Neurocognitive and Quality-of-life Outcomes Following Intensive Care Admission: A Prospective 6-month Follow-up Study

Viswesvaran Balasubramanian, Jagdish C Suri, Pranav Ish, Nitesh Gupta, Debasis Behera, Pankaj Gupta, Shibdas Chakrabarti

ABSTRACT

Background: Post-intensive care survivors have decreased quality-of-life scores and prolonged cognitive dysfunction due to baseline factors and events related to intensive care unit admission, which remain largely unrecognized.

Materials and methods: A prospective observational cohort study to assess the quality of life and occurrence of cognitive dysfunction, 3 and 6 months following discharge from the intensive care unit, was carried out. We enrolled 136 adults presenting to the intensive care unit with no prior cognitive dysfunction or depression and followed up and assessed them with repeatable battery for the assessment of neuropsychological status (RBANS) and quality of life with short Form-36 (SF-36) health survey.

Results: The incidence and prevalence of cognitive dysfunction was 100% at 3 and 6 months, respectively, as assessed by RBANS with a global cognition scores at 3 and 6 months of 71 (IQR 68.5–73) and 74 (IQR 72–86), respectively. Higher Charlson's comorbidity score, increased severity of illness, longer duration of mechanical ventilation, pain, delirium, coma, and hospital stay were associated with statistically significant lower scores at 3 months. The median SF-36 mental component score (MCS) and physical component score (PCS) at 3 months were 38.4 and 32.5 and at 6 months were 38.2 and 32.6, respectively. Poor score was associated significantly with advancing age, poor functional parameters at baseline as evidenced by clinical frailty, poor baseline Katz ADL scores, increased severity of illness, longer duration of mechanical ventilation, occurrence and duration of delirium, coma, pain, and usage of sedatives with or without analgesics.

Conclusion and clinical significance: Patients discharged from the intensive care unit are at high risk for persistent cognitive impairment and poor quality of life score. Poor baseline patient characteristics and events occurring in ICU are associated with worse cognition and quality of life scores. There is an urgent need to prevent, diagnose, and manage these patients by optimizing intensive care practices.

Keywords: Neurocognitive impairment, Post-intensive care, Quality of life.

INTRODUCTION

Advances in medical technology and therapeutics have reduced mortality rates and extended lives of critically ill patients. Millions of patients who survive critical illnesses each year are burdened with acquired impairment in cognition, mental health, and/or functional disability, which remains largely underrecognized. While some patients do return back to their precritical illness level of health and functional status functioning, many patients experience impairments in mental health, cognition, physical health, and quality of life. Critical illness survivors can have a persistent and often underestimated cognitive dysfunction, which is characterized by fresh deficits or worsening of preexisting deficits in cognition and/or executive function. This long-term cognitive impairment postrcritical illness is an emerging public health issue, given the enormous number of acutely ill patients who are under treatment in intensive care units (ICUs). Among elderly, cognitive decline is associated with prolonged hospitalization also.

Understanding the epidemiology and risk factors is essential as the subsequent interventions should be initiated at the earliest to prevent the cognitive impairment, improve mental, physical health and quality of life, and reduce the long-term morbidity and mortality rates of ICU survivors. We conducted a prospective observational cohort study to evaluate the quality of life and occurrence of cognitive dysfunction, 3 and 6 months following discharge from ICU.

