS; TMT_Part A; TMT_Part B; and MMSE), adjusting for possible covariates (age; sex; highest level of education; ICU LOS; APACHE II; APACHE III; and total dose of Propofol, Benzodiazepine, and Opioids in ICU). Variables with $p<0.2$ in univariate analysis were entered into multivariate models with the exception of age and education, which were entered in all models regardless of significance due to known associations with the outcomes. Multivariate models were constructed using a manual backward (at $p<0.05$) model building technique. Correlation between covariates and model assumptions (distribution of the residuals, influential observations) were checked. Regarding the MMSE outcome, it was not possible to fit a regression model due to the low number (below or near 10 cases per independent variable) of participants who were classified as cognitively impaired with this outcome. Thus, regression model results are only presented for the RBANS (total score after adjusting for age, remaining in natural scale) and TMT_Part A and Part_B (transformed to approximately normal distributions using the formula: inverse square root of time, (in

seconds)). Regarding the covariates, age was centered around the mean for easier interpretation, whilst sex, ICU LOS, APACHE II, and APACHE III were entered into regression models in their natural scale.[36] Education was recoded into three categories (secondary education or less; certificate/diploma; and university). The variables indicating propofol, benzodiazepine and opiates doses were coded into ordinal variables with six approximately balanced groups (analysis was repeated with propofol, benzodiazepine and opiates doses expressed as average daily values).

Delirium was expressed in days, and defined as at least one positive delirium assessment made in the day using the CAM-ICU. In the study by Girard et al,[3] delirium was analyzed as a continuous variable; however, few patients experienced ≥2 days of delirium in our current study (7%) and, for statistical integrity, delirium was analyzed as a dichotomous variable.

The effect of multiple comparisons was considered when evaluating the results. Statistical significance was declared at $p<0.05$. All data analyses were performed using STATA version 12.1 (StataCorp, Texas, USA).

Results

During the recruitment period, 421 patients met the eligibility criteria and 148 participants were enrolled into the study between November 2011 and the end of 2014. Ninety-one (61%) participants completed an outcome measure assessment at either one or both time points: 88 were successfully assessed at three months, 79 at six months, and 76 were tested at both time points (Figure 1).

Sample Characteristics

Most of the study participants were males, aged 43 - 65 years, with varied educational backgrounds (Table 1), and a mean severity of illness (APACHE II) score of 18.

Participants' length of ICU stay was 4.3 days and they were mechanically ventilated for 2.2 days. The incidence of ICU delirium was 19%, and just 7% of participants experienced delirium on multiple days.

There was no difference in the characteristics of the 91 study participants who completed at least one cognitive test when compared with the 57 participants enrolled but not tested at either the three or six-month time points (due to withdrawal, loss to follow-up or deceased), and the incidence of delirium was comparable (17% for those tested vs. 14% for those not tested at either time points, results not presented).

Cognitive Impairment at Three and Six Months Follow-Up

Using the RBANS, cognitive impairment remained for 36 (41%) participants at three-months, and 19 (24%) at six-months post ICU discharge (Table 2). Similar patterns were observed for the TMT_Parts A and B, with the frequency of impairment reducing over time but persisting in more than a quarter of participants. Using the MMSE, there was a slight increase in the number of participants assessed as cognitively impaired from three to six months (*n*=2 vs. n=4).

When considering only the 76 participants who were tested at both time points, 27 (36%) participants had cognitive impairment on the RBANS at three-months, and 17 (22%) participants remained impaired when tested at six- months post ICU discharge. Using the TMT_Part A, 20 (30%) participants had impaired information processing speed at three-months, with 16 (24%) participants remaining impaired when tested at six- months. Similarly, for the TMT_Part B, 31 (48%) participants had impaired executive functioning at three-months, reducing to 25 (38%) participants with impaired executive functioning at six- months. However, the number of participants assessed as impaired on the MMSE rose slightly from 2 (2.7%)

participants at three months testing to 4 participants (5.9%) when tested at six months post ICU discharge (Table 2).

