Approaches to Addressing Post–Intensive Care Syndrome among Intensive Care Unit Survivors

A Narrative Review

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Abstract

Critical illness can be lethal and devastating to survivors. Improvements in acute care have increased the number of intensive care unit (ICU) survivors. These survivors confront a range of new or worsened health states that collectively are commonly denominated post–intensive care syndrome (PICS). These problems include physical, cognitive, psychological, and existential aspects, among others. Burgeoning interest in improving long-term outcomes for ICU survivors has driven an array of potential interventions to improve outcomes associated with PICS. To date, the most promising interventions appear to relate to very early physical rehabilitation. Late interventions within aftercare and recovery clinics have yielded mixed results, although experience in heart failure programs suggests the possibility that very early case management interventions may help improve intermediate-term outcomes, including mortality and hospital readmission. Predictive models have tended to underperform, complicating study design and clinical referral. The complexity of the health states associated with PICS suggests that careful and rigorous evaluation of multidisciplinary, multimodality interventions—tied to the specific conditions of interest—will be required to address these important problems.

Keywords: acute respiratory distress syndrome; post–intensive care syndrome; long-term outcomes; critical care outcomes

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The past two decades have seen significant improvements in mortality among patients admitted to intensive care units (ICUs), despite an increase in overall severity of illness (1). Promising improvements in quality of care have engendered a growing population of ICU survivors who confront a wide range of difficulties that may persist for years after their discharge from hospitals. These difficulties that ICU survivors face have recently been termed—for heuristic and strategic rather than biological or mechanistic reasons—the "post–intensive care syndrome" (PICS) (*see* Figure 1). The term "PICS" is intended to draw attention to new and/or worsening impairments in physical, cognitive, or mental health status arising after critical

	Acute Illness	Hospital Recovery	Early Post-discharge Recovery	Late Post-discharge Recovery
Desired Outcome:	Survival	Discharge Home	Stay Home and Improving	Return to Baseline
Examples of impediments to desired outcome:	• Late antibiotics or source control for sepsis • Hospital-onset infection (e.g., ventilator-associated pneumonia) • Lack of venous thromboembolism prophylaxis • High-tidal volume ventilation for ARDS	• Immobility • Delirium • Lack of rehabilitation • Polypharmacy • Prolonged catheterization • Disruption of circadian rhythms	• Post-Intensive Care Syndrome • Caregiver misinformation • Fragmented care or inadequate follow-up • Vague or incomplete discharge instructions • Inadequate medication reconciliation • Missing DME • Inadequate rehabilitation • Lack of subspecialist follow-up • Polypharmacy	• Post-Intensive Care Syndrome • Inadequate vocational rehabilitation • Disrupted employment • Socioeconomic barriers to care (insurance, transport) • Patient and family financial burden • Fragmented or inadequate family support • Polypharmacy
Location:	ICU	Hospital ward	Home	Home
Supervising clinician:	Intensivist	Hospitalist	PCP	PCP
Timeframe:	Days to weeks	Days to weeks	Months	Years

Figure 1. The phases of critical illness. ARDS = acute respiratory distress syndrome; DME = durable medical equipment; ICU = intensive care unit; PCP = primary care provider.

illness and persisting beyond acute hospitalization (2, 3).

By way of example, acute respiratory distress syndrome (ARDS), a common cause of ICU admission (4), affects approximately 200,000 people and results in approximately 75,000 deaths, accounting for approximately 2.2 million ICU days annually in the United States alone (5). Over 100,000 ARDS survivors confront the long-term sequelae of critical illness every year in the United States. Similarly, every year, over 14 million patients survive sepsis hospitalizations worldwide; a majority of these patients experience sequelae of PICS (6).

The National Heart, Lung, and Blood Institute (7, 8), the National Institute on Aging (9), and critical care professional societies (2, 10, 11) have identified long-term functional outcomes after critical illness as a crucial target for research and clinical improvements (12). The societal burden of PICS among survivors is substantial, is anticipated to increase, and therefore represents a research priority for the critical care community. In this narrative review, we highlight existing evidence and experience with strategies aimed at preventing and treating the impairments associated with PICS and additional areas of focus that could potentially ameliorate the burdens of critical illness survivors.

