

Long-term outcomes after critical illness

A Concise Clinical Review

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Abstract

Impairments in function after resolution of critical illness are common and may be under-recognized. Cognitive dysfunction, mood disorders, respiratory impairment, physical debility and reduced quality of life, occur at high rates among survivors of critical illness, with important clinical and public health implications. The elderly, patients with preexisting comorbidities, and those experiencing delirium during hospitalization are at elevated risk for impairment after critical illness resolves. Predicting impairment after critical illness and developing interventions to prevent impairment are areas of ongoing research.

Introduction

In the United States, approximately 5.7 million adults are admitted to the intensive care unit (ICU) each year and greater than 4.8 million individuals survive.¹ Although the incidence of common critical illness syndromes such as severe sepsis and acute respiratory distress syndrome (ARDS) have increased, improvements in treatment have also led to increases in survival.^{2,3,4,5,6}

While some survivors do return to their pre-critical illness level of functioning and health, many experience impairments in cognition, mental health, and physical and quality of life functions.⁷ A new impairment in one or more of these domains is referred to as post-intensive care unit syndrome (PICS).⁸ PICS excludes patients admitted with traumatic brain injury and stroke and is identified in the immediate period following critical illness.

As more individuals survive critical illness, the goals of critical care extend well beyond mortality outcomes and clinicians are challenged with the task of understanding and managing the pathologic consequences of surviving critical illness. The purpose of this review is to describe the incidence, risk factors, clinical manifestations, management, and outcomes for each domain of PICS.

Impairments in Cognition After Critical Illness

Cognitive and mental health impairments encompass post-ICU neuropsychiatric disabilities (figure 1). Post-ICU cognitive impairments are reported to occur between 25-78%.^{9,10,11,12,13,14} Impairment has been demonstrated across a range of cognitive domains with deficits consistently observed in memory, attention, concentration, mental processing speed, and executive function.¹⁵ The most common impairments are deficits in memory and executive functioning, both necessary for independent living.

Most studies report onset of cognitive deficits immediately post-discharge, at 3 months, 6 months, and up to 1-year, with the suggestion of a plateau effect beyond 1 year.^{9,15}

