

COMMENTARY

Depression, delirium, and post-intensive care syndrome

Commentary on “Delirium, depression, and long-term cognition” by Andrews *et al.*

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Patients admitted to intensive care units (ICUs) are susceptible to several short and long-term consequences of their ICU stay. These can include physical, mental, and emotional symptoms that often persist after leaving the ICU, in what is known as post-intensive care syndrome (PICS). Depression, cognitive impairment, and delirium can aggravate PICS, leading to decreased motivation, memory complaints, anxiety, and sleeping disorders, and require targeted measures to minimize such unwanted complications (Needham *et al.*, 2012).

Depression has been shown in the past to affect approximately one in three ICU patients, and although depressive symptoms are frequently first reported in the hospital, they are often present during the first year after discharge (Davydow *et al.*, 2009). However, a recent multicenter study in the United Kingdom (UK), including more than 13 thousand ICU survivors, reported that more than half of their participants had significant symptoms of depression, anxiety, or post-traumatic stress disorder (PTSD) (Hatch *et al.*, 2018).

Age and length of ICU stay are some of the factors that appear to be associated with depression in this context. Liao *et al.* found in a retrospective nationwide population-based ICU cohort, with over 320 thousand participants, that depression was more common in adults aged 20 to 49 years than those aged 50 to 65 years (Liao *et al.*, 2020). They also observed that the risk of depression was U-shaped, with higher risks associated with ICU stays of 1 to 3 days and more than 15 days. Regrettably, older adults were not included in this study, and its results cannot be extrapolated to patients over the age of 65.

ICU neuropsychiatric complications can go far beyond depression. In a summary of existing data regarding the potential long-term physical, cognitive and mental health problems after intensive care, experts listed as other adverse outcomes:

pathological grief, anxiety, PTSD, cognitive changes affecting memory and attention, physical changes including myopathy and neuropathy, chronic respiratory changes, increased disability in activities of daily living, and decreased performance in the six-minute walk test (Needham *et al.*, 2012).

Notably, delirium is increasingly recognized as both a complication and predictor of complications of ICU patients. A recent systematic review based on 48 studies found a pooled prevalence of delirium of 31%, with a pooled incidence of 22% (Krewulak *et al.*, 2018). Having delirium in the ICU is associated with longer time on mechanical ventilation, increased length of hospital and ICU stay, higher mortality, and higher risk of institutionalization (Poulsen *et al.*, 2021). Delirium is also associated with long-term cognitive impairment (LTCGI) (Wang *et al.*, 2018). Other risk factors for ICU-acquired LTCI include neurologic dysfunction, infection or severe sepsis, and acute kidney injury. Additionally, delirium duration is a risk factor for LTCI in adults of any age (Girard *et al.*, 2010).

Less data are available on the association between post-ICU depression and adverse outcomes, with often inconclusive and conflicting results (Schofield-Robinson *et al.*, 2018). Even so, Hatch *et al.* found in their UK cohort that participants with depressive symptoms were 47% more likely to die during the first two years after ICU discharge (Hatch *et al.*, 2018). Besides, it is well known that depression can influence clinical health. Generally speaking, patients with major depression can die five to 10 years earlier than their counterparts, while patients with bipolar disorder are estimated to die 10 to 20 years earlier (Chang *et al.*, 2010; Katon, 2011; Roshanaei-Moghaddam and Katon, 2009). Also, although post-ICU depression and LTCI are different conditions, they certainly can overlap (Wang, 2018). Depression impairs executive functioning and can aggravate existing cognitive deficits.

Therefore, it is reasonable to expect that further studies specifically designed to investigate depression as a predictor of ICU complications might uncover clinically meaningful associations.

In their paper, Andrews *et al.* (2021) seek to investigate essential issues related to the presence of pre-existing depression. They examine pre-admission history of depression as a predisposing factor for delirium/coma, one-year depression severity, and LTCI in adults admitted to two ICUs in Nashville, Tennessee, between 2007 and 2010. The authors evaluated 821 eligible patients for possible inclusion, of which 261 had a history of depression (Andrews *et al.*, 2021). A total of 448 and 382 participants underwent the study assessments 3 and 12 months after discharge, respectively.