Associations between Cognition, and Delirium and Duration of Mechanical Ventilation

The presence of delirium in the ICU was significantly associated with TMT_Part A (processing speed) and B (executive functioning) scores at six-months in multivariate modelling (Table 3). However, delirium was not associated with variation in the TMT_Part A and B scores at three-months, or the RBANS total scores at either time points. Specifically, participants who experienced delirium in the ICU had a mean TMT_Part A score that was 7.86 seconds longer than those with no delirium (p=0.03), when holding age, education and Apache III levels fixed (Figure 2a). Further, participants who experienced delirium in the ICU had a mean TMT_Part_B score that was 24.0 seconds higher than those with no delirium (p=0.04), when holding age and education fixed (Figure 2b).

Although not statistically significant, duration of mechanical ventilation demonstrated a trend of positive association with TMT_Part B scores (executive functioning) at six-months (Table 3). Delirium was not associated with the variation in TMT_Part B at three-months, nor for the TMT_Part A scores (processing speed) and RBANS total scores at either assessment time points. Specifically, the mean TMT_Part B score was 1.69 seconds longer (p=0.05) for those who received mechanical ventilation one day longer than the average duration (or, for example, 9.1 seconds longer for those who received mechanical ventilation 5 days longer than the average duration), when holding age and education level fixed (Figure 2c).

Discussion

The incidence of delirium in Australian general ICU patients and its association with patients' cognition at post ICU discharge was assessed in this prospective cohort study. To our knowledge it is the first Australian study that has examined the relationship between delirium and long-term cognitive impairment. This study included a mixed cohort of medical, surgical and trauma ICU patients requiring mechanical ventilation thus broadening previous research beyond medical patients. [5] We used well-known, psychometrically robust assessment tools for both delirium and cognitive impairment, and a design similar to a previously conducted study[3] to enable international comparison.

The incidence of delirium in this study was low, with one in five (19%) patients experiencing delirium of up to two days during their ICU stay. Whilst this is consistent with other Australian studies,[6, 7, 11, 17] it is lower than that reported internationally, with Girard et al[3] finding 84% of patients experience delirium for up to five days (50% ≥2 days; 25% ≥5 days) and others studies with 74% of ICU patients with respiratory failure or shock evaluated as delirious.[4] Differences in the clinical characteristics of the patient populations including the severity of illness and diagnoses between the current study and others may explain some of the disparity. Our participants had lower APACHE II scores indicating a lesser severity of illness that other studies[3, 4] with APACHE II scores of 18 in our study versus 29 and 25 respectively. In addition, our study had a mixed cohort whereas Girard et al's study[3] participants were solely medical patients. Our lower rates of delirium may also reflect the heterogeneity in international ICU nursing practices, with differences including a higher registered nurse/patient ratio in Australia than the USA (1:1 vs 1:2 or 1:3 respectively). Although levels of registered nursing staff have been demonstrated to

influence adverse events such as hospital acquired pneumonia and unplanned extubation, links to delirium have not been investigated.[37]

Consistent with previous research, the current study found that, whilst improvements in cognitive functioning occurred in the six-months post ICU discharge, many patients remained cognitively compromised.[3, 4, 21, 22, 38] Notably, the rates of cognitive impairment found in the current study were much lower than that reported by others[3, 4] and again, this disparity may be attributable to the older and sicker profile of their patients.

When looking at the detection of cognitive impairment using the RBANS, the TMT_Parts A and B, and the MMSE, there were differences. When using the MMSE, only a minority were classified as impaired at three and six-months (1%; 3% respectively), which is in marked contrast to the rates reported when using the RBANS (41%; 24% respectively), and the TMT_Part A (32%; 26% respectively) and Part B (49%; 38% respectively). This distinction is an important finding as TMT_Part A and B have been found to be both sensitive and clinically significant in predicting functional independence in other cohorts.[39, 40] Further, no one in the current study was assessed as severely impaired on the MMSE, with the lowest score at both assessment periods being 23, which is indicative of mild impairment. MMSE is a short, screening test that uses a small number of items in a restricted number of cognitive areas. The items used are simple in nature and are sensitive in detecting more severe or obvious cognitive problems. By contrast, RBANS and TMT_Part A and B have more items that range in difficulty levels. Consequently, for cognitive deficits caused by delirium, RBANS and TMT_Part A and B may be better in detecting more subtle deficits. We advocate the use of RBANS and TMT in future studies due to their greater sensitivity

in detecting cognitive impairment (globally and regarding information processing speed and executive functioning) in comparison to MMSE in this cohort.

