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Review: Post-Intensive Care Syndrome: Unique Challenges in the Neurointensive Care Unit

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Abstract

Within the last couple of decades, advances in critical care medicine have led to increased survival of critically ill patients, as well as the discovery of notable, long-term health challenges in survivors and their loved ones. The terms post-intensive care syndrome (PICS) and PICS-family (PICS-F) have been used in non-neurocritical care populations to characterize the cognitive, psychiatric, and physical sequelae associated with critical care hospitalization in survivors and their informal caregivers (e.g., family and friends who provide unpaid care). In this review, we first summarize the literature on the cognitive, psychiatric, and physical correlates of PICS and PICS-F in non-neurocritical patient populations and draw attention to their long-term negative health consequences. Next, keeping in mind the distinction between disease-related neurocognitive changes and those that are associated directly with the experience of a critical illness, we review the neuropsychological sequelae among patients with common neurocritical illnesses. We acknowledge the clinical factors contributing to the difficulty in studying PICS in the neurocritical care patient population, provide recommendations for future lines of research, and encourage collaboration among critical care physicians in all specialties to facilitate continuity of care and to help elucidate mechanism(s) of PICS and PICS-F in all critical illness survivors. Finally, we discuss the importance of early detection of PICS and PICS-F as an opportunity for multidisciplinary interventions to prevent and treat new neuropsychological deficits in the neurocritical care population.

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Keywords

Post-intensive care syndrome; PICS; PICS-family; Critical care

Introduction

Admission to an intensive care unit (ICU) is often a sudden, devastating, and life-threatening event. Discharge from the ICU marks the end of this hyperacute phase, but is just the beginning of the recovery journey for many patients and their informal caregivers.

Critical care advances have meant that more patients are surviving their critical care illness (CCI) [1]. Until recently, the primary focus during hospitalization was on physiological parameters and markers of recovery (e.g., vital sign stability). However, CCI affects survivors' and caregivers' health in unanticipated ways [2]. Survivors often suffer from new or worsened physical, cognitive, and emotional sequelae despite making good recovery of their CCI; informal caregivers can experience substantial emotional distress. These CCI-related sequelae—termed post-intensive care syndrome (PICS) and PICS-family (PICS-F) by the Society of Critical Care Medicine (SCCM) [3]—often become chronic and increase risk for morbidity and mortality [3–5].

Traditionally, PICS and PICS-F have been considered distinct from the sequelae observed in survivors of acute brain injuries (ABI; e.g., traumatic brain injury, TBI; stroke). In order to avoid the confounding effect of the neurological injury on the classical symptoms of PICS, the neurocritical care population has largely been excluded from "PICS"-related research, and neurocritical care physicians have largely been absent from the SCCM PICS stakeholder conferences regarding development and dissemination of information.

The main goal of this paper is to familiarize healthcare providers with PICS and how it might relate to our patients and their informal caregivers. We begin by concisely reviewing the PICS and PICS-F literature in the non-neurosciences population to provide a general understanding of PICS as an acquired phenomenon *in the absence* of known neurological injury. Next, we review the additional impact of neurological injury on cognitive, physical, and emotional outcomes among neurocritical care patients and families, address challenges in studying PICS in this population, and discuss ways to advance the science of recovery among critically ill patients and their families.

PICS and PICS-F in Critical Care Patients Without Acute Brain Injury

Physical Effects of Critical Illness

The most common CCI-related physical impairment is weakness. This includes critical illness polyneuropathy and/or myopathy, which occurs in at least a quarter of medical ICU (MICU)/surgical ICU survivors without preexisting neuromuscular disease [4], and has associated pathological changes [5]. The acquired weakness is independently associated with multiorgan failure (e.g., severe sepsis), sedation, pharmacological (e.g., steroid) treatment, and prolonged mechanical ventilation (> 4–7 days) [5, 6]. Joint contractures can

also occur as a result of limited mobility [7]. These physical impairments increase in-hospital morbidity and also mortality at one year [8].

Cognitive Effects of Critical Illness

Prolonged cognitive impairment is common among survivors of CCI and occurs with a frequency greater than expected when compared with normative data. The most commonly reported domains of cognitive impairment are attention, executive functioning/verbal fluency, visual and working memory, and visuospatial skills [9–12]. Several high-quality prospective studies are worth mentioning.