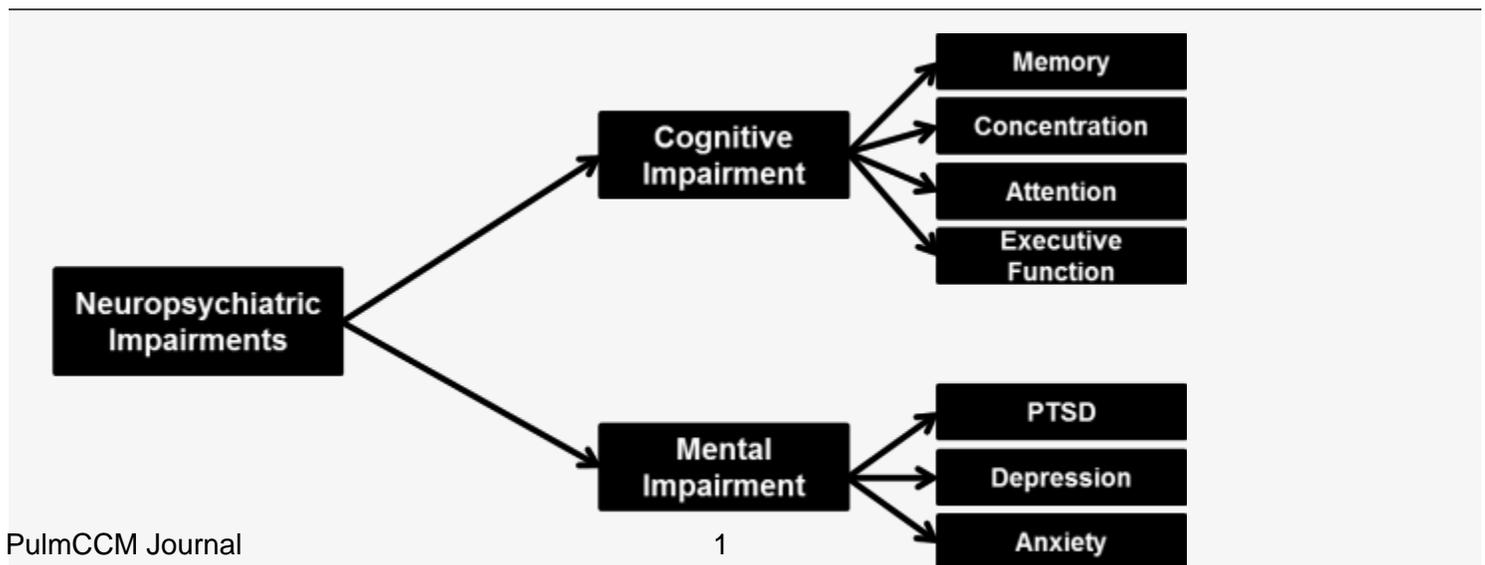


Figure 1. Post intensive care unit neuropsychiatric impairments. PTSD, post-traumatic stress disorder

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Pandharipande and colleagues enrolled 821 patients with respiratory failure or shock, evaluated them for in-hospital delirium, and assessed their global cognition and executive function at 3 and 12 months. At 3 months, 40% of patients had global cognition scores that were worse than those typically seen in patients with moderate traumatic brain injury, and 26% had scores similar to scores for patients with mild dementia.¹¹ The deficits persisted at 12 months in a substantial minority (24-34%) of patients.¹¹

Hopkins and colleagues recruited 55 survivors of severe ARDS and found that at the time of hospital discharge, 100% had difficulty with memory, concentration, attention, or global loss of cognitive function. At 1 year, 78% still had impairment of at least one cognitive function.¹⁶

Studies demonstrate cognitive dysfunction improves but can persist for years. In elderly patients with severe sepsis, Iwashyna and colleagues demonstrated >4-fold increase in post-ICU moderate or severe cognitive impairment lasting up to 8 years.¹⁴ Using a short cognitive performance test, Rothenhausler demonstrated 100% of ARDS survivors had cognitive dysfunction at the time of discharge. Cognitive dysfunction persisted in 30% at 1-year and 24% had mild to moderate impairments in attention skills at 6-year median follow-up, particularly in speed of information processing.¹⁸

Early identification of cognitive impairment could theoretically expedite appropriate evaluations and treatment, although beneficial effects are yet to be demonstrated. In the critical care setting, an evaluation for cognitive dysfunction must be brief, easy to administer, and widely applicable.¹⁹ Validated impairment screening tests include the Modified Mini-Mental State examination (MMSE), the Mini-Cog, and the Montreal Cognitive Assessment (MoCA).^{20,21,22} However, the MMSE and Mini-Cog do not predict long-term cognitive sequelae at 6-month follow-up, and these tests cannot be recommended to evaluate for long-term cognitive impairment.¹⁹ The MoCA is a 10-minute cognitive screening tool with greater sensitivity than the MMSE to detect mild cognitive impairment.²² However, the MoCA's predictive accuracy for long-term cognitive dysfunction is likewise unknown.

Management strategies to preserve cognitive function have been promoted, although strong evidence does not exist to support or refute their use. These include screening for and minimizing delirium, reducing sedation, providing sedation holidays, and prevention and mitigation of risk factors such as hypoglycemia, hypoxemia, and hypotension.¹⁵

The presence and duration of delirium is a risk factor for the development of post-ICU cognitive dysfunction.^{10,11,13} However, it remains unproven whether delirium is itself deleterious, or is merely a marker for more severe illness and preexisting dysfunction.

