ICU Survivorship—The Relationship of Delirium, Sedation, Dementia, and Acquired Weakness

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ABSTRACT: The advent of modern critical care medicine has revolutionized care of the critically ill patient in the last 50 years. The Society of Critical Care Medicine (was formed in recognition of the challenges and need for specialized treatment for these fragile patients. As the specialty has grown, it has achieved impressive scientific advances that have reduced mortality and saved lives. With those advances, however, came growing recognition that the burden of critical illness did not end at the doorstep of the hospital. Delirium, once thought to be a mere by-product of critical illness, was found to be an independent predictor of mortality, prolonged mechanical ventilation, and long-lasting cognitive impairment. Similarly, deep sedation and immobility, so often used to keep patients "comfortable" and to facilitate mechanical ventilation and recovery, worsen mortality and lead to the development of ICU-acquired weakness. The realization that these outcomes are inextricably linked to one another and how we manage our patients has helped us recognize the need for culture change. We, as a specialty, now understand that although celebrating the successes of survival, we now also have a duty to focus on those who survive their diseases. Led by initiatives such as the ICU Liberation Campaign of the Society of Critical Care Medicine, the natural progression of the field is now focused on getting patients back to their homes and lives unencumbered by disability and impairment. Much work remains to be done, but the futures of our most critically ill patients will continue to benefit if we leverage and build on the history of our first 50 years.

KEY WORDS: critical illness; delirium; early mobility and exercise; intensive care unit–acquired weakness; post intensive care syndrome; survivorship

Over the past 50 years, since the founding of the Society of Critical Care Medicine (SCCM) and under its leadership, we have witnessed profound advances in our understanding of how critical illness impacts the human body and a dramatic evolution in the care of the world's sickest patients. If one peers across the span of critical care medicine's history, there is a significant change in mindset with regard to the best way to care for patients who receive mechanical ventilation (MV) and other forms of life support with an eye toward preserving the brain and neuromuscular system from life-altering disabilities and impairments. This shift is founded in the rapid advancement in knowledge of the long-term impact of critical illness as a systemic disease process and the collateral iatrogenic damage that our medical interventions can have on the human body and brain. The research-chiseled progression of critical care medicine over these 50 years allows us to adjust an early myopic focus on survival to one that includes implementing early steps in the ICU needed to improve survivorship. These fresh aims ultimately help critical illness survivors return to their preillness quality of life, hobbies, social interactions, and employment.

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We now know that the admission diagnosis is just the beginning of the family of diseases that define critical illness. We understand that from the moment a person is placed in our hands in the ICU with organ failure, he or she is very often developing new disease processes that are both organic and iatrogenic. A majority of ICU survivors develop a new or worsening form of cognitive impairment, physical impairment, and/or mental health impairment. This syndrome, now called the "postintensive care syndrome (PICS)," was coined originally by an SCCM-sponsored expert panel led by Dale Needham et al (1). Through basic science, cohort studies, and expertly designed and conducted randomized controlled trials, critical care medicine has advanced to realize that the physiology of acute disease cannot define our entire approach to the human in medical and surgical crisis. We must also attend to the entire person and not just the etiology of their ICU admission. Indeed, once under our care, it is the entire body, mind, and spirit of the person involved that are affected by the illness and our own clinical decision-making, strongly influenced by the culture of the ICU. In response to this growth in knowledge, the SCCM built the "ICU Liberation Campaign." It began with a series of adapted and bundled aspects of care to improve the entire culture of critical care, incorporating a holistic approach that improved upon a mechanistic approach to care that frequently led to oversedation and immobilization. We came to understand that acquired dementia and weakness are major components of the legacy of our patients' survivorship that needed addressing on the "front-end" of care, rather than the "back-end." We know now that delirium and oversedation, so common in critical illness, lead to acquired dementia and neuromuscular weakness. We also know now that the first steps to preventing these long-lasting impairments start in the ICU, preventing and treating delirium, targeting light sedation, and exercising our patients, all with the goal of accelerating the recovery of survivors. Our goal in this article is to outline this part of the story of critical care medicine. The history, and the lessons learned from it, is vital to the story of critical care medicine and particularly poignant in the face of the global coronavirus disease 2019 (COVID-19) pandemic that has placed *Critical Care Medicine* at the forefront of an international public health crisis (2, 3).

THE EVOLUTION OF CRITICAL CARE MEDICINE AND ICU SURVIVORSHIP

The European polio epidemic of the 1950s gave rise to much of the what we have come to understand as critical care medicine. Similar previous epidemics in the 1940s were the sparks that generated the development of negative pressure ventilation, the "iron lung," as an effort to combat respiratory failure. The precursor to the modern positive pressure ventilator was developed during the European epidemic of the 1950s, when Ibsen (4), an innovative anesthesiologist from Denmark, developed the first technique for applying positive pressure ventilation through a tracheostomy for a young patient in respiratory failure (5). From those first efforts to develop a new treatment for respiratory failure, numerous innovative advancements have emerged in the techniques of MV to keep patients alive during periods of critical illness. These initial machines, however, were very rudimentary and often intolerable for patients (6), frequently leading physicians to take complete control of the body via the perfunctory use of deep sedation and paralysis. Although this new technology was undoubtedly life saving, the subsequent use of deep sedation and paralysis bore new complications such as delirium, new-onset dementia or cognitive impairment, and acquired weakness, the consequences of which we have come to understand more clearly in the following years.

Toward the end of the century, there was a paradigm shift in our understanding of the ramification of critical illness. Landmark studies shed light on the fact that patients were developing a profound myoneuropathy due to critical illness and that a large percentage of acute respiratory distress syndrome (ARDS) survivors were suffering from significant neurocognitive deficits, even though they were admitted for with primary respiratory failure and had not experienced any catastrophic neurologic events while in the ICU (7–10). Research in the ensuing 2 decades confirmed and elucidated these long-term ramifications of critical illness (i.e., PICS) and provided insight into their societal implications. This led to a focus on understanding those mechanisms and designing interventions to reduce the prolonged burden of critical illness among survivors (11–13). It became apparent that, although leveraging our best technology to keep people alive during sepsis and other life-threatening illness, millions of people were acquiring a "neck-up"

brain disease and "neck-down" neuromuscular diseases that dramatically affected their lives after the ICU (7–9, 14–18).