The Health and Retirement Study (HRS), a national cohort of individuals > 50 years, showed that among 516 surviving respondents with incident sepsis from the HRS, only 6.1% had moderate-to-severe cognitive impairment prior to incident sepsis, with that number increasing to nearly 17% afterward [13]. Similarly, among previously unimpaired MICU patients younger than 55 who require mechanical ventilation, 32% show cognitive impairment in 2 or more cognitive domains 6 months later [9], without any newly appreciated in-hospital neurological injury to explain these new impairments.

In another large, single-center cohort of 821 patients, 40% of the patients had global cognition scores that were similar to scores of patients with moderate TBI (1.5 SD below the population mean), while approximately 25% of individuals had cognitive performance scores similar to patients with mild Alzheimer's disease (2 SD below the population mean) at 3 months post-discharge. At 12 months, these numbers were 34% and 24% [13] indicating some improvement, though a clinically significant number of individuals still do not reach near-normative values [14]. Moreover, these ICU admissions do not need to be long-lasting for onset of short-term and long-term cognitive difficulty; in the Sukantarat et al. [14] study, patients needed to be admitted to the ICU for only 72 hours to be included.

Despite a lack of any known neurological injury in these critically ill patients, there does seem to be an anatomic correlation for these new cognitive deficits. Computed tomography head imaging reveals significant atrophy in acute respiratory distress syndrome survivors compared with age- and sex-matched controls [15]. Using magnetic resonance imaging, VISIONS researchers noted brain atrophy in the frontal lobes and hippocampi of CCI survivors, as well as decreased fractional anisotropy scores (a marker of white matter integrity) in the corpus callosum and anterior limb of the internal capsule using diffusion tensor imaging at 3-month follow-up [11, 16]. These volume and white matter changes correlated with delirium duration, and the white matter changes further correlated with cognitive impairment at 12 months.

Psychiatric Effects of Critical Illness in Patients and Caregivers

Symptoms of depression, post-traumatic stress (PTSD), and anxiety are common after CCI and often become chronic, negatively impacting physical recovery and increasing risk for morbidity and mortality. Lasting neuropsychiatric effects may also occur in patients' informal caregivers, *up to years* following a loved one's illness [17–19], and appear related to the patient's post-ICU disability [20, 21] but independent of whether the patient survived [21]. These effects then impact caregivers' own health-related quality of life [22].

Post-Traumatic Stress—PTSD is a response to a life-threatening event that continues for at least four weeks post-trauma and includes avoidance of trauma reminders, physiological hyperarousal, re-experiencing, and negative cognitions [23]. Since admission to the ICU is often sudden and life-threatening, many patients develop post-traumatic stress (PTS) symptoms that can transition to PTSD. Caregivers who witness life-threatening CCI can also develop PTSD [24–26].

Symptoms of PTS are seen following medical, cardiovascular, surgical, trauma, and burn CCI [27, 28], encompassing a host of diagnoses (e.g., respiratory failure, sepsis, cardiac arrest). The prevalence of post-traumatic stress disorder in CCI survivors is high and persists over time [29]. More than 75% of mixed ICU patients referred for neuropsychological evaluation report at least one stressful in-ICU experience (e.g., nightmares, severe pain, breathing difficulty, or a feeling of suffocation) [30]. A recent meta-analysis in 36 unique cohorts of patients surviving critical illness found a pooled prevalence of PTSD of 25–44% at 6 months depending on the severity cutoff used for the Impact of Event Scale [31]. At one-year follow-up, PTSD symptoms are still reported in upwards of 20% of survivors [31]. Rates of PTSD in caregivers of CCI survivors range between 11.1 and 57.1% depending on the instrument used and timepoint of assessment [18, 20, 22, 24, 32]. These high prevalence rates are corroborated by studies using the PTSD Checklist for DSM-V (PCL-V), which has a high concordance with diagnostic interviews [33].

Depression—There are similar clinical risk factors for depression as for other psychiatric disorders, for example, hypoglycemia [34], sepsis [21], and acute respiratory distress syndrome (ARDS) [12, 35]. Some researchers have noted a long-lasting comorbidity between CCI-associated depression and PTSD [36].

In a large, multicenter study investigating neuropsychological health after critical illness, the reported prevalence of depression was high at 37% ($N = 406$) [4]. In patients with no preexisting history of depression, depressive symptoms still occur in nearly 30% at 12 months and are even higher in patients with preexisting depression. At five years, prevalence is still nearly 20% in a multicenter cohort study of ARDS survivors [37]. Smaller cohorts have a wider range of rates of depression, though they are still significantly higher than the general population prevalence of < 10% [12, 38, 39]. Similarly, rates of depression in caregivers range between 4.7 and 36% [17, 18, 20, 24].