Whilst this study did not find an association between ICU delirium and long-term global cognitive impairment using the RBANS, it did find that ICU delirium was positively associated with impaired information processing speed and executive functioning at six-months post-discharge. In addition, whilst just outside of statistical significance, there was a positive association between executive functioning speed and mechanical ventilation.

Implications for practice and future research

These findings add to the body of evidence [3,4, 19-22, 38, 41] of a relationship between ICU delirium and long-term cognitive impairment and support the need for interdisciplinary approaches to both screen for, and reduce delirium in ICU patients. Clinical care strategies that focus on modifiable factors including sensory impairment, immobilisation, metabolic derangement, pain and sedative management, emotional distress and sustained sleep deprivation are recommended.[42,43]

ICU stay is clearly associated with psychological disorders,[44] which in turn may have an effect on cognitive functions and visa versa. The potential complex relationship between delirium, cognitive impairment and psychological states such as anxiety, depression and post-traumatic stress syndrome is worthy of further study. Future well-resourced multi-centre studies assessing the potential predictive value of ICU delirium in terms of patient outcomes are needed to fully understand the impact on patients' long-term cognition up-to and beyond the period of six-month and whether interventions to reduce the incidence and duration of delirium also impact on long term cognition. This study achieved a high retention of participants. Of those who were tested at the three-month period, 86% were retained at six-months and,

therefore, the feasibility of longitudinal cognitive testing of ICU patients is supported. In addition, understanding patient and family experiences of the impact of reduced cognition post ICU discharge is another area for investigation that would benefit from a qualitative research approach. Preliminary feasibility research supports further studies which include family members in the delivery of cognitive interventions within ICU to reduce delirium.[45] Research into cognitive focused interventions across the spectrum of ICU, wards and post-hospital discharge are recommended.

Limitations

The low incidence of delirium forced us to dichotomously classify ICU delirium, which may have reduced the study's statistical power and prevented a stronger association between delirium and cognitive compromise from being found.[19] Further, a CAM-ICU assessment was missing for 16% (*n*=24/148) of patients, which reduced the sample size and may also have contributed to reduced statistical power to detect differences. However, our sample size is comparable to that included in the Girard et al's study at three- (n=76) and 12-month (n=52) assessment time-points. [3] Patients' pre-existing cognitive impairment was not assessed (as is the case with any non-elective ICU populations), which limits understanding of any effect that this may have had on the observed impairments post-discharge. Data on any re-hospitalization during the six-month prior to assessment was not collected and may have influenced participants' health status. Finally, this was a single-site study and therefore limits the generalizability of findings beyond this site.

Conclusions

The relationship of delirium and long term cognitive impairment in general ICU patients was examined in this Australian study. ICU delirium was positively

associated with impaired information processing speed and executive functioning at six-months post-discharge for this cohort. Testing for cognitive impairment with RBANS and TMT should be considered due to its greater sensitivity in comparison to the MMSE. In light of the growing number of patients surviving ICU each year, strategies to reduce and prevent delirium and potentially improve long-term cognitive function are imperative.

