Long-term complications of critical care

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Objectives: **As critical care advances and intensive care unit mortality declines, the number of survivors of critical illness is increasing. These survivors frequently experience long-lasting complications of critical care. As a result, it is important to understand these complications and implement evidence-based practices to minimize them.**

Data Sources: **Database searches and review of relevant medical literature.**

Data Synthesis: **Critical illness and intensive care unit care influence a wide range of long-term patient outcomes, with some impairments persisting for 5–15 yrs. Impaired pulmonary function, greater healthcare utilization, and increased mortality are observed in intensive care survivors. Neuromuscular weakness and impairments in both physical function and related aspects of quality of life are common and may be long-lasting. These complications may be reduced by multidisciplinary physical rehabilitation initiated early and continued throughout the intensive care unit care stay and by providing patient education for self-rehabilitation after hospital discharge. Common neuropsychiatric complications, including cognitive impairment and symptoms of depression and posttraumatic stress disorder, are frequently associated with intensive care unit sedation, delirium or delusional memories, and long-term impairments in quality of life.**

Conclusions: **Survivors of critical illness are frequently left with a legacy of long-term physical, neuropsychiatric, and quality of life impairments. Understanding patient and intensive care risk factors can help identify patients who are most at risk of these complications. Furthermore, modifiable risk factors and beneficial interventions are increasingly being identified to help inform practical management recommendations to reduce the prevalence and impact of these long-term complications. (Crit Care Med 2011; 39:371–379)**

Key Words: critical care; outcome assessment (health care); quality of life; neuromuscular diseases; mental disorders; respiratory function tests; respiratory distress syndrome; adult

Despite a reduction in acute care beds, utilization of critical care has grown over the past 2 decades (1, 2). With an aging baby boomer population, intensive care is expected to further expand in the next 2 decades (1). This increase in critically ill patients, along with improvement in intensive care unit (ICU) mortality, is creating a growing number of ICU survivors (2).

As a consequence of these trends, clinicians face an increasingly important challenge of addressing the long-term complications of critical care. The goals of critical care must extend beyond patient survival and include shared, multidisciplinary collaboration to prevent and manage the long-term complications of critical care (3). In this concise definitive review, we summarize data on the most widely studied patient complications after critical care and, where possible, provide evidence-based management recommendations for mitigating these complications (Table 1). To maintain a focus specifically on complications of critical care, patients with primary neurologic injuries (e.g., traumatic brain injury) are excluded from this review, since the nature of such pre-ICU injuries can affect many of the outcomes evaluated in this article.

Mortality

Cumulative mortality over the first year after ICU ranges from 26% to 63% (4), with four large studies providing important data regarding long-term mortality. Studies from the United States, Canada, and Australia, each following ~20,000–35,000 ICU survivors for 3 to 15 yrs, demonstrated that survivors are 2 to 5 times more likely to die compared with age- and sex-matched population controls (5–7). A Finnish study, in contrast, showed that mortality in >12,000 ICU survivors was similar to the general population within 2 yrs after illness (8). However, these Finnish findings varied by the subpopulation of ICU patients studied, with respiratory failure patients having worse survival during the full 5-yr follow-up period.

Multiple risk factors for post-ICU mortality have been reported, including age, comorbidity, and ICU severity of illness (5, 7, 9). The duration of ICU delirium also has been associated with increased mortality in the first year after ICU (9, 10). Sepsis also may be a risk factor since sepsis survivors experience a 5% to 14% absolute increase in mortality compared to survivors of other critical illnesses in the first year after discharge (11), with most deaths occurring early during follow-up (12).