MATERIALS AND METHODS

The study was conducted in the ICU of a tertiary care center over a time period of 18 months. All adult patients above 18 years of age presenting to ICU with respiratory failure, septic shock or cardiogenic shock, and consent for follow-up were included in the study.
Neurocognitive and Quality-of-life Outcomes Following Intensive Care

study. We excluded individuals with a past history of ICU exposure in recent times (i.e., mechanical ventilation in the preceding 2 months before the current admission; >5 ICU days stay in the month before the present ICU admission); patients who could not be reliably assessed for delirium owing to deafness and blindness; and patients at risk for preexisting cognitive deficits due to neurodegenerative disease, severe dementia, suspected anoxic brain injury, or out-of-hospital cardiac arrest. We also excluded patients with score >3.3 in Short Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) during screening for preexisting cognitive impairment in patients >50 years of age and for patients <50 years but with known memory disorders. An informed consent was obtained from patients or next to kin. If consent was initially obtained from next to kin, then informed consent was obtained from the patient when he/she was competent. The questionnaires were administered by the intensivist in the patient’s or next to kin's own language of understanding as and when needed. The study was approved by the institutional ethics committee. All the questionnaires were administered by the intensivist with translation into Hindi as and when needed.

We obtained data on baseline demographics, history of depression, preexisting cognitive impairment, and other mental health illnesses as told by patient or next to kin (including psychiatric conditions diagnosed previously by a healthcare professional), education, activities of daily living (ADL), and instrumental ADL (IADL) at the time of enrolment with the Katz ADL Scale and Pfeffer functional activities questionnaire (PFAQ) questionnaires (though a healthcare proxy), clinical frailty score (CFS), illness severity according to the acute physiology and chronic health evaluation (APACHE) II score, sequential organ failure assessment (SOFA) score, comorbidities according to the Charlson comorbidity index (CCI), and admission diagnosis. Up to the entire duration of stay in hospital, we evaluated the patients twice a day in the ICU and once a day in the wards for the level of consciousness using the Richmond agitation-sedation scale (RASS) and for delirium with the confusion assessment method for the ICU (CAM-ICU). Patients were considered to be delirious if they were responding to verbal stimuli (RASS score value –3 or more) and CAM-ICU positive. They were considered comatose if they were not responding to verbal stimuli (RASS score value of -4 or -5). For patients in ICU, SOFA score was calculated every day and the use of sedatives and analgesics was documented from the medication records for entire duration of hospital stay.

At 3 and 6 months after hospital discharge (with a leeway of 15 days allowed on both sides of the target date), patients were assessed for cognitive dysfunction with the RBANS Update questionnaire and quality of life with the Short Form-36 (SF-36) Health Survey—Mental Component Score (MCS) and Physical Component Score (PCS) questionnaire.

Statistical Analysis
All reported confidence intervals were two-sided with a p value of less than 0.05 considered and recorded significant. Continuous variables in the study were expressed as median and interquartile range, with correlation between qualitative data was performed using the Pearson Chi-square test and Fisher’s exact test. Correlation between qualitative and quantitative data was performed using the Kruskal–Wallis test and Mann–Whitney test. Correlation between two quantitative variables was performed using the Spearman’s rho test. The analysis was performed using the SPSS (Statistical Package for the Social Sciences) software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM).

Results
Over a span of 18 months, 136 patients were enrolled of which 18 (13.2%) patients died prior and 14 patients (10.3%) did not return for follow-up at 3 months. Of the 104 patients followed up after 3 months, 19 (18.3%) patients died and 10 (9.61%) patients did not return to follow-up and a total of 75 patients had complete data at the end of 6 months. The 136 patients enrolled in the study had a median age of 56 years (IQR 49.2–65.7) at baseline. None of the patients having preexisting or past cognitive impairment as assessed by short IQCODE (score of 3.6 or greater) or by medical history of depression in the past as told by patient’s attendee was enrolled. Baseline characteristics of cohort at baseline, 3-month, and 6-month follow-up are given in Table 1. Delirium was observed in 70 (51.5%) of 136 patients during the period of hospital stay with a median duration of 2 days. Data regarding the cognitive and QOL outcomes at 3 and 6 months’ follow-up are given in Table 2.

