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Potentially Modifiable Risk Factors for Long-Term Cognitive Impairment After Critical Illness: A Systematic Review

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Abstract

Long-term cognitive impairment is common in survivors of critical illness. Little is known about the etiology of this serious complication. We sought to summarize current scientific knowledge about potentially modifiable risk factors during intensive care unit (ICU) treatment that may play a substantial role in the development of long-term cognitive impairment. All searches were run on October 1, 2017. The search strategy included Ovid MEDLINE, Ovid Embase, Ovid CDR, Cochrane Central Register of Controlled Trials and Database of Abstracts of Reviews of Effect, Scopus, and Web of Science, and included MeSH headings and keywords related to *intensive care, critical care*, and *cognitive disorders*. Searches were restricted to adult subjects. Inclusion required follow-up cognitive evaluation at least 2 months after ICU discharge. Studies assessing patients with cardiac arrest, traumatic brain injury, and cardiac surgery history were excluded. The search strategy resulted in 3180 studies. Of these, 28 studies (.88%) met our inclusion criteria and were analyzed. Delirium and duration of delirium were associated with long-term cognitive impairment after ICU admission in 6 of 9 studies in which this factor was analyzed. Weaker and more inconsistent associations have been reported with hypoglycemia, hyperglycemia, fluctuations in serum glucose levels, and in-hospital acute stress symptoms. Instead, most of the studies did not find significant associations between long-term cognitive impairment and mechanical ventilation; use of sedatives, vasopressors, or analgesic medications; enteral feeding; hypoxia; extracorporeal membrane oxygenation; systolic blood pressure; pulse rate; or length of ICU stay. Prolonged delirium may be a risk factor for long-term cognitive impairment after critical illness, though this association has not been entirely consistent across studies. Other potentially preventable factors have not been shown to have strong or consistent associations with long-term cognitive dysfunction in survivors of critical illness.

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Long-term cognitive impairment after critical illness remains a significant public health burden. Each year, millions of patients are treated in intensive care units (ICUs) across the United States, and many of them end up being cognitively impaired.[1] The incidence of cognitive decline after critical illness has been highly variable (4%-64%) in different studies.[2-5] Cognitive impairment after ICU admission can be greatly taxing to patients and their families, and it has enormous societal cost, with a total estimate of $18 billion per year.[6,7]

To date, a number of studies have evaluated the incidence of long-term cognitive impairment after critical illness.[8] However, risk factors, particularly preventable ones, are not well understood. We sought to summarize current knowledge about potentially modifiable risk factors during ICU treatment that may influence the development of long-term cognitive impairment.

PATIENTS AND METHODS

With the assistance of an expert librarian, we developed search strategies and applied them to Ovid MEDLINE, Ovid Embase, Ovid CDR, Cochrane Central Register of Controlled Trials and Database of Abstracts of Reviews of Effects, Scopus, and Web of Science. All

searches were run on October 1, 2017. There were no restrictions on publication date; searches were restricted to adult subjects. The search strategy included MeSH headings and keywords related to intensive care, critical care, and cognitive disorders (Supplemental Table 1, available online at http://www.mayoclinicproceedings.org). Each study abstract was evaluated independently by 2 investigators. We excluded studies in languages other than English, case reports and case series with less than 10 patients, animal studies, reviews, comments, editorials, letters to the editor, studies that assessed cognitive function only within 2 months of ICU discharge, and studies focused on patients admitted to the ICU because of cardiac arrest, traumatic brain injury, or cardiac surgery history.

To compare and reconcile independent evaluations, we used Covidence, an online tool for systematic reviews.[9] This software allows searches of abstracts and full texts to be uploaded and evaluated by each investigator blinded to the other evaluator's determinations. Disagreements are flagged for resolution. We resolved such cases using third reviewer adjudication. After screening abstracts, full texts were obtained and evaluated in the same way. We then abstracted data from each study using a standardized form. Because the primary aim of our systematic review was to evaluate potentially modifiable risk factors during the ICU stay, we focused on ICU exposures such as delirium and duration of delirium, mechanical ventilation and duration of mechanical ventilation; use of sedatives, analgesic medications, or vasopressors; extracorporeal membrane oxygenation; presence of in-hospital acute stress symptoms; blood product transfusion; blood loss; hematocrit level; hypoglycemia, hyperglycemia, and fluctuations in blood glucose levels; enteral feeding; hypoxia; and length of ICU stay. We used the Downs and Black checklist[10] to assess the quality of each included study.

RESULTS

Our search strategy identified 3180 studies. Of these, 28 studies met our inclusion criteria. Details are provided in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram shown in the Figure.

