**Appendix to the AID-ICU cohort study statistical analysis plan for cognitive follow-up 6 month after ICU discharge**

**Introduction**

ICU survivors are at risk of cognitive impairment up to at least 1 year after the ICU stay to a level that equals that of patients with moderate traumatic brain injury or mild Alzheimer’s disease1. Several nonmodifiable and modifiable risk factors for cognitive impairment after critical illness have been suggested but knowledge remains incomplete2. Prolonged delirium in ICU have been identified as the main modifiable risk factor for cognitive impairment but this association is not consistent across studies3. Hypoxia, duration and mechanical ventilation use of sedatives, opiates end other psychotropics drugs, dysglycemia, blood pressure and blood transfusion has been suggested as potential modifiable risk factors also in the ICU2.

The STROBE statement will be used to report the results of this study4.

The Danish AID-ICU cohort patients were included in a sub-study of cognitive functions at 6-month assessed with Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).

**Research question**

Is cognitive impairment frequent and is time in delirium, length of mechanical ventilation and ICU stay risk factors for cognitive impairment in adult ICU patients 6 month after discharge?

**Hypothesis:** We hypothesise that cognitive impairment is frequent 6 months after ICU stay and that prolonged delirium, ICU length of stay and mechanical ventilation are risk factors for impaired cognitive function.

**AIM:** To describe the incidence of and the risk factors for impaired cognitive function in adult ICU survivors.

This is a descriptive and hypothesis generating study embedded in a large inception cohort study and sample size calculation was not performed5.

**Definitions of variables**

**Cognitive function**

Cognitive function is the mental action or process of acquired knowledge and understanding through thought, experience and the senses. With RBANS we can assess the global function and five executive functions (immediate and delayed memory, attention, visuospatial construction and language6. The population age-adjusted mean (±SD) for the RBANS global cognition score and for the individual domains is 100 ±15 SD (on a scale ranging from 40 to 160, higher score indicating better performance).

**Delirium**

We considered a patient being in delirium if they at some point during ICU stay had a positive delirium screening. Duration of delirium is defined as number of days with at least one positive test for delirium. If delirium days are not consecutive, the days between delirium days will be subtracted from total days in delirium.

**Mechanical ventilation**

We considered a patient mechanical ventilated (MV) if they at some point during ICU stay were MV. Days of MV is defined as number of days where MV was used. If MV days were not consecutive, the days between MV days will be subtracted from total days of MV.

**ICU length of stay**

Number of days admitted to ICU from time of admission to time of discharge from ICU.

**Severity of illness**

We will assess overall disease severity by modified Simplified Acute Physiology Score (SAPS) II (excluding PaO2/FiO2 ratio, urinary output and s-bilirubin level) at ICU admission.

**ICU survivors**

All patients that were alive 90 days after the ICU admission during which they were included in the study.

**Primary outcome**

The Global cognitive function (RBANS) score (mean ± SD) assessed in ICU survivors 6 month after ICU stay.

**Secondary outcome**

* Individual domains (mean ± SD/median IQR) for each patient with a complete RBANS
* Number of patients with a score lower than 65 (equal to Alzheimer’s disease)7, number of patients with a score between 65 to 71 (equal to moderate to severe brain injury)8, and number pf patients with a score between 71 to 92,4 (equal to mild cognitive impairment)9.
* The association between the cognitive impairment (point estimates (95% CI) and the co-variates: days in delirium, days on mechanical ventilation, days in ICU for ICU survivors, alone and together in a multivariate model including SAPS II.

**Data presentation**

Numeric data will be given as medians with inter-quartile ranges (IQR) or ranges where relevant and frequencies as numbers with percentages and 95% confidence intervals (CI) where relevant.

**Descriptive statistics**

We will present the number of patient who were invited and who were an RBANS (Repeatable Battery for the Assessment of Neuro-psychological Status) assessed.

We will compare differences in baseline characteristics between patients with and without an RBANS assessment using Wilcoxon’s or Chi-square tests.

We will report time from ICU admission until RBANS score as median number of days (IQR).

We will report the number of delirium days as median number of days (IQR), the number of patient with delirium also mechanically ventilated and hospital length of stay as median number of days (IQR).

### Follow-up and outcome analyses

To assess if delirium duration, mechanical ventilation or ICU length of stay may predict cognitive impairment 6 month after ICU stay, we will do a linear regression analysis adjusting for the above chosen covariates defined as modified SAPS II (continuous), delirium duration (number of days), mechanical ventilation (number of days) and ICU length of stay (number of days).

We will do all statistical tests 2-tailed and consider p<.05 statistically significant.

**Missing data**

Missing data will be presented in an appendix of the main manuscript. We expect only few individuals with missing data on covariates but as presented there will be a fair number of patients with missing RBANS score. We will, therefore, employ complete case analyses.3 All details will be presented in a supplement to the primary publication.

Referenses

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