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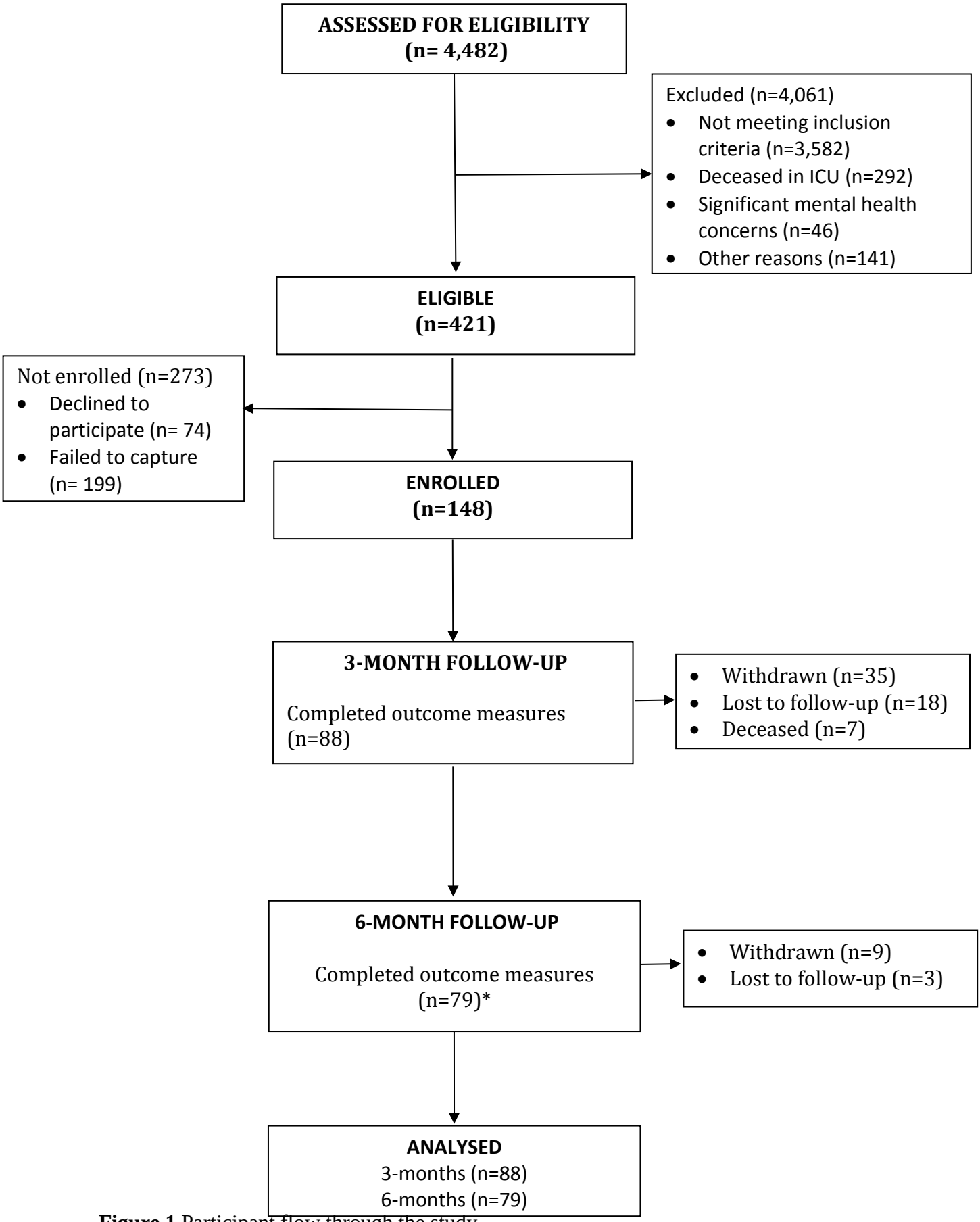


Figure 1 Participant flow through the study

*Three participants were unable to complete three month testing (deemed lost to follow-up), but were able to complete the six month testing; n=76 completed testing at both three and six months.

Table 1 Participant and clinical characteristics

Characteristic	Cohort, *n*=91
Age (years)[a]	57 (43-65)
Sex (male)	63 (69%)
Education:	
12 years of education or less	27 (36%)
Certificate/diploma	27 (36%)
University degree or higher	21 (28%)
Admission diagnosis:	
Cardiac surgical	19 (21%)
Cardiac non-surgical	20 (22%)
Surgical	16 (18%)
Medical	18 (20%)
Trauma	15 (16%)
Other	3 (3%)
APACHE II score[b,c]	18.1 (5.97)
APACHE III score[b,d]	56.5 (22.4)
Length of stay in ICU (days)[a]	4.3 (2.1-7.9)
Length of stay in hospital (days)[a]	17.7 (12.1-27.1)
Propofol dose (mg)[a]	3,820 (1,500-9,190)
Benzodiazepine dose (mg lorazepam eq.)[a]	15 (0-90)
Opioid dose (mg fentanyl eq.)[a]	3.7 (1.5-8.8)
Days of mechanical ventilation (days)[a]	2.2 (1.0-5.1)
Delirium in ICU (days):	
zero	62 (82%)

one	9 (12%)
two	5 (7%)

n (%) shown unless otherwise indicated. Continuous variables reported as mean and standard deviation (SD) if normally distributed, or as median and $25^{th}/75^{th}$ percentiles otherwise.

