Received: 28 June 2022 | Revised: 21 January 2023 | Accepted: 23 January 2023

DOI: 10.1111/acps.13534

Acta Psychiatrica Scandinavica WILEY

SYSTEMATIC REVIEW

Delirium-related psychiatric and neurocognitive impairment and the association with post-intensive care syndrome—A narrative review

Dharmanand Ramnarain[1,2,3] | **Sjaak Pouwels**[1,4] | **Sol Fernández-Gonzalo**[5,6,7] | **Guillem Navarra-Ventura**[5,8] | **Vicent Balanzá-Martínez**[6,9]

[1]Department of Intensive Care Medicine, Elisabeth-Tweesteden Hospital, Tilburg, The Netherlands

[2]Department of Intensive Care Medicine, Saxenburgh Medical Center, Hardenberg, The Netherlands

[3]Departmentof Medical and Clinical Psychology, Center of Research on Psychological and Somatic disease (CoRPS), Tilburg University, Tilburg, The Netherlands

[4]Department of General, Abdominal and Minimally Invasive Surgery, Helios Klinikum, Krefeld, Germany

[5]Critical Care Center, Hospital Universitari Parc Taulí, Institut d'Investigació i Innovació Parc Taulí I3PT, Universitat Autònoma de Barcelona, Sabadell, Spain

[6]Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain

[7]Department of Clinical and Health Psychology, Universitat Autònoma de Barcelona, Bellaterra, Spain

[8]Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Madrid, Spain

[9]Teaching Unit of Psychiatry and Psychological Medicine, Department of Medicine, University of Valencia, Valencia, Spain

Correspondence
Vicent Balanzá-Martínez, Teaching Unit of Psychiatry and Psychological Medicine, Department of Medicine, University of Valencia, 46010 Valencia, Spain.
Email: vicente.balanza@uv.es

Abstract

Introduction: Delirium is common among patients admitted to the intensive care unit (ICU) and its impact on the neurocognitive and psychiatric state of survivors is of great interest. These new-onset or worsening conditions, together with physical alterations, are called post-intensive care syndrome (PICS). Our aim is to update on the latest screening and follow-up options for psychological and cognitive sequelae of PICS.

Method: This narrative review discusses the occurrence of delirium in ICU settings and the relatively new concept of PICS. Psychiatric and neurocognitive morbidities that may occur in survivors of critical illness following delirium are addressed. Future perspectives for practice and research are discussed.

Results: There is no "gold standard" for diagnosing delirium in the ICU, but two extensively validated tools, the confusion assessment method for the ICU and the intensive care delirium screening checklist, are often used. PICS complaints are frequent in ICU survivors who have suffered delirium and have been recognized as an important public health and socio-economic problem worldwide. Depression, anxiety, post-traumatic stress disorder, and long-term cognitive impairment are recurrently exhibited. Screening tools for these deficits are discussed, as well as the suggestion of early assessment after discharge and at 3 and 12 months.

Conclusions: Delirium is a complex but common phenomenon in the ICU and a risk factor for PICS. Its diagnosis is challenging with potential long-term adverse outcomes, including psychiatric and cognitive difficulties. The implementation of screening and follow-up protocols for PICS sequelae is warranted to ensure early detection and appropriate management.

KEYWORDS

delirium, emotional symptoms, ICU, neurocognitive impairment, post-intensive care syndrome

1 | INTRODUCTION

Delirium is a very common neuropsychiatric syndrome, which affects a signification proportion of patients in the hospital.[1,2] The prevalence of delirium varies enormously according to the studied populations.[2–4] Several studies showed an estimated prevalence of delirium of 23% in hospitalized patients, 4%–38% of patients in a nursing home, around 35% of patients in palliative care, and 8%–17% in patients presented at the Emergency department.[2,4–6] In addition, delirium is a common complication seen after surgery (especially in older adults), with incidence rates ranging from 15% to 25% after major elective surgery and even higher rates (up to 50%) after emergency surgery or high-risk surgeries.[2,4–6] The prevalence of delirium in the intensive care unit (ICU) varies even more, with rates ranging from 11% to 89%, depending on the patient population.[7–10] Delirium symptoms can even persist for several months after ICU and hospital discharge.[11] However, in clinical practice delirium can be difficult to diagnose and often goes unrecognized by clinicians, in up to 65% to 88% of cases.[2] Besides increased mortality,[12,13] delirium has also been associated with prolonged mechanical ventilations during ICU treatment, prolonged hospitalization and increased healthcare costs,[4,14,15] impaired physical functioning,[4–6,15] and cognitive disturbances and long-term cognitive decline.[7,14,16] Psychological symptoms such as anxiety, depression and posttraumatic stress have also been reported.[17]

All above mentioned complications of delirium, short-term as well as long-term cognitive dysfunction, physical impairment, and psychological symptoms are also recognized as being part of post-intensive care syndrome (PICS). While delirium is an acute condition that occurs during hospitalization and/or ICU care, PICS is diagnosed after hospital discharge, has a longer duration, and presents with physical symptoms, such as pain and muscle weakness. Symptoms can occur as early as 24 h of ICU treatment and can persist for up 5 to 15 years after discharge.[18–21] Notwithstanding, approximately half of ICU survivors have psychiatric and cognitive disturbances, which can significantly affect the functioning of these patients.[22–24] PICS has been recognized as affecting the wellbeing of post-ICU patients and their caregivers.[18,19,25]