Median RBANS global cognition scores recorded at 3 and 6 months were 71 (IQR 68.5–73) and 74 (IQR 72–86), respectively. The median scores for individual domains of cognitive were low in comparison to age-adjusted population mean (100). Thus, the incidence and prevalence of cognitive dysfunction was 100% at 3 and 6 months’, respectively, as assessed by RBANS update. Median scores were lower in patients with age >65 years at 3 and 6 months (Fig. 1). Higher Charlson’s comorbidity score, increased severity of illness as evidenced by higher APACHE and SOFA scores, longer duration of mechanical ventilation, pain, delirium, coma, and hospital stay were associated with statistically significant lower RBANS global cognition scores at 3 months. All the above parameters except for longer duration of mechanical ventilation, baseline APACHE and SOFA scores were associated with poorer cognitive scores at 6 months (Table 3).

The median SF-36 mental component score (MCS) and physical component score (PCS) at 3 months were 38.4 and 32.5 and at 6 months were 38.2 and 32.6, respectively. Poor SF-36 Mental component score at 3 and 6 months was associated significantly with advancing age, poor functional parameters at baseline as evidenced by clinical frailty, poor baseline Katz ADL scores, increased severity of illness as evidenced by higher APACHE and SOFA scores, longer duration of mechanical ventilation, occurrence and duration of delirium, coma, pain, and usage of sedatives with or without analgesics. In addition, poor SF-36 MCS at 6 months was also found to be associated with poor baseline PFAQ scores.

The SF-36 physical component score at 3 and 6 months was found to be associated with advanced age, clinical frailty, baseline poor Katz score and PFAQ, and higher Charlson comorbidity index. In addition, poor SF-36 (PCS) at 6 months was also found to be associated with longer duration of hospital stay (Table 3).

Discussion
To the best of our review and knowledge, this study is one of the few studies undertaken in Indian population to assess the risk factors associated with cognitive dysfunction and poor quality of life scores following discharge from the ICU. Though incidence, risk factors, prevalence, and outcome of delirium were studied in Indian population, the influence of such events in mental...
health on a long-term basis of post-ICU survivors is unknown. The BRAIN-ICU cohort study analyzed the depression, long-term cognitive impairment, posttraumatic stress disorder, and functional disability in patients of critical illness discharged from ICU.20,21 However, the study was conducted in only U.S. population and hence the generalizability of the data to people of different racial and demographic backgrounds remains questionable. Hence, it was imperative to assess the long-term mental and physical health parameters in Indian population as we believe that early identification and intervention may help in improving the long-term outcomes of post-ICU survivors.

In the current study, cognition was affected in all patients of the follow-up cohort across all age groups. Since none of the patients with prior cognitive dysfunctions were included in this study, these

Table 1: The baseline characteristics of the patients in hospital and in the cohorts of follow-up