Pulmonary

Long-term pulmonary function has been studied most frequently in acute respiratory distress syndrome (ARDS) survivors. Impairments in pulmonary function have been predominantly mild, with variability in the type of impairment(s) observed (i.e., obstructive, restrictive, and reduced diffusion capacity) (13–17). Fully understanding the degree of impairment directly attributable to ARDS is difficult because pre-ICU pulmo-

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Table 1. Long-term complications, selected risk factors, and management suggestions

Complication	Description	Selected Risk Factors	Natural History	Management Suggestions
Pulmonary	Impairment in spirometry, lung volumes and diffusion capacity	Diffusion capacity: duration of mechanical ventilation	Generally mild and improves during first year, but can persist to ≥5 yrs	
Neuromuscular	Includes critical illness polyneuropathy and myopathy	Hyperglycemia Systemic inflammatory response syndrome Sepsis Multiorgan dysfunction	Polyneuropathy may recover more slowly than myopathy; can extend to 5 yrs	Glycemic control Limit corticosteroids and neuromuscular blockers
	Disuse atrophy	Immobility/bed rest		Early rehabilitation (below)
Physical function	Impairment in activities and instrumental activities of daily living and 6-min walk distance	Systemic corticosteroids ICU-acquired illnesses Slow resolution of lung injury Age Preexisting impairment of instrumental activities of daily living	Some improvement within months, but impairments in activities of daily living may be seen at 1 yr and in instrumental activities of daily living at 2 yrs Long-lasting impairment in 6-min walk distance vs. population norms	Early rehabilitation in ICU continued throughout post-ICU recovery
Psychiatric symptoms	Depression	Traumatic/delusional memories of ICU, sedation, psychiatric symptoms at discharge, impairment of physical function	May decrease over first year	Prevent hypoglycemia
	Posttraumatic stress disorder	Sedation, agitation, physical restraints, traumatic/delusional memories	Little improvement in first year	Limit use of sedation
	Anxiety	Unemployment, duration of mechanical ventilation	May persist past first year	
		Overall risk factors: female sex, younger age, lower education, and pre-ICU psychiatric symptoms and personality		
Cognitive	Impairments in memory, attention, executive function	Lower pre-ICU intelligence ICU delirium Sedation Hypoglycemia	Significant improvement during first year, with residual deficits up to 6 yrs later	Delirium prevention Prevent hypoglycemia
Quality of Life	Deficits most observed in physical domains	Older age Severity of illness Critical illness polyneuropathy Psychiatric symptoms Delusional memories of ICU Pulmonary function abnormalities	Physical deficits improve over first year, but could recur or persist during 5-yr follow-up	Handbook for self-guided rehabilitation

ICU, intensive care unit.

nary function is not typically available. However, because these pulmonary impairments generally improve over time, some impairment is likely a reversible consequence of critical illness or ICU care, perhaps reflecting slow resolution of lung injury and ongoing lung remodeling. Impairment in diffusion capacity is the most common pulmonary complication, with one study observing that median diffusion capacity was initially mildly impaired, almost normal by 2 yrs, and normalized by 5 yrs among those surviving at each time point (17, 18). Median spirometry and lung volume values in the same cohort improved quickly, with mild abnormalities at 3 months normalizing by 6 months (16). However, other studies report long-term impairments: mild spirometry abnormalities were observed in one cohort through the first year after ARDS (19), while a separate study reported at least one pulmonary function abnormality in 27 of 50 ARDS survivors at a median follow-up of >5 yrs (13). Little information is known about risk factors for these impairments. Diffusion capacity was inversely associated with the duration of mechanical ventilation (13); however, existing small-sized studies have not demonstrated that specific ventilation strategies can reduce long-term pulmonary complications (15, 20).

Neuromuscular

Neuromuscular complications of critical illness are increasingly recognized (16, 21–23), with a recent international

roundtable meeting specifically focused on many aspects of this topic (24). A taxonomy for these abnormalities has been proposed, with patients having clinically apparent weakness attributable to critical illness designated as having "ICU-acquired weakness" (25). The subsets of these patients with ICU-acquired weakness who have electrophysiologically documented axonal polyneuropathy have "critical illness polyneuropathy" (CIP), and those with documented myopathy have "critical illness myopathy." Most commonly, CIP and critical illness myopathy occur together and are designated "critical illness neuromyopathy" (25).