ARTICLE HIGHLIGHTS

- Long-term cognitive impairment is common in survivors of critical illness. It can be greatly taxing to patients and their families, and it has enormous societal cost, with a total estimate of $18 billion per year.
- Little is known about the etiology of this serious complication. Available evidence suggests that prolonged delirium is the potentially modifiable factor most strongly associated with post–intensive care unit (ICU) cognitive impairment. Weaker and more inconsistent associations have been reported with hypoglycemia, hyperglycemia, fluctuations in serum glucose levels, and in-hospital acute stress symptoms. Instead, most of the studies did not find significant associations between long-term cognitive impairment and mechanical ventilation; use of sedatives, vasopressors, or analgesic medications; enteral feeding; hypoxia; extracorporeal membrane oxygenation; systolic blood pressure; pulse rate; or length of ICU stay.
- High-quality research on a large cohort of critically ill patients is necessary to better characterize potentially modifiable risk factors for persistent cognitive impairment after ICU hospitalization.

Of the 28 included studies, 13 evaluated patients admitted to mixed (medical and surgical) ICUs, 6 included patients from medical ICUs, 7 studied patients from surgical or trauma ICUs, and the remaining 2 studies did not report the type of ICU. Study designs were prospective observational in 23 articles, retrospective in 3, case-control in 1, and randomized controlled trial in 1. Study design and characteristics are summarized in Table 1.[11-13,15-35]

The definition of cognitive impairment varied in different studies, and there was a wide range of neuropsychological tools used to evaluate cognitive function (Table 1). Most of the studies performed both univariate and multivariate analyses adjusted for age and severity of acute illness. Outcome data for exposures are summarized in Table 2. Quality assessment is provided in Supplemental Table 2 (available online at http://www.mayoclinicproceedings.org). Overall, the studies meeting our inclusion criteria had a moderate risk of bias, primarily because of limitations in the measurement of the variables

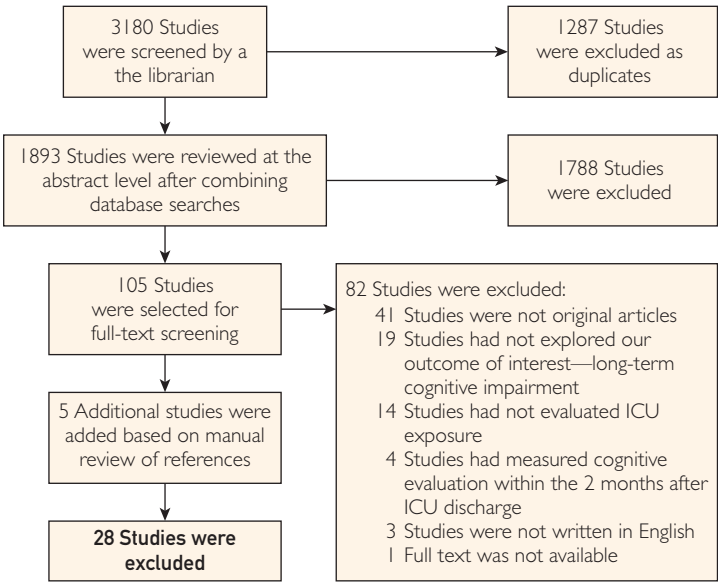

FIGURE. The search flow diagram. ICU = intensive care unit.

under investigation and the outcome as well as in the selection of the reported results.

Delirium and Duration of Delirium

Acute delirium in the ICU has been highlighted as a predictor of subsequent cognitive impairment in several studies. Pandharipande et al[29] assessed 448 ICU patients diagnosed with respiratory failure, septic shock, or cardiogenic shock with cognitive evaluations 3 months after ICU discharge. A total of 382 patients survived and were reevaluated at 12 months. A significant proportion of patients remained cognitively impaired both at 3 and 12 months after ICU discharge (66% and 58%, respectively), and longer duration of delirium was found to be independently associated with worse cognitive performance at 3 and 12 months in tests of global cognition (P=.001 and P=.04) and executive function (P=.004 and P=.007).[29]

A high rate of delirium during the ICU stay (84%) was reported in a prospective study conducted in 77 ICU patients with in-person cognitive evaluation by an expert 3 months and 12 months after ICU discharge. Duration of delirium was an independent risk factor for cognitive decline at both time points. After adjusting for preexisting cognitive impairment, age, severity of illness, education, severity of sepsis, treatment group, and total exposure to sedatives, longer duration of delirium was still associated with worse cognitive performance.[20]

A 2-center prospective cohort study found that patients with longer duration of delirium had a greater degree of brain atrophy on magnetic resonance imaging obtained 3 months after discharge as well as worse cognitive performance at 12 months follow-up.[18]

van den Boogaard et al[35] compared 171 patients who experienced delirium during the ICU stay with 745 ICU patients who had not developed delirium. Patients who experienced delirium exhibited worse performance in all cognitive dimensions. After adjusting for covariates, the difference between the groups remained significant.[35] Acute brain dysfunction during chronic critical illness, defined by the placement of tracheostomy tubes after at least 10 days of difficulty weaning from mechanical ventilation, was shown to be substantially associated with an increased risk of long-term cognitive impairment (odds ratio, 2.14; 95% CI, 1.02-4.52) in 1 prospective cohort study.[17]

Delirium in the ICU was positively associated with impaired information processing