| Characteristic                              | In-hospital cohort (n = 136) | Follow-up cohort at 3 months (n = 104) | Follow-up cohort at 6 months (n = 75) |
|--------------------------------------------|------------------------------|----------------------------------------|---------------------------------------|
| Age—median (IQR)                           | 56 years (49.2–65.7)         | 55 years (49–64.75)                    | 54 years (46–59)                      |
| Male—number (%)                            | 90 (66.2%)                   | 74 (71.2%)                             | 53 (70.7%)                            |
| CCI—median (IQR)                           | 3 (1–5)                      | 3 (1–5)                                | 2 (1–4)                               |
| APACHE—median (IQR)                        | 25.5 (22–28)                 | 24 (20–26)                             | 22 (19–24)                            |
| SOFA—median (IQR)                          | 12 (10–14)                   | 11 (10–13)                             | 11 (9–12)                             |
| Diagnosis—no (%)                           |                              |                                        |                                       |
| Sepsis                                     | 16 (12%)                     | 5 (4.8%)                               | 4 (5.3%)                              |
| ARDS                                       | 21 (15.4%)                   | 12 (11.5%)                             | 6 (8%)                                |
| AECOPD                                     | 32 (23.5%)                   | 29 (27.9%)                             | 26 (34.7%)                            |
| Asthma                                     | 7 (5.1%)                     | 5 (4.8%)                               | 5 (6.7%)                              |
| Pulmonary edema                            | 19 (14%)                     | 15 (14.5%)                             | 10 (13.5)                             |
| Pulmonary embolism                         | 4 (2.9%)                     | 3 (2.9%)                               | 2 (2.6%)                              |
| Intersitial lung disease                   | 3 (2.2%)                     | 3 (2.9%)                               | 2 (2.6%)                              |
| Post-tubercular sequelae                   | 23 (16.9%)                   | 22 (21.1%)                             | 16 (21.3%)                            |
| Obstructive sleep apnea                    | 7 (5.1%)                     | 7 (6.7%)                               | 4 (5.3%)                              |
| Cardiogenic                                | 4 (2.9%)                     | 3 (2.9%)                               | 0                                     |
| Duration of hospital stay—median (IQR)     | 12 days (8–14)               | 10 days (7.25–12)                      | 9 days (6–12)                         |
| Mechanical ventilation (n%)                | 122 (89.7%)                  | 97 (93.2%)                             | 69 (92%)                              |
| Median duration (IQR)                      | 6 days (4–8)                 | 5 days (4–8)                           | 4 days (3–7)                          |
| Delirium—no (%)                            | 70 (51.5%)                   | 44 (42.3%)                             | 27 (36%)                              |
| Median duration (IQR)                      | 2 days (0–3)                 | 0 days (0–2)                           | 0 days (0–2)                          |
| Coma—no (%)                                | 49 (36%)                     | 32 (30.8%)                             | 16 (21.3%)                            |
| Median duration (IQR)                      | 0 days (0–1)                 | 0 days (0–1)                           | 0 days (0–0)                          |
| Use of sedative or analgesic agents—no (%) |                              |                                        |                                       |
| Benzodiazepine                             | 52 (38.2%)                   | 32 (30.7%)                             | 16 (11.8%)                            |
| Morphine                                   | 12 (8.8%)                    | 5 (3.7%)                               | 4 (5.3%)                              |
| Fentanyl                                   | 51 (37.5%)                   | 32 (30.7%)                             | 16 (11.8%)                            |
| Dexmedetomidine                            | 5 (3.7%)                     | 1 (0.9%)                               | 1 (1.3%)                              |
| History of ADL disability                  |                              |                                        |                                       |
| Full function                              | 68 (50%)                     | 55 (52.9%)                             | 50 (66.7%)                            |
| Moderate impairment                        | 68 (50%)                     | 49 (47.1%)                             | 25 (33.3%)                            |
| Severe impairment                          | 0                            | 0                                      | 0                                     |
| PFAQ                                       |                              |                                        |                                       |
| Impairment                                 | 68 (50%)                     | 49 (47.1%)                             | 25 (33.3%)                            |
| No impairment                              | 68 (50%)                     | 55 (52.9%)                             | 50 (66.7%)                            |
| PFAQ—median score (IQR)                    | 10.5 (8–15)                  | 9 (8–15)                               | 9 (8–13)                              |
| Clinical frailty scale                     |                              |                                        |                                       |
| Frail                                      | 67 (49.2%)                   | 49 (47.1%)                             | 25 (33.3%)                            |
| Not frail                                  | 69                            | 55 (52.9%)                             | 50 (66.7%)                            |
| Duration of pain—median (IQR)              | 2 days (1–5)                 | 1 days (1–4)                           | 1 days (0–4)                          |

IQR, interquartile range; CCI, Charlson comorbidity index; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; ARDS, acute respiratory distress syndrome; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; no, number; ADL, activities of daily living; PFAQ, Pfeffer functional activities questionnaire
profound cognitive impairments were newly acquired. A systematic review observed the incidence of cognitive decline after critical illness to vary between 4 and 64% in adult patients evaluated and followed up to a time frame between 2 and 156 months after critical illness and attributed such highly variable incidence to varied definitions of cognitive impairment used in individual studies.
different time frame of follow-up, failure to adjust for the pre-ICU
cognitive function, and comorbidities.22