The Plight of Critical Illness Survivors

Survivors of critical illness often confront residual disability after their critical illness, impairments from preexisting illness, and risks for the onset of new illnesses (especially sepsis). Added to these burdens are iatrogenic complications (especially from polypharmacy and care fragmentation) and mismatches between supports needed and supports provided during the vulnerable period after hospital discharge. Extensive studies have identified substantial, persistent impairments in physical, cognitive, and mental health outcomes; limitations in ability to perform activities of daily living; and impaired quality of life among ICU survivors (6, 13–28).

Each domain of post-ICU impairment may impact the other domains. Symptoms of depression adversely impact physical function (25), and ICU-acquired weakness is associated with reduced quality of life (29, 30). A number of studies have shown relationships between cognitive impairments and psychological outcomes. Depression, anxiety, and post-traumatic stress disorder are associated with worse cognitive function (31–34). Conversely, cognitive impairments are associated with development of worse depression and anxiety (35). Cognitive impairments are also associated with new or worsening dependencies in instrumental activities of daily living, such as shopping, food preparation, and management of medications and finances (36).

Relatedly, many survivors incur substantial healthcare costs, lose employment, and find their social networks reconfigured at high rates (37–42). Many ICU patients are readmitted to the hospital within the first 3–12 months, often for potentially preventable complications (43–45). The first two years after hospital discharge are especially costly for ICU survivors (14, 18, 46–49). A longitudinal cohort study of ARDS survivors in Maryland reported a 1-year readmission rate of 40% among survivors, with an associated median hospital cost of $18,756 (interquartile range [IQR], $7,852–$46,174) (49). The costs to patients and families are

similarly high: ICU survivorship is associated with decreased return to work, and both patients and caregivers are plagued by loss of earnings (39, 50, 51). In addition, some survivors report an existential threat that comes from feeling abandoned in the face of great need (52, 53).

Conceptual Framework for the Phases of Post-ICU Recovery

The different phases of critical illness and recovery can be empirically classified as acute illness, hospital recovery, and early and late postdischarge recovery. Each phase can be thought of as a distinct epoch with a mix of unique and similar problems. Figure 1 summarizes the various phases of critical illness and its aftermath, which may be amenable to interventions that attempt to prevent, ameliorate, or treat the underlying impairments of PICS. Identification of the issues associated with each phase encourages development of targeted strategies to mitigate the impediments to complete recovery. Interventions relevant to each of these phases have been studied, albeit with variable rigor and replicability.

Of all these phases, the early postdischarge period is perhaps the least well explored and represents a vulnerable period in the recovery from critical illness. Although some morbidity (e.g., cognitive dysfunction, lung injury) may be intrinsic to the disease processes underlying critical illness, other aspects of post-ICU morbidity may result from therapeutic exposures and decisions in the ICU. Still others will result from fragmented or inadequate care after discharge, leading to potentially modifiable risk of poor outcome. These varied etiologic mechanisms for the range of post-ICU morbidity and mortality likely have a substantial influence on the possible efficacy of preventive or therapeutic interventions to limit post-ICU disability. We structure the balance of this narrative review around these varied etiologies, and we attempt to address them and future directions for optimizing outcomes after ICU discharge.

Acute Mechanistic Interventions

Little work has been done to explore acute mechanisms underpinning the impairments observed in PICS. Most critical care randomized trials measure only short-term organ dysfunction outcomes, with survival or organ-free days as the primary outcome of interest. Generally, randomized trials of ICU-based interventions have only evaluated outcomes after hospital discharge as secondary or safety signals. This strategy is insensitive in determining the impact of interventions across the continuum of care for the critically ill population, which becomes a key issue as survivorship increases.

Some notable exceptions in which researchers have attempted to explore PICS-relevant outcomes after ICU-based interventions (e.g., early enteral nutrition [23, 24], rosuvastatin [54, 55], or haloperidol and ziprasidone for delirium [56]) have not suggested efficacy. Admitting the risk of α-inflation when emphasizing possible efficacy signals on secondary outcomes, several pivotal ICU trials focused on sedation- and/or mobilization-related interventions have suggested improvement in key outcomes, including functional outcomes at hospital discharge or survival to 1 year (57–59). The ROSE (Reevaluation of Systemic Early Neuromuscular Blockade) trial of neuromuscular blockers in ARDS includes a carefully selected panel of postdischarge outcomes (60); results suggested no difference in outcomes to 12 months (61). More interventional trials that focus on the long-term outcomes of acute interventions are needed.