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TABLE 1. Study Design and Characteristics

Reference, year	Study design	Setting	Cases	Controls	Cognitive evaluation/time of cognitive assessment	Definition of cognitive impairment
Ambrosino et al,[11] 2002	Prospective controlled cohort study	Respiratory ICU	63 Patients with COPD at their first episode of acute or chronic respiratory failure required mechanical ventilation	34 Stable patients with COPD receiving long-term oxygen therapy	MMS at discharge and 3 and 6 mo after ICU discharge	Maximum score is 30; score <24 indicates cognitive impairment
de Azevedo et al,[12] 2017	Prospective observational cohort study	Medical and surgical ICUs	206 ICU survivors with cognitive impairment	207 ICU survivors without cognitive impairment	FTT, RAVLT, clock-drawing test, verbal fluency test, MMSE	1.5 SD below the mean on 2 of the index scores or 2 SD below the mean on 1 of the index scores—mild cognitive impairment; 1.5 SD below the mean on ≥3 of the index scores or 2 SD below the mean on ≥2 of the index scores—severe cognitive impairment
Davydow et al,[13] 2013	Prospective cohort study	Medical and surgical ICUs	120 Nontraumatic ICU patients completed cognitive evaluation 12 mo after discharge	Patients with IHASS vs those without IHASS (specific number, not reported)	Modified Telephone Interview for Cognitive Status at 12 mo after ICU discharge	Not precisely defined/cognitive impairment was assessed using a cutoff score of ≥3 errors on the 6-item cognitive screen. Maximum possible score is 39, with higher scores indicating better cognitive status
Duning et al,[5] 2010	Case-control study	Surgical ICU	37 Patients with hypoglycemia	37 Patients with hypoglycemia vs matched controls (those without hypoglycemia)	Battery of validated neuropsychological tests investigating 5 areas of cognitive functioning at least 1 y after ICU discharge	Test results were compared with the published normative data[14]

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TABLE 1. Continued

Reference, year	Study design	Setting	Cases	Controls	Cognitive evaluation/time of cognitive assessment	Definition of cognitive impairment
Girard et al,[15] 2010	Prospective control study	Medical ICU	65 Patients who experienced delirium during the ICU stay	12 Patients without delirium	In-person cognitive evaluation by neuropsychologists at 3 and 12 mo after discharge; comprehensive battery of 9 neuropsychological tests designed to measure 7 main domains of cognitive functioning used for the assessment	2 cognitive test scores 1.5 SD below the mean or 1 cognitive test score 2 SD below the mean—mild to moderate cognitive impairment. ≥3 cognitive test scores 1.5 SD below the mean or ≥2 cognitive test scores 2 SD below the mean—severe cognitive impairment. Scores better than 1.5 SD below the mean on all 9 tests—no cognitive impairment
Gunther et al,[16] 2012	Prospective cohort study	Medical and surgical ICUs	47 ICU survivors with respiratory failure or shock	Comparison was made using the RBANS	RBANS at 12 mo after ICU discharge	≤69, extremely low; 70-79, borderline; 80-89, low average; 90-109, average; 110-119, high average; 120-129, superior; ≥130, very superior
Hope et al,[17] 2013	Prospective cohort study	Respiratory ICU	108 Patients with cognitive impairment after chronic critical illness	59 Patients without cognitive impairment after chronic critical illness	Telephone Confusion Assessment Method at 6 mo after discharge	Too cognitively impaired for the telephone Confusion Assessment Method or delirious by telephone—alive with brain dysfunction Not delirious by the telephone Confusion Assessment Method —alive without brain dysfunction
Hopkins et al,[18] 1999	Retrospective study	Medical and surgical ICUs	30 Patients with cognitive impairment	36 Patients without cognitive impairment	Battery of neuropsychological tests (WAIS-R, WMS-R, RAVLT, ROCF, immediate recall and 30-min delayed recall, TMT Parts A and B, verbal fluency test) at 1 y after discharge	≥2 cognitive test scores that were >1.5 SD or 1 test score that was >2 SD below the normative population mean values