The aim of this narrative review is to discuss the latest screening and follow-up options of delirium-related psychiatric and cognitive impairment as being part of PICS. We discuss the following topics: (1) Delirium in the ICU; (2) PICS definition and epidemiology; (3) Delirium-associated psychiatric impairment; (4) Delirium associated long-term cognitive impairment (LTCI); (5) Assessment of neurocognitive and psychiatric morbidities in post-ICU patients; and (6) Future perspectives and research agenda. These topics were chosen based on the evidence that PICS may result from delirium in the ICU and psychiatric and neurocognitive impairments are two core features of PICS. To that end, we conducted a targeted literature search on these topics and synthesized findings in a narrative review. An unstructured literature review was conducted in PubMed database from inception up to June 2022 using the key terms (and their possible combinations) "delirium," "post-intensive care syndrome," "ICU," "ICU survivor," "anxiety," "depression," "PTSD," and "cognitive impairment." For the purpose of this article, "ICU" was used as a general term covering all critical care units (e.g., medical, surgical). The term "ICU survivor" was used to refer to all persons who have suffered a critical illness and critical care hospitalization not resulting in death. Clinical experience was incorporated with the evidence to

Summations

- Delirium is the main risk factor for post-intensive care syndrome (PICS)-related neurocognitive impairment; further studies analyzing its relationship with psychiatric outcomes is needed.
- Characterization of PICS-related sequelae is limited by factors such as the different follow-up intervals and assessment tools used; a scientific consensus needs to be reached.
- We propose early follow-up no later than 2–4 weeks after hospital discharge and long-term follow-up at 3 and 12 months in patients at high risk for post-intensive care unit delirium-associated neurocognitive and psychiatric sequelae.
- The use of brief instruments, such as the Montreal cognitive assessment test and the hospital anxiety and depression scale, is recommended to screen for neurocognitive and psychological components of PICS, respectively.

Limitations

- The narrative nature of this review does not allow for a comprehensive analysis of the current evidence, which might have been identified in a systematic review.
- The clinical experience element is subjective and may vary according to different standards and clinical settings.

suggest some prospects to advance the field. Since the assessment and follow-up of physical impairment are commonly implemented in the routine ICU discharge protocols (see recent reviews[26,27]), this narrative review was intended to focus on the psychiatric and neurocognitive aspects of the critically ill patient.

2 | DELIRIUM IN THE INTENSIVE CARE UNIT

In the ICU, delirium is a common phenomenon that presents with fluctuations in the level of consciousness and an acute decline in cognitive functioning.[28] Different studies report different incidence rates of delirium in the ICU, but approximately 75% of patients will develop delirium at some point during their ICU stay.[29] Delirium is a known predictor of longer duration of both invasive mechanical ventilation (IMV) and length of ICU stay, as well as LTCI.[30]

On the other hand, several comorbidities have been reported to increase the risk of delirium, including frailty,[31] cardiac disease,[32] hypertension,[33] premorbid psychiatric disorders,[34] and lifestyle behaviors such as alcohol use and smoking.[35,36] Elderly patients with pre-existing cognitive impairment have also been found to have an increased risk for developing delirium.[35]

Delirium can be classified into three subtypes: hyperactive, hypoactive, and mixed subtype.[37]

Hyperactive delirium subtype is more easily identified due to its florid clinical presentation of agitation and restlessness. However, this subtype of delirium only occurs in about 10%–25% of cases, leaving 75%–90% to the hypoactive and mixed delirium, which is more prevalent in older patients, often unnoticed. The hypoactive delirium is characterized by lethargic with reduced motor activity. Patients with mixed delirium show both signs of hypoactive and hyperactive delirium.[5,6,37] A fourth type of delirium has been described recently. This "rapidly reversible" delirium subtype is sedation-related, may occur after cessation of sedation and appears not to affect clinical outcomes.[38] In prospective study in 102 adult ICU patients, rapidly reversible, sedation-related delirium showed fewer ventilator and hospital days than patients with persistent delirium.[38] Patients without delirium and rapidly reversible sedation-related delirium were more likely to be discharged home. Patients with persistent delirium had increased 1-year mortality versus those with no delirium and rapidly reversible, sedation-related delirium.[38] A large cohort study of ICU patients compared the risk for mortality associated with delirium subtypes.[39] The overall prevalence of delirium was 25%. Patients with rapidly reversible delirium had the lowest risk for 90-days mortality, whereas those with mixed subtype had the highest risk.

Although there is no "gold standard" for diagnosing delirium in the ICU, two extensively validated tools are often used, namely the Confusion Assessment Method for the ICU (CAM-ICU) and the intensive care delirium screening checklist (ICDSC). Both have good sensitivity and specificity and are easy to use.[8,14,40] Moreover, the CAM-ICU has been also validated in different populations of ICU patients, such as pediatric, emergency and neurocritical care.[41] Despite the availability of these validated diagnostic tools, several studies have shown that the occurrence of delirium is often underestimated.[42] A reliable tool like the CAM-ICU has shown sensitivity levels for the diagnosis of delirium that may depend on several factors, of which the patient population and the nursing team are the most important.[40,43,44] It must be considered that the sensitivity of the diagnosis of delirium varies between 40% and 80%, regardless of clinicians' training and patient population.[40,43,44] A disadvantage of the CAM-ICU is that it can be difficult to use in patients who are deeply sedated.[40,43,44] This was demonstrated by the study conducted by van Eck van der Sluijs et al.[42] In this single-center study, 103 ICU patients were followed (a total of 502 days) and the results showed that CAM-ICU could not be used for patient with a high Richmond agitation sedation scale (RASS) score or a comatose state. In sum, delirium is difficult to diagnose, especially seen in the ICU.

Recently, promising research has been published using single or two leads EEG-based monitoring for detecting delirium. Normal EEG registration is time consuming and therefore not suited for bedside screening. Two lead frontal lobe EEG monitoring has demonstrated high sensitivity and specificity for detection of delirium in post-operative cardiothoracic patients.[45] Moreover, delirium and possible delirium could be detected in older postoperative patients using a brief single-channel EEG recording.[46] In another study in non-intubated adult inpatients, routine clinical EEG findings were associated with delirium and delirium severity.[47] Typical registration of theta or delta EEG slowing strongly correlated with delirium severity across various types of delirium. The typical EEG slowing of background activity pattern predicted poor clinical outcomes such as increased hospital length of stay, and increased mortality. However, to date there are no studies regarding single lead EEG monitoring and short- or long-term, delirium-associated cognitive impairment.