Interventions to Mitigate PICS

A number of interventions have been attempted in heterogeneous groups of critical care survivors to ameliorate the different impairments associated with PICS. Table 1 summarizes the various interventions that have been studied to mitigate the effects of PICS. These interventions can be broadly classified into four domains—physical, mental and social health, cognitive, and care coordination. Various combinations of interventions across these domains have been studied through different time frames, such as during hospitalization and in early discharge and late discharge periods. Unfortunately, very few interventions have demonstrated efficacy. Much work remains to be done.

Rehabilitation-based Interventions Have Yielded Mixed Results

Randomized controlled trials of physical rehabilitation interventions initiated several days after ICU admission have generally yielded no consistent evidence of benefit (2, 62–69). Clinical trials that focused on functional mobility, conducted by nurses, physical therapists, and/or occupational therapists and started within days of ICU admission, have demonstrated statistically significant benefits (59, 70–72). Beyond ICU discharge, studies have included in-hospital, outpatient, and home-based focused rehabilitation interventions—either formal or self-directed (using a rehabilitation manual)—without consistent evidence of significant efficacy (64, 73–76). Table 1 highlights exemplary interventions that have been studied. The most recent large meta-analyses suggest that exercise interventions may in fact be effective in terms of increased strength and decreased duration of mechanical ventilation (77, 78). The incremental benefits of adding nutritional therapy to rehabilitation interventions are a research priority (74, 79, 80); at least one controlled trial addressing this question is underway (NEXIS [Nutrition and Exercise in Critical Illness]; www.clinicaltrials.gov identifier NCT03021902).

Approaches to Fragmented or Inadequate Postdischarge Care

In the current healthcare system, patients and families often experience unmet needs after hospital discharge. Such unmet needs include durable medical equipment (e.g., oxygen, noninvasive ventilation, mobility assistive devices), coordination with government assistance and community health programs, rehabilitation therapy, medication management, and psychotherapy/counseling. At one healthcare system, 68% of patients at an ICU aftercare and recovery clinic (A&R), a term we introduce to describe post-ICU clinics and similar activities, required targeted care not otherwise being provided—especially physical therapy, psychotherapy, and nutrition services (81). The range of common needs in the early discharge period are displayed in Figure 2. Especially important is

Table 1. Examples of interventions studied or proposed to ameliorate aspects of post–intensive care syndrome

Intervention	Time Frame		
	In the Hospital	Early after Discharge	Late after Discharge
Physical	Physical therapy and mobilization interventions (59, 68, 71, 73, 77, 119–121), nutrition assessment and treatment (79)	Outpatient physical therapy (63, 74, 75), nutritional supplementation (74), recovery manual (74), home-based rehabilitation (64, 67)	Rehabilitation manual (62), nurse-led clinic/care coordination (76), home-based rehabilitation (64)
Mental and social health	ICU diaries (122–132), early psychological intervention (133), nurse-led preventive psychological intervention (134), open visitation (135), animal-assisted intervention (136)	ICU diary debrief (137, 138), internet-based cognitive behavioral writing therapy for patients and partner (87), rehabilitation manual, occupational (62) rehabilitation (39)	Peer support for patients and families (139, 140)
Cognitive	Cognitive intervention (141)	Cognitive therapy (73), in-home cognitive therapy (67), computerized cognitive rehabilitation (142)	
Care coordination/ care plan	Transfer of elderly ICU patients to geriatric ward (143)	Hospitalist discharge clinic (88), multidisciplinary recovery clinic/ center/program (85, 89, 144–146), medication management (84, 144), disease management support (147, 148)	Nurse-led mobile multidisciplinary care coordination (86)

Definition of abbreviation: ICU = intensive care unit.

addressing the risk of polypharmacy, especially overuse of (and failure to discontinue) proton pump inhibitors, antihistamines, corticosteroids, antibiotics, bronchodilators, anticholinergics, antidepressants, hypnotics, opioids, and antipsychotics (82–84).