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TABLE 1. Continued

Reference, year	Study design	Setting	Cases	Controls	Cognitive evaluation/time of cognitive assessment	Definition of cognitive impairment
Hopkins et al,[19] 2004	Prospective longitudinal outcome study	Medical and surgical ICUs	30 ARDS ICU survivors with cognitive sequelae	36 ARDS ICU survivors without cognitive sequelae	Neuropsychological tests (WAIS-R, WMS-R, RAVLT, ROCF, TMT Parts A and B, verbal fluency test) at 1 y after hospital discharge	Scores on ≥2 neuropsychological tests that were >1.5 SD or 1 test score that was >2 SD below the normative population mean
Hopkins et al,[20] 2010	Prospective study	Shock-Trauma Intermountain Respiratory ICU	55 ARDS survivors who have reached 1 y follow-up	Normative population mean	WAIS-R, WMS-R, RAVLT, ROCF (copy, immediate recall, and 30-min delayed recall), TMT Parts A and B at 1 y after entry into the ARDS study	Compared with normative population data
Hopkins et al,[21] 2005	Longitudinal prospective cohort study	Type of ICU was not reported	66 ARDS survivors who have reached 1 y follow-up; 62 ARDS survivors who have reached 2 y follow-up	Normative population mean	WAIS-R, WMS-R, RAVLT, ROCF (copy, immediate recall, and 30-min delayed recall), TMT Parts A and B, verbal fluency test at 2 y after hospital discharge	≥2 neuropsychological tests scored ≥1.5 SDs below the mean or ≥1 tests scored ≥2 SDs below the mean
Jackson et al,[22] 2011	Prospective cohort study	Trauma ICU	71 Severely injured trauma ICU survivors	37 Moderately injured trauma ICU survivors	Comprehensive battery of neuropsychological tests (MMSE, ROCF, TMT Parts A and B, Digit Span subtest, Digit Symbol subtest, FAS, IQCODE-SF) at 1 y after hospital discharge	Cognitive impairment was defined as having 2 neuropsychological test scores that were 1.5 SD below the mean or 1 neuropsychological test score that was 2 SD below the mean
Jackson et al,[3] 2007	Prospective observational pilot study	Trauma ICU	58 Adult ICU survivors without intracranial hemorrhage with injury severity score >25	Normative population mean	Comprehensive battery of cognitive instruments (MMSE, ROCF, TMT Parts A and B, Digit Span subtest, Digit Symbol subtest, FAS, IQCODE-SF) at 12 and 24 mo after ICU discharge	2 neuropsychological test scores that were 1.5 SD below the mean or 1 neuropsychological test score that was 2 SD below the mean were defined as cognitively impaired
Jackson et al,[4] 2003	Prospective cohort study	Medical ICU	11 Cognitively impaired and mechanically ventilated ICU patients	23 Cognitively normal and mechanically ventilated ICU patients	Battery of neuropsychological tests (APACHE II, CAM-ICU, GCS, GDS-SF, MMSE, RASS, SOFA) at 6 mo after ICU discharge	2 neuropsychological test scores that were at least 2 SD below the norm-referenced mean or 3 scores that were at least 1.5 SD below the norm-referenced mean

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TABLE 1. Continued

Reference, year	Study design	Setting	Cases	Controls	Cognitive evaluation/time of cognitive assessment	Definition of cognitive impairment
Jackson et al,[23] 2010	Single-center randomized trial	Medical ICU	89 Patients undergoing a wake-up and breathe protocol that paired daily spontaneous breathing trials	91 Patients with usual care (patient-targeted sedation) and undergoing a spontaneous breathing trial protocol	Battery of neuropsychological tests (Digit Span subtest, Digit Symbol subtest—Coding, MMSE, RAVLT, ROCF, TMT Parts A and B, verbal fluency test, Psychological Assessments Awareness Questionnaire, BDI-II, PTSD-10 for the ICU, Functional Assessment Screening Questionnaire, Katz ADL, SF-36)	≥2 neuropsychological tests scored ≥1.5 SDs below the mean or ≥1 tests scored ≥2 SDs below the mean
Jones et al,[24] 2006	Prospective study	Medical and surgical ICUs	16 Nondelirious ICU patients who underwent tracheal intubation and without sedation	Comparison was made according to the CANTAB	CANTAB at 1 wk after ICU discharge, on the general ward, and 2 mo after discharge	Not reported
Mikkelsen et al,[25] 2012	Prospective multicenter cohort study	Type of ICU was not reported	41 Acute lung injury survivors with cognitive impairment	34 Acute lung injury survivors without cognitive impairment	Telephone-administered battery of standardized neuropsychological tests	Score that was >2 SD below the normative population data
Mitchell et al,[26] 2017	Prospective cohort study	Medical and surgical ICUs	15 ICU survivors who experienced delirium during the ICU stay	64 ICU survivors without delirium during the ICU stay	RBANS, TMT Parts A and B, MMSE	1.5 SD below the mean on 2 of the index scores or 2 SD below the mean on one of the index scores—mild cognitive impairment; 1.5 SD below the mean on ≥3 of the index scores or 2 SD below the mean on ≥2 of the index scores—severe cognitive impairment