In terms of clinical outcomes, several studies have shown that ICU survivors who had delirium of longer duration have also significantly worse cognitive impairment at 1-year follow-up.[22,30] Several other studies show that

patients who experienced delirium during their ICU stay are at increased risk of developing psychiatric disorders.[48,49]

The exact pathophysiological mechanisms linking delirium with short- and LTCI and mental symptoms are not fully understood, although they are likely multifactorial in nature.[50] Previous literature has suggested the role of genetic predisposition, inflammatory cytokines, decreased cerebral blood flow, and acute breakdown of neural networks in the brain.[2,51] Delirium has also been associated with an atrophy of brain regions involved in executive functioning and memory.[52]

3 | POST-INTENSIVE CARE SYNDROME DEFINITION AND EPIDEMIOLOGY

Despite attempts to improve awareness of PICS, it is still a difficult-to-research phenomenon due to the lack of a clear definition and well-established diagnostic criteria. Furthermore, it is extremely difficult to assess whether reported symptoms are new or worsening. The current expert consensus-based definition is: "all new or worsened impairments in physical, cognitive or mental health impairment originating after critical illness and persisting beyond acute care hospitalization."[53] One or more PICS-related complaints were reported in 64% of ICU survivors after 12 months.[23] When PICS is defined as complaints in all three domains the prevalence is much lower (approximately 4% after 12 months).[23] As stated above, cognitive impairment is often seen in ICU survivors. Approximately 30% of these patients reported cognitive deficits at some point after ICU admission.[22–24] Even socioeconomic problems are present after ICU admission. ICU survivors have more frequent consultations with their general practitioner (up to 5 more times compared to the period before ICU admission). In addition, one third of patients have to deal with reduced income, and even 12 months after discharge, 50% are unable to work at their previous level.[54] Moreover, about 25% of patients need assistance for their daily activities.[54]

Growing evidence suggests that physical and psychological symptoms are correlated in ICU survivors. Patients with physical sequelae may feel more disabled after discharge compared to patients without. Moreover, sequelae such as pain and fatigue have shown its impact on patients' emotional and cognitive state.[55] Among ICU survivors, persistent pain was associated with a higher risk for long-term psychological symptoms, including anxiety, depression, posttraumatic stress, and sleep problems.[56] This suggests that these patients may benefit from interventions aimed to alleviating the burden of pain.

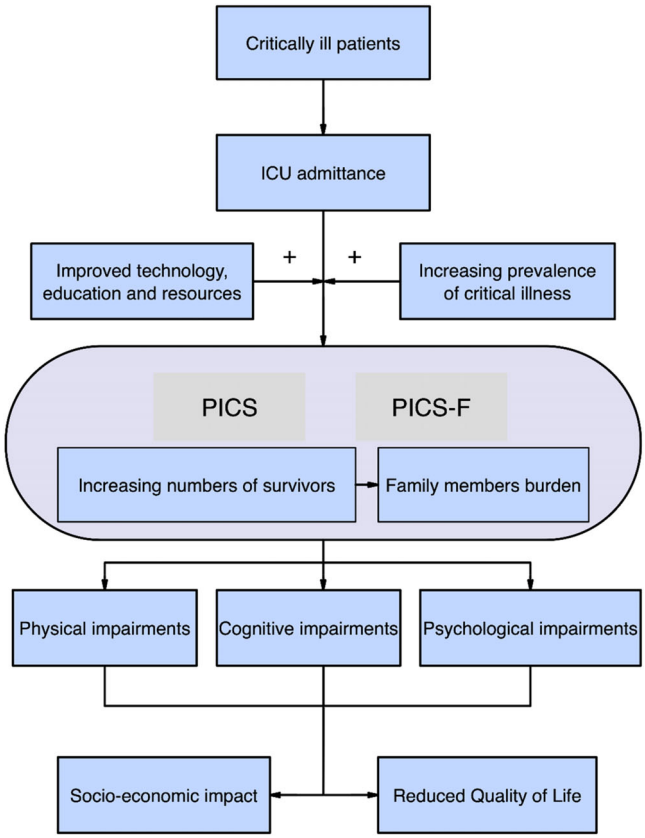

FIGURE 1 Overview of the components of PICS and PICS-F and their relationship to socio-economic impact and quality of life. ICU, intensive care unit; PICS, post-intensive care syndrome; PICS-F, post-intensive care syndrome-family; QoL, quality of life

PICS has been recognized as an important public health and socio-economic problem as millions of patients are discharged from ICUs over the world annually.[20,53,57] A large cohort study from the UK showed that the prevalence of PICS and its psychiatric domains, such as anxiety, depression, and post-traumatic stress disorder (PTSD) were 46%, 40%, and 22%, respectively.[23,58] A recent systematic review points to a prevalence of PICS-related cognitive deficits of around 50% in critical illness survivors.[59] Further, PICS may also be present in significant others and/or caregivers of the former ICU patients mentioned above, which is known as PICS-family (PICS-F).[60] Figure 1 provides an overview of the PICS and PICS-F components and their relationship to socioeconomic impact and poorer quality of life (QoL).

4 | DELIRIUM-RELATED PSYCHIATRIC MORBIDITY

Delirium is currently considered both a complication and a predictor of complications for critical illness patients.[61]

While there is consistent evidence that delirium increases the risk of mortality, physical problems and cognitive dysfunction, interest in adverse mental health outcomes is more recent.