Early experience with A&R services has suggested some of the limitations in current systems of health care. Experience at a prominent A&R clinic has identified medication reconciliation as a key unmet need and has suggested alternative approaches to integration of rehabilitation activities (85). In a small prospective cohort study of ICU survivors, all participants required at least one pharmacy intervention (e.g., dose adjustment, stopping or starting medications, administration of prophylactics, or monitoring for adverse drug reactions) with the median number of intervention per patient being 4 (IQR, 2–5) (84). Others have observed disorganized care among uncoordinated clinicians as a stumbling block for patients recovering from acute respiratory failure (86). Several innovative multidisciplinary interventions are currently being tested, including a mobile aftercare clinic (86) and early efforts at telehealth aimed at mitigating sequelae of critical illness (87).

Early experience at a Veterans Affairs hospital suggested that decreasing fragmentation through a hospitalist-run clinic for patients recently discharged from the hospital was associated with decreases in death and hospital readmission; although this was not specific to the ICU, generalizability may be possible (88). Early suggestive evidence from a collaboration of acute care physicians and geriatricians further supports the potential utility of ICU A&R clinics (89). In Germany, a prospective randomized trial examined the impact of structured A&R services on postdischarge outcomes among sepsis survivors (90). A structured primary care intervention did not improve mental health–related quality of life at 6 months after hospital discharge (the prespecified primary endpoint); however, those in the intervention group may have had better physical function and fewer impairments in activities of daily living (91).

Three randomized controlled trials have explored the utility of outpatient ICU A&R clinics specifically. The PRaCTICaL trial (A Pragmatic Randomised, Controlled Trial of Intensive Care postdischarge review clinics in improving Longer-term outcomes from critical illness) showed no increase in health-related quality of life with a nurse-led clinic in the United Kingdom (76). However, Jones and colleagues demonstrated benefit to a rehabilitation manual-guided recovery program within the context of an A&R clinic in Liverpool (62). The RECOVER (Evaluation of a Rehabilitation Complex Intervention for patients following Intensive Care Discharge) trial showed that patients randomized to A&R support were more satisfied, but there was no difference across the various outcome measures evaluated (79). Notably, both intervention and control groups received a rehabilitation manual (62), which may have blunted the difference between control and intervention groups. A nurse-led intervention to improve psychological health through narrative construction (i.e., cocreating a meaningful story about the ICU admission) administered in conjunction with follow-up visits showed no benefit in its primary outcomes of health-related quality of life, sense of coherence, depression, or anxiety (92). Of note, these investigational A&R clinic models were generally associated with visits more than 3 months after hospital discharge, well after a relevant window of vulnerability.

A recent Cochrane review of five studies examining the impact of ICU A&R clinics suggested insufficient evidence to determine whether ICU A&R clinics were effective in identifying