Wolters and colleagues prospectively analyzed data on 1102 survivors of critical illness over a 2-year period at a single-center ICU. Thirty-seven percent of patients had delirium during their ICU stay. Patients with any delirium during their ICU stay experienced significantly greater mild or severe self-reported problems in cognitive functioning compared to those without delirium during their ICU stay.¹³ Girard and colleagues demonstrated the duration of delirium amongst mechanically ventilated medical patients was independently associated with long-term cognitive impairment.¹⁰ Conversely, significant cognitive impairment has also been demonstrated in those who never experienced delirium during their ICU stay.¹⁷

Other risk factors for post-ICU cognitive dysfunction include pre-existing factors such as anxiety, depression, prior cognitive deficits, diagnoses such as severe sepsis and ARDS, and ICU acquired factors such as hypoxemia, hypoglycemia, hypotension, and sedation (figure 2).¹⁵

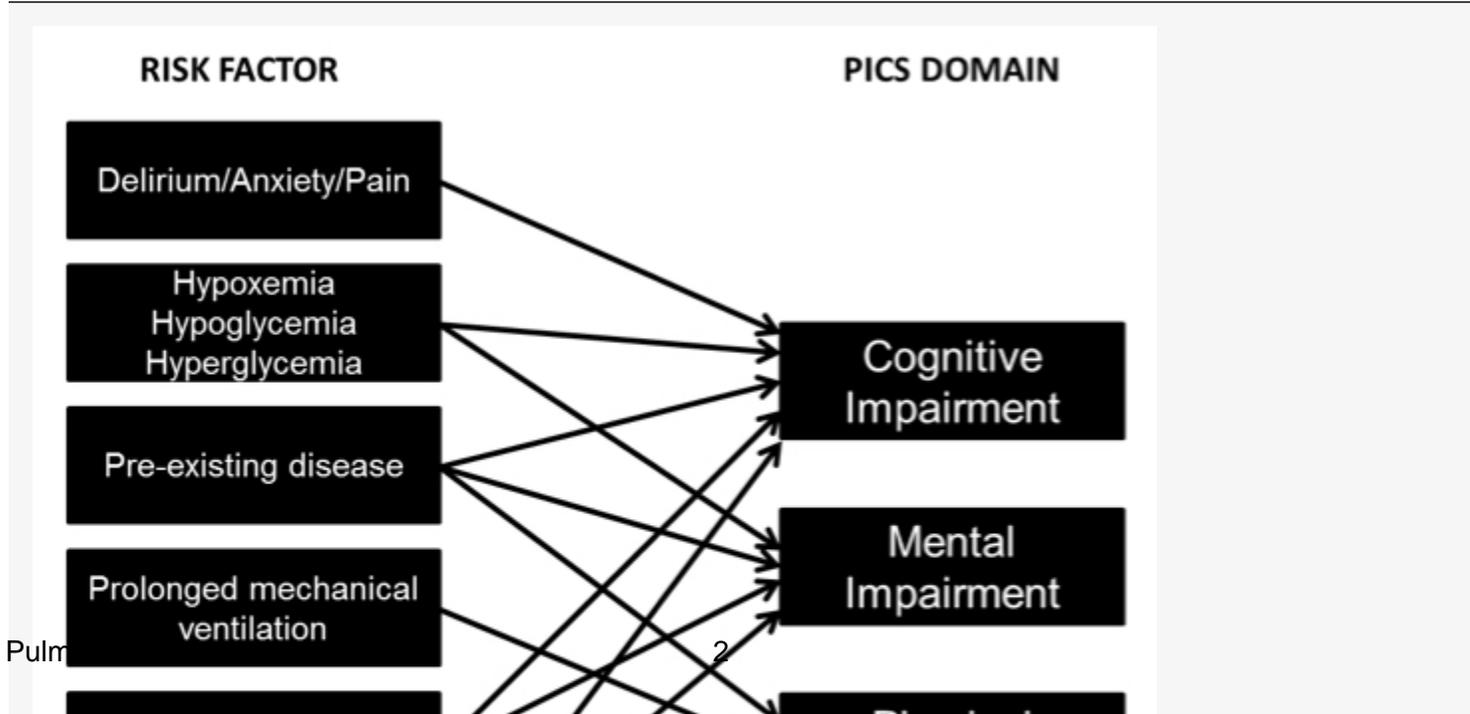


Figure 2. Risk factors for post-intensive care unit syndrome (PICS). ARDS, acute respiratory distress syndrome; MOF, multiple organ failure; NMB, neuromuscular blocker.