Evidence suggests that the relationship between delirium and psychiatric symptoms and disorders evolves over time. Several mental health symptoms can occur during the acute phase of critical illness, including intrusive memories, delusions, panic attacks, and nightmares.[50] In ICU settings, psychological distress encompasses "any painful emotional, mental, and physical symptoms that are linked with anticipated mood fluctuations."[62] This ICU-related psychological distress includes symptoms of anxiety, depression, and perceived stress, and may correlate with delayed physical and psychological recovery.[62] Three months after discharge, 46% of ICU survivors had probable depression, 44% had anxiety, and 27% had PTSD symptoms.[63]

Moreover, patients who experience delirium often develop long-term psychiatric problems.[64] The major mental health outcomes post-delirium are depression, anxiety, and PTSD, which are collectively considered stress-related or emotional conditions.[50] However, the association between delirium and these emotional problems is controversial. Indeed, both the occurrence of delirium and the duration of delirium have been inconsistently associated with subsequent psychiatric symptoms.[65] In critically ill patients, the combination of delirium and coma during ICU stay increased the risk for the incidence of composite psychiatric symptoms and autonomous functioning at 3 and 12 months after discharge.[66] Moreover, the combination was also independently associated with the presence of anxiety and PTSD symptoms at 12 months.[66] However, in a relatively large study,[67] up to 45% of critical care survivors showed symptoms of depression, anxiety, and/or PTSD at 1 year, but developing delirium during the ICU stay was not associated with emotional outcomes. Still, a systematic review concluded that delirium might predispose ICU survivors to developing psychiatric symptoms, especially depression.[68] In the long term, ICU patients with lived experience of delirium have ever-present feelings of fear and agony,[69] and anxiety symptoms may persist in up to 62% of patients 1 year after discharge.[70]

The relationship between delirium and acute stress disorder and PTSD is complex. Evidence is sparse and controversial regarding delirium as a risk factor for the development of PTSD.[64] Research on post-delirium PTSD has been conducted mostly in general ICUs, where both conditions are prevalent. PTSD symptoms have been found in up to 60% of ICU survivors, prevalence similar to that described among the survivors of a natural disaster.[71] In patients with acute respiratory distress syndrome (ARDS) requiring a very long ICU stay, prolonged duration of delirium (>40 days) was significantly correlated with PTSD symptoms, but not with anxiety and depression.[72]

In contrast, far fewer studies have examined a wider range of psychiatric disorders. A nationwide, retrospective cohort study from Korea found that experiencing in-hospital delirium increased the risk of psychiatric disorders within 2 years of discharge, especially for substance abuse disorder, sleep disorder, and depression in patients requiring ICU care.[73]

Beyond delirium, several risk factors for developing post-ICU psychiatric problems have been described.[74] Modifiable risk factors include length of sedation, and use of benzodiazepines and vasopressors, whereas non-modifiable risk factors include disturbed memories or frightening experiences in the ICU, and preexisting psychiatric problems, and absence of social support across the illness.[74,75] Several risk factors can be used to identify patients who should be screened for long-term PICS symptoms.[75] Specifically, factors before (frailty and pre-existing functional impairments) during (delirium duration, sepsis and adult respiratory distress syndrome) and after (early symptoms of anxiety, depression, or PTSD) critical illness have been suggested in a recent consensus.[75]

5 | LONG-TERM COGNITIVE IMPAIRMENT

Cognitive dysfunction in the course of critical illness spans a continuum ranging from acute ICU admission to months and even years after hospital discharge.[76] Acute impairment of the cognitive sphere, embodied in confused thinking and reduced awareness of the environment, is a central feature of delirium very common in ICU patients undergoing IMV.[77] Beyond this transient state of global brain dysfunction, survivors of a critical illness may also experience LTCI,[78] which represents one of the most prominent sequelae related to PICS due to its high personal and social impact. Indeed, LTCI is a well-established predictor of unemployment status and decreased QoL at 12 and 24 months after ICU discharge,[79,80] which is also associated with functional dependency states that can even affect families' finances.[81]

In ICU survivors, delirium is the leading clinical risk factor associated with LTCI after adjusting for age, education, preexisting cognitive function, and severity of illness.[82–84] Delirium has even been found to be a predictor of post-ICU cognitive deficit over surgery or exposure to sedatives.[85] At the neuroanatomical level, longer duration of delirium has been associated with smaller brain volumes up to 3 months post-discharge, as well as with white matter abnormalities at both discharge and

3 months.[52,86] At the clinical level, especially a longer duration of delirium, but also greater severity, are independent predictors of more severe cognitive deficits both at discharge[8,87–89] and in the long term.[22,82,90–92] Although the literature findings are robust, the relationship between delirium and cognition is influenced by other mediating factors, as not all patients are equally vulnerable to developing LTCI. For example, the APOE4 allele, which is associated with the development of dementia in the general population, represents the first demonstrated genetic predisposition to increased duration of delirium in critically ill patients.[93] With respect to the different subtypes of delirium, sedative-associated, hypoxic, septic, and hypoactive delirium, but not metabolic or hyperactive delirium, appear to have the greatest impact on LTCI.[90,94]

More specifically, LTCI refers to a set of mild to severe deficits circumscribed to specific cognitive domains that appear after ICU discharge, or worsen in the case of previous cognitive impairment, and persist for more than 3 months.[77] Deficits have been observed in attention and working memory, learning and memory, visuospatial ability, executive functions, and processing speed.[95,96] However, consistent with transient neurological changes at the cortical and subcortical levels detected by brain imaging during ICU admission in delirious patients,[97] post-ICU cognitive impairment appears to adopt a frontal-subcortical pattern, characterized by greater impairments in processing speed, executive functions, and memory-related processes.[98] Taken together, these results suggest that modern neuroimaging techniques coupled with neuropsychological testing can help detect patients at risk for cognitive impairment after ICU, thereby predicting outcomes and guiding rehabilitation.[86,99]