Anxiety—Anxiety has been less studied. Published rates of anxiety most often use the Hospital Anxiety and Depression Scale (anxiety subscale) questionnaire, and, in general, range from 16 to 24% in long-term survivors of CCI, though rates as high as 62% have been reported [12, 29, 35]. These prevalence rates of anxiety are higher than the general population [39], and there are no differences in prevalence between medical, surgical, and trauma ICU patients even a year after discharge [29]. Caregivers experience anxiety with rates similar to patients (15–25%) [24].

Risk Factors as Defined in Non-Neurocritical Population

Several risk factors interact with CCI to contribute to the development of PICS and PICS-F with subsequent decreased health-related quality of life (see Fig. 1).

Non-Modifiable Factors—Younger patients may be at higher risk for PTSD [27, 40, 41]. Female gender is regularly reported as a risk factor for depression in both patients and family members following CCI [21, 30, 35]. One of the most robust predictors of PICS- or PICS-F-related psychiatric illness is lifetime history of mental illness [18, 20, 34–36, 42], with a relative risk of 3.9 (95% CI 1.5–6.5) [34]. Prior cognitive impairment is also a risk factor for post-ICU worsened cognitive function [43].

Modifiable Factors: Sedation, Delirium and Agitation, and Length of Stay—The pathophysiological relationship between sedation, delirium, and cognitive impairment is multifactorial and outside the scope of this paper, but sedation and delirium may impact future development of PICS.

With delirium, patients can experience psychotic symptoms, and delusional memories of an ICU admission predict PTSD, so delirium may be a risk factor [27]. Additionally, in hundreds of patients enrolled in the BRAIN-ICU study, a longer duration of delirium was independently associated with both worsened global cognitive and executive function [13]. A British pathology-based study reported that the odds ratio for developing dementia at > 85 years old was 8.7 in patients with delirium [44], and in patients without prior cognitive impairment, this incident dementia was not mediated by traditional neuropathological changes. If delusional, fragmented memories contribute to PTSD, then processing those memories may decrease the vulnerability to developing PTSD. ICU diaries used to address memory gaps have shown benefits (mostly in single-center trials) in PICS and PICS-F in Europe, Canada, and the USA [45–49] with a large prospective multicenter trial ongoing in France [50].

Data on the relationship between sedation and PICS are mixed. Several studies have reported a relationship between benzodiazepine sedation and PICS [34, 40, 42, 51]. One study reported increased relative risk of depression in patients with a mean daily ICU benzodiazepine dose > 100 mg of midazolam-equivalent agent [34], and another noted increased PTSD with larger total dose of lorazepam [40]. This correlation was not seen in the larger BRAIN-ICU cohort [13], which was completed more recently and may reflect a growing interest in sedation reduction [52, 53]. It may be that the higher doses of sedation—and in particular benzodiazepines and opiates, rather than propofol and dexmedetomidine [40, 42, 54]—or lack of sedation holidays are more detrimental to downstream cognitive impairment and mental illness, especially PTSD [31, 42, 55]. Kress and colleagues suggested daily sedation holidays until a patient is reliably following commands or uncomfortable/agitated [52]. Conversely, agitation or placement of restraints (especially without sedation) is a risk factor for PICS [42, 54]. This agitation may be a marker or prodrome of PTS, and benzodiazepines might reflect the management of this anxiety/agitation [27].

Length of stay (LOS) is another risk factor for PICS and a significant predictor of PTSD [56]. Mechanical ventilation [41], a longer time to develop delirium, and immobility [7] are likely a few mediators of this risk *rather* than severity of illness [14, 38, 40, 41].

PICS and PICS-F in Patients with Acute Brain Injury

Within the neurointensive care unit (NeuroICU), research on PICS is emerging. It is well known that certain neurological diagnoses are associated with neurocognitive changes, for instance stroke [57, 58]. However, many disorders are heterogenous, with only a fraction of patients experiencing associated CCI; admission to the NeuroICU is more complicated than having a specific diagnosis. To the extent that neurological diagnoses do not universally require intensive care, these studies are not pertaining to PICS (or PICS-like) effects. This approach is not errant; however, it negates the effect that CCI can have on the trajectory of disease and recovery. PICS is related to the *experience* of critical illness.

