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Long-term Neurocognitive Function After Critical Illness*

Ramona O. Hopkins, PhD; and James C. Jackson, PsyD

Background: Until relatively recently, critical care practitioners have focused on the survival of their patients and not on long-term outcomes. The incidence of chronic neurocognitive dysfunction has been underestimated and underreported, and only recently has it been studied in critically ill patients. However, neurocognitive outcomes have been the subject of extensive investigation in other medical populations for many years.
Methods: Review of the current literature regarding long-term neurocognitive outcomes following critical illness.
Results: Data from studies to date indicate that critical illness can lead to significant neurocognitive impairments. The neurocognitive impairments persist for months and years, and may have important consequences for quality of life, the ability to return to work, overall functional ability, and substantial economic costs. The mechanisms of the neurocognitive impairments are not fully understood but likely include delirium, hypoxia, glucose dysregulation, metabolic derangements, inflammation, and the effects of sedatives and narcotics among other factors. The contributions of these factors may be particularly significant in patients with preexisting vulnerabilities for the development of cognitive impairments such as mild cognitive impairment, dementia, prior traumatic brain injury, or other comorbid disorders associated with neurocognitive impairments.
Conclusions: Current research indicates that neurocognitive sequelae following critical illness are common, may be permanent, and are associated with impairments in daily function, decreased quality of life, and an inability to return to work. Research needs to be done to better understand the prevalence, nature, risk factors, and nuances of the neurocognitive impairments observed in ICU survivors. *(CHEST 2006; 130:869–878)*

Key words: critical care outcomes; critical illness; neurocognitive impairments

Abbreviations: APACHE = acute physiology and chronic health evaluation; IQ = intelligence quotient

Despite a reduction in the total number of US hospital beds over the last 15 years, there has been a 26% increase in critical care beds in the last 2 decades.[1] Advances in critical care medicine have led to improved survival rates among those patients admitted to the ICU. In the United States, approximately 55,000 patients are treated in ICUs each day.[2] At least 40% of adult ICU patients require mechanical ventilation.[3] Patients who require long-term mechanical ventilation (*ie*, > 3 days) represent 4 to 10% of critical care hospital admissions and consume 30 to 50% of critical care resources.[4] Although the age range of ICU populations varies widely, approximately 60% of all days spent in the ICU occur in patients > 65 years of age.[5]

Critical illness often results in multiple system organ dysfunction, including neurologic dysfunction, and is associated with poor neurologic outcomes.[6] Investigations of the effects of critical illness on neurologic dysfunction have been relatively neglected compared to the effects on other organ systems. The incidence of neurologic dysfunction has

been underestimated and underreported, and only recently has it been studied in critically ill patients. Neurologic outcome, including neurocognitive function, has been the subject of extensive investigation for many years in other medical populations.[7] A study[8] that assessed neurologic organ dysfunction found that a higher severity of the initial neurologic dysfunction (eg, lower Glasgow coma score) was associated with a higher 30-day mortality rate. In addition, no change or worsening of the severity of the neurologic dysfunction from the first to third ICU day was also associated with higher 30-day mortality rate.[8] Some more recent data have suggested that neurologic dysfunction following critical illness may be due to neuropathologic changes. Structural and quantitative MRI in patients who are mean (± SD) time of 16 ± 12 days from ARDS onset showed significant brain atrophy and ventricular enlargement, and 53% of the patients had atrophy or lesions, as determined by radiologic report.[9] Neurologic dysfunction following critical illness involves both the CNS and peripheral nervous system, and contributes to mortality and morbidity.[10] Neurologic morbidity includes polyneuropathy, encephalopathy, and neurocognitive impairments.

Prevalence and Nature of Chronic Neurocognitive Impairments

Medical and surgical management of critical illnesses can, and frequently does, result in *de novo* neurocognitive impairments. Research is limited regarding neurocognitive outcomes in survivors of critical illness; however, these patients are at risk for delirium (eg, acute cerebral dysfunction) during ICU treatment and chronic neurocognitive impairments.[11–15] Early reports of chronic neurocognitive impairments after critical illness have been concerning, although additional research is needed. In ICU survivors, approximately one third of patients or more will develop chronic neurocognitive impairment.[13] While it is difficult to make comparisons across studies due to different definitions of neurocognitive sequelae, neuropsychological tests administered, time to follow-up, patient population, study design (prospective vs retrospective), or inclusion of a control group, the current data suggest that neurocognitive impairments are extremely common in survivors of critical illness.