DELIRIUM

At the end of the 20th century, most clinicians assessed consciousness in critically ill patients only qualitatively at the bedside, frequently in very rudimentary ways. Although the pathology of "acute encephalopathy" was recognized, a developed approach to describing clinical manifestations, such as delirium, was lacking (19). Much of the documentation described a patient's general orientation to person, place and time, or whether or not they had intact brain function. There was little to no formal assessment describing how clearly a patient was thinking. One component of consciousness, "arousal," was sometimes measured with poorly validated instruments, but we were not accurately measuring the other major component, "content of consciousness," except perhaps to note those patients who were very agitated with hallucinations and delusions. These patients were frequently referred to as having "ICU psychosis," a term now considered both a misnomer and antiquated (20). At the time, staff often deemed delirium to be a benign side effect of critical illness, assumed to clear up when a patient was transferred from the ICU. Little was known of the cause or if it truly was benign. Ultimately, our field came to understand this particular manifestation of acute encephalopathy in the critically ill as a spectrum of disease, now called ICU delirium. Delirium's primary presentation can include hyperactive symptoms and agitation, but it more often manifests with symptoms of lethargy, inattention, and disorganized thinking, the cardinal components of hypoactive delirium.

For many years, ICU delirium was brushed off as a natural consequence of critical illness. Although clinicians had anecdotal experiences demonstrating that alteration in brain function often delayed liberation from MV and ICU discharge, it was not until the development and validation of delirium assessment tools designed specifically for the ICU setting, and the subsequent studies finding delirium to be a robust and independent predictor of mortality and morbidity, that the critical care world began to take notice (11–13, 21). The two most widely used delirium assessments tools are the Confusion Assessment Method for the ICU and the Intensive Care Delirium Screen Checklist, both of which were initially published in 2001 (11, 13). They are built to be easy, quick, valid, and reliable in patients who were critically ill and both verbal (i.e., off MV) or nonverbal on MV (11, 13). These tools assess for the cardinal features of delirium, including acute, fluctuating consciousness and inattention (22). These findings are caused by organic diseases like sepsis (or coronavirus infection), coagulopathy, and hypoxemia or iatrogenically by receipt of potent psychoactive medications such as gamma-aminobutyric acid (GABA) modifying sedatives or opioid analgesics. Once delirium is diagnosed with these tools, then it is up to the clinical team to determine the differential diagnosis of potential causes and address them accordingly. These instruments create a common and validated, reliable language by which to communicate this form of organ dysfunction on rounds in the ICU. This allows coma and delirium to be part of routine organ function monitoring, serving as both an early warning system for changes in clinical status and a catalyst for emerging literature on prognostication (23). As a result, across the hospital, from medical and surgical wards (24, 25), to step down units and postoperative recovery area (26), and the emergency department (27), as well as in pediatric populations (28–30), we "now" use consistent delirium assessment methods to understand that delirium is a phenomenon not just unique to the ICU, but that it is seen across the spectrum of acutely ill patients.

Delirium develops in up to three quarters of mechanically ventilated patients during critical illness (11, 24, 25, 31). Data consistently show that the development and duration of delirium in ICU patients is a "canary in the coal mine," as it is an independent predictor of untoward outcomes including higher mortality (**Fig. 1**), longer time on the ventilator, and longer time in the ICU and the hospital (12, 21). Delirium is also predictive of increased healthcare costs (32, 33). For survivors of critical illness, the burdens of delirium do not end at hospital discharge. The duration of delirium is a primary risk factor for a form of acquired dementia that lasts years following the ICU stay (23, 34), and this long-term cognitive complication of critical illness is a major component of the PICS.

At the same time that we as a field came to understand the numerous negative consequences associated with delirium, the hunt for modifiable risk factors quickened, and practices began to change. In