In a systematic review of 19 studies dated between 1980 and 2012, cognitive deficits were present in 4%–62% of patients after a follow-up of 2–156 months.[95] More recently, the prevalence of LTCI determined by objective cognitive testing was estimated to be 79% and 71% at 3 and 12 months in the study by Jackson et al.[100] involving 180 medical ICU patients undergoing IMV, 66% and 58% in the study by Pandharipande et al.[22] which included 821 medical/surgical ICU patients with respiratory failure, cardiogenic shock or septic shock, and 47% and 41% in the study by Haddad et al.[92] which included 1040 medical/surgical ICU patients with respiratory failure or shock. Against this background of highly variable data, a systematic review of 49 articles without date restrictions points to a mean prevalence of 61% and 43% at 3 and 12 months, respectively.[59] However, the diagnostic heterogeneity in critically ill patient limits our ability to draw firm conclusions that can be extrapolated to all patients. In fact, patients with respiratory failure, especially ARDS, are known to show the highest prevalence of LTCI, which can be as high as 80% of cases 1 year after hospital discharge.[101,102] Similarly, a study involving 2345 individuals reports that cognitive complaints 12 months after ICU discharge are more frequent in emergency surgery patients (13%), followed by medical patients (11%) and elective surgery patients (6%).[103] Overall, these studies point to the existence of different pathophysiological mechanisms for the development of cognitive impairment among different ICU populations. In this regard, there is evidence that, as a consequence of lung-brain crosstalk,[104] patients who have undergone IMV and/or experienced delirium during admission are more prone to develop chronic sequelae (>24 months) compared to other clinical subgroups not affected by these conditions.[59] It is also worth mentioning that the use of benzodiazepines has been associated with an increased risk of post-ICU cognitive impairment.[75]

Interestingly, the prevalence of LTCI differs when objective or subjective cognitive measures are applied. Objective cognitive assessment is administered by a neuropsychology professional and involves the use of standardized tests. Subjective assessment of cognitive status involves the administration of self-reported measures of perceived deficits or cognitive complaints. Brück et al.[105] observed in 100 survivors of a general ICU that the prevalence of objective cognitive deficits decreased from 34% to 18% and 16% at 3, 6, and 12 months after discharge, while there were no significant differences in deficit perception, indicating a discrepancy between objective and subjective cognitive performance already described in other clinical populations.[106] Still, there is agreement in considering that while objective deficits tend to decrease over time, subjective deficits remain stable or even increase depending on the emotional state of patients.[59]

6 | ASSESSMENT OF NEUROCOGNITIVE AND PSYCHIATRIC MORBIDITIES IN POST-ICU PATIENTS

In the early 2000 s, an expert consensus highlighted the need to include neuropsychological assessment as a patient-centered outcome.[107] Since then, a large body of scientific literature has verified the presence of post-ICU, delirium-associated cognitive impairment, calling for the inclusion of objective cognitive assessment as part of the standard of care for the critical illness survivor. To this end, two trends have been followed: (1) the use of screening assessment tools and (2) the administration of comprehensive neuropsychological batteries.

The use of screening techniques allows a quick and brief assessment (10–15 min) that can be performed by different health professionals linked to the ICU but without specific training in neuropsychology. On the downside, screening tests do not allow an accurate multidomain assessment and offer a less comprehensive result, which could mask subtle deficits and make it difficult to monitor the evolution of cognitive status. Although different screening tools have been used, such as the clock drawing test,[108] the Mini-Cog[65] or the Montreal cognitive assessment (MoCA),[109] the mini-mental state examination (MMSE) has been the most widely utilized. However, the MMSE may not be the most optimal tool for assessing PICS-related cognitive deficits, as it was designed to detect cognitive impairment in the context of Alzheimer's disease. In fact, as recently highlighted by a systematic review,[59] the use of the MMSE in ICU survivors underestimates the actual prevalence of cognitive impairment by almost half compared to studies that administered comprehensive neuropsychological batteries (36% vs. 61% at ICU discharge). In contrast, the MoCA instrument better matches the frontal-subcortical pattern observed in ICU survivors, making it a preferable option. Moreover, it has been recently recommended by PICS experts for the assessment of LTCI, as it allows a rapid and accurate screening for mild cognitive deficits, regardless of etiology.[70] It broadly assesses short-term memory, visuospatial abilities, executive functions, attention, concentration and working memory, language, and temporal and spatial orientation. In addition, it has several versions to avoid the learning effect when used repeatedly on the same person and can be used with individuals of different ages, educational levels, and cultures. However, a brief training and certification are required prior to its administration.[110]

Comprehensive neuropsychological batteries (approximately 60 min) consist of different selected tests that allow an in-depth evaluation of brain functions, assessing multiple cognitive domains and detecting subtle deficits that may go unnoticed in screening tests despite being reported by some patients, particularly those with a high educational level. In ICU studies, the most commonly used battery is the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).[22,37] The RBANS has been shown to be sensitive for the detection of cognitive impairment in a wide range of clinical populations[111] and enables to obtain five independent indexes (immediate memory, visuospatial/constructive, language, attention, and delayed memory) as well as a global cognition score. However, it does not include measures of information processing speed or executive functions, which are core features in the frontal-subcortical pattern observed in ICU survivors, so studies are often forced to administer it together with some complementary tests (e.g., the trail making test). The alternative to the use of ready-made neuropsychological batteries is the generation of test compendia specifically designed by a neuropsychology professional.[17,108] This option can allow tailoring the assessment to the neuropsychological profile described in post-ICU survivors and the individual patient needs as well as refining the interpretation of the results. Considering the above information, we suggest a neuropsychological test battery that integrates the most relevant literature on neurocognitive assessment in critically ill patients going beyond the RBANS[100,112] and supported with the authors' clinical and research experience[98,113] (Table 1). This is only intended to be an indicative proposal that reflects the authors' recommendation based on clinical and research practice and the most frequently used tests and procedures in the scientific literature.