Frequencies and proportions may not add up to *n*=91 and 100% due to missing data or rounding

APACHE Acute Physiology and Chronic Health Evaluation, ICU Intensive Care Unit, mg Milligram, eq. Equivalent

[a]median ($25^{th}/75^{th}$)

[b]mean (SD)

[c]APACHE II scores range 0 – 71 with higher scores indicating more severe disease

[d]APACHE III scores range 0-299 with higher scores indicating more severe disease

Table 2 Cognitive outcomes at three and six months

Measure	3 months *n*=88	6 months *n*=79
RBANS:		
list learning[b]	25.1 (4.9)	26.6 (4.7)
story memory[a]	14.0 (11.0-16.0)	17.0 (13.0-19.0)
figure drawing[a]	20.0 (19.0-20.0)	20.0 (19.0-20.0)
line orientation[a]	19.0 (17.0-20.0)	19.0 (17.0-20.0)
picture naming[a]	10.0 (10.0-10.0)	10.0 (10.0-10.0)
semantic fluency[b]	19.8 (4.7)	20.3 (4.2)
digit span[a]	10.0 (8.0-12.0)	10.0 (8.0-12.0)
coding[b]	39.5 (11.3)	41.3 (10.1)
list recall[b]	4.56 (2.6)	5.49 (2.5)
list recognition[a]	19.0 (18.0-20.0)	20.0 (19.0-20.0)
story recall[a]	8.0 (4.5-10.0)	9.0 (7.0-11.0)
figure recall[a]	15.0 (12.0-18.0)	17.0 (14.0-19.0)
Immediate Memory Scale Score[b]	84.8 (16.4)	93.2 (15.9)
Visuospatial/Constructional Scale Score[a]	112 (102-126)	121 (102-126)
Language Scale Score[a]	98.5 (90.0-104)	99.0 (92.0-105)
Attention Scale Score[b]	88.7 (15.7)	94.1 (13.7)
Delayed Memory Scale Score[b]	93.7 (16.4)	100 (14.2)
Total Scale Score[b]	93.3 (13.5)	99.8 (12.7)
RBANS impairment[c,d]	36/88(40.9%)	19/79 (24.1%)
TMT_Part A impairment[c,e]	24/75 (32.0%)	18/68 (26.5%)
TMT_Part B impairment[c,f]	36/73 (49.3%)	26/68 (38.2%)
MMSE impairment[c,g]	2/75 (2.7%)	4/68 (5.9%)

RBANS impairment – participants tested at each time point		
No impairment	52 (59.1%)	60 (75.9%)
Mild/moderate impairment	14 (15.9%)	11 (13.9%)
Severe impairment	11 (12.5%)	1 (1.3%)
One of the five RBANS domains 1.5 SDs below the mean	1 (12.5%)	7 (8.9%)
RBANS impairment – participants tested at both time point (*n*=76)		
No impairment	49 (64.5%)	59 (77.6%)
Mild/moderate impairment	10 (13.2%)	10 (13.2%)
Severe impairment	10 (13.2%)	1 (1.3%)
One of the five RBANS domains 1.5 SDs below the mean	7 (9.2%)	6 (7.9%)

Continuous variables reported as mean and standard deviation (SD) if normally distributed, or as median and $25^{th}/75^{th}$ percentiles otherwise

RBANS Repeatable Battery for the Assessment of Neuropsychological Status, MMSE Mini Mental State Examination, TMT= Trail Making Test, SD Standard Deviation

[a]median ($25^{th}/75^{th}$)

[b]mean (SD)

[c]*n* (%)

[d]includes mild to moderate, severe, and one domain score 1.5 standard deviations below the mean

[e]completion time 40 seconds or longer

[f]completion time 92 seconds or longer

[g]score of 26 or below

Table 3 Associations of ICU exposures (positive assessment of delirium; number of days of mechanical ventilation), with long-term cognitive outcomes (at three and six months)