Though cognitive dysfunction was spread across all age groups
and was more severe at 3 months, 32% of 6-month follow-up had
scores worse than those occurring in Alzheimer’s disease indicating
that events occurring in ICU can lead to long-term impact in
patient’s cognition. In our study, the univariate analysis revealed
poor baseline factors such as higher Charlson’s comorbidity score,
higher APACHE and SOFA scores at presentation, longer duration
of mechanical ventilation, pain, delirium, coma, and hospital stay
to have a statistically significant association with lower RBANS global
cognition scores at 3 months. However, duration of mechanical
ventilation and APACHE and SOFA scores were not associated with
significant poorer cognitive scores at 6 months. This implies that
the cognition deficits occurring at 3 months secondary to initial
severity of illness and mechanical ventilation might be reversible
as evidenced by improved cognition scores at 6 months.

However, other parameters like poor baseline CCI scores,
duration of pain, delirium, coma, and hospital stay had long-term
impacts on cognitive functions. This was similar to the findings
from systematic review, which found inconsistent or no associations
of cognitive dysfunction with hypoglycemia, hyperglycemia,
variations in serum glucose levels, in-hospital stay acute stress
symptoms, mechanical ventilation, use of sedatives, analgesic or
vasopressors medications, enteral feeding, extracorporeal
membrane oxygenation, hypoxia, systolic blood pressure, pulse
rate, or length of ICU stay.22 However, in the present study, poor
baseline CCI, duration of pain, coma, and length of hospital stay
had impact on cognitive outcomes at 3 and 6 months.

In the present study, the presence and the duration of delirium
was associated with worsening cognition scores at 3 and 6 months
suggesting a long-term impact of delirium. Investigators in the
BRAIN-ICU cohort also observed that the duration of delirium was
associated with poor long-term global cognition and executive
function and this association was independent of sedative or
analgesic usage, age, preexisting cognitive impairment, the
comorbidities, and other organ system failures during ICU care.20
Similar observations were also observed in studies involving acute
respiratory distress syndrome (ARDS) survivors and post-critical care
survivors where delirium developing during the intensive care unit
stay had significantly more cognitive issues even after adjusting
for various covariates.23 In addition, the duration of delirium was
associated with long-term cognitive dysfunction.24

The association of delirium with poor cognitive functions is
multifactorial and complex. Various neurotoxic, neuromodulatory,
and neuroinflammatory mediators have been implicated. It
is speculated that several factors including disturbed sleep,
medications, hypoxia, and dysglycemia alter and affect the
neurotransmitter production, action, and availability, which may
have a role in psychological manifestations occurring during
critical illness.25,26 Such neuroinflammation was observed to be
precipitated by sepsis and ARDS27 due to an increased release of
cytokines and reactive oxygen species, which affect the microglia
and leads to synaptic and neuronal signal disruption.28,29 In
addition to this, it may also be associated with structural changes
like cerebral atrophy19 and reduced white-matter integrity.30 A
prospective cohort study observed that patients with delirium of
longer duration had a greater brain atrophy when evaluated with
magnetic resonance imaging carried out 3 months after discharge
besides worse cognitive function at 12 months’ follow-up.3

Similarly, the median MCS and PCS of SF-36 at 3 and 6 months
were lower in comparison to data available for Indian population
(MCS: 51.68 ± 5.5, PCS: 47.87 ± 8.17).31 Poor SF-36 at 3 and 6 months
was found to be significantly associated with advancing age, poor
baseline physical functional status, clinical frailty, and other ICU
events like higher APACHE and SOFA scores, longer duration of
mechanical ventilation, occurrence and duration of delirium, coma,
pain, and usage of sedatives with or without analgesics.