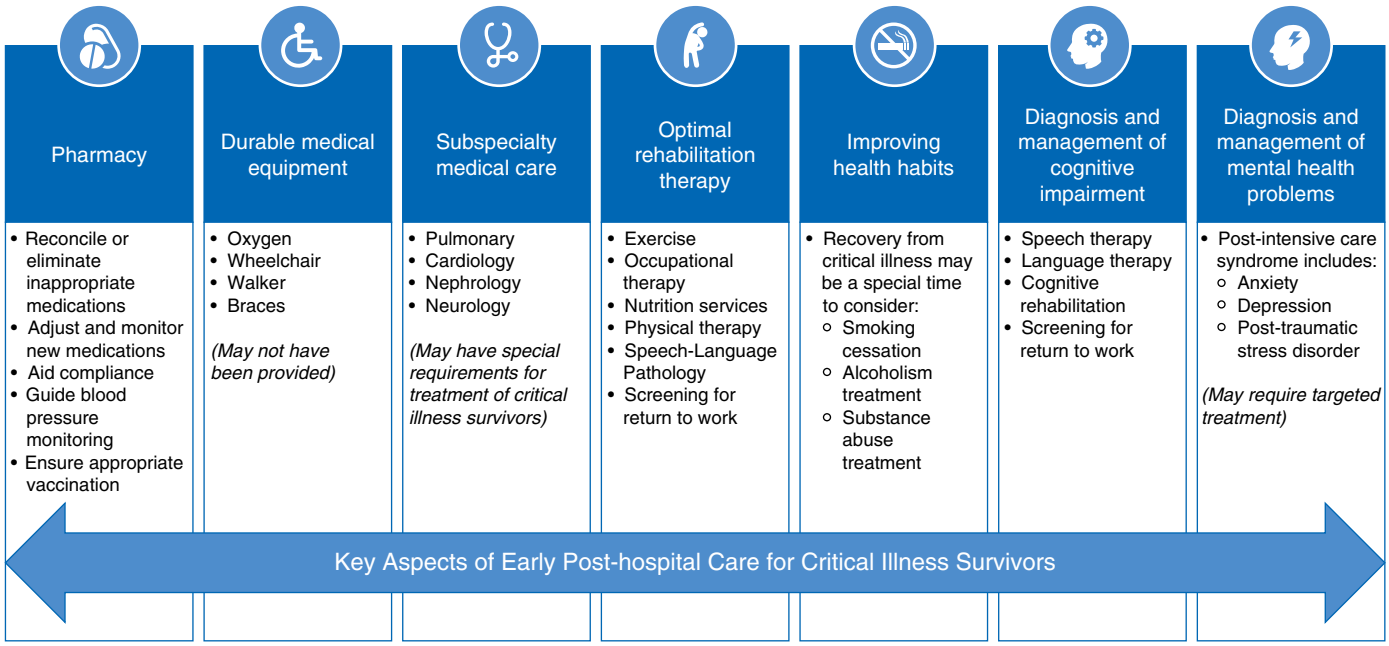

Figure 2. Key aspects of early post-hospital care for critical illness survivors.

and addressing new impairments across multiple domains of recovery (93). Whether support and coordination applied much earlier in the postdischarge course would be efficacious is not yet known. How best to staff such clinics is also unknown. Some advocate routine integration into primary care clinics (94), whereas others advocate for the presence of ICU clinicians in the design and staffing of clinics (95). Physical medicine and rehabilitation clinicians historically provide care for stroke survivors and others who have moved through inpatient rehabilitation. No comparative, quantitative data exist on the question, although patient and family identification with ICU clinicians, the analogy to surgical follow-up clinics, and some prospect of decreasing ICU clinician burnout favor, in our view, involving ICU clinicians (95). Whatever the conclusion, a multidisciplinary structure, with consultation as needed, seems prudent and is currently the most frequently encountered model for these clinics (personal communication, December 2018, Society of Critical Care Medicine THRIVE Post ICU Clinic Collaborative).

Despite the relative lack of firm efficacy data, the academic societies and many healthcare systems have supported A&R clinics. The Society of Critical Care Medicine (SCCM) has prioritized innovation and development of A&R services, including clinics and peer support programs. After establishment of the THRIVE Task Force, dedicated to improving care for ICU survivors and their families, two learning collaboratives within THRIVE have exemplified the high interest in evaluating feasibility and effectiveness of ICU aftercare interventions. The two collaboratives are comprised of nearly 50 unique centers in the United States and abroad. Initial work includes surveying current models of peer support in use around the world and early infrastructure building to test innovative models of ICU aftercare in multidisciplinary outpatient clinics (96, 97). The Collaborative Assessment of ICU Recovery Needs study (NCT03513289), funded by SCCM, is the largest qualitative study of ICU survivors, carers, and clinicians to date, and it will serve as a signpost to the testing of promising ideas that patients and families suggest may work to optimize recovery after critical illness (98). The other academic societies have not undertaken similar activities; no current relevant society guidelines exist.

Possible Analogous Evidence from Oncology

In cancer care, survivorship clinics have become common. Survivor clinics have been suggested to provide incremental benefit over usual follow-up care, and attendance has been associated with decreased healthcare use (99, 100). Although the evidence base continues to evolve, the field is clinically well established and received (101, 102). Although cancer survivors are distinct from survivors of critical illness, they bear similar burdens of postacute morbidity across multiple domains (103). Whether the benefits seen with cancer survivor clinics could be realized among ICU survivors through a similarly multidisciplinary outpatient approach remains unclear.

Early Postdischarge Interventions Work in Patients with Congestive Heart Failure

In congestive heart failure, coordinated A&R activities, such as structured telephone support, home visits, daily weights, educational materials, review of discharge plans, and related interventions, have improved readmission rates (104, 105). Because

heart failure is a reasonably coherent disease with protocol-driven treatments, these observations may not be fully generalizable to ICU survivors, who represent a heterogeneous group with largely syndromic presentations. Whether the specific techniques used in congestive heart failure will be relevant for ICU survivors is not known. To date, though, case management strategies appear to be among the most promising options, at least for improvement in healthcare use and readmission.