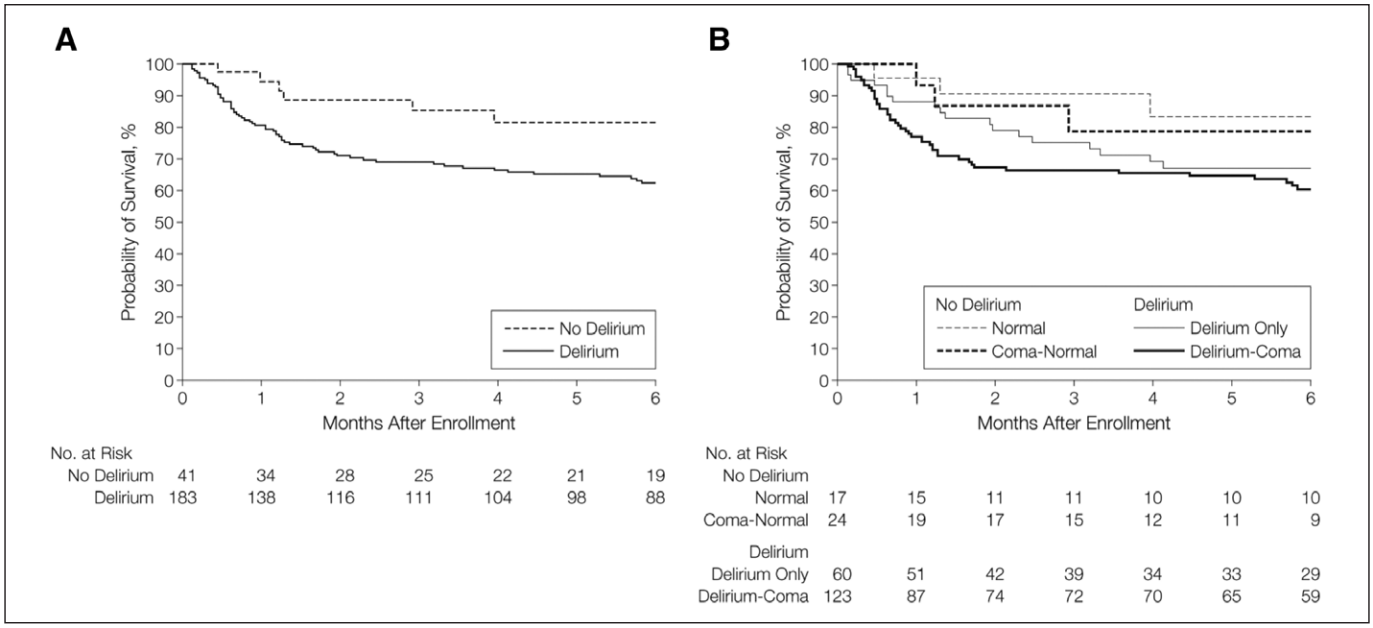

Figure 1. Delirium and coma are associated with 6-mo mortality in critically ill patients. **A**, Kaplan-Meier curves of survival to 6 months in patients with delirium versus no delirium. **B**, Survival according to both delirium and coma. Reproduced with permission from Ely et al (12).

2002, the clinical practice guidelines for sedative and analgesic use in critically ill adults were developed by the Task Force of the American College of Critical Care Medicine as part of the SCCM, in conjunction with the American College of Chest Physicians. They introduced delirium assessment as an important aspect of appropriate analgesic and sedative use (35). In the mid-2000s, standard clinical practices at the time came under scrutiny with respect to delirium. The administration of long-acting sedatives, such as benzodiazepines, was found to independently predict of the development of delirium and hence be an important modifiable risk factor (36–38). These discoveries turned conventional wisdom within the field upside down. By 2013, with rapidly increasing knowledge surrounding delirium, the SCCM updated its directives with a focus on pain, agitation, and delirium, all interdependent symptoms that need close monitoring in all critically adults, as the Pain, Agitation, and Delirium, or "PAD" guidelines in an ongoing effort to reduce human suffering (39).

Now, with the SCCM's most recent 2018 Pain, Agitation, Delirium, Immobility, and Sleep, or "PADIS" guidelines, delirium assessment, and prevention have come of age as an ICU standard and remain an important focus within the field. These guidelines, along with the development of the ICU Liberation Campaign and the ABCDEF bundle **(Table 1)**, have redefined how critical care medicine approaches delirium. No longer is it an expected and overlooked side effect of the ICU environment, but now it is recognized as a significant clinical syndrome representing a valid and reliable phenotype of acute encephalopathy with wide-reaching impact on patient outcomes. This growing recognition has also led to a broader hunt for effective pharmacologic treatments over the last 2 decades. The evidence surrounding pharmacologic management of delirium, however, is to date disappointing. Several large randomized controlled trials demonstrate no benefit to antipsychotics in treating delirium despite their persistent use in critically ill patients (40–42). Similarly, studies of other pharmacologic agents have demonstrated limited benefit in studies to date (43). Future research in the discovery of effective pharmacologic treatments for delirium, in addition to best practices such as the ABCDEF bundle, are an important area for future investigation.

These developments and advances in the management of delirium were not in isolation. They coincided with other advances in within the field, including ventilator management and improved sedation practices, the recognition of ICU-related cognitive impairment in survivors, and the promotion of early rehabilitation and mobility in response to critical illness-related neuromuscular impairments. These aspects of critical illness are no longer seen as disparate, individual issues to be addressed, but instead as linked, interdependent processes to be managed in a symbiotic manner.

Assessment for and management of delirium is an indispensable part of usual clinical care among all critically ill patients, particularly during the COVID-19 pandemic (44, 45). Critically ill patients with COVID-19 are experiencing extremely high rates of delirium and coma that persist for several days, a significant setback from prior progress made in the field (46).

DEEP SEDATION AND PARALYSIS FOLLOWING ADVANCES IN VENTILATOR MANAGEMENT

Fifty years ago, Ashbaugh et al (47) published their landmark article describing the ARDS and the potential benefits of positive end-expiratory pressure (PEEP). In the 5 decades since, synchronous with many other changes in critical care medicine, there have been significant advances in the use and design of mechanical ventilators. With those advances, however, also came the understanding that inappropriate use of MV paired with deep sedation can lead to significant iatrogenic harm.

Concomitant with the increasing capabilities of ventilators, there was exponential growth in our understanding of the risks associated with MV. The 1960s and 1970s revealed the harms of oxygen toxicity, atelectasis, and barotrauma heralding the era of high tidal volume ventilation to offset those deleterious effects (48, 49). Fast-forward into the 1990s, we learned that over distention of the alveoli was also detrimental. Volutrauma leads to lung injury, including the release of inflammatory mediators in the lung, increased permeability, translocation of mediators, bacteria, and endotoxin into the systemic circulation, resulting in multiple organ dysfunction syndrome (50, 51). During that time, there was also a growing body of evidence that deep sedation (often with neuromuscular blockade), used to keep patients "comfortable" on MV, contributed to increased mortality (**Fig. 2**) and worsened clinical outcomes, including delirium and immobilization (7, 36, 52). These short-term outcomes from deep sedation and paralysis created larger, long-term problems, ultimately leading to worse long-term cognitive and physical impairments. The syndrome "PICS" was defined to describe these cognitive, functional, mental health, and neuropsychologic consequences of critical illness (1) and with PICS entered a new metric of successful management in the ICU and hospital that focused on the quality of survivorship. Understanding and revising our approach to sedation use has been key in improving outcomes in critical illness survivors.