Cognitive dysfunction in post-ICU patients may change over the recovery phase, so cognitive assessment in critically ill patients should also be based on continuous and dynamic assessment methods that adjust to the patient's stage of recovery and specific needs (e.g., altered emotional state), the potential risk of chronification, relevant events within the recovery process (e.g., return to work), and available clinical resources. In this context, in frail patients or those with suspected pre-existing cognitive impairment or emotional disturbances, it is also advisable to administer screening tools for premorbid status (such as the Informant Questionnaire on Cognitive Decline in the Elderly or the short form of the Geriatric Depression Scale)[114,115] early at hospital stay, to estimate their baseline status and consider them directly as candidates for a PICS assessment at hospital discharge. With this instrument, we found a high prevalence of cognitive dysfunction showing a slight decline in 64.3%, moderate decline in 27.4% and severe decline in 8.2% from a consecutive series of 213 patients prior to ICU admission.[116]

Despite being different conditions, psychiatric morbidity and LTCI are intertwined in several ways.[117] In cohort studies, one or more PICS problems are present in most critical illness survivors, and co-occurrence is relatively common.[23] Moreover, it is well known that stress-related conditions, especially depression, are associated with executive dysfunction and impaired memory, and can worsen previous cognitive deficits, and vice versa. In ICU survivors, executive dysfunction has been correlated with depression and poorer mental health-related QoL.[118]

The association between delirium and emotional problems is somehow controversial.[119] The timing of assessment likely influences the prevalence of late-onset psychological conditions, such as PTSD, which must be distinguished from acute stress disorder. Symptoms of

TABLE 1 Summary of the most used tests and proposal for a comprehensive neuropsychological examination

Cognitive domain	Neuropsychological test	Administration time (minutes)	Recommendation level
Attention	Forward digit span WAIS-IV	5	Recommended
	Forward spatial span WMS-III	5	Optional
	Continuous performance test 3	15	Optional
Working memory	Backward digit span WAIS-IV	5	Recommended
	Backward spatial span WMS-III	5	Optional
	Mental control WMS-III	5	Optional
Learning and memory	Rey auditory verbal learning test	15	Recommended
	Logical memory WMS-III	15	Optional
	10/36 spatial recall test	15	Optional
	Rey–Osterrieth complex figure	15	Optional
Executive functions	Trail making test	5	Recommended
	Phonetic verbal fluency	5	Recommended
	Stroop color and word test	5	Optional
	Semantic verbal fluency	2	Optional
Visuomotor and processing speed	Symbol digit modality test	5	Recommended
	Symbol search WAIS-IV	5	Optional
	Coding WAIS-IV	5	Optional
Motor speed	Grooved pegboard test	5	Recommended
	Finger tapping test	10	Optional

Note: Different tests are offered per cognitive domain, although the recommendation for the composition of the neuropsychological assessment battery is to select one test per domain (two in the case of executive functions).
Abbreviations: WAIS, Wechsler adult intelligence test; WMS, Wechsler memory scale.

acute stress disorder present immediately after the traumatic event and last up to a month, whereas PTSD symptoms present slower, up to 6 months after the trauma, and last longer, up to several months or years.[3] Thus the incidence of late-onset psychological symptoms may not be fully captured in follow-up studies up to 6 months after delirium.[68] Moreover, the evaluation of PICS-related psychological problems should begin in the early recovery phase, within 2–4 weeks of hospital discharge. Additional follow-up assessments should be prioritized for high-risk patients, and positive screening tests should be used for referral to specific outpatient clinics and/or more detailed evaluations.[75] There is evidence that screening with validated tools as early as 1 week after ICU stay correlates with psychological outcomes at 3 months and thus can enable early intervention.[120]

In most cases, emotional symptoms are assessed by self-report with screening questionnaires and less so by clinical diagnostic interviews. Despite being more burdensome, clinical interviews represent a more fine-grained diagnostic procedure. Moreover, conducting a comprehensive assessment is critical because the three major psychological symptoms (anxiety, depression, and PTSD), is critical because they usually co-occur with each other. Indeed, patients showing symptoms of one psychiatric condition have a 64% chance of comorbidity with symptoms of another.[31]

Several expert recommendations on the screening tools to detect psychiatric morbidity after critical illness have been issued in recent years.[75,121] According to a consensus conference,[75] the hospital anxiety and depression scale (HADS)[122] was strongly recommended for anxiety and depression, and the impact of event scale-revised (IES-R)[123] or the abbreviated IES-6[124] were weakly recommended as screening tools for PTSD.[75] Another expert consensus[121] proposed a two-step evaluation in outpatient care settings. The patient health questionnaire-4 (PHQ-4)[125] was recommended as a first-step assessment of broad domain of mental health. An extended, second-step assessment is warranted for ICU survivors with a significant impairment on the PHQ-4. In this case, the patient health questionnaire-8 (PHQ-8),[126] the generalized anxiety disorder scale-7 (GAD-

TABLE 2 Summary of the most used screening questionnaires and proposal for a comprehensive psychological examination

Psychological symptoms	Questionnaire	Number of items	Administration time (minutes)	Recommendation level
Depression and anxiety (broad domain)	Hospital anxiety and depression scale (HADS)	14	5	Recommended
	Patient health questionnaire, 4 items (PHQ-4)	4	2	Recommended
Depression	Patient health questionnaire, 8 items (PHQ-8)	8	4	Optional
Anxiety	Generalized anxiety disorder, 7 items (GAD-7)	7	4	Optional
PTSD	Impact of event scale-revised (IES-R)	22	10	Recommended
	Davidson trauma scale (DTS)	17	8	Recommended

Abbreviation: PTSD, post-traumatic stress disorder.