Impairments in Mental Health After Critical Illness

Mental health impairments occur frequently after critical illness and are comprised of depression, anxiety, and post-traumatic stress disorder (PTSD) (figure 2). A national database of 24,000 survivors of critical illness reported that 1% of survivors of nonsurgical critical illness had a new psychological disorder, and 19% received one or more prescriptions for psychoactive medications.²³ The prevalence of major depression amongst the general population in the United States is 17%.²⁴ In comparison, two systematic reviews identified the median prevalence of depressive symptoms to be 28% in general ICU survivors.^{15·25·26}

More recent data from the BRAIN-ICU cohort suggests an even greater prevalence of depressive symptoms, occurring in 30% at 3 months and 29% at 12 months post-ICU survival.²⁷ The most common findings include fatigue, loss of interest, poor appetite, a sense of hopelessness, and insomnia. Since all of these studies excluded patients with pre-existing depression, these findings suggest critical illness contributes to the development of depression.¹⁵

A systematic review by Davydow and colleagues identified five studies evaluating the prevalence of anxiety in ARDS survivors. The median prevalence of anxiety was 24% (range 23-48%).²⁶ In the same study, the authors identified five studies evaluating the prevalence of PTSD in ARDS survivors. The median prevalence of PTSD as evaluated by questionnaire was 28% (range 21-35%), significantly higher than the general population at 3.5%.^{24·26}

Griffiths and colleagues also found an association between PTSD and sexual dysfunction. One-hundred and eight survivors of critical illness completed a full questionnaire at 12-months. Fifty of 108 reported sexual dysfunction, and of these, 64% had PTSD ($p=0.019$).²⁸ There are several overlapping risk factors for the post-ICU psychiatric complications. Patient-level risk factors include pre-ICU psychiatric symptoms, younger age, lower educational status, and female gender.¹⁵

One study demonstrated a personality trait of pessimism to be a risk factor for PTSD, anxiety, and depression.²⁹ Disease related factors include severe sepsis and ARDS, trauma, hypoglycemia, and hypoxemia.^{9·15·16·30·31·32·33·34} ICU related factors such as duration of sedation, mechanical ventilation, and ICU stay each predicted later depressive symptoms.²⁶ Particular risk factors for PTSD include traumatic or delusional ICU memories, duration of sedation and opiates, breathing difficulties, and nightmares.^{26·35}

The mechanisms surrounding post-ICU psychiatric complications are unclear. Sedatives such as benzodiazepines may be primarily implicated in the development of depression and PTSD, perhaps by contributing to the development of delirium.³⁶ Data indicates lighter sedation may be protective for PTSD.^{15·30·31·37·38} Reduced cortisol level has been implicated in the development of PTSD.³⁵ Retrospective data and a small randomized controlled study of 20 patients have suggested augmentation of cortisol in critical illness may reduce the risk of PTSD.^{39·40}

All patients suspected of having a post-ICU psychiatric complication should undergo a formal mental health screening. Numerous screening tests for depression and PTSD are available, but none have been validated for use in post-ICU psychiatric complications. These include a hospital anxiety and depression scale, the Beck Depression Inventory and the post-traumatic stress syndrome 10-question inventory.^{41·42·43}

Based on the known risk factors, reducing ICU sedation and preventing hypoglycemia and hypoxemia may reduce post-ICU psychiatric complications.¹⁵ Maintaining an ICU diary by family members has also been shown to decrease symptoms of PTSD by fostering the formation of factual memories.^{44·45} Jones and colleagues randomized 352 patients at 1-month post-ICU discharge to receive their diary (written by healthcare workers and family during the ICU stay) immediately or after 3-months. The incidence of PTSD was significantly less at 3 months (5 vs 13%, $p=0.02$) in the group receiving the diary at time of randomization.⁴⁵ Garrouste-Orgeas et al demonstrated in a prospective before-after study an ICU diary reduced PTSD symptoms at 12-months, though the reduction was greater in relatives than in patients.⁴⁴

Impairments in Physical Function and Quality of Life

Post-ICU physical impairments are broadly divided into pulmonary and extra-pulmonary complications. The spectrum of extra-pulmonary impairments include ICU acquired weakness (ICU-AW), impairments in activities of daily living (ADL), renal dysfunction, ischemic digits, heterotopic ossification, and cosmesis secondary to ICU procedures or contractures.⁴⁶ Discussion of extra-pulmonary complications will be limited to ICU-AW and ADL impairments.