Interprofessional collaborative work has paved the way to better our understanding of managing patients on MV, particularly with regard to sedation strategies. We have learned over the years what to do and what to avoid. Maintaining light levels of sedation, in conjunction with low tidal volume ventilation using optimal PEEP, daily spontaneous awakening trials (SATs) and spontaneous breathing trials (SBTs) (**Fig. 3**), and

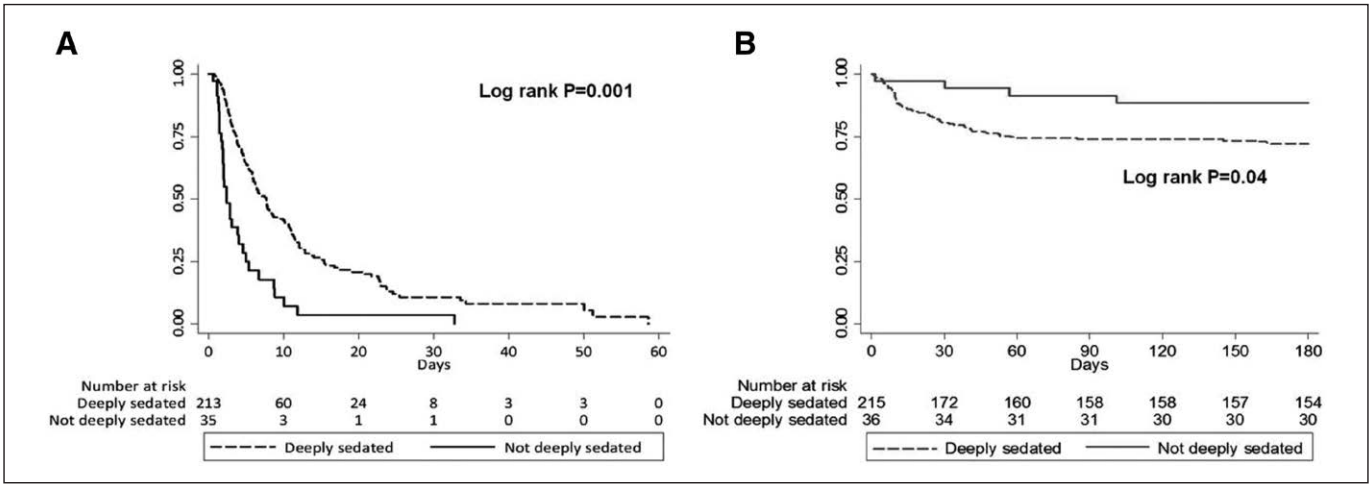

Figure 2. Kaplan-Meier curves for time to extubation and mortality at 180 d. **A**, Time to extubation was significantly longer among patients who were deeply sedated early in the ICU compared with those who were not. Median (interquartile range), 7.7 (6.0–8.6) versus 2.4 days (1.9–4.0 d) (log-rank $p < 0.001$). **B**, Those who were deeply sedated early (first 48 hr) showed significantly reduced survival (log-rank $p = 0.048$) compared with patients who were not deeply sedated. Reproduced with permission from Shehabi et al (53). Copyright © 2020 American Thoracic Society—all rights reserved. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.

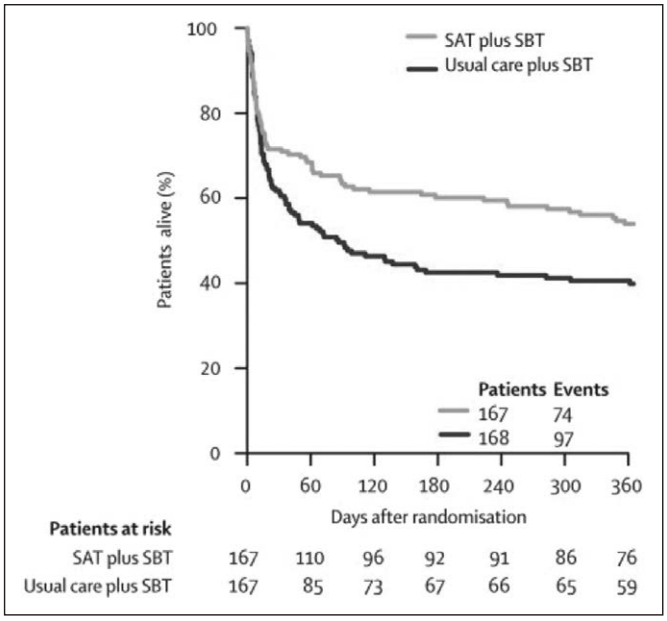

Figure 3. Performance of paired spontaneous awakening trials (SATs) and spontaneous breathing trials (SBTs) compared with usual care with spontaneous breathings trials is associated with a significant reduction in mortality. Reproduced with permission from Girard et al (54). All rights reserved.

early mobilization and exercise have all been associated with improved outcomes in mechanically ventilated patients (50, 54–57). There has been a paradigm shift, with these supportive "back-end" therapies now being catapulted to the "front-end." These elements of care are now prioritized and have a central role as part of safe and effective ICU care starting as soon as a patient is in the ICU or put on MV. Substantial questions remain unanswered, however, in our sedation strategies and represent important areas of future research. Recent studies have failed to identify a preferred nonbenzodiazepine sedation agent among the most commonly used drugs (58). Similarly, the optimal "dose" of light sedation (or none at all) remains unclear (59). Further questions regarding the ideal management of analgosedation to promote ventilator synchrony with low tidal volume ventilation and early mobilization are catalysts for ongoing studies on the "front-end" to improve "back-end" outcomes.

Although 1 day we may have a magic bullet to treat ARDS, or sepsis leading to acute respiratory failure, the last 50 years have taught us that a methodical approach with attention to the little things early in a patient's critical illness makes the greatest difference in outcomes. As critical care medicine deals with the current severe acute respiratory syndrome coronavirus 2 pandemic, this fact has never been more true or relevant. There is no magic drug or treatment, but patients managed with guideline-driven light sedation strategies along with lung-protective MV and evidence-based critical care will continue to survive, with the goal of thriving, after their critical illness (2, 60).

ACQUIRED DEMENTIA

Similar to the understanding of the complications of MV and deep sedation, much has been learned in recent decades about the challenges and complications that linger in the brains of survivors of critical illness. Cognitive concerns shape narratives, bend trajectories, and often become permanent fixtures in the lives of bewildered men and women who struggle to make sense of changes they neither anticipated nor asked for. They take many expressions, including deficits in cognition which, in turn, lead to functional disabilities and diminished quality of life, among a panoply of other maladies (14, 15, 23, 61). When considering the many conditions that define PICS, cognitive problems are reported by many patients to be extremely debilitating in the course of their daily attempts to go back to work or be the matriarchs and patriarchs of their families (62).