With that limitation in mind, some diagnoses often include a portion of their hospital stay in the ICU: status epilepticus (SE), malignant cerebral edema following ischemic stroke, aneurysmal subarachnoid hemorrhage (aSAH), non-traumatic intracerebral hemorrhage (ICH), and moderate-to-severe TBI. We will focus on these ABI diagnoses here.

Status Epilepticus

SE can be either convulsive or non-convulsive (NCSE); it is considered a risk factor for future cognitive impairment [59]. In a retrospective study of outcomes following NCSE, approximately 15% of patients evidenced new cognitive impairment; however, it is unclear if some of these neurocognitive changes were related to the NCSE itself, the underlying trigger for NCSE, or medication effects [60]. The same research group found that SE patients performed poorer than controls on memory, learning, and executive functioning tasks; the SE patients also performed significantly worse on tests of motor latency than did patients with > 10 lifetime seizures (but never SE) [59].

Ischemic Stroke

Admission to the ICU following stroke depends on severity and treatment history. However, malignant edema from ischemic stroke is often treated in the ICU. In a case series evaluating long-term outcomes following decompressive hemicraniectomy in these patients, we see that 100% evidenced impairments in multiple cognitive domains and 40% endorsed clinically significant depressive symptoms [61]. When asked directly, 80% of patients considered surgery as a favorable course of action despite these deficits; 20% had aphasia too severe to answer for themselves. Similar multi-domain cognitive dysfunction has been reported in less detail elsewhere in a retrospective study with a larger cohort [62].

Non-Traumatic ICH

In the multicenter, double-blind FAST trial, researchers noted a high prevalence of depression (20%) that independently and negatively impacted quality of life (QoL) [63]. Clinical severity and disability appear to impact development of depression [63]. Taking all non-traumatic ICH together, one study found a prevalence of depression and anxiety of 23% and 8%, respectively, in 48 patients who presented for formal neuropsychological assessment; cognitive impairment (memory > psychomotor > executive functioning > language > visuospatial) was noted in 77%, and 13% met criteria for dementia [64]. This effect may be further exacerbated by delirium and agitation, as seen in a prospective study

measuring Neuro-QoL scores up to 1 year after surviving ICH [65]. Within the prospective PITCH cohort, 37% without preexisting dementia showed cognitive decline following their ICH, which was associated with severity of cortical atrophy [66]. A separate single-center study investigated early versus late *incident* dementia in ICH and found that different risk factors were influential at different times during recovery [67].

Aneurysmal SAH

In a single-center study of 111 patients, 95% reported at least one subjective cognitive or emotional complaint that affected everyday life [68]. The most commonly cited objective cognitive impairments in aSAH are related to attention, memory, and executive functioning despite reports of "good outcomes" on traditional measures (e.g., Modified Rankin) [69–71]; in the large, multicenter prospective ISAT trial cohort, 32% of patients with a "good outcome" had cognitive impairment (performance at < 5%ile in ≥ 2 cognitive domains) [72]—rates of neuropsychological impairment similar to prior studies [73, 74]. We also see a high prevalence of depression (23– 44%) in aSAH patients [69, 75–78]. In combination with cognitive impairment, these emotional complaints contribute to decreased health-related QoL and inability to return to work [72, 75, 79]. In studies that have prospectively investigated it, reported rates of anxiety and PTSD after aSAH are > 30% and > 35%, respectively [76, 78, 79]. Additionally, even in perimesencephalic SAH—which is thought to have a good prognosis—approximately one-quarter of patients ($N = 39$) could not return to work in a prospective study over 8 years [80]; this was attributed to new neuropsychological changes and fatigue [69, 80, 81].

Traumatic Brain Injury

Focusing on civilian studies of moderate/severe TBI, cognitive dysfunction has an inconsistent pattern of cognitive impairment [82]. Moreover, these neuropsychological changes evolve over time with different risk factors at different times [83]. In querying the Traumatic Brain Injury Model Systems dataset, researchers reported an age-related impact on decline after TBI, with patients > 26 years having an increased likelihood of decline than younger patients (16–26) [84]. At in-person 4-year follow-up of over 100 patients from the Paris-TBI cohort with severe TBI, cognitive complaints were noted in up to 68%; 43% had anxiety and 25% were noted to have depression despite nearly 80% of the cohort being independent in ADLs [85] and more than 33% being gainfully employed [86]. A separate single-center cohort of 108 moderate-to-severe patients without intracranial hemorrhage found high rates of new cognitive impairment (52%), clinically significant depression (40%), and PTSD (26%), without a relationship seen between severity of injury and cognitive outcomes [38].