Post-intensive care syndrome (PICS) is defined as new or
worsening underlying impairment in physical, cognitive, or mental
health status arising and persisting after hospitalization for critical
illness. Understanding the epidemiology and risk factors is essential
as the subsequent interventions to prevent PICS should be initiated
at the earliest to prevent the cognitive impairment, improve mental,
physical health and quality of life of ICU survivors, and reduce their
long-term morbidity and mortality rates.

Our results highlight the importance of addressing cognitive
impairment, mental health difficulties, and functional disabilities,
which need to be monitored vigilantly. Since delirium is associated
with long-term cognitive disability and functional limitations,
interventions aimed at reducing delirium may help prevent
brain injury associated with critical illness. Prevention of delirium
with judicious use of sedative agents, following adequate pain
management protocols, routine monitoring of delirium for all
patients in ICU, and interventions like early mobilization and sleep
protocols followed in ICU have been shown to mitigate the risk
of delirium. However, it is unknown whether any preventive or
management strategies can mitigate the risk of PICS, which needs
further large-scale studies.

Strengths and Limitations
The strengths of our study include the availability of a follow-up
cohort at 3 and 6 months. The attrition rate excluding the
mortality was only 18.1%, though mortality accounted for 28% of
the missing cases at 6 months’ follow-up. An important
limitation of the current study was our inability to evaluate
the patients’ cognition before their current illness. We tried to
address this limitation by excluding patients who were found
to have severe dementia and preexisting cognitive dysfunction
with a well-validated and objective Short IQCODE assessment
tool. Another limitation of our study is that the questionnaires
used were primarily validated for English-speaking population
and hence application of such questionnaires and using their
reference values for Indian population might not be a true
representation of underlying cognitive dysfunction. The
questionnaires were administered by intensivist with translation
into Hindi in a subset of population, the validation of which is not
available. We were not able to evaluate the risk of confounding
by death or withdrawal during the study period. Finally, being
an observational study, the risk of bias due to confounders not
measured cannot be excluded.

Conclusion
In conclusion, cognitive impairment and decreased quality of
life scores following critical illness is not uncommon and may
persist. Baseline functional characteristics and various events
occurring during intensive care admission may adversely affect
the neurocognitive functions and quality of life of these post-ICU
survivors.
REFERENCES

1. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders’ conference. Crit Care Med 2012;40:502–509.

2. Ehlenbach WJ. The sobering reality of outcomes when older adults require prolonged mechanical ventilation. J Am Geriatr Soc 2014;62:183–185.

3. Hopkins RO, Weaver LK, Pope D, Orme JF, Bigler ED, Larson-LOHR V. Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. Am J Respir Crit Care Med 1999;160:50–56.

4. Jackson JC, Hart RP, Gordon SM, Shintani A, Truman B, May L, et al. Six-month neuropsychological outcome of medical intensive care unit patients. Crit Care Med 2003;31:1226–1234.

5. Ehlenbach WJ, Hough CL, Crane PK, Haneuse SJ, Carson SS, Curtis JR, et al. Association between acute care and critical illness hospitalization and cognitive function in older adults. JAMA 2003;303:763–770.

6. Adhikari NK, Fowler RA, Bhagwanjee S, Rubenfeld GD. Critical care and the global burden of critical illness in adults. Lancet 2010;376:1339–1346.

7. Chodosh J, Seeman TE, Keeler E, Sewall A, Hirsch SH, Guralnik JM, et al. Cognitive decline in high-functioning older persons is associated with an increased risk of hospitalization. J Am Geriatr Soc 2004;52:1456–1462.

8. Rockwood K, Brown M, Merry H, Sketris I, Fisk J. Vascular Cognitive Impairment Investigators of the Canadian Study of Health and Aging. Societal costs of vascular cognitive impairment in older adults. Stroke 2002;33:1605–1609.

9. Jorm AF. The Inforant Questionnaire on cognitive decline in the elderly (IQCODE): a review. Int Psychogeriatr 2004;16:275–293.

10. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. The index of Adl: a standardized measure of biological and psychosocial function. Jama 1963;185:914–919.