While systematic epidemiologic data are limited, CIP and/or critical illness myopathy have been observed in nearly 50% of ICU patients with sepsis, multiorgan failure, or prolonged mechanical ventilation and are associated with increased ICU and hospital stay (26) and severe disability impeding independent walking or spontaneous ventilation after ICU discharge (27). Furthermore, 84% to 95% of ICU survivors with CIP continue to have neuromuscular abnormalities almost 5 yrs after discharge (28, 29). Persistent abnormalities can include muscle atrophy and weakness, impaired deep tendon reflexes, entrapment neuropathies, stocking and glove sensory loss, painful hyperesthesia, foot drop, and heterotopic ossification (16, 27). Some limited data suggest that recovery from CIP may be slower than from critical illness myopathy (30, 31), but both require prolonged rehabilitation compared with ICU patients without these neuromuscular complications (32). Although less well characterized, muscle atrophy occurring in part from ICU immobilization is becoming recognized as a common and likely meaningful factor in neuromuscular complications (33–35).

Abnormalities with the axon, neuromuscular junction, and muscle caused by ICU illness and/or interventions have all been implicated in these neuromuscular complications (36). Relevant mechanisms include inflammatory axonal injury, muscle breakdown, reduced nerve excitability from sodium channelopathy, and bioenergetic failure (36–39). Commonly cited risk factors include hyperglycemia, systemic inflammatory response syndrome, sepsis, and multiorgan dysfunction (26, 40). Furthermore, controlled mechanical ventilation and diaphragm inactivity were associated with diaphragm atrophy and proteolysis after only 18–69 hrs of ventilation in a study of brain-dead organ donors (41).

Intensive insulin therapy targeting tight glucose control has reduced some electromyographic evidence of muscle abnormality (42, 43). However, in separate studies, it has also been associated with increased rates of hypoglycemia and 90-day mortality (44, 45). Hence, avoiding hyperglycemia, without implementing tight glucose control, may balance the benefits and risks of this intervention. Additionally, while exposure to corticosteroids and neuromuscular blocking agents is not consistently associated with critical illness neuromyopathy, judicious use of these medications is generally recommended (22, 26, 40, 46) (Fig. 1).

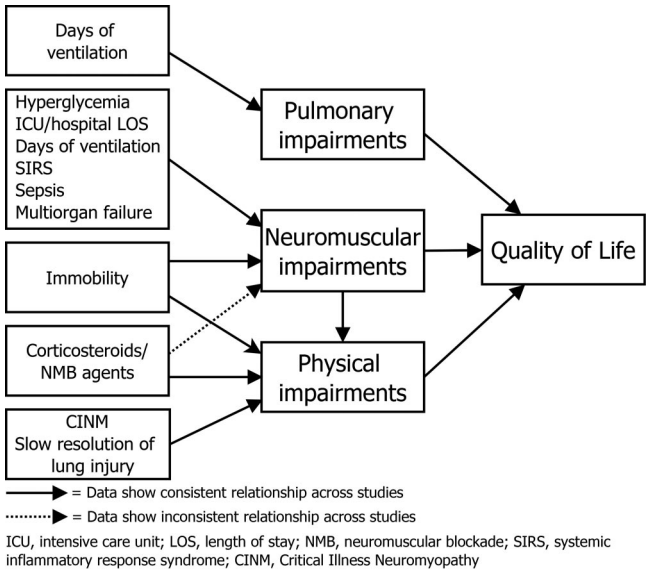

Figure 1. Patient and ICU risk factors for long-term physical complications.

Physical Function

Many ICU survivors report limitations in physical function which, despite showing slow improvement over time, may be long-lasting. Commonly used measures of physical function in ICU survivors include surveying patients' activities of daily living (ADLs) and instrumental activities of daily living and evaluating their 6-min walk distance (6MWD).

Impairment in ADLs was reported in virtually all ICU survivors assessed in the first week after discharge from ICU (47). Similarly, a cohort of previously healthy ARDS survivors had a mean decrement in ADLs of 40% at 28-day follow-up, which had not returned to baseline 1 yr after illness (48). This functioning may improve with time; however, impairments still occur in >50% of ICU survivors in the first year after illness, and almost one-third may have severe impairment at 1-yr follow-up (49, 50). ADL impairments may be more prevalent in mechanically ventilated patients because 86% and 69% of patients ventilated for >48 hrs had limitations in physical function at 3 and 12 months, respectively. Approximately 75% of these limitations were severe at 12 months (51). ADL impairments have been correlated with physical impairments after ICU discharge, including difficulty with walking and grip strength (47).