A literature search for all articles pertaining to critical illness and neurocognitive outcome was conducted using the US National Library of Medicine MEDLINE database. Terms used to search the database included "critical illness and cognitive sequelae," "critical illness and cognitive impairment,"

"critical illness and neuropsychological impairment," "ICU and cognitive impairment," "ICU and cognitive sequelae," and "ICU and neuropsychological impairment." In addition, we reviewed relevant critical care journals for relevant abstracts, as well as the references used in these sources. Studies were required to meet the following two criteria for inclusion in this review: (1) to assess neurocognitive outcomes in critically ill patients; and (2) to employ objective measures of neurocognitive functioning. Our search identified six studies that met our inclusion criteria. Four additional studies were identified from published abstracts, resulting in a total of 10 studies that assessed neurocognitive outcome in critically ill patients.

Currently, there are 10 cohorts totaling approximately 455 patients that have assessed chronic neurocognitive impairments following critical illness.[16–26] The populations of the patient cohorts include five studies in ARDS patients,[16,19,20,23,27,28] one study in patients with acute lung injury,[25] one study in patients with respiratory failure,[28] one study in medical ICU patients,[24] and two studies in general ICU patients.[17,21] The time to neurocognitive assessment was variable, with the majority of the follow-up occurring during the first year post-hospital discharge (Fig 1). Three studies assessed patients beyond 1 year. A prospective longitudinal study[28] followed up patients at hospital discharge, 1 and 2 years post-hospital discharge, and two retrospective studies[25,29] assessed the patients at approximately 6 years post-hospital discharge.

The evidence from the 10 cohorts suggests that 25 to 78% of ICU survivors experience neurocognitive impairments.[16,18–26,28] Among specific populations, such as patients with ARDS, the prevalence of neurocognitive impairments is even greater, and may be as high as 78% at hospital discharge, 46% at 1 year,[16] and 25% at 6 years.[25] Hopkins and colleagues[28] assessed the premorbid estimated intelligence quotient (IQ) in ARDS patients and found that it was significantly lower than their measured IQ at hospital discharge. However, the patients' measured IQs improved to their premorbid levels by the 1-year follow-up, with no additional improvement found at 2 years. The finding that patients recovered over time with regard to intelligence does not necessarily suggest a comparable recovery in all cognitive domains, as data from the literature on traumatic and anoxic brain injury suggest that some neurocognitive abilities are more likely to improve than others.[28]

A recent study[28] found that neurocognitive impairments occur in 70% of ARDS patients at hospital discharge, in 45% at 1 year, and in 47% at 2 years. The neurocognitive test scores of the ARDS survi-
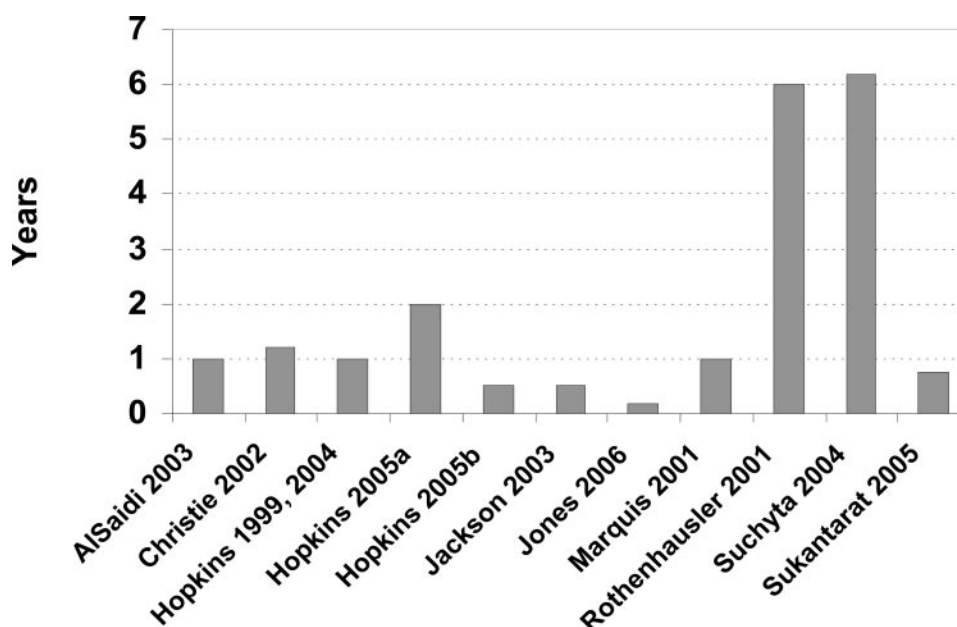
FIGURE 1. The mean time to neurocognitive assessment by study listed in alphabetical order by first author.

vors with neurocognitive sequelae (approximately 50% of survivors) fell below the sixth percentile of the normal distribution of cognitive function. These ARDS survivors had marked difficulty with tasks that require executive function, memory, attention, or quick mental processing speed. The neurocognitive impairments in critically patients are similar to those reported in medical ICU survivors[13] following carbon monoxide poisoning,[30] and several years after elective coronary artery bypass graft surgery.[31]