These data should indicate that our neurocritical patients may survive their CCI yet continue to have unmet needs. It appears that PICS (or a PICS-like phenomenon) exists, but the neurological literature uses a different language to describe it. Moreover, there is a distinction between the disease-related neurocognitive changes and the neurocognitive changes associated with the hospitalization. As illustrated in the non-neurological critical care population, the neuropsychiatric effects of critical illness appear to represent a separate

insult (see Fig. 2). In neurocritical care, perhaps this experiential injury is over and above that of the primary neurological injury.

Challenges of Addressing PICS in Neurocritical Care Patients

There is a fundamental difficulty in addressing PICS in the NeuroICU population, though our patient population may be at a high risk of developing PICS-like symptoms.

Primary Brain Injury

NeuroICU patients are admitted with ABI, sometimes in addition to other diagnoses known to be implicated in PICS (e.g., sepsis). Unfortunately, this new neurological injury makes it profoundly difficult to study PICS in this population since differentiating new neuropsychological changes related to primary neurological injury from symptoms related to critical illness is near impossible. Although studies using functional MRI can identify general locations involved in cognitive functioning, it is artificial to try to conclude that a new neuropsychological deficit can be attributed to a particular lesion rather than critical illness. It is more straightforward to attribute new neuropsychological findings to known brain injury, and this may leave PICS unattended in the NeuroICU population.

In addition, many neurological injuries leave patients with new neurological symptoms (e.g., aphasia, impaired decision-making, and decreased arousal) that may make it difficult to study patients' mental health using common methods (e.g., surveys). As providers, we need to tailor our assessment and treatments for individual ability to participate.

Although ABI makes it harder to understand PICS in our patient population, it also makes it more important to identify ways of studying our patient population's risk. Some neuropsychological changes are related to ABI, but it is possible that there is additional impairment related to the experience of CCI itself. The interrelationship among biological and psychological factors challenges our understanding of new neuropsychological impairment because there may be a component of post-NeuroICU impairment that is preventable based on an understanding of PICS pathophysiology and risk factors.

Prolonged Sedation

Sedation holidays and daily awakenings show benefit in mitigating neuropsychological impairment [52, 55], but patients in the NeuroICU often have pathologies that preclude weaning of sedation. For instance, management escalation often necessitates anesthetic infusions and cerebral suppression using propofol, benzodiazepines, or barbiturates in the treatment of status epilepticus, uncontrolled intracranial pressure, and severe drug or alcohol withdrawal [87–90]. Thus, relative to the medical ICU, the NeuroICU disproportionately has patients who are not candidates for daily sedation interruption, which may increase the risk for neuropsychiatric sequelae.

Lack of Noninvasive Monitoring

Although some diagnoses require prolonged cerebral suppression, in many cases attempts are made to minimize sedation to optimize the neurological exam. This may affect our PICS patients' risk, however.

First, the Pain, Agitation, Delirium, Immobility and Sleep guidelines [91] are not adapted to a NeuroICU population. They recommend adjunctive non-opioid medications to reduce sedation and opioid needs, for example ketamine, which can increase intracranial pressure, thus being potentially detrimental in the NeuroICU. Neuropathic pain medications are also recommended, but their sedative and cognitive effects prevent their use in many neurological patients [92].

Secondly, the neurological examination is the gold standard for noninvasive neuro-monitoring. Unlike the cardiac (i.e., telemetry) or pulmonary (i.e., O2 saturation) systems, the neurological system lacks a highly sensitive way to continuously and noninvasively monitor neuroclinical status. While continuous electroencephalography (EEG) is utilized in the NeuroICU, and quantitative EEG can offer information regarding changes in cerebral activity, these are not universally used nor relied upon to determine clinically significant changes. Thus, patients are examined every one to four hours. The sleep disturbances that occur are an unfortunate corollary to frequently waking patients up for an interactive examination, often times for days in a row.

Although nebulous, the link between sleep and delirium is theorized to include common pathophysiologic pathways, shared mechanisms, shared neurotransmitters, or a potential cause–effect relationship [93]. This is relevant because if our frequent neurological examinations are contributing to a heightened risk for delirium, then we may also be contributing to an increased risk of neuropsychological sequelae in our patient population.