At 1-yr follow-up, instrumental activity of daily living impairments, such as difficulty taking medication or shopping, were present in >70% of ICU survivors ventilated for >48 hrs. These impairments were associated with age and preexisting instrumental activity of daily living dependencies (52). At a mean of 2 yrs after illness, good instrumental activity of daily living outcomes were reported for >50% of survivors >80 yrs old (53).

Using 6MWD as a measure of physical function, a longitudinal study of ARDS survivors reported that 6MWD was impaired and changed little with time, from 66% of predicted at 1 yr, to 68% at 2 yrs, and 77% at 5 yrs (17, 54).

Specific ICU-related risk factors for physical impairment may include exposure to systemic corticosteroids, new

ICU-acquired illnesses, and slow resolution of lung injury in the ICU (16). Early rehabilitation interventions in the ICU and after hospital discharge are beneficial in improving short-term physical function and have been demonstrated as safe and feasible (55–60). However, the timing of these interventions is important. Specifically, a two-site trial demonstrated that mechanically ventilated patients randomized to early occupational and physical therapy starting within 72 hrs of intubation were more likely to return to independent functional status at hospital discharge than patients who received similar rehabilitation care starting at a median of 7 days after intubation (61). In addition, patients randomized to routine physical therapy plus cycling exercises starting as early as ICU day 5 had significantly improved quadriceps force, 6MWD, and physical quality of life (QOL) measurements at hospital discharge vs. controls who received only routine physical therapy (62). Use of other technology-based rehabilitation therapies in the ICU, such as neuromuscular electrical stimulation and a dynamic tilt table, also may have benefit (63–67). However, a randomized trial of general ICU survivors receiving an individualized, home-based physical rehabilitation program showed no difference in improvement in 6MWD vs. a control group without structured postdischarge rehabilitation, raising questions regarding whether such efforts should be refined, focused on specific patient subgroups (e.g., prolonged mechanical ventilation), or evaluated using different outcome measures (68).

Observed limitations in physical function are likely caused, in part, by critical illness neuromyopathy, muscle atrophy, joint contractures, and other negative effects of immobility, which occur even in healthy individuals (16, 33–35, 69–72). Given these data, it seems prudent to minimize deep sedation and allow early rehabilitation as soon as possible after ICU admission (57, 73). Recently published guidelines in the United Kingdom recommend the initiation of an individualized, structured rehabilitation program early during ICU care, with continuation upon transfer to the ward along with education on self-guided rehabilitation (74). A European task force also emphasized the need for structured and individualized rehabilitation in the ICU (75) (Fig. 1).

Psychiatric

Psychiatric complications after critical illness occur frequently, with symptoms of depression and anxiety (including posttraumatic stress disorder [PTSD]) being most common. A systematic review of general ICU survivors reported a median 28% (range 8%–57%) point prevalence of clinically significant depressive symptoms in studies using a validated questionnaire, and a 33% point prevalence in a single study using a clinical diagnostic interview (76). In a separate systematic review of ARDS survivors, the median point prevalence of depressive symptoms, by questionnaire, was similar at 28% (range 17%–43%) (77). More recent studies in both ICU and ARDS survivors have also observed prevalence estimates within the ranges reported in these reviews (49, 78–82). These prevalence findings are markedly higher than in the general population (7%–8%) (83, 84) and after myocardial infarction (14%) (85). Since many of these studies excluded patients with preexisting psychiatric history, these findings suggest that critical illness or ICU care contributes to the development of depression. The duration of depressive symptoms after critical illness is unclear, but some studies show attenuation during the first year after ICU discharge (86–89).