In addition to ARDS survivors, neurocognitive impairments have been reported in the general population of critically ill patients. Jackson et al[13] studied 34 medical ICU survivors at 6 months and found that 33% had chronic neurocognitive impairment (which was defined using a very conservative definition of the impairment of two test scores 2 SDs below the mean or three test scores 1.5 SDs below the mean). The neurocognitive impairments were similar to those reported in ARDS survivors, and included mental processing speed, memory, language, and visuospatial abilities. The neurocognitive deficits were mild to moderate in severity. While 34 patients completed a 6-month neurocognitive follow-up, 128 patients, all without preexisting cognitive impairment assessed using the Informant Questionnaire of Cognitive Decline in the Elderly, were administered an initial Mini Mental State Examination at ICU discharge. The mean Mini Mental State Examination scores of the critically ill survivors who did not complete neurocognitive follow-up were below the impairment cutoff of 24 and were significantly lower than those of the patients who completed follow-up, suggesting that neurocognitive impairments may be more common than previously reported.[13] Additional support for neurocognitive impairment in the general critically ill population came from a prospective cohort[18] of 32 critically ill medical patients who underwent long-term mechanical ventilation (ie, ≥ 5 days). The patients were evaluated at hospital discharge and 6 months later. Of the patients receiving long-term mechanical ventilation, 91% had neurocognitive impairments at hospital discharge and 41% had neurocognitive impairments at 6 months, primarily in attention, memory, mental processing speed, and executive function.[18]

Neurocognitive impairments in ICU survivors occur in a variety of neurocognitive domains, although information regarding the specific nature of these impairments is incomplete. The studies conducted to date have inconsistently assessed neurocognitive domains, with some investigations focusing a wide range of neurocognitive functioning and others focusing on a narrower range of capacities. The neuropsychological test batteries employed across studies have generally been fairly brief (they were designed to accommodate the fatigue that is common in ICU survivors) rather than comprehensive batteries designed to investigate all neurocognitive abilities. The neurocognitive domains that are impaired in ICU survivors may depend on the nature of

the insult experienced during critical illness and its treatment, as well as on the presence of preexisting neurologic abnormalities and individual vulnerabilities such as older age or comorbid disorders that might render specific domains more vulnerable to critical illness-induced brain injury. In general, memory is the most frequently observed deficit, followed by executive function and attention deficits (Fig 2). Support for impaired memory following critical illness comes from a prospective cohort of 87 ARDS survivors who were administered a memory questionnaire. Twenty percent of the ARDS survivors rated their memory as poor 18 months after ICU discharge.[23] A study[21] that predominantly evaluated executive function (*eg*, planning, organization, behavioral inhibition, and decision making) in general ICU survivors at 3 and 9 months found executive dysfunction in 35% of the patients. Mechanically ventilated nondelirious patients, in whom delirium was assessed just prior to neurocognitive testing, had impaired memory and problem solving abilities (*ie*, executive function) during ICU treatment, during hospital treatment, and at the 2-month follow-up.[17] While in the ICU, 100% of patients had impaired executive function, and 67% had impaired memory. At the 2-month follow-up, 50% of patients had impaired executive function and 31% had impaired memory.[17]

DURATION OF THE NEUROCOGNITIVE IMPAIRMENTS

Many critically ill patients have significant chronic neurocognitive impairments at 2 months,[17] 6 months,[18,24] 9 months,[21] 1 year,[16,19,23] 2 years,[28] and up to 6 years.[20,25] Neurocognitive impairments im-prove during the first 6 to 12 months post-hospital discharge. For example, 70% of ARDS survivors had neurocognitive impairments at hospital discharge, but only 45% had neurocognitive impairments at 1 year. There was no additional improvement in neurocognitive sequelae from the 1-year follow-up to the 2-year follow-up.[28] Data regarding neurocognitive outcomes > 2 years after the critical illness have come from two studies. A retrospective cohort study[25] of 46 ARDS survivors found that 25% had impairments 6 years following ICU treatment; only 21 patients returned to full-time employment, and all patients with neurocognitive impairments were disabled. A second study[20] of 30 ARDS survivors found impaired memory, attention, concentration, executive dysfunction, and motor impairments 1 to > 6 years after hospital discharge (mean time, 6.2 years). The above studies suggest that the neurocognitive impairments in survivors of critical illness are long-lasting and likely permanent. The persistent effects of critical illness on neurocognitive function may be particularly striking in geriatric patients with preexisting mild neurocognitive impairment or dementia, as critical illness-related neurologic insults may serve to heighten their cognitive decline and lead to what could be characterized as an "ICU-accelerated dementia." Such a pattern (*eg*, medical illness accelerating the trajectory of dementia) has been observed in other populations but has not been investigated in critically ill cohorts.[32,33]

REMOTE ASSESSMENT OF NEUROCOGNITIVE FUNCTION