	Multivariable regression results		
Predictor	**Point estimate**	**95% CI**	***p* value**
RBANS (total score)			
Delirium (yes/no)			
Association with 3 month outcome[a]	1.88	-6.14 to 9.90	0.641
Association with 6 month outcome[a]	-2.23	-10.0 to 5.57	0.569
Ventilator days			
Association with 3 month outcome[b]	-0.36	-1.12 to 0.41	0.353
Association with 6 month outcome[c]	0.27	-0.71 to 1.24	0.586
TMT_Part A (seconds)			
Delirium (yes/no)			
Association with 3 month outcome[d]	0.86	-3.32 to 6.44	0.713
Association with 6 month outcome[a]	7.86	0.68 to 17.9	0.030
Ventilator days			
Association with 3 month outcome[d]	0.02	-0.38 to 0.43	0.918
Association with 6 month outcome[a]	0.27	-0.28 to 0.83	0.331
TMT_Part B (seconds)			
Delirium (yes/no)			
Association with 3 month outcome[a]	17.9	-8.02 to 58.7	0.203
Association with 6 month outcome[a]	24.0	0.92 to 59.5	0.040
Ventilator days			
Association with 3 month outcome[a]	1.64	3.70 to -0.35	0.106

Association with 6 month outcome[a]	1.69	0.00 to 3.45	0.050

The point estimate indicates the change in scores on the respective cognitive tests, back-transformed where necessary