The median point prevalence of ICU-related anxiety symptoms is 24% (range 23%–48%) (49, 77, 80, 81). For PTSD symptoms specifically, the median point prevalence in general ICU survivors is approximately 22% (range 8%–51%) by questionnaire or 19% (range 10%–39%) by clinical diagnostic interview (49, 80, 90). In ARDS survivors, the PTSD point prevalence was similar, with a median value of 28% (range: 21%–35%) by questionnaire (77) and 44% by clinical interview (91). These results are markedly higher than PTSD symptoms, from all causes, in the general population (3.5%) (84), and in post-myocardial-infarction and post-cardiac-surgery patients (16%–17%) (92). Unlike with depressive symptoms, PTSD symptoms may not improve over the first year (80, 90), with symptoms being reported up to 8 yrs after ARDS (91).

Several risk factors for these psychiatric symptoms overlap. Patient-level risk factors include pre-ICU psychiatric symptoms (76, 79, 82, 90), younger age (81, 90, 93), education (80, 82), and female sex (76, 81, 90). Commonly reported ICU-related risk factors include poor recall of the ICU stay, traumatic or delusional ICU memories, and ICU sedation (76, 77, 79, 82, 90, 94). Pre- or post-ICU impairment in physical function also may be associated specifically with depressive symptoms (49, 95), along with psychiatric symptoms at hospital discharge (76) and post-ICU cognitive impairment (81). Risk factors specifically associated with anxiety symptoms at 1 yr after critical illness include being unemployed at 1 yr and the duration of mechanical ventilation, while an optimistic personality trait was protective (80, 81). ICU-related risk factors for PTSD include agitation and physical restraint in the ICU (90). Understanding these risk factors is important in identifying which patients may be at greatest risk for post-ICU psychiatric complications.

The mechanisms of post-ICU psychiatric symptoms are largely unknown. For depression, biological factors such as cerebral hypoxia, inflammation, or hypoglycemia may contribute (76, 77, 79). For PTSD, ICU admission alone had an independent contribution in trauma patients, even after controlling for other potentially relevant variables, suggesting possible stressors in the ICU environment itself (96). A common in-ICU risk factor is benzodiazepine use; however, it is unclear if higher doses are mainly a marker for patients with pre-ICU psychiatric risk factors (i.e., anxious patients receive more sedation) or if they truly cause psychiatric symptoms, possibly through their effect on ICU delirium (79, 82, 90, 97, 98). However, preliminary data indicate that lighter sedation or daily interruption of sedation infusions may be protective (or at least not harmful) for PTSD (97, 99–101). Preliminary data also suggest that hydrocortisone administration in the ICU may be protective, potentially because of its effect on memory formation and retrieval (90, 102, 103). Based on these risk factors, preventing ICU hypoglycemia and reducing ICU sedation may reduce psychiatric complications (99) (Fig. 2). Two interesting trials demonstrated that patients who received dexmedetomidine experienced less delirium than those receiving benzodiazepines, but any long-term psychiatric benefits are still unknown (104–106).