Frightening Memories

Frightening and delusional memories are symptoms of acute distress, and several studies have also identified them as risk factors for post-CCI psychiatric symptoms including PTSD [42, 51, 54, 56]. Some of the non-pharmacological mechanisms for preventing PTSD include rest, minimal stimulation, and explanations of *any* procedure being performed no matter how minimal (e.g., suctioning, serial examinations). However, many neurological patients have language impairment and struggle with comprehension. As such, routine care might be frightening, especially in someone who is unable to communicate or otherwise encephalopathic.

Mobility

Early mobility is known to improve physical outcomes after critical illness [94–96] and may also have some positive effects on delirium [97]. Mobility challenges are complex in the NeuroICU, though many of these complexities—such as appropriate staffing, availability of physical and occupational therapists, mechanical ventilation, prevalence of tubes and lines—are shared with other ICU populations [98]. Many patients in the NeuroICU also have external ventricular drains, lumbar drains, or other intracranial monitoring, which, though not a contraindication to mobility, add a degree of complexity. In addition, many patients with ABI also have motor impairment related to their primary injury, which may confound early mobility and rehabilitation efforts.

Effects on Neurocritical Care Families

To fully discuss PICS in the neurocritical population, we must also address the effects of neurocritical illness on families and caregivers. There is evidence to support a PICS-F phenomenon [99–101], although the literature refers to it using different terminology. In a prospective study investigating caregivers of patients with advanced neurological illness, Trevick and Lord [102] found that signs of a traumatic response could be seen in 33% of caregivers at one month, with 17% of family members ($N = 23$) meeting criteria for PTSD at 6 months; these results were not explained by whether a patient died. The prevalence of depression and anxiety in family members has been reported as high as 8.6% and 20.7%, respectively, with no difference based on LOS [100]. Vranceanu et al. [103] conducted a series of cross-sectional and prospective studies showing that ineffective coping, mindfulness [103], self-efficacy and social support [101], and the interpersonal patient–caregiver relationship [101] are important modifiable [104] factors associated with depression, anxiety, and PTS in patients and caregivers, and that early emotional distress tends to remain chronic over time [33].

Perhaps, as a result of increased recognition of family and caregiver effects from neurocritical illness, there has been an increased focus on family-centered care in the NeuroICU. Hwang et al. [105] found increased satisfaction in families who participate in family meetings and also identified areas for improvement in family satisfaction including support during decision-making and control over the care of their loved ones. Shared decision-making also seems to be important; however, shared decision-making is difficult due to discordance between the kind of information decision-makers desire and that which is provided to them by physicians [106], as well as the limitations of decision aids available for use in the NeuroICU [107, 108]. No single intervention seems to be universally successful in preventing PICS-F [109], and a recent article noted that recovery interventions aimed at the patient alone are unsuccessful [110]. To recognize the importance of patient–family and patient–caregiver dyads is to recognize the impact that psychosocial factors can make on recovery and neuropsychological outcomes for both the patient *and* their loved ones.

Discussion

Millions of critical illness survivors are discharged every year, yet neither they nor their informal caregivers are prepared for the new challenges that await them [111], including lengthy rehabilitation and new or worsened cognitive, psychiatric, and physical problems. These neuropsychological changes represent a CCI process that can be seen *in the absence* of objective neurological injury, which is why understanding neurocognitive changes in the non-neurological population is critical. To the extent that the neurosciences population also experiences CCI, our patients' outcomes may improve with increased prevention and treatment of this CCI-related injury. If one accepts that there are potential neuropsychological effects of CCI, it raises the question: *what are the next steps?*

Firstly, in order to move this field of inquiry forward, we must reframe our expectations for neurocritical care patients' outcomes and better clarify the ways in which PICS is relevant in the NeuroICU (even though it may be difficult to parse out). Ultimately, a more complete understanding of these neuropsychological outcomes will be required for an effective

assessment/treatment framework. To this end, the Neurocritical Care Society and Deutsche Gesellschaft für NeuroIntensivund Notfallmedizin held a joint session at Arbeitstagung NeuroIntensivMedizin on the topic of “Post ICU Syndrome—what happens in the NICU … stays with the patient” [112] with a position paper published [113]. Although critical care physicians are increasingly aware of PICS and PICS-F, there are many opportunities for advancing our understanding within neurocritical care (and with those providers who follow our patients long-term). Limited awareness may lead to reduced quality of life [114].