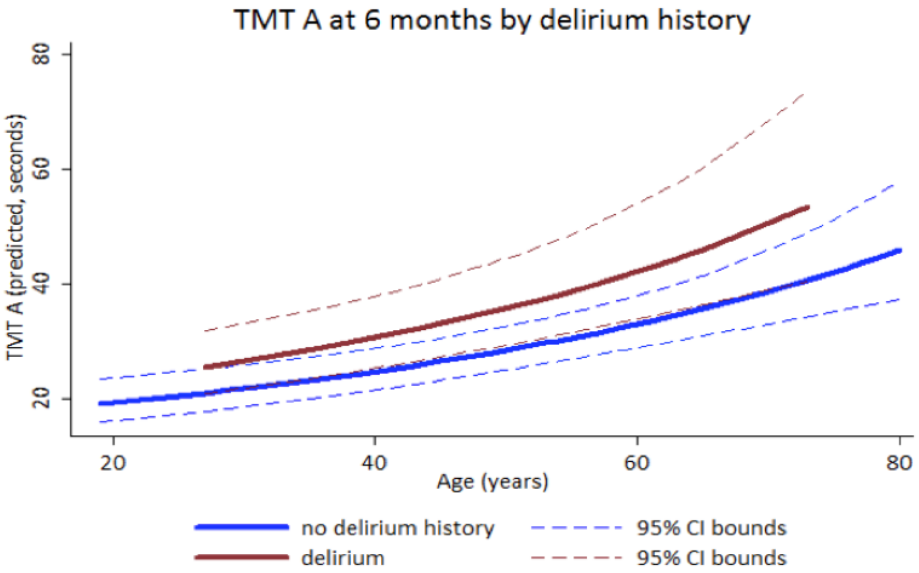
[a]adjusted for age and education

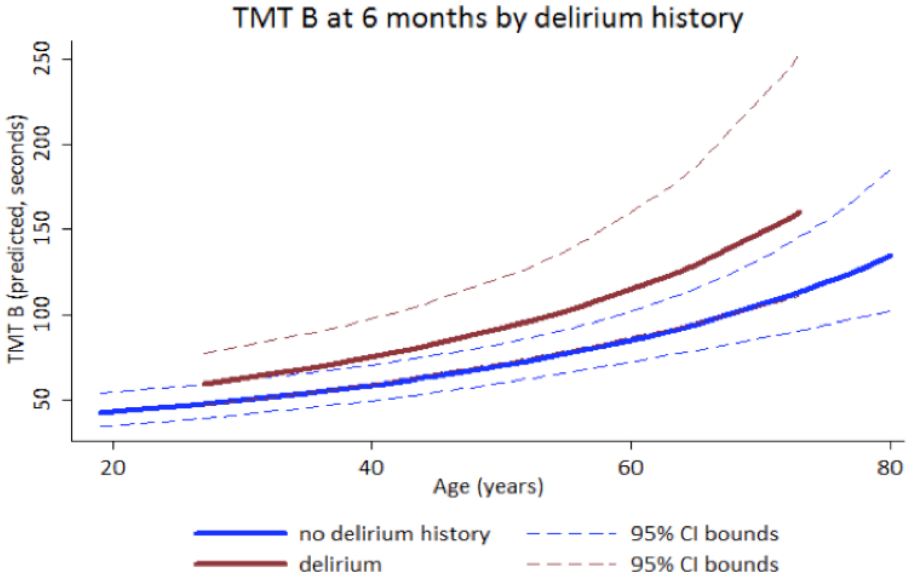
[b]adjusted for age, education, and sex

[c]adjusted for age, education, sex and benzodiazepine

[d]adjusted for age, education and APACHE III

ICU Intensive Care Unit, CI Confidence Interval, RBANS Total score of the Repeatable Battery for the Assessment of Neuropsychological Status, TMT Trail Making Test (seconds)


TMT A at 6 months by delirium history
TMT A (predicted, seconds)
20
40
60
80
20
40
60
80
Age (years)
no delirium history
95% CI bounds
delirium
95% CI bounds


TMT B at 6 months by delirium history
TMT B (predicted, seconds)
50
100
150
200
250
20
40
60
80
Age (years)
no delirium history
95% CI bounds
delirium
95% CI bounds

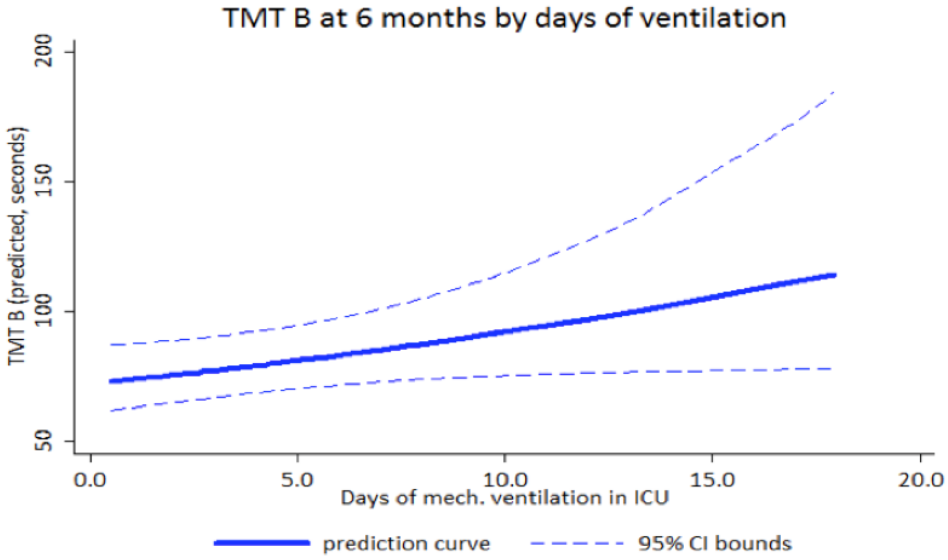

TMT B at 6 months by days of ventilation
TMT B (predicted, seconds)
50
100
150
200
0.0
5.0
10.0
15.0
20.0
Days of mech. ventilation in ICU
prediction curve
95% CI bounds

Figure 2 Relationship between delirium, cognition and duration of mechanical ventilation

Figure 2a Relationship between positive assessment of delirium in the ICU and mean TMT_Part A scores at six months

p=0.03, TMT_Trail Making Test, ICU Intensive Care Unit, CI Confidence Intervals.

Figure 2b Relationship between positive assessment of delirium in the ICU and mean TMT_Part B scores at six months

p=0.04, TMT_Trail Making Test, ICU Intensive Care Unit, CI Confidence Intervals.

Figure 2c Relationship between duration of mechanical ventilation in the ICU and mean TMT_Part B scores at six months

p=0.05, TMT_Trail Making Test, mech. mechanical, ICU Intensive Care Unit, CI Confidence Intervals