7)[127] and the IES-R were recommended to separately screen for depression, anxiety, and PTSD. In clinical practice, the HADS is the most used screening tool for anxiety and depression, and the IES and the Davidson trauma scale (DTS)[128] are among the most frequently used tools to assess PTSD. In Table 2 we summarize the most used screening tools and suggest a comprehensive examination of PICS-related psychiatric morbidity.

7 | FUTURE PERSPECTIVES AND RESEARCH AGENDA

Current research on the detection and follow-up of psychological and cognitive sequelae in patients who have experienced delirium during ICU admission and are at risk of PICS is limited by several factors. These include differences in study design and methodology (e.g., disparity in the timing and frequency of follow-ups, assessment tools, and cut-off scores), the heterogeneity of the critically ill patient (e.g., disparity in diagnoses and reasons for admission), how LTCI is conceptualized (e.g., objective performance versus subjective perception), and how physical, emotional, and cognitive states interact with each other.

According to a systematic review, most of the available screening tools do not have suitable psychometric properties to predict PICS-related outcomes after critical illness.[129] For instance, it is unclear whether these tools are feasible in specific populations of critical illness patients, such as those with delirium, stroke, and sedation.[62] Therefore, further refining screening instruments should be prioritized in clinical practice and research. Specifically in relation to LTCI, there are promising initiatives based on the use of computerized batteries. Such tools have been shown to be effective as screening instruments for cognitive assessment and can characterize the profile of cognitive deficits. Although their use in critical illness survivors is still in its infancy, digital assessment tools should be considered due to their potential cost–benefit advantage compared to the use of paper-and-pencil tests.[130,131] Some recent initiatives have also emerged that focus on the prevention and rehabilitation of the cognitive and psychological sequelae using both paper-and-pencil and computerized strategies.[113,132,133] Given the high personal, social, and economic impact of these deficits, efforts to develop and improve such initiatives may be worthwhile.

From a more clinical point of view, it is important to start establishing assessment processes and healthcare circuits that allow early detection of cognitive and psychological deficits, the identification of late-onset emotional symptoms (e.g., PTSD), and monitoring ICU survivors along the entire recovery process. Ideally, these conversations should involve critical illness survivors, their significant ones, and clinicians of different specialties, e.g., intensive care medicine, neuropsychology, psychiatry, surgery, and internal medicine, among others.

Based on our clinical and research experience as well as recent expert recommendations,[75,134] we provide a potential example of a hybrid face-to-face and remote assessment process regarding neurocognitive and psychiatric outcomes specifically designed for critical illness survivors at risk of PICS (e.g., delirium during ICU). This proposal is based on the administration of the screening tools and instruments recommended in previous sections at different points over 1 year (e.g., hospital discharge or during the 2–4 first weeks, 3 and at 12 months) (Figure 2). The algorithm is a suggestion for a potential assessment and follow up process that may need further testing.