Cognitive

Cognitive impairment, including delirium occurring during and after the

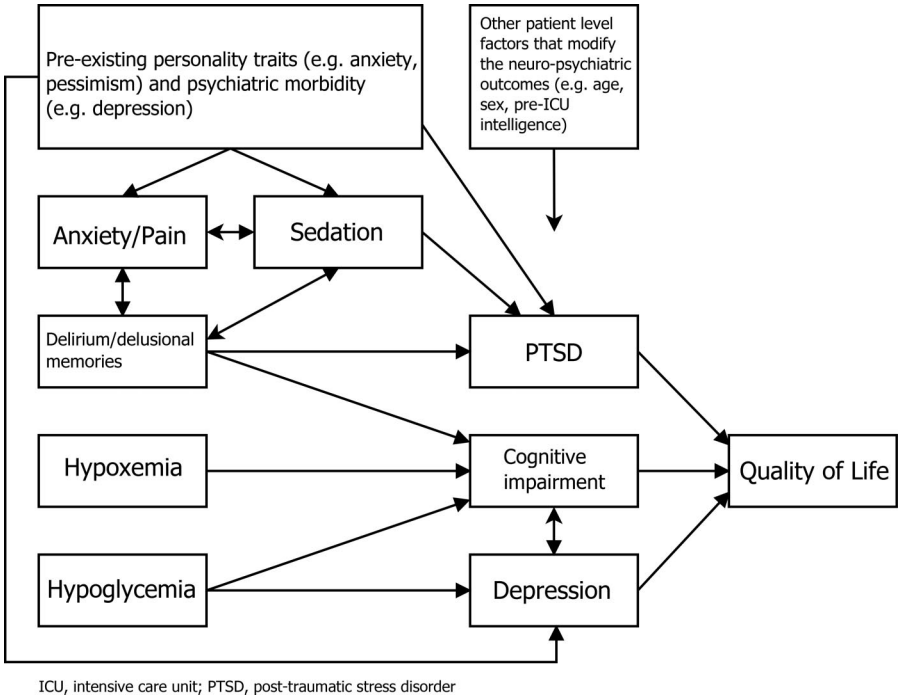

Figure 2. Patient and ICU risk factors for long-term neuropsychiatric complications.

ICU, is very common (107, 108) but improves partially over the first year post-ICU. Of 54 ARDS survivors, 73% had cognitive sequelae at hospital discharge, but only 46% had sequelae at 1 yr (109). However, there were no important changes in cognitive function between 1- and 2-yr follow-up of this patient cohort, suggesting a plateau beyond 1 yr (109). More recently, a study of 77 medical ICU patients demonstrated that 79% and 71% had cognitive impairment at 3 and 12 months, respectively (110). In another study of 51 general ICU survivors, 35% scored lower than the fifth percentile in at least two of three standardized cognitive tests at 3 months, but only 4% had such severe impairment at 9 months (111). Despite such improvements, a cross-sectional study demonstrated that impairments can be long-lasting, with 24% of ARDS survivors having at least mild to moderate cognitive impairment at a median follow-up time of 6 yrs (range: 1–12 yrs) (112). Furthermore, a study of patients ≥65 yrs old with severe sepsis showed a >4-fold increase in new, post-ICU moderate or severe cognitive impairment lasting up to 8 yrs (113). Impairment after critical illness occurs across a range of cognitive domains with deficits consistently observed in memory, attention, and executive function (78, 109, 111, 112, 114–116).

In one large patient cohort with cognitive screening before illness, cognitive decline was observed during posthospital follow-up. This decline was greatest in critically ill patients but also apparent in those with non-critical-illness hospitalizations when compared to nonhospitalized controls (117). The duration of ICU delirium also has been associated with cognitive impairment at 1 yr (110); however, significant impairment has been observed even in patients who were apparently never delirious, suggesting additional mechanisms independent of delirium (114). Brain atrophy has been observed on MRIs of critically ill patients with delirium, but it is unclear whether atrophy is a risk factor for, or an effect of, a common neurologic insult (118). Furthermore, brain CT imaging could not predict cognitive impairment in hospital (119). Lower pre-ICU intelligence ("cognitive reserve") and an inability to recall ICU events after critical illness (120) may be risk factors for post-ICU cognitive impairment. Other potential ICU-related risk factors include hypoglycemia (121), hypoxemia (89), hypotension (109, 114), and sedation (101). Management recommendations to potentially help preserve cognitive function should focus on screening for and minimizing delirium (e.g., reducing benzodiazepine use), and preventing hypoglycemia (Fig. 2).

Quality of Life

Given the unexpected nature of critical illness, QOL outcomes generally cannot be prospectively measured before critical illness. As a result, many studies compare ICU survivors' QOL with population norms. However, patients who become critically ill may not be at the population norm before illness (122, 123), making it difficult to fully understand the impact of critical illness on QOL. With this caveat, existing research indicates that QOL is commonly impaired after ICU discharge, potentially for long durations.