11. Pfeffer RI, Kuroski TT, Harrah CH Jr, Chance JM, Filos S. Measurement of functional activities in older adults in the community. J Gerontol 1982;37:323–329.

12. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173(5):489–495.

13. Ferreira FL, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373–383.

14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373–383.

15. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, Linde-LOHR V. Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. Am J Respir Crit Care Med 1999;160:50–56.

16. Jackson JC, Hart RP, Gordon SM, Shintani A, Truman B, May L, et al. Six-month neuropsychological outcome of medical intensive care unit patients. Crit Care Med 2003;31:1226–1234.

17. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA 2001;286:2703–2710.

18. Ware JE. SF-36 Physical and Mental Health Summary Scales: a user’s manual. Boston, MA: Health Assessment Lab, New England Medical Center, 1994.

19. Sharma A, Malhotra S, Grover S, Jindal SK. Incidence, prevalence, risk factor and outcome of delirium in intensive care unit: a study from India. Gen Hosp Psychiatry 2012;34:639–646.

20. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, et al; BRAIN-ICU Study Investigators. Long-term cognitive impairment after critical illness. N Engl J Med 2013;369:1306–1316.

21. Jackson JC, Pandharipande PP, Girard TD, et al. Depression, post-traumatic stress disorder, and functional disability in survivors of critical illness in the BRAIN-ICU study: a longitudinal cohort study. Lancet Respir Med 2014;2(5):369–379. doi:10.1016/S2213-2600(14)70051-7.

22. Sakusic A, O’Horo JC, Dziadzko M, Volha D, Ali R, Singh TD, et al. Potentially Modifiable Risk Factors for Long-Term Cognitive Impairment After Critical Illness: A Systematic Review. Mayo Clin Proc 2018;93:68–82.

23. Hopkins RO, Suchyta MR, Snow GL, Jephsan A, Weaver LK, Orme JF. Blood glucose dysregulation and cognitive outcome in ARDS survivors, Brain Inj 2010;24:1478–1484.

24. Van den Boogaard M, Schoonhoven L, Evers AW, van der Hoeven JG, van Achterberg T, Pickkers P. Delirium in critically ill patients: impact on long-term health-related quality of life and cognitive functioning. Crit Care Med 2012;40:112–118.

25. Jevtovic-Todorovic V, Absalom AR, Blomgren K, Brambrink A, Crosby G, Culley DJ, et al. Anaesthetic neurotoxicity and neuroplasticity: an expert group report and statement based on the BJA Salzburg Seminar. Br J Anaesth 2013;111:143–151.

26. Trzepacz PT. Is there a final common neural pathway in delirium? Focus on acetylcholine and dopamine. Semin Clin Neuropsychiatry 2000;5:132–148.

27. Dilger RN, Johnson RW. Aging, microglial cell priming, and the discordant central inflammatory response to signals from the peripheral immune system. J Leukoc Biol 2008;84:932–939.

28. Reidel B, Browne K, and Silbert B. Cerebral protection: inflammation, endothelial dysfunction, and post-operative cognitive dysfunction. Curr Opin Anesthesiol 2014;27:89–97.

29. Hovens IB, Schoemaker DP, van der Zee EA, Heineman E, Ikazaki G, van Leeuwen BL. Thinking through postoperative cognitive dysfunction: How to bridge the gap between clinical and pre-clinical perspectives. Brain Behav Immun 2012;26:1169–1179.

30. Gunther ML, Morandi A, Krauskopf E, Pandharipande P, Girard TD, Jackson JC et al. The association between brain volumes, delirium duration, and cognitive outcomes in intensive care unit survivors: the VISIONS cohort magnetic resonance imaging study. Crit Care Med 2012;40:2022–2032.

31. Agarwal R, D’Silva C. Assessment of quality of life in normal individuals using the SF-36 questionnaire. IJCCR 2017:3:43–47.