Another natural arena for collaboration with our non-neurosciences colleagues is to better elucidate the mechanisms that underlie the constellation of neuropsychological symptoms afflicting CCI survivors. One hypothesis is that patients with non-neurological critical illness are actually experiencing new neurological injury related to systemic organ dysfunction, and this new injury is simply below the threshold of identification using current technology (for instance, there is emerging literature on the pathophysiology of cerebral dysfunction in sepsis [115, 116] that could be built upon). Thus, investigation into the mechanism of PICS in non-NeuroICU patients is an area where neurological expertise and collaboration may be beneficial, and it may help us to understand neuropsychological outcomes in our own neurocritical patients. In this way, neurocritical care is an extension of critical care rather than a separate entity.

Additionally, we need to have a better understanding of the prevalence of PICS-like outcomes in NeuroICU patients. One goal is to identify modifiable and non-modifiable risk factors in order to detect patients at risk of neuropsychological sequelae, with interventions designed to mitigate those risks. In some circumstances, this may require reassessing clinical trial results or landmark recommendations (e.g., pain, agitation, and delirium guidelines [53], ABCDE bundles [117]) with attention paid to the NeuroICU population. For example, a trial is currently underway to evaluate the effects of non-sedation (versus sedation with a daily wake-up trial) on cognitive and physical outcomes [118]. Although some neurocritical patients (e.g., those with status epilepticus or head trauma requiring therapeutic coma) will be excluded, neurological patients will not broadly be excluded. Moreover, when conducting trials, we propose keeping these neuropsychological outcomes in mind, because—all things being equal—our patients and their families will likely prefer treatments that improve quality of life [119]; “mortality rates alone are no longer a sufficient guide to quality of care” [120].

More than any of the above, however, is potential for collaboration in addressing outcomes in both patients (PICS) and their family members (i.e., PICS-F). Multidisciplinary post-ICU clinics [2]—as in the THRIVE initiative—may be a valuable objective within neurocritical care. However, current efforts at preventive interventions for patients alone, without including the caregiver, have not been successful in preventing chronic emotional distress in patients [110]. Upon critical reflection, this makes sense given research showing that patient and caregiver coping and emotional distress are interrelated and may travel together over time [121]. Many caregivers feel that they are not always understanding the needs of the patient [122, 123], and this negatively impacts their mood and the care they provide [124, 125]. Additionally, the quality of care that a caregiver provides influences the trajectory of psychiatric illness in patients [126–128]; for example, overprotection and patronization

predict greater depression in patients [124]. Caregiver psychological distress also affects the functional and psychosocial recovery of the patient [129, 130] (as well as medical costs insofar as caregivers' poor mental health is associated with patients' rehospitalization and increased health-related costs [131–133]). A recent systematic review from the American Heart Association recommended that interventions during stroke recovery should be dyadic (patient and caregiver together) and should address patient and caregiver outcomes (rather than just teaching caregivers how to help patients, or how to cope with caring for patients) [134, 135]. We believe this dyadic framework is applicable to all NeuroICU diagnoses.

Given that emotional distress at hospitalization is the best predictor of future emotional distress [31] in both patients and their families, a focus on prevention may be the most efficient and effective way to improve outcomes in both patients and caregivers. The level of patient involvement will depend on degree of neurologic impairment; for those with cognitive deficits, skills such as mindfulness meditation can be emphasized. Early dyadic interventions starting at hospitalization and focusing on skills such as resiliency and interpersonal communication are underway in some institutions, including Massachusetts General Hospital's "Recovering Together" initiative [136], which was developed through qualitative feedback from dyads and nurses [104]. Pilot data show good feasibility and improvement in emotional distress and resiliency, with a subsequent single-blind randomized controlled trial funded by the National Institute of Nursing Research underway. As critical care physicians, we need to unite our efforts to develop interventions that address the "critical care experience" and its effect on patients and caregivers regardless of the acute injury.

Given the interrelation among patient and caregiver factors, the documented chronicity of depression, anxiety, and PTS, and the interaction between the physical, emotional, and cognitive recovery in PICS and PICS-F, we recommend the development of screening methods to identify dyads of patients and caregivers who are at risk, and the development of preventive, tailored interventions for these dyads. Both NeuroICU survivors and caregivers definitively deserve our attention on long-term recovery and the prospect of a better life.