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TABLE 1. Continued

Reference, year	Study design	Setting	Cases	Controls	Cognitive evaluation/time of cognitive assessment	Definition of cognitive impairment
Morandi et al,[27] 2012	Two-center prospective cohort study	Medical, surgical, and cardiac ICUs	47 Adult patients admitted to ICUs with respiratory failure or shock	Comparison was made using the RBANS	RBANS at 3 and 12 mo after ICU discharge	Not reported
Needham et al,[28] 2013	Multicenter prospective longitudinal study	Medical ICU	81 Adult ICU patients who survived acute lung injury and were receiving trophic feeding	82 Adult ICU patients who survived acute lung injury and were receiving full enteral feeding	HSCT, COWAT, Logical Memory I and Logical Memory II age-adjusted scaled scores, Digit Span subtest age-adjusted scaled score at 12 mo after discharge	1 Cognitive test within the battery with a score at least 2 SDs below population norms or 2 tests with a score $\geq$1.5 SDs below population norms
Pandharipande et al,[29] 2013	Prospective study	Medical and surgical ICUs	448 Patients with respiratory failure, cardiogenic shock, or septic shock were cognitively evaluated at 3 mo after ICU discharge; 382 patients were evaluated at 12 mo after ICU discharge (59 died in between)	Normative population mean	RBANS at 3 and 12 mo after ICU discharge	Global cognition scores 1.5 SD below the population means (similar to scores for patients with moderate traumatic brain injury) and scores 2 SD below the population means (similar to scores for patients with Alzheimer disease)
Richards et al,[30] 2011	Prospective observational study	Trauma ICU	59 Cognitively impaired trauma ICU patients with multiple trauma (Injury Severity Score>15) without evidence of intracranial hemorrhage	49 Cognitively normal trauma ICU patients with multiple trauma (Injury Severity Score>15) without evidence of intracranial hemorrhage	MMSE, RAVLT, ROCF, Digit Symbol subtest—Coding, TMT Parts A and B, Digit Span subtest at 1 y after hospital discharge	2 Neuropsychological test scores 1.5 SD below the mean or 1 neuropsychological test score 2 SD below the mean
de Rooij et al,[31] 2008	Retrospective cohort study	Medical and surgical ICUs	178 Patients who underwent planned surgery	15 Patients who underwent unplanned surgery; 11 patients with medical treatment without surgery	IQCODE-SF at 1-6 y after ICU discharge	IQCODE-SF score >3.9, dementia; IQCODE-SF score 3.1-3.9, mild to moderate cognitive impairment; IQCODE-SF score <3.1, normal cognition
Rothenhäusler et al,[32] 2001	Exploratory retrospective study	Multidisciplinary ICU	11 ARDS survivors with cognitive impairment	35 ARDS survivors without cognitive impairment	SKT at a median time of 6 y after ICU discharge	Profound cognitive impairment, 24-27; severe cognitive impairment, 19-23; moderate cognitive impairment, 14-18; mild cognitive impairment, 9-13; subthreshold, 5-8; no cognitive deficits, 0-4

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TABLE 1. Continued

Reference, year	Study design	Setting	Cases	Controls	Cognitive evaluation/time of cognitive assessment	Definition of cognitive impairment
Semmler et al,[33] 2013	Two-center prospective study with follow-up	Surgical ICU	25 Septic ICU survivors	19 Nonseptic ICU survivors	NeuroCogFX (computerized assessment battery) at 6-24 mo after discharge	Not reported
Torgersen et al,[2] 2011	Prospective study	Surgical ICU	28 ICU patients with >24 h ICU length of stay	24 Surgical patients without ICU admission	MMSE at hospital discharge; CANTAB at 3 and 12 mo after discharge	*z* Score below −2.0 SD on 2 out of 10 results or below −1.5 SD on 3 out of 10 results obtained from the CANTAB
Woon et al,[34] 2012	Prospective study	Shock trauma ICU and respiratory ICU	53 ICU survivors who were mechanically ventilated for >48 h completed cognitive evaluation after discharge	Normative population mean	MMSE and Mini-Cog at hospital discharge; WASI and standardized neurophysiological tests (SCWTGV, FTT, COWAT, WMT-III, LMS, CVLT, ROCF, WAIS-R, TNT Parts A and B, HSCT) at 6 mo after discharge	Scores on ≥2 neuropsychological tests that were >1.5 SD or 1 test score that was >2 SD below the normative population mean
van den Boogaard et al,[35] 2012	Prospective study	4 Mixed ICUs	171 Patients who were delirious during the ICU stay	745 Patients who were not delirious during the ICU stay	Cognitive failure questionnaire	Total score 0-100, with higher scores indicating greater cognitive impairment

APACHE II = Acute Physiology and Chronic Health Evaluation II; ARDS = acute respiratory distress syndrome; BDI- II = Beck Depression Inventory Two; CAM-ICU = Confusion Assessment Method for the Intensive Care Unit; CANTAB = Cambridge Neuropsychological Test Automated Battery; COPD = chronic obstructive pulmonary disease; COWAT = Controlled Oral Word Association Test; CVLT = California Verbal Learning Test; FAS = Verbal fluency test, generating as many possible words with F,A,S; FTT = finger tapping test; GCS = Glasgow Coma Scale; GDS-SF = Geriatric Depression Scale – Short Form; HSCT = Hayling Sentence Completion Test; ICU = intensive care unit; IHASS = in-hospital acute stress syndrome; IQCODE-SF = Informant Questionnaire on Cognitive Decline – Short Form; Katz ADL = Katz Activity of Daily Living; LMS = Logical Memory subtest; MMSE = Mini-Mental State Examination; PTSD = post traumatic stress disorder; RASS = Richmond Agitation-Sedation Scale; RAVLT = Rey Auditory Verbal Learning Test; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; ROCF = Rey-Osterrieth Complex Figure Test; SCWTGV = Stroop Color-Word Test-Golden Version; SF-36 = Short Form 36 SKT = short cognitive performance test for assessing deficits of memory and attention; SOFA = Sepsis-related Organ Failure Assessment; TMT Parts A and B = Trail Making Test Parts A and B; WAIS-R = Wechsler Adult Intelligence Scale – Revised; WASI = Wechsler Abbreviated Scale of Intelligence; WMS-R = Wechsler Memory Scale – Revised; WMT-III = Wechsler Memory Test—Third Edition.