Since the late 1990s, when the first modern neuropsychologically oriented investigation of individuals after critical illness ensued, over 50 studies of cognition functioning following critical illness have been conducted (9, 14, 23, 34, 63–67). These studies vary widely in size, in comprehensiveness, and in methodology, among many other variables, making sweeping generalizations difficult. Nevertheless, a variety of durable findings emerge. In general, cognitive impairment affects a quarter to a third of ICU survivors and occurs in numerous neuropsychologic domains including attention, executive functioning, memory, processing speed, and visuospatial construction (although language abilities are typically preserved) (23). Such impairments are of a severity commensurate with mild-to-moderate Alzheimer's dementia (**Fig. 4**). Cognitive impairment frequently persists over time, yet the epidemiology of its natural history is still being described (23). It is sometimes progressive and marked by neuroanatomical abnormalities such as hippocampal atrophy although amyloid deposits are not a major component of the findings in one case series (68, 69).

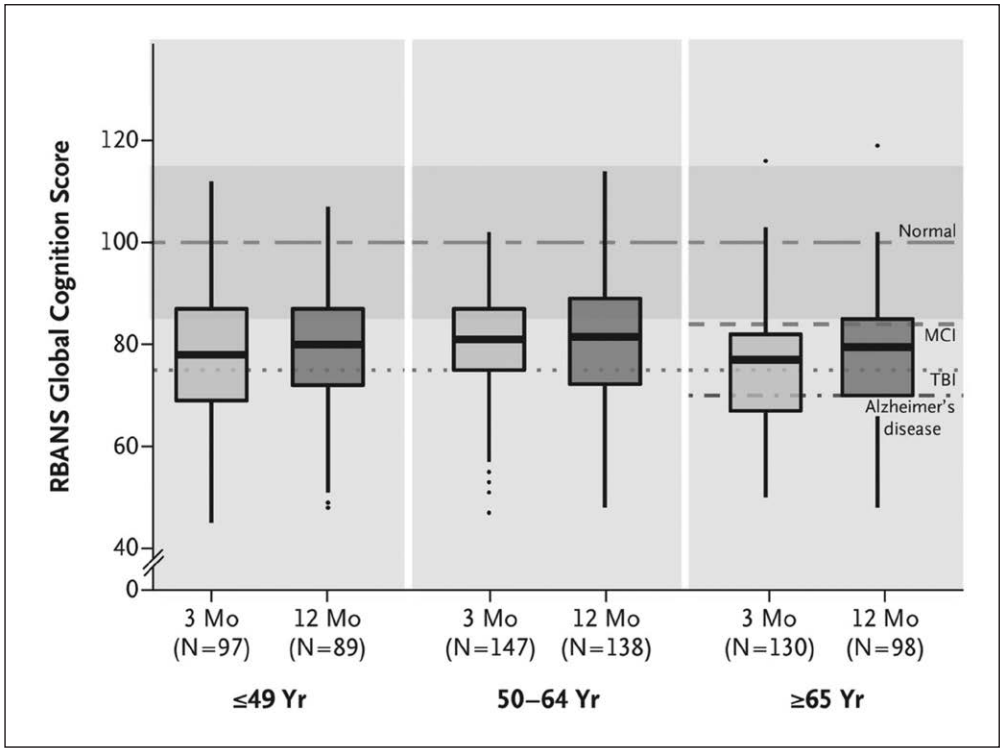

Figure 4. Critical illness is associated with significant cognitive impairment across all age ranges in the year following hospitalization. Reproduced with permission from Pandharipande et al (23). All rights reserved. MCI = mild cognitive impairment, RBANS = Repeatable Battery for the Assessment of Neuropsychological Status, TBI = traumatic brain injury.

Cognition impairment, a form of acquired dementia, is a common and, indeed, even pervasive problem in survivors of critical illness. Although decades of efforts have succeeded in identifying this condition and describing it in broad and sometimes rich and vivid strokes, crucial "next steps" await in the neuropsychologic arena. Chief among these is that we must describe the neurologic sequelae in greater detail– that is, we must mature in the depth, sophistication, and granularity of our work, which necessarily involves a renewed focus on issues of mechanism and basic science models. Furthermore, we must strive assiduously to create and implement preventive strategies and approaches to cognitive rehabilitation to overcome memory and executive function deficits.

Risk factors for cognitive impairment have been extensively described, though which ones are causal versus merely "markers" is somewhat unclear. Frequently identified risk factors include delirium duration, duration of MV, emergent disease, severity of illness, age, education, and the presence of preexisting cognitive impairment, among several others (**Fig. 5**) (70). Many mechanisms of injury have been hypothesized and, in some instances, demonstrated in animal models, including the direct effects of inflammation in the context of blood brain barrier permeability, cytokine-mediated neuronal injury, and activation of microglia (71–73). A number of conceptual models have been advanced that highlight the dynamic interplay between risk factors and prior vulnerabilities—not surprisingly, individuals with cognitive reserve are likely better able to withstand the "storms" of critical illness, whereas even minor insults may create cognitive problems in those without social and biological "protections" at baseline (74, 75). Ongoing studies to understand factors related to both these protections against cognitive dysfunction and the biological mechanisms of cognitive resiliency after critical illness are an important and active area of ongoing research.