Respiratory impairment

Pulmonary abnormalities include radiographic and abnormal pulmonary function testing. Radiographic pulmonary abnormalities

following ARDS survival are often limited to minor, nondependent pulmonary fibrotic changes identifiable on interval follow-up computed chest tomography (CT).⁴⁷ Pulmonary function abnormalities include reduction in diffusion capacity, abnormal spirometry, and abnormal lung volumes.^{15,36,48} Amongst ARDS survivors, diffusion abnormality is the most commonly seen pulmonary function test impairment, with normalization at 5-years post-ICU.³⁶ Spirometry and lung volumes in ARDS survivors were abnormal at 3 months with normalization at 6 months post-critical illness.¹⁵ The pulmonary abnormalities are not believed to be related to parenchymal abnormalities. Rather, these changes are thought to be related to extra-pulmonary respiratory and diaphragmatic weakness.^{49,50} In fact, the decrease in physical functioning 5-years post-ICU, as measured by the 36-item short form health survey (SF-36), is related to extra-pulmonary muscle weakness.⁴⁷ Using the 76-item pulmonary disease specific St. George's Respiratory Questionnaire, Davidson and colleagues demonstrated ARDS survivors had significantly worse scores than similarly ill critical care controls, concluding there was an ARDS-specific, pulmonary component to physical impairment.⁵¹ Evaluations for pulmonary impairments include spirometry, lung volumes, and diffusion capacity.

Non-respiratory physical impairment

Intensive care unit-acquired weakness is the most common non-pulmonary physical impairment, occurring in 25% of ICU survivors.^{11,53,54} Clinical manifestations include abnormal exercise endurance, muscle weakness, poor mobility, paresis, polyneuropathy, contractures, and weight loss with malnutrition.^{36,47,48,55} These non-pulmonary impairments can be measured by 6-minute walk distance (6MWD), electromyography and nerve conduction studies, and evaluation by physical and occupational therapists. Hermans et al, in a prospective trial, demonstrated ICU-AW worsens 1-year mortality.⁵⁴ The etiology of increased mortality is associated with diaphragmatic and pharyngeal muscle weakness promoting respiratory infection, sarcopenia, and gait disturbances promoting falls.

Herridge et al demonstrated ARDS survivors had 24% reduction in walk distance, as compared to age and sex-matched controls in critical illness.⁴⁷ Worse, ARDS survivors had a 6MWD which was impaired up to 5-years post-ICU.⁴⁷ ICU-AW also increases hospital morbidity and increase healthcare utilization.¹⁵ Risk factors for non-pulmonary physical impairments such as ICU-AW include severe sepsis, ARDS, multiple organ failures, older age, corticosteroid use, and prolonged mechanical ventilation (PMV).^{14,47,48,56} PMV is defined as mechanical ventilation for ≥4 days with tracheostomy placement or mechanical ventilation for ≥21 days without tracheostomy. PMV is a substantial marker for post-ICU physical impairment. A study from Duke University Medical Center revealed PMV was associated with a 47% incidence of moderate or complete functional dependency one year post-ICU.⁵² A retrospective evaluation of Medicare administrative database concluded that PMV is a marker of both in-hospital morbidity and long-term morbidity and mortality.⁵⁷ Overall, physical function impairments are most pronounced for older patients and those with ≥2 coexisting illnesses at the time of ICU admission.^{14,47,52}

Impairments in activities of daily living are common in ICU survivors. Severe sepsis survivors >50 years old were shown to have 1.5 new functional impairments following their episode of severe sepsis and to be at-risk for developing new limitations each following critical illness.¹⁴ A study by van der Schaaf et al demonstrated impairments in ADLs in nearly all ICU survivors the first week after discharge.⁵⁸ Angus et al showed 40% of ARDS survivors had reductions in ADLs persisting at 1-year post-ICU.^{15,59} Chelluri et al reported >70% of ICU survivors who were mechanically ventilated >48 hours had impairments in ADLs such as difficulty shopping and taking medications.⁶⁰