speed and executive functioning 6 months after discharge in adult ICU survivors who were ventilated for more than 12 hours during their ICU hospitalization.[26]

However, not all studies have found an association between delirium and subsequent cognitive impairment. Davydow et al[13] did not find a significant association between delirium and worse cognitive performance in 120 nontraumatic ICU patients who completed a Modified Telephone Interview for Cognitive Status 12 months after discharge. In another study conducted in 108 patients who completed a comprehensive battery of neuropsychological tests 12 months after discharge from a trauma ICU, delirium during ICU hospitalization (present in 23.2% of the patients) was not associated with long-term cognitive impairment.[24] In unselected population of 413 ventilated and nonventilated ICU patients, delirium did not seem to contribute the development of long-term cognitive impairment.[12]

Mechanical Ventilation and Duration of Mechanical Ventilation

The influence of mechanical ventilation during ICU hospitalization on long-term cognitive impairment was inconsistent across studies. Of the 28 studies included in our analysis, 14 evaluated the influence of mechanical ventilation on long-term cognitive impairment after ICU admission. Twelve of these studies did not find any significant association.[2-4,11,13,18,21,24,25,32-34]

Only 2 studies reported an association between mechanical ventilation and cognitive impairment. In a prospective observational study that evaluated 108 trauma ICU patients without evidence of intracranial hemorrhage, 57.4% of the patients were mechanically ventilated for a mean duration of 3.4 days. Duration of mechanical ventilation was shown to be significantly longer in patients with worse cognitive outcomes (P=.004).[30] In a retrospective study conducted in 66 acute respiratory distress syndrome (ARDS) survivors, intubation time longer than 23.6 days increased the odds of cognitive impairment by 1.8 times in multivariate analysis.[18]

Use of Sedatives or Analgesic Medications

Sedation and analgesia did not appear to influence the risk of long-term cognitive impairment. Pandharipande et al[29] did not find a consistent association between the use of sedatives or analgesic medications and cognitive impairment 3 and 12 months after ICU discharge. In a single-center randomized trial that compared 89 patients managed according to a protocol of daily sedation holidays paired with spontaneous breathing trials against 91 patients receiving usual care (patient-targeted sedation), the cognitive scores at 12 months follow-up were similar in both groups (P=.61).[23] The use of vasopressors,[25] benzodiazepines, opioids, antipsychotic agents, and antidepressant drugs did not play a significant role in the incidence of cognitive decline in 120 nontraumatic ICU patients.[13]

In-Hospital Acute Stress Symptoms (Posttraumatic Stress Disorder Checklist – Civilian Version)

The Modified Telephone Interview for Cognitive Status was used to evaluate a cognitive function in 120 nontraumatic ICU survivors 12 months after ICU discharge to assess the role of in-hospital acute stress symptoms in the development of cognitive impairment. The 17-item Posttraumatic Stress Disorder Checklist – Civilian version was used to evaluate the presence of in-hospital acute stress symptoms such as intrusive thoughts, nightmares, avoidance of thoughts, emotional numbing, impaired sleep, and hypervigilance. The investigators concluded that the presence of in-hospital acute stress symptoms was an independent risk factor for long-term cognitive decline (P=.03).[13]

Blood Product Transfusion, Blood Loss, and Hematocrit Level

Davydow et al[13] did not find any significant correlation between blood transfusion and persistent cognitive impairment in general ICU patients. Similarly, blood loss did not appear to have any effect on the risk of subsequent cognitive impairment in patients admitted to a trauma ICU.[3] Meanwhile, another study in trauma patients found that hematocrit level in the emergency department (P=.03) and blood transfusion during the first 24 hours (P=.04) were more common in patients who subsequently had cognitive decline impairment.[30]

TABLE 2. Outcome Data for Exposures[a]