IMMOBILIZATION AND ICU-ACQUIRED WEAKNESS

The burdens of critical care survivors also reach beyond the brain and mind, with many survivors experiencing significant neuromuscular weakness and muscle wasting leading to physical impairments. Collectively, this phenomenon is called "ICU-acquired weakness" (ICU-AW), referring to multifactorial and complex disease processes that afflict both the muscle and nervous system of the critically ill (76). Impairments in neuromuscular function related to critical illness have long been identified (7), with reports Osler (77) describing the phenomenon in patients with sepsis. Following on the heels of the advent of modern critical care medicine, however, there has been greater recognition of myopathies and neuropathies in the critically ill patient (8, 78). This increasing recognition is concurrent with the evolution of diagnostics in ICU-AW,

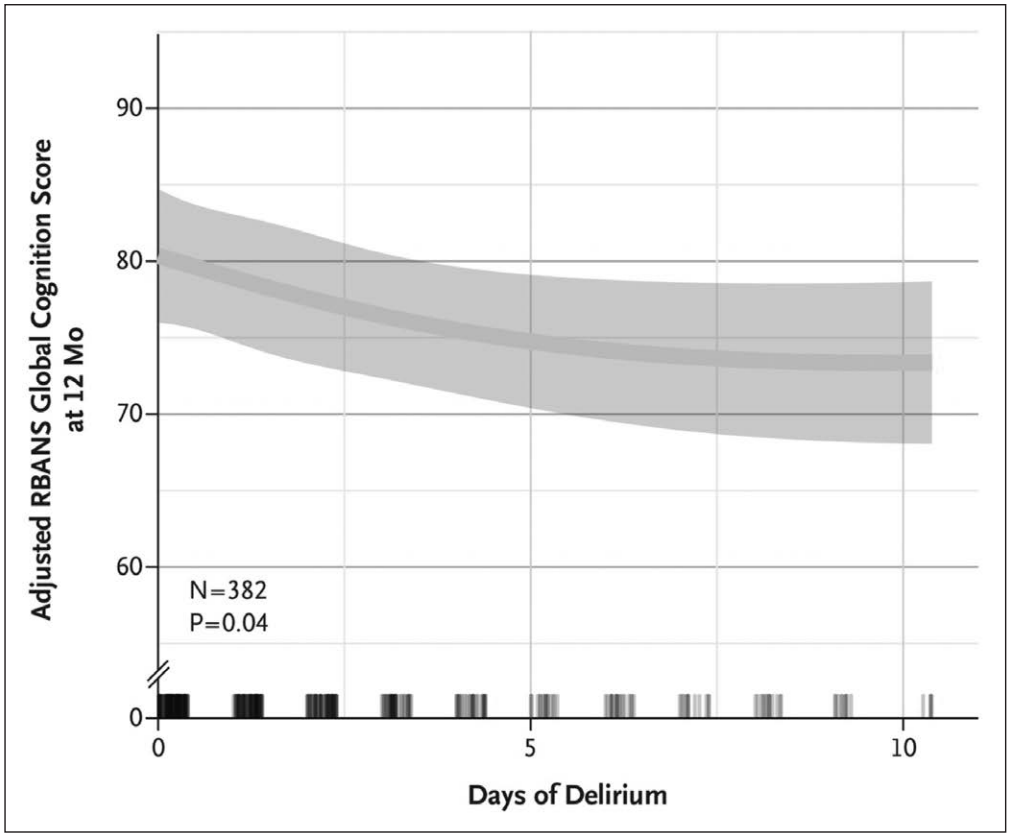

Figure 5. Duration of delirium strongly predicts deficits in global cognition at 12 mo after critical illness. Reproduced with permission from Pandharipande et al (23). All rights reserved. RBANS = Repeatable Battery for the Assessment of Neuropsychological Status.

including the use of the Medical Research Council manual muscle testing scale complemented by the occasional use of electromyography, nerve conduction studies, and muscle biopsies (79). Although mortality from critical illness has fallen, the acknowledgment of physical impairments stemming from iatrogenic insults such as immobilization and deep sedation has increased, burdening ICU survivors and limiting their return to normal lives.

Critically ill patients frequently receive sedative medications while in the ICU, particularly when receiving MV (80). As the use of MV was adapted from practices in the operating room to the ICU, so was the use of sedation. As a result, the original reflex was to deeply sedate patients to facilitate "recovery" and synchrony with the mechanical ventilator, most often with drugs prone to accumulation and long-acting effects such as benzodiazepines (81, 82). With such deep sedation, however, patients are immobile for significant periods of time (83). Over time, it became increasingly clear that deep and continuous sedation, with subsequent patient immobilization, precipitated negative downstream consequences, including ICU-AW and muscle wasting as well as prolonged MV, all of which are associated with increased mortality (53, 84–86). With the use of deep sedation and paralysis, more severe muscular weakness is seen, likely as a result of the concomitant immobility these medications wrought (87). The burden of muscle wasting and weakness during critical illness is not limited to limb muscles, however. The diaphragm is also impacted by muscle wasting and weakness (17), leading to prolonged MV and complicating ventilator liberation.

In addition to poor short-term outcomes, such as increased hospital mortality and length of stay (88, 89), ICU-AW is also associated with long-term mortality, disability, and poor physical function for many years to follow (16, 90–92). Realization of these facts laid the foundation for investigations into "early rehabilitation," including mobility interventions and aggressive physical and occupational therapy while patients were still in the ICU. These foundational studies demonstrated that early exercise and mobility is safe and associated with improved physical function (56, 93, 94), galvanizing an "early rehabilitation" movement. Randomized clinical trials evaluating ICU rehabilitation interventions demonstrated mixed results, however, with some trials showing improved physical function (**Fig. 6**) (56, 57, 93), whereas others showed no improvement over usual care, even when therapy is administered early during an ICU stay (95–97). Novel approaches to mitigate the impact of acquired weakness, such as in-bed cycling and electrical stimulation, have been pursued (98), but to date, such approaches have not yielded consistent improvements in outcomes.

