ORIGINAL ARTICLE

Neurocognitive and Quality-of-Life Outcomes Following Intensive Care Admission: A Prospective 6-Month Follow-Up Study

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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.

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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.[1] 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.[2]

Critical illness survivors can have a persistent and often underestimated cognitive dysfunction,[3–5] which is characterized by fresh deficits or worsening of preexisting deficits in cognition and/or executive function. This long-term cognitive impairment postcritical illness is an emerging public health issue, given the enormous number of acutely ill patients who are under treatment in intensive care units (ICUs).[6] Among elderly, cognitive decline is associated with prolonged hospitalization also.[7,8]

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.

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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. 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)[9] 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[10] and Pfeffer functional activities questionnaire (PFAQ) questionnaires[11] (though a healthcare proxy), clinical frailty score (CFS),[12] illness severity according to the acute physiology and chronic health evaluation (APACHE) II score, sequential organ failure assessment (SOFA) score,[13] comorbidities according to the Charlson comorbidity index (CCI),[14] 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)[15] and for delirium with the confusion assessment method for the ICU (CAM-ICU).[16] 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[17] and quality of life with the Short Form-36 (SF-36) Health Survey—Mental Component Score (MCS) and Physical Component Score (PCS) questionnaire.[18]

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[9] (score of 3·6 or greater) or by medical history of depression in the past as told by patient's attender 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,[19] the influence of such events in mental

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%)
Interstitial lung disease	3 (2.2%)	3 (2.9%)	2 (2.6%)
Post-tubercular sequalae	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

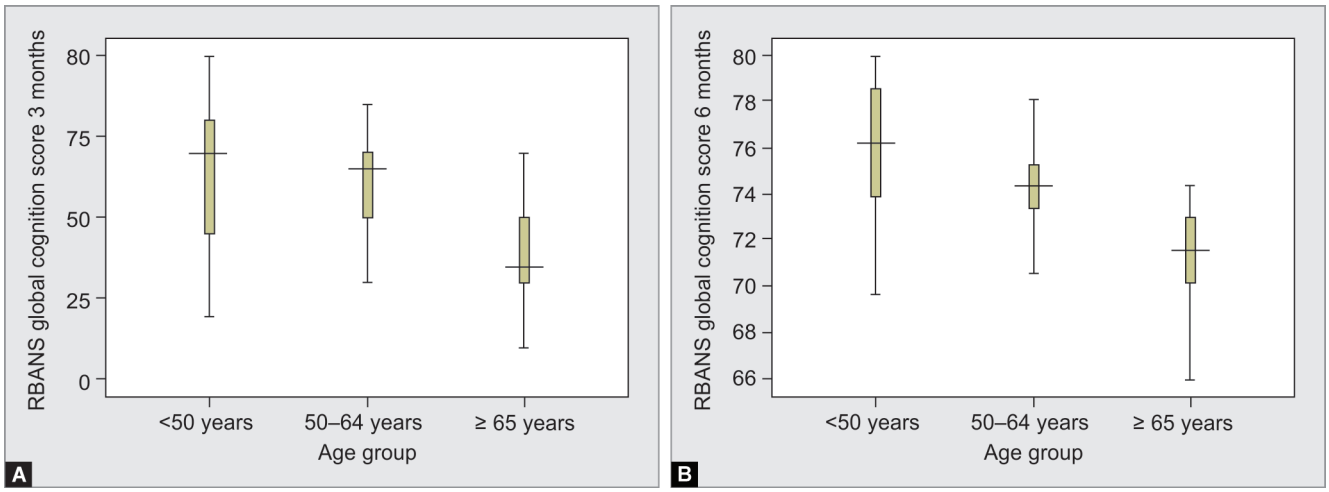
health on a long-term basis of post-ICU survivors is unknown. The BRAIN-ICU cohort study analyzed the depression, long-term cognitive impairment, posttraumatic stress disorder, and functional disability in patients of critical illness discharged from ICU.[20,21] However, the study was conducted in only 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 2: Long-term cognitive and QOL outcomes at 3 and 6 months

Outcome	*At 3 months (n = 104)*	*At 6 months (n = 75)*
Cognition		
RBANS global cognition score	71 (68.5–73)	74 (72–76)
RBANS immediate memory score	79.5 (77–81.5)	80 (78–82)
RBANS delayed memory score	82 (80–84)	84 (82–86)
RBANS attention score	80 (78–82)	84 (82–86)
Quality of life [SF–36]		
Mental component	38.4	38.2
Physical component	32.5	32.6

RBANS, repeatable battery for the assessment of neuropsychological Status; SF-36, short form survey 36. The RBANS is a brief, individually administered test measuring attention, language, visuospatial/constructional abilities, and immediate and delayed memory. It consists of 12 subtests, which yield 5 index scores and a total scale score. Index scores have a mean of 100 and standard deviation of 15. SF-36 scores range from 0 to 100. Higher scores indicate better quality of life



Figs 1A and B: Box and whisker plot showing correlation between RBANS global cognition score and age in the cohort at 3 and 6 months

Table 3: Correlation of baseline parameters with outcome parameters at 3 and 6 months

Baseline parameters	*Age adjusted RBANS global cognition score at 3 months*	*6 months*	*SF-36 (PCS) at 3 months*	*6 months*	*SF-36 (MCS) at 3 months*	*6 months*
Gender	–	–	0.469	0.549	0.343	0.343
Age	–	–	**<0.001**	**<0.001**	**0.019**	**0.019**
Duration of mechanical ventilation	**<0.001** (rho–0.468)	0.114 (rho–0.184)	0.383	0.383	**<0.001**	**<0.001**
Duration of delirium	**<0.001** (rho–0.544)	**0.006** (rho–0.312)	0.774	0.121	**<0.001**	**<0.001**
Duration of coma	**<0.001** (rho–0.425)	**0.012** (rho–0.260)	0.159	0.102	**<0.001**	**<0.001**
Sedative ± analgesia	–	–	1.000	0.771	**<0.001**	**<0.001**
Clinical frailty score	–	–	**0.018**	**<0.001**	**0.008**	**0.008**
Baseline KATZ ADL score	–	–	**<0.001**	**<0.001**	**0.027**	**0.027**
Baseline PFAQ score	–	–	**<0.001**	**<0.001**	0.109	**<0.05**
APACHE score	**<0.001** (rho–0.570)	0.092 (rho–0.196)	0.938	0.328	**<0.001**	**<0.001**
SOFA score	**<0.001** (rho–0.512)	0.092 (rho–0.196)	0.369	0.194	**<0.001**	**<0.001**
Number of hospital days	**<0.001** (rho–0.675)	**0.009** (rho–0.300)	0.142	**0.018**	**<0.001**	**<0.001**
Charlson Comorbidity Index	**<0.001** (rho–0.334)	**0.002** (rho–0.352)	**<0.001**	**<0.001**	0.249	0.249
Duration of pain	**<0.001** (rho–0.552)	**0.024** (rho–0.260)	0.986	0.053	**<0.001**	**<0.001**

RBANS, repeatable battery for the assessment of neuropsychological status; SF-36, short Form Survey 36; ADL, activities of daily living; PFAQ, Pfeffer functional activities questionnaire; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment
Bold values signify the *p*-value <0.05; It represents the statistically significant. Correlation of baseline parameters with outcome parameters

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 ARDS[27] 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 atrophy[19] 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 treatment 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.

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