After completing their analyses, Andrews *et al.* found a significant relationship between the presence of pre-existing depression and a greater severity of depressive symptoms in the year after hospitalization. Although that might seem a self-evident result at first glance, it highlights the importance of neuropsychiatric assessments during and after ICU stays. Recently, a population-based cohort study from Ontario, Canada, reported that ICU survivors had a higher risk of suicide and self-harm, and patients with a previous history of depression had almost six times the odds of those outcomes compared to patients without depression (Fernando *et al.*, 2021).

Conversely, the authors did not find significant associations between pre-existing depression and delirium/coma-free days or post-discharge cognitive impairment.

It stands to notice that the cognitive assessment protocol was particularly well designed in this study. Delirium and level of consciousness were respectively assessed using the Confusion Assessment Method for the ICU and level of the Richmond Agitation-Sedation Scale, which are widely accepted and used instruments. Patients were evaluated twice daily while in the ICU and daily when in the wards, and delirium episodes were unlikely to have been lost (the fact that 73% of the study sample experienced delirium is indicative of this fact). Furthermore, cognitive performance was measured at different time points after discharge, using the Repeatable Battery for the Assessment of Neuropsychological Status, which tests immediate memory, visuospatial/constructional, language, attention, delayed memory, and is also a well-validated tool.

The analysis plan is another strength of this study. The authors adequately addressed missing data using model-based imputations and maximized their power using continuous measures whenever possible. They were also careful to use outcome-specific multivariable models, including logistic

regressions, proportional odds logistic regressions, and linear regressions. All models were adjusted for relevant confounders such as age, sex, years of education, comorbidities, and baseline cognition.

In spite of these strengths, some limitations might have affected the study results. The diagnosis of pre-existing depression was based on information given by health proxy and did not follow a validated interview, screening, or diagnostic tool. Time of diagnosis and previous treatment were also not taken into consideration in the study's analyses of depression. Likewise, combining delirium/coma into a single variable might have impacted the results. Although delirium and coma often coexist in admissions, they do not represent the same phenomena, especially in the context of critical care and sedation. A sensitivity analysis restricting the outcome to delirium-free days could have clarified this point.

Understandably, candidates with pre-existing cognitive impairment were excluded from the study since it would have been harder to define the presence of depression in these patients. Nevertheless, this decision, combined with the relatively low mean age of the participants, ranging from 51 to 71, possibly restricted the sample vulnerability to long-term cognitive decline and contributed to the negative findings.

Finally, aspects of the study might compromise its generalizability. It was completed in two centers of the same American city, in a mostly White population, using data from more than ten years ago. There were substantial improvements during this period in depression treatment and follow-up and in ICU conditions and resources. Results should be interpreted in light of such specificities.

The study's negative results do not empty the discussion regarding depression, delirium, and LTCI. Oldham *et al.* reported in a cohort of 131 subjects undergoing coronary artery bypass graft surgery that, although a lifetime history of depression was not predictive of delirium, preoperative depression was independently associated with delirium (Oldham *et al.*, 2019). Nordness *et al.* recently showed in a five-center nested prospective cohort of 1047 critically ill patients that depression was independently associated with LTCI (Nordness *et al.*, 2021).

Andrews *et al.*'s paper addresses issues that have become increasingly relevant in the context of the COVID-19 pandemic. Delirium has been reported to be common and associated with a worse prognosis in hospitalized patients with severe COVID-19 (Garcez *et al.*, 2020). Mood disorders and memory complaints have also increased during the pandemic (Søraas *et al.*, 2021). With the ongoing waves of SARS-CoV-2 infection, leading to increased hospitalizations and ICU admissions, Andrews *et al.* draw attention to concerning outcomes, which might have long-lasting effects.

One particular gap in their discussion is the relevance of these complications to older adults. Geriatric patients are frailer and more vulnerable to ICU complications. They have lower cognitive reserve and are at a higher risk of delirium and cognitive decline. On the other hand, older adults often present with atypical forms of depression and require differentiated analyses for a more granular understanding of its effects on their health. PICS is more and more common, and the rising group of older ICU survivors poses an unparalleled clinical challenge to critical care medicine (Wang *et al.*, 2018).

In conclusion, clinicians should be aware of the importance of neuropsychiatric conditions in the context of critical care and post-ICU discharge. Researchers must continue to work on this line of inquiry, hopefully collaborating in multicenter studies that would benefit from the boosted resources and participants to generate conclusive results.

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