MAYO CLINIC

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

Amra Sakusic, MD; John C. O'Horo, MD, MPH; Mikhail Dziadzko, MD, PhD; Dziadzko Volha, MD; Rashid Ali, MD; Tarun D. Singh, MBBS; Rahul Kashyap, MBBS; Ann M. Farrell, MLS; John D. Fryer, PhD; Ronald Petersen, MD, PhD; Ognjen Gajic, MD, MSc; and Alejandro A. Rabinstein, MD

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.

 ■ Mayo Clin Proc. 2018;93(1):68-82

From the Department of Physiology, Faculty of Medicine, University of Tuzla, Tuzla, Bosnia and Herzegovina (A.S.); University Clinical Center Tuzla, Tuzla, Bosnia and Herzegovina (A.S.); Multidisciplinary Epidemiology and Translational Research in Intensive Care (METRIC), Emergency and Perioperative Medicine (A.S., J.C.O., D.V., R.A., T.D.S., R.K., O.G., A.A.R.), Division of Infectious

Affiliations continued at the end of this article.

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