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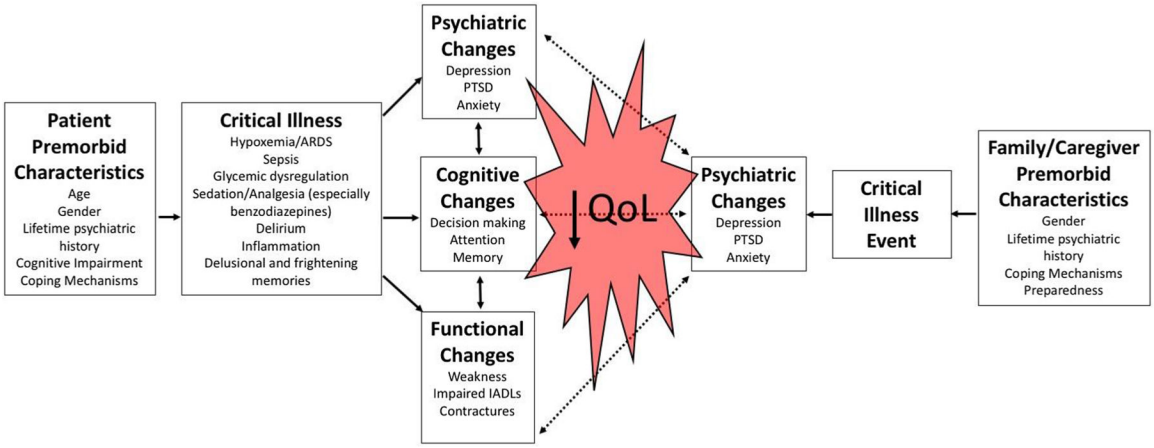

Fig. 1.

Patient premorbid and ICU risk factors for long-term cognitive, functional, and psychiatric effects of critical illness, as well as family/caregiver risk factors for long-term psychiatric consequences after the patient's critical illness. There are important areas of interrelationship between changes seen in patients and caregivers (dashed lines), highlighting the interplay and influence between the two groups. The downstream effect for each group is decreased quality of life. *ARDS* acute respiratory distress syndrome, *PTSD* post-traumatic stress disorder, *QoL* quality of life

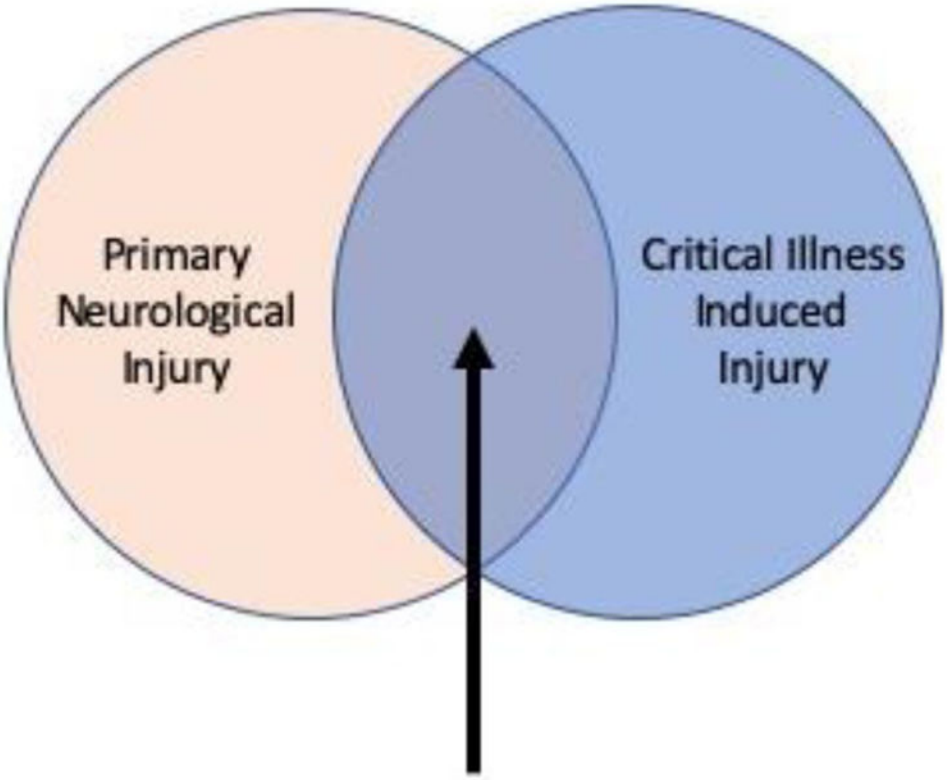

Fig. 2.

Neurocognitive findings observed following neurological injury requiring ICU level of care exist at the intersection between primary neurological injury and critical illness induced injury (arrow). If even some of the experiential injury related to critical care illness can be mitigated, then perhaps some of the neurocognitive deficits we see in our patient population may be preventable or treatable. *Not drawn to scale*