A systematic review of 21 studies with >7,000 ICU survivors found significantly lower QOL, with most studies demonstrating impairments in all QOL domains except bodily pain (124). Impairments in both ICU and ALI/ARDS survivors are most commonly found in the domains related to physical QOL (11, 49, 124, 125) and generally improve, to some degree, within 3–12 months after discharge (124, 126). However, this physical recovery may not be durable. A longitudinal study assessing QOL in 300 ICU patients reported impairment at 3 months that recovered by 1 yr, but another impairment occurring between 2.5 and 5 yrs (122). Throughout the 5-yr follow-up, the mean physical component QOL score of this cohort remained below population norms. However, the pre-ICU baseline QOL, according to family estimates, was lower for these patients vs. population norms, and virtually all domains of post-ICU QOL surpassed these proxy estimates of baseline QOL at 6 months after illness. This finding may be due to the positive influence of surviving critical illness on patients' perceived QOL or discrepancies between family and patient estimates of baseline QOL (122, 123, 127).

A variety of factors have been associated with QOL impairments, including age, preexisting disease (128), ICU severity of illness (124), and PTSD and depression symptoms (76, 90). Physical QOL deficits were specifically associated with CIP (49), the loss of muscle mass (129), and impaired pulmonary function (19) (Fig. 1). A study of trauma survivors identified that delusional memories of the ICU were associated with long-lasting impairments in all QOL domains evaluated (130, 131).

QOL may be improved with specific interventions. For example, in a randomized trial, ICU survivors receiving a rehabilitation handbook, which included self-

directed exercises and a patient diary, in addition to routine follow-up had improved physical function-related QOL at 6 months (132). However, the optimal content, timing, and duration of post-ICU interventions need further clarification because other randomized trials of nurse-led or home-based rehabilitation programs initiated after hospital discharge failed to improve QOL (68, 133).

Healthcare Utilization

While the majority of direct medical costs for ICU survivors are incurred during patients' initial hospitalizations, >40% require ongoing medical care for ≥2 yrs (17). Within the United States, utilization of long-term acute care hospitals for patients recovering from critical illness has substantially increased with a three-fold increase in long-term acute care admissions between 1997 and 2006 (134). Post-ICU costs are primarily related to inpatient rehabilitation and hospital readmissions and associated with age and organ dysfunction in the ICU (17, 48). In a cohort of 92 ARDS survivors in Canada, 33% received inpatient rehabilitation and >50% used home care services in the first 2 yrs, while almost 40% were readmitted to the hospital, with half being readmitted multiple times (17). This increased healthcare utilization reinforces the prior findings that the effects of critical illness are far reaching, creating an important burden for patients and their families for years after ICU discharge. Given the profound dependencies that survivors of critical illness experience, substantial caregiver burden, including depression (135, 136) and lifestyle or employment disruption (136), has been reported 1 to 2 yrs (137) after ICU survivors' illness.

Of note, a subset of ICU patients have chronic critical illness, typically requiring prolonged mechanical ventilation, sometimes for weeks or months following their initial illness. A recent comprehensive review highlights the particularly poor outcomes of these patients compared with other survivors of critical illness (138). Nearly half of these patients remain on mechanical ventilation after hospital discharge, with most of those ventilated >60 days remaining so until death (138–140). Survivors tend to be extremely physically and cognitively disabled and require considerable ongoing care (141–143), with two-thirds readmitted to the hospital within 1 yr of ICU discharge (144). The ongoing nature of treatment and frequent readmissions represent a substantial burden on healthcare resources. A prospective study of 126 survivors of prolonged mechanical ventilation demonstrated inpatient or home-care services were required, on average, during 74% of all days in the first year after illness (144). Furthermore, fewer than 10% were alive and without functional dependency at 1 yr. Hence, resource utilization is especially high among the chronically critically ill.

CONCLUSIONS

The number of survivors of critical illness is growing and expected to further increase with the aging population and improving ICU mortality. It is increasingly clear that there is a formidable legacy of critical illness (145)—that ICU survivors experience significant long-term complications in physical and psychological function that are associated with impairments in QOL. As we learn more about these complications and their natural history, our understanding of their high prevalence, magnitude, and impact grows. Continued investigation of both modifiable and nonmodifiable risk factors, and underlying mechanisms, are essential for identifying which patients are most likely to experience these complications and for designing effective ICU and post-ICU interventions to mitigate them. With an understanding of the long-term complications of critical care, ICU clinicians can begin to modify factors that influence these complications and support interventions demonstrated to reduce them.

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