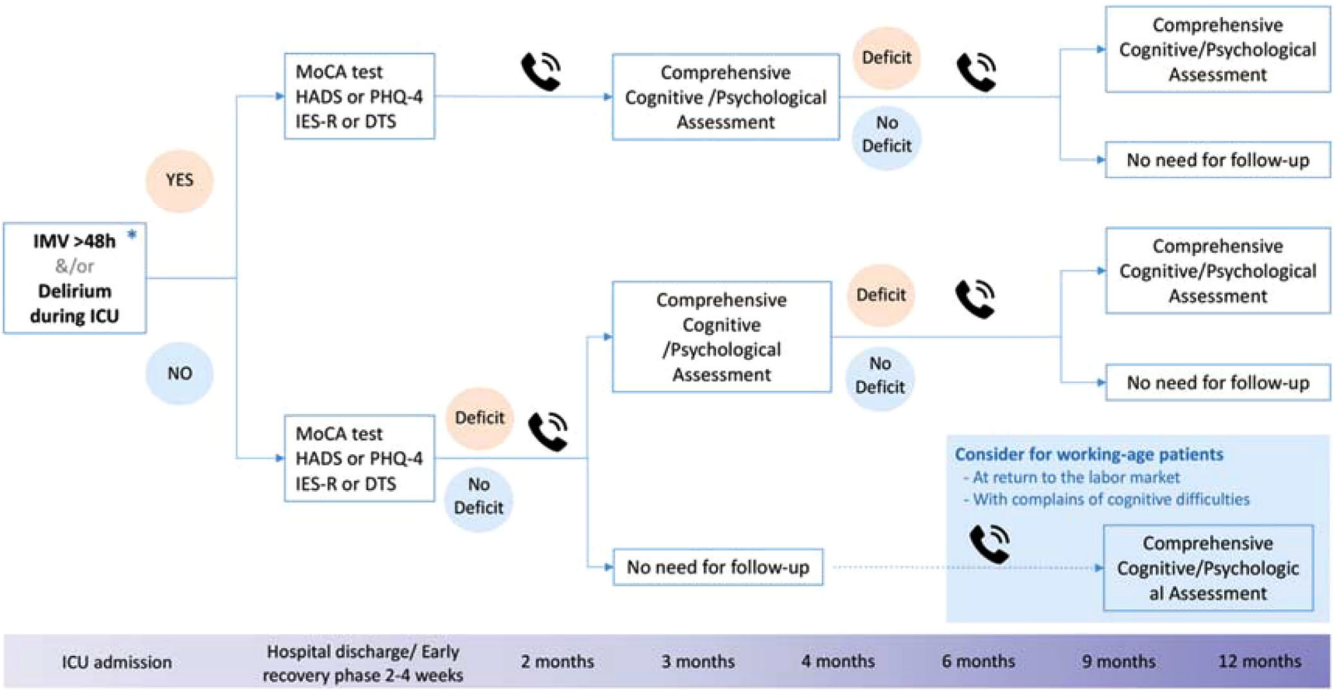

FIGURE 2 Proposed cognitive and psychological assessment algorithm. DTS, Davidson trauma scale; HADS, hospital anxiety and depression scale; ICU, intensive care unit; IES-R, impact of event scale-revised; IMV, invasive mechanical ventilation; MoCA, Montreal cognitive assessment; PHQ-4, patient health questionnaire, 4 items. * Other risk factor for cognitive/psychological deficit (e.g., cognitive impairment prior to the ICU admission, preexisting psychiatric conditions, older age, etc.) should be also considered. Consider telephonic psychological screening in high-risk patients (see "Delirium-related psychiatric morbidity" section). In all ICU survivors it is advisable to administer a screening battery for the detection of psychological and cognitive alterations at hospital discharge or within the first 2–4 weeks of the recovery phase. In *critically ill patients with the presence of risk factors for PICS* sequelae during ICU admission, regardless of the result of the screening tests, it is recommended to perform a comprehensive assessment of the cognitive and psychological status at 3 months post ICU discharge. In case of a positive result (presence of deficits), assessment at 12 months would be mandatory. In the critically ill patients with risk factors for PICS, a brief telematics follow-up of the state of psychological and cognitive difficulties should be carried out at 2- and 6-months post ICU discharge in order to monitor their evolution and rule out incident symptoms (e.g., PTSD symptoms). In *critically ill patients without the presence of risk factors for PICS* sequelae during their ICU stay, if the results of the screening tests at hospital discharge (or in the initial 2–4 weeks of the recovery phase) are negative, it would not be necessary to carry out subsequent follow-ups. However, it may be advisable to consider telephone screening, and even more extensive evaluations, at 6 and/or 12 months in working-age patients. In case of positive results in the screening tests, continuing the same flowchart as in patients with risk factors during ICU admission would be advisable. Presence of cognitive deficit should be defined by the cut-off of the MoCA test (<26 points) or by the interpretation of the neuropsychologist professional in the case of the comprehensive neuropsychological battery. However, as suggested by Jackson et al.[101] cognitive deficit can be considered attending to the z-score results as moderate alteration (≤1.5 SD below the mean) on two or more cognitive domains or else when patient scored severe (≤2 SD below the mean) on one or more of cognitive domains. Presence of psychological problems should be defined by the cut-off of screening questionnaires to assess depression and anxiety symptoms (HADS >7 or PHQ-4 >5) and PTSD symptoms (IES-R > 1.5 or DTS >40).

An efficient management of PICS-related outcomes consists of the early identification and treatment of cognitive and psychiatric comorbidities. Early identification includes the recognition and the assessment of symptoms as early as possible after delirium and, when indicated, conducting serial evaluations over time, also during the transition of critical illness survivors to outpatient care settings.[75,134] It is expected that addressing some of the suggestions above may increase clinicians' awareness and decrease the complications associated with PICS, and ultimately enhance patients' functional outcomes and QoL.[68] Finally, it is acknowledged that systematic reviews, rather than narrative reviews, can provide more robust evidence for this purpose.

To conclude, delirium is a complex, but common phenomenon in the ICU and its morbidity is significant. Delirium, as a main risk factor for developing PICS, is a challenging diagnosis, although clinicians should focus on its early detection and the already well-known delirium preventative measurements. Therefore, the neuropsychiatric status of critically ill patients should currently be understood as a continuum encompassing the acute

stage, the hospitalization, and the survival phase after discharge. It is necessary to develop follow-up programs and neuropsychiatric evaluation batteries that allow us to approach both the delirium and the PICS-related sequelae from a comprehensive and patient-centered perspective with the aim of reducing its impact on a personal, medical, and economic level.

AUTHOR CONTRIBUTIONS

The initial idea for a project was generated by a team consisting of Dharmanand Ramnarain, Sjaak Pouwels, and Vicent Balanzá-Martínez. The team then conducted a comprehensive literature search, which included the contribution of all authors. The article was written collaboratively by all the members of the team. All authors gave their final approval to the article.

ACKNOWLEDGMENTS

We thank Mercè Jodar, PhD, for her contribution to the design of a comprehensive neuropsychological battery and the algorithm for emotional and cognitive follow-up of the surviving ICU patient.

FUNDING INFORMATION

No funding is received for this work.

CONFLICT OF INTEREST STATEMENT

Sol Fernández-Gonzalo and Guillem Navarra-Ventura are authors of the early neurocognitive rehabilitation in intensive care (ENRIC) platform (source code protected under copyright and duly registered at SafeTheProof with registration number 960–951, 848, 947, 944–940). The other authors declare no conflict of interests.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/acps.13534.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ORCID

Dharmanand Ramnarain https://orcid.org/0000-0001-8005-2780
Sjaak Pouwels https://orcid.org/0000-0002-6390-7692
Sol Fernández-Gonzalo https://orcid.org/0000-0003-0267-0617
Guillem Navarra-Ventura https://orcid.org/0000-0001-9839-7357
Vicent Balanzá-Martínez https://orcid.org/0000-0001-7772-7396

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How to cite this article: Ramnarain D, Pouwels S, Fernández-Gonzalo S, Navarra-Ventura G, Balanzá-Martínez V. Delirium-related psychiatric and neurocognitive impairment and the association with post-intensive care syndrome—A narrative review. *Acta Psychiatr Scand*. 2023;147(5):460-474. doi:10.1111/acps.13534