Reference, year	Delirium and duration of delirium	Mechanical ventilation (MV) and duration of MV	Length of ICU stay	Use of sedatives or analgesic medications	Vasopressors	ECMO	In-hospital acute stress symptoms	Blood product transfusion, blood loss, or HCT level	Hypoglycemia, hyperglycemia, or fluctuations in glucose levels	Trophic feeding vs enteral feeding	Hypoxia	Pulse rate or systolic blood pressure
Ambrosino et al,[11] 2001	Not tested	No association	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested
de Azevedo et al,[12] 2017[b]	No association	Not tested	No association	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested
Davydow et al,[13] 2013[b]	No association	No association	Not tested	No association	Not tested	Not tested	Positive association	No association	Not tested	Not tested	Not tested	Not tested
Duning et al,[5] 2010[c]	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Positive association	Not tested	Not tested	Not tested
Girard et al,[15] 2010[b]	Positive association	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested
Gunther et al,[16] 2012[b]	Positive association	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	No association
Hope et al,[17] 2013[b]	Positive association	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested
Hopkins et al,[18] 2010[b]	Not tested	Positive association	Positive association	Not tested	Not tested	Not tested	Not tested	Not tested	Positive association	Not tested	Not tested	Not tested
Hopkins et al,[19] 2004	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	No association	Not tested
Hopkins et al,[20] 1999	Not tested	No association	No association	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Positive association	Not tested
Hopkins et al,[21] 2005	Not tested	No association	No association	No association	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	No association	No association
Jackson et al, 2011[b]	No association	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not Tested	Not tested	Not tested	Not tested
Jackson et al,[3] 2007	Not tested	No association	Not tested	Not tested	Not tested	Not tested	Not tested	No association	Not tested	Not tested	Not tested	Not tested
Jackson et al,[4] 2003[b]	Not tested	No association	No association	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested
Jackson et al,[23] 2010[d]	Not tested	Not tested	Not tested	No association	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested
Jones et al,[24] 2006	Not tested	Not tested	Positive association	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested
Mikkelsen et al,[25] 2005	Not tested	No association	No association	Not tested	No association	Not tested	Not tested	Not tested	Not tested	Not tested	Positive association	No association

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TABLE 2. Continued

Reference, year	Delirium and duration of delirium	Mechanical ventilation (MV) and duration of MV	Length of ICU stay	Use of sedatives or analgesic medications	Vasopressors	ECMO	In-hospital acute stress symptoms	Blood product transfusion, blood loss, or HCT level	Hypoglycemia, hyperglycemia, or fluctuations in glucose levels	Trophic feeding vs enteral feeding	Hypoxia	Pulse rate or systolic blood pressure
Mitchell et al,[26] 2017[b]	Positive association	No association	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested
Morandi et al,[27] 2012	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested
Needham et al,[28] 2013[d]	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	No association	Not tested	Not tested
Pandharipande et al,[29] 2013[b]	Positive association	Not tested	Not tested	No association	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested
Richards et al,[30] 2011[b]	Not tested	Positive association	Not tested	Not tested	Not tested	Not tested	Not tested	Positive association	Not tested	Not tested	Not tested	No association
de Rooij et al,[31] 2008[b]	Not tested	Not tested	No association	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested
Rothenhäusler et al,[32] 2001	Not tested	No association	No association	Not tested	Not tested	No association	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested
Semmler et al,[33] 2013	Not tested	No association	No association	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested
Torgersen et al,[2] 2011	Not tested	No association	No association	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested
Woon et al,[34] 2012	Not tested	No association	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested
van den Boogaard et al,[35] 2012[b]	Positive association	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested

[a]ECMO = extracorporeal membrane oxygenation; HCT = hematocrit; ICU = intensive care unit.
[b]An analysis adjusted for multiple variables was performed.
[c]A matched case-control design.
[d]Randomized design.

Hypoglycemia, Hyperglycemia, and Fluctuations in Glucose Levels

Glucose levels have been associated with cognitive impairment after the ICU stay in a few small studies. Duning et al[5] compared 37 ICU patients with hypoglycemia vs 37 matched controls without hypoglycemia to assess the influence of low serum glucose levels on long-term cognitive impairment. The results indicated that cognitive impairment was persistent in both groups, but cases performed worse in visuospatial skills ($P=.01$). Interestingly, hyperglycemia and fluctuations in blood glucose levels were significantly associated with worse outcomes in the same domain ($P<.005$ and $P<.008$, respectively).[5]

A retrospective study conducted in 66 ARDS survivors found that blood glucose dysregulation, in particular moderate hyperglycemia, was associated with long-term cognitive impairment. Having a blood glucose level greater than 153.5 mg/dL (to convert to mmol/L, multiply by 0.0259) during ICU hospitalization was associated with a greater likelihood of having long-term cognitive impairment after ICU discharge.[18]

Hypoxia

Mikkelsen et al[25] compared acute lung injury survivors who developed cognitive impairment (n=41) with those who remained cognitively well (n=34) 12 months after ICU discharge. Lower partial pressure of oxygen during ICU admission was detected in patients with cognitive impairment ($P<.02$).[25]

A small study by Hopkins et al[20] reported a significant correlation between cognitive impairment and hypoxemia in 17 ARDS survivors who experienced generalized cognitive decline 1 year after discharge. Yet, the same group of researchers later put into question the relationship between degree of acute hypoxemia and subsequent cognitive decline. When comparing the mean duration of oxygen desaturation less than 90% between 30 ARDS ICU survivors with cognitive impairment and 39 ARDS ICU survivors without cognitive impairment, they did not find any significant difference (110.6 and 113.8 hours, respectively) ($P=.89$).[19] Furthermore, although evaluating the influence of hypoxemia on neurocognitive sequelae in ARDS survivors 2 years after ICU discharge, they did not find any significant correlation and suggested that this may be due to cognitive recovery over time.[21]