Quality of life impairment

The combination of cognitive, mental, and physical impairments has led to a reduction in post-ICU QOL, as compared to normal controls. Independently, pre-existing disease such as malignancy and chronic lung disease are associated with reduction in QOL post-ICU.⁶¹ Furthermore, ICU related factors such as severe ARDS, PMV, severe trauma, and severe sepsis appear to have the greatest reductions in QOL.⁶¹ Furthermore, QOL impairments persist. In a study of 1663 patients, Pandharipande et al demonstrated impairment in QOL up to 36 months without significant improvement.¹¹ And in those with QOL recovery, critical illness survivors are prone to develop new QOL impairments 5-years post-ICU.⁶²

Quality of life measures include specific instruments such as the Euro-QOL-5D (EQ-5D), and Nottingham Health Profile (NHP).⁶¹ Consensus does not exist as to which instrument should be employed; however, the SF-36 and EQ-5D are considered valid and reliable for critically ill patients.⁶¹

Risk stratification and interventions

Developing predictive models to risk stratify and identify patients who are prone to post-ICU physical impairments is an area of ongoing research. Shandle et al developed a screening instrument utilizing variables such as educational level, core stability at ICU discharge, presence of fractures, and ICU stay longer than 2 days each to predict new-onset physical disability following critical illness.⁶³ Carson et al also described a simplified prognostic scoring rule (ProVent score) to aide in predicting long-term outcomes in patients requiring PMV. Age, platelet count, vasopressor requirement, and hemodialysis were shown to represent a reproducible model to identify patients requiring PMV who are at high risk of 1-year mortality.⁶⁴ The use of these predictive

models, as well as regular communication to patients and their families or surrogate decision-makers, have been proposed as methods to reduce unintended ICU sequelae.⁶⁴

Interventions aimed at reducing post-ICU physical impairment should target risk factors. First, since PMV is a significant risk factor for post-ICU physical impairment, current best practices to avoid longstanding impairment of physical function following ICU stay include direct and indirect measures to decrease time on mechanical ventilation. These include limiting sedation, using low tidal volume ventilation, proper oral care, and elevation of the head-of-bed.⁶⁵⁻⁶⁶ Second, avoiding hyperglycemia, corticosteroids, and paralytic agents, whose presence has been associated with ICU-AW, could decrease resultant physical dysfunction.⁶⁷ Third, since physical impairments are likely caused by critical illness polyneuropathy, muscle atrophy, and joint contractures, early and regular mobilization of critically ill patients has been recommended in an attempt to improve functional outcomes.¹⁵⁻⁶⁸ A two-site trial demonstrated mechanically ventilated patients randomized to early occupational and physical therapy within 72 hours of intubation were more likely to return to independent functional status at hospital discharge, compared to patients who received similar rehabilitation starting at a median of 7 days after intubation.¹⁵⁻⁶⁹ Fourth, QOL may be improved with specific interventions such as ICU survivors receiving a rehabilitation handbook, which includes directed exercises and a patient diary.¹⁵ Lastly, PICS clinics have been proposed as a means to integrate specific rehabilitation expertise targeting post-ICU impaired function,⁸ though data on their efficacy is lacking and remains an open area for research.

Conclusions

Over the past 30 years, improvements in the management of critical care syndromes such as severe sepsis and ARDS has led to an increase in survival. The increase in survival has led to the acquisition of cognitive, mental health, and physical dysfunctions. The most common cognitive impairments are memory deficits and abnormal executive functioning. Depression, anxiety, and PTSD encompass mental health impairments, with depression identified in nearly one-third of ICU survivors. Physical impairments include pulmonary and non-pulmonary abnormalities. The most common non-pulmonary abnormalities is ICU-AW with the greatest risk factor being PMV. Impairments in both QOL and ADL are common post-ICU, persisting years after critical illness. Healthcare utilization has increased for post-ICU survivors and this utilization reinforces the effects of critical illness are far reaching, creating a burden for patients and the healthcare system for years beyond ICU discharge¹⁵. As we begin to understand the prevalence, risk factors, and overall effect of post critical illness consequences, further research is crucial in alleviating risk factors and attenuating the impact.

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