Parallels between patients with heart failure and sepsis survivors—suggested by inclusion of sepsis aftercare in the Centers for Medicare & Medicaid Services bundled payment care initiative—may exist. These concepts are part of the broader approach to postacute therapy that is tied to the specific needs and impairments of hospital survivors. It remains to be seen whether strategies motivated by the bundled payment care initiative and related programs are successful in improving patient-centered outcomes among sepsis survivors.

Predictive Modeling and Personalization

One key void in the literature is a careful map of the needs of ICU survivors. Understanding the interface between individual patients and the healthcare system is a crucial next step. What services do patients require? Which specialists do they see? What needs remain unmet in the current healthcare environment? Do distinct groups of patients have distinct patterns of unmet needs and adverse outcomes after hospitalization? Despite the accumulation of data documenting extensive functional impairments after an ICU stay, the specific prevention and treatment needs of individuals with PICS spectrum conditions are not well defined.

As with much of critical illness, patient selection is almost certainly central to efficacy. Not only will some conditions (or some aspects of conditions) be unresponsive to treatment, but also patients will vary in their proportion of treatable conditions, and the etiology of each may influence response to interventions. Although severity of acute illness and hospital-based physiology are strongly associated with hospital mortality (as exemplified by the myriad predictive models for ICU mortality), it is unclear which factors specifically drive postdischarge mortality and readmission among, for example, ARDS or sepsis survivors. One large predictive model identified preexisting chronic illness features as most predictive but had relatively poor discrimination for predicting 90-day unplanned readmission (106). In general, typical severity-of-illness scores and critical illness attributes are not strongly or consistently associated with functional outcomes in the months after hospital discharge (106, 107). Existing studies have identified possible associations between a few clinical predictors and individual outcomes (25, 33), including psychological outcomes (35, 108–113). Early work on phenotyping ARDS suggests a septic/inflammatory phenotype and a less inflammatory phenotype (114). Although that phenotype may affect response to ventilation with higher positive end-expiratory pressure and is associated with higher mortality, whether such phenotypes of acute inflammation map onto different postdischarge trajectories is not known (115). Distinct clusters with different clinical outcomes have similarly been identified among patients with severe sepsis or septic shock (116). Whether patients in such clusters have distinct postdischarge needs is unknown, nor is it known whether, for example, various causes of ARDS (e.g., trauma vs. pneumonia vs. pancreatitis) put patients at differential risk for PICS-related outcomes.

These realities emphasize the importance of methods to improve applications of interventions, including how best to select or enrich patient referrals to an A&R clinic. In the absence of reliable predictive models, many clinics have employed convenience definitions, including shock, respiratory failure requiring mechanical ventilation (especially if $\geq$48 h), and delirium (85, 117). Others use the presence of sepsis, prolonged ICU stay, receipt of extracorporeal membrane oxygenation, new organ failure, or the presence of tracheostomy or feeding tube at ICU discharge to prompt ICU A&R referral (personal communication, December 2018, SCCM THRIVE Post-ICU Clinic Collaborative).

Finally, seamless care integration appears to be a key factor in ensuring optimal continuum of care for survivors of critical illness. With growing ICU survivorship and increasing burden of PICS, it is imperative to integrate post–acute care services targeting residual impairments into the discharge process. It is anticipated that this strategy may not only aid postdischarge recovery but also optimize resource use at a time when bundled episode-based care is becoming increasingly influential.

Conclusions

Survivors of critical illness experience impairments across multiple domains that may persist long after their index episode of illness. The critical care community has labeled this phenomenon "PICS" to draw attention to a range of important problems confronting survivors and their families. Multiple interventions have been attempted to ameliorate PICS-related impairments. There is no "silver bullet" for a problem as complex and multifaceted as the spectrum of impairments frequently encountered within PICS. Observations regarding the lack of "steady, intimate" (118) care in contemporary medicine in general and congestive heart failure interventions in particular suggest that A&R activities may help address unmet discharge needs among ICU survivors. This aspect of post-ICU care remains poorly understood and therefore represents a research priority. A multicenter prospective cohort study (APICS-01 [Addressing Post-Intensive Care Syndrome]; www.clinicaltrials.gov identifier NCT03738774) is currently underway to systematically examine the impact of care fragmentation on readmission and survival among survivors of acute respiratory failure, which is one of the major causes of PICS. ■

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