Length of ICU Stay

Studies published so far have shown contradictory results on the relationship of the length of stay in the ICU and cognitive decline. Hopkins et al[18] reported that a total length of stay in the ICU longer than 27.4 days was associated with 2.7 times higher odds of cognitive decline. The length of stay in the ICU correlated with the degree of difficulty in problem solving 2 months after discharge in another small prospective study.[19] Conversely, most of the other studies did not find significant associations between the length of ICU stay and cognitive dysfunction.[2,4,20,31-33]

DISCUSSION

Long-term cognitive impairment after critical illness is a challenging research and clinical problem. To date, many studies have discussed this topic, yet little is truly known about potentially preventable risk factors for this disabling complication.

Our review shows that delirium, particularly when prolonged, may be associated with an increased likelihood of persistent cognitive impairment after ICU hospitalization. Of the 9 studies that assessed the role of delirium in cognitive impairment, 6 reported a significant association.[15-17,26,29,35] Evidence linking other potentially preventable ICU factors with long-term cognitive impairment is much weaker or even more inconsistent. Because delirium is a significant and independent risk factor for developing cognitive impairment, putting an effort to prevent delirium in the ICU may be an important prevention strategy.

For instance, mechanical ventilation and duration of mechanical ventilation were not significantly associated with cognitive impairment after critical illness in many studies,[2-4,11,13,20,26,32-34] but still 2 studies found positive associations.[18,30] One of them emphasized the influence of long duration of mechanical ventilation (>23 days),[18] yet 2 other studies did not find such correlation.[13,22] Most of the studies did not find an association between the length of ICU stay and cognitive dysfunction.[2,4,20,31-33]

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Dysglycemia has been reported to be associated with subsequent cognitive decline, but the studies supporting this association are small and methodologically limited.[5,18] Multiple other evaluated factors were not found to influence the likelihood of post-ICU cognitive impairment, including use of sedatives and analgesic medications, extracorporeal membrane oxygenation, trophic feeding, intraoperative hypotension, and hypoxia.[12,23,28-30,32]

Although our study focused on the influence of potentially modifiable risk factors during critical illness on long-term cognitive impairment after discharge, it is pertinent to note that nonmodifiable factors, such as age, level of education, comorbidities, severity of illness and injury, and sepsis, can affect the risk of cognitive impairment. Age was significantly associated with long-term cognitive dysfunction in a prospective cohort study of 167 survivors of chronic critical illness.[17] Yet, age was not significantly associated with cognitive impairment in several other studies.[2-4,22,29,31,32] Data on the relationship of age with cognitive impairment after ICU admission needs to be interpreted with caution because the higher rates of mortality in older patients may create a form of selection bias, by which only patients at lower risk of cognitive impairment get to survive. The severity of acute illness assessed by Sepsis-related Organ Failure Assessment, Acute Physiologic and Chronic Health Evaluation II, or Simplified Acute Physiology score did not appear to influence the risk of long-term cognitive impairment in most of the studies published so far.[2,4,13,31,32] However, Acute Physiologic and Chronic Health Evaluation II score was associated with long-term cognitive decline in 1 study of 108 survivors of chronic critical illness.[17] In a large cohort of subjects who underwent serial cognitive evaluation, Iwashyna et al[36] found that hospitalization for severe sepsis (though not necessarily in the ICU) was associated with new moderate or severe cognitive impairment.

The literature on cognitive impairment after critical illness has marked limitations. None of the articles had addressed all issues, making it tough to draw effective conclusions. Chief among them is the lack of baseline assessment of cognitive function before ICU hospitalization in most studies. Most of the studies were also likely underpowered to assess for associations between possible risk factors and cognitive outcomes reliably. The discrepant results across studies may in part be caused by variable cognitive assessments, in terms of both definitions and timing. Also, most of the studies do not permit discrimination between transient and persistent cognitive impairment because they do not provide information on serial cognitive examinations at various times after discharge from the ICU. Overall, the included studies had moderate risk of bias, mostly related to limitations in the measurement of the examined variables and the end point as well as in the selection of the results reported.

CONCLUSION

The influence of potentially modifiable risk factors during ICU treatment on long-term cognitive impairment needs further investigation. Available evidence suggests that prolonged delirium is the potentially modifiable factor most strongly associated with post-ICU cognitive impairment. Yet, the literature on this important clinical problem is generally suboptimal and the results are inconsistent across studies. High-quality research on a large cohort of critically ill patients is necessary to better characterize potentially modifiable risk factors for persistent cognitive impairment after ICU hospitalization.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at: http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **ARDS** = acute respiratory distress syndrome; **ICU** = intensive care unit

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