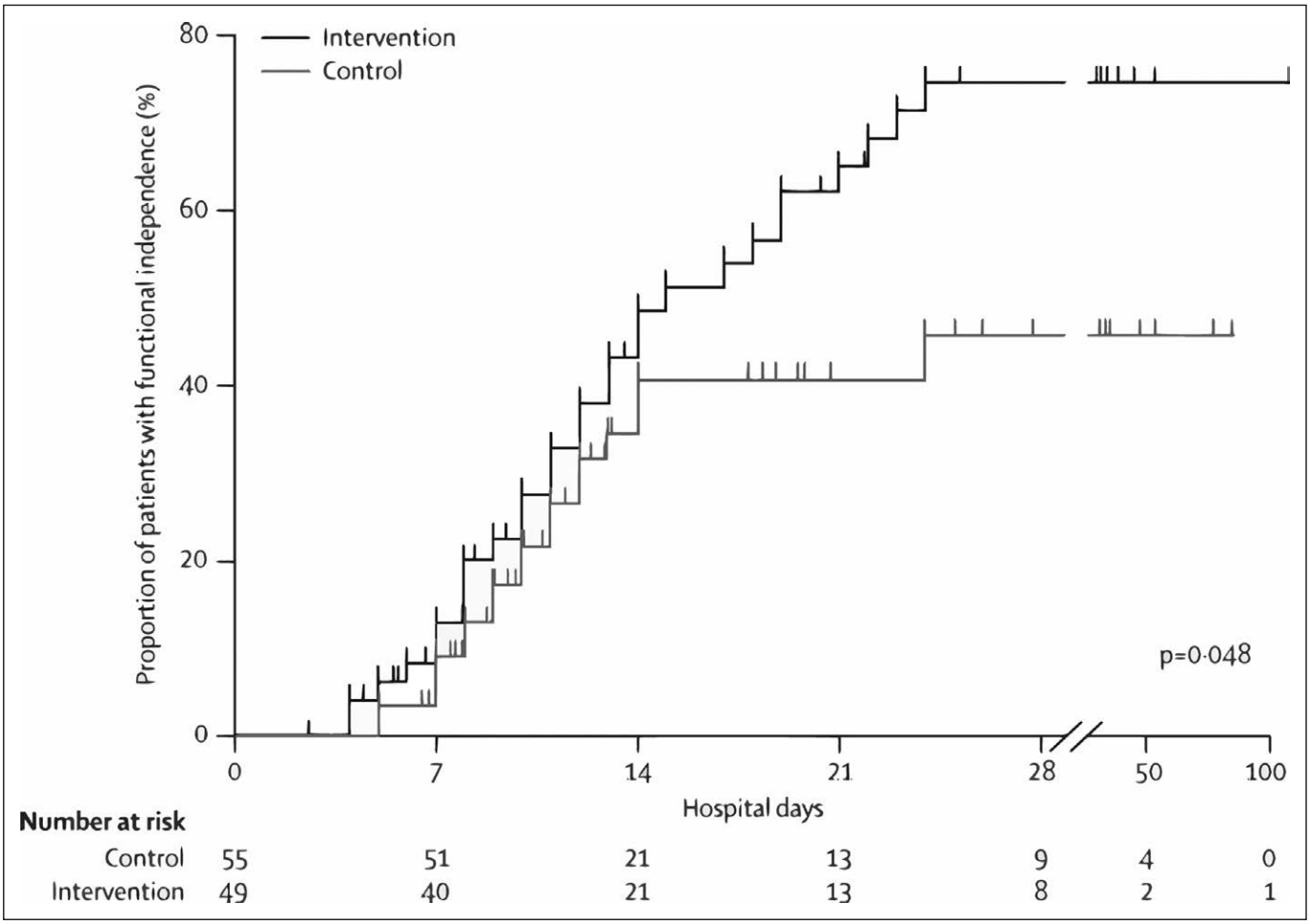

Figure 6. Early physical therapy intervention improves the functional independence at hospital discharge in critically ill patients. Reproduced with permission from Schweickert et al (56).

Notably, each of these trials varied in their approach to rehabilitation as well as the "dose" and timing of interventions. Despite the potentially mixed findings in trials of early rehabilitation, when similar interventions are combined with light sedation and the mitigation of pain and delirium, there is consistent evidence of improved patient outcomes. Dose-dependent compliance with the ABCDEF bundle, which includes early exercise and mobility as a core component, is associated a lower likelihood of discharge to a facility, less delirium, and lower in-hospital death (**Fig. 7**) (99, 100). The combination of early mobility with other complementary care processes creates a holistic approach to clinical care, combining physical, cognitive, and family engagement to help patients recover, creating a philosophy of care that is greater than the sum of its parts. This paradigm shifts from a culture of deep sedation and immobility to one of early physical activity, and light sedation has revolutionized critical care medicine over the past 25 years, all in response to the realization that the "back-end" of critical care has long-lasting impact on ICU survivors.

Many unanswered questions and ripe areas for investigation remain regarding the mobilization and rehabilitation of critically ill patients, a need amplified by the COVID-19 pandemic. Like the neurologic burdens suffered by ICU survivors, further study of ICU-AW and neuromuscular impairment is needed to facilitate both prevention and treatment. Developing successful approaches to improving the implementation and uptake of early rehabilitation and mobilization, along with ongoing rehabilitation efforts after the ICU, remains a priority as well. Describing the impact that light sedation and early physical rehabilitation have on ICU-AW and other physical outcomes several months to years after critical illness will be an important avenue of research, as patients' burdens sometimes accelerate at the time of discharge to home without their medical team's presence. Similarly, rehabilitation following discharge from the hospital remains an area that lacks robust data and is

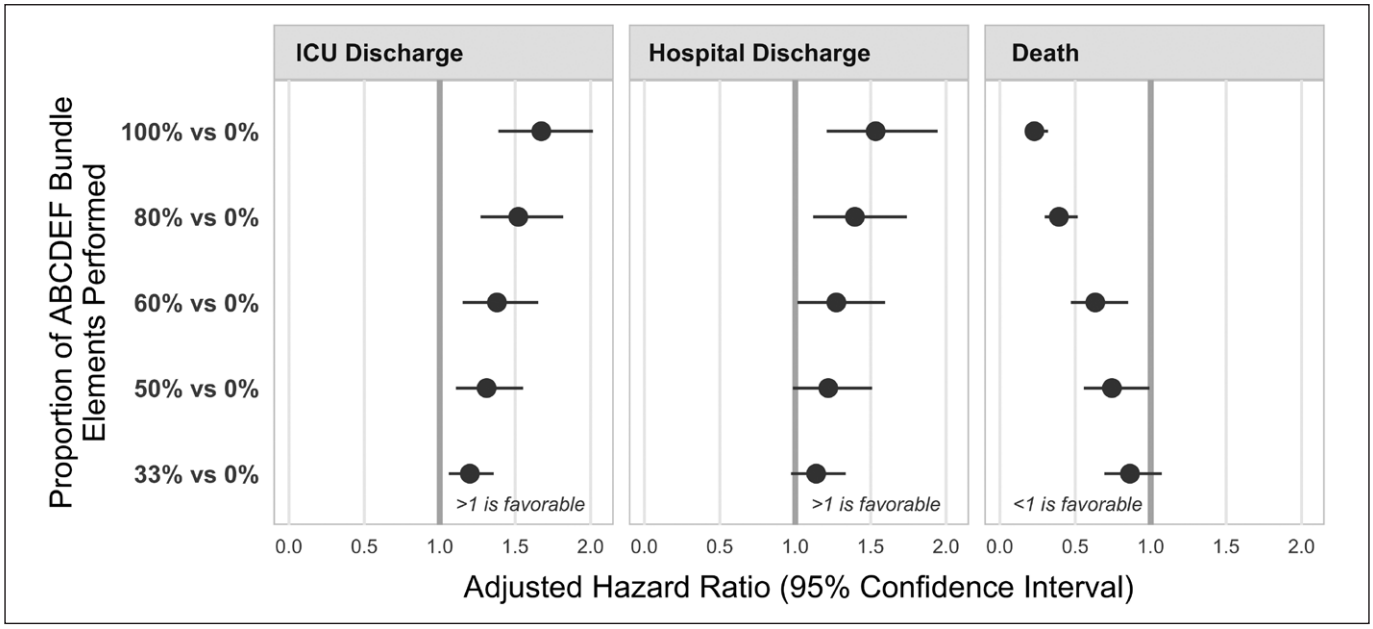

Figure 7. Based on an *n* greater than 15,000 patients, these data show that increased performance of elements of the ABCDEF bundle is associated with lower hospital mortality and increased odds of discharge from the hospital and the ICU. Reproduced with permission from Pun et al (99) ABCDEF = Assess, Prevent, and Manage Pain; Both Spontaneous Awakening Trials and Breathing Trials; Choice of Analgesia and Sedation; Delirium: Assess, Prevent, and Manage; Early Mobility and Exercise; Family Engagement and Empowerment.

an area in urgent need of further research. Eliminating the burden of ICU-AW, and improving legacy of critical care survivorship, will be built upon heeding the aphorism by Barcroft (101) that "the condition of exercise is not a mere variant of the condition of rest, but it is the essence of the machine." Which is to say, enabling and encouraging our patients to be awake, interactive, and mobile, as is the natural state of our minds and bodies, will accelerate the recovery of our survivors.

LOOKING FORWARD AND CONCLUSIONS

The 50 years of critical care medicine since the launch of SCCM has been an exemplar of the marvel of modern medicine, yet it has also been a humbling reminder of the very human impact of our work. During the first half of those formative years, we saw our field evolve remarkably in ways that allowed us to keep people alive despite a degree of disease never before thought survivable. However, in the process, our approach to sedation, paralysis, and immobilization precipitated development of a tremendous amount of acquired disease in the human body, now known as PICS, which is the primary determinant of the ICU survivor's long-term quality of life, disability, and return to normalcy. PICS affects all aspects of the patient's brain and body, including neurocognitive and psychiatric disease, particularly in the form of acquired dementia, as well as ICU ICU-AW, a devastating form of systemic myoneuropathy. These injuries incurred during care in the ICU are at least partially preventable by focusing on evidence-based, PADIS guideline-supported approaches such as those in the ABCDEF bundle and championed by the ICU Liberation Campaign (**Table 1**). Reflecting the development of critical care as a field and the knowledge of long-term outcomes related to treatment in the ICU, the SCCM has identified several care practices that represent best value care (102). Integral to such are several elements of the ABCDEF evidence-based safety bundle. Tailoring sedation targets toward light sedation, waking patients up using paired SATs and SBTs, and mobilizing patients early are recognized as key components of value-based care. These recommendations reflect the evolution of critical care and the acknowledgement that delirium prevention and management, sedation stewardship, and early mobilization are key priorities for every ICU patient who has long-reaching impacts on cognitive and physical recovery.

The future of research in survivorship after critical illness will continue to be focused on both optimizing care practices in the ICU and the wards as well as confronting the complex and often fragmented care that survivors experience once leaving the hospital. The development

TABLE 1.
Evidence-Based Management of ICU Complications

Clinical Problems	ABCDEF Bundle Interventions
Delirium	**A**ssess/prevent/manage pain
	Both SATS and SBTs
	Choice of analgesia and sedation
	Delirium–assess, prevent, and manage
	Early mobility and exercise
	Family engagement and empowerment
Deep Sedation and Paralysis	**A**ssess/prevent/manage pain
	Both SATS and SBTs
	Choice of analgesia and sedation
	Delirium–assess, prevent, and manage
Immobility and ICU-acquired weakness	**A**ssess/prevent/manage pain
	Both SATS and SBTs
	Early mobility and exercise
	Family engagement and empowerment

SAT = spontaneous awakening trial, SBT = spontaneous breathing trial.

of ICU survivor clinics, focused on multidisciplinary specialty care after the ICU, is an active area of research and may represent another tool to improve the recovery trajectory after critical illness. Understanding both the fundamental biological mechanisms of PICS and uncovering promising new treatment approaches across the spectrum of care venues will be vital.

Thousands of peer-reviewed scientific manuscripts have been published on topics related to delirium, sedation, ventilator management, and early mobilization over the course of the last 50 years of critical care medicine. And yet, for our patients, it is not and cannot be the end of the story. Faced with the ongoing threat of critical illness, the next steps forward for our field are to march forward in our clinical care, armed with evidence and best practices while continuing to search and gain knowledge, all in the service of accelerating the recovery of our patients and improving the legacy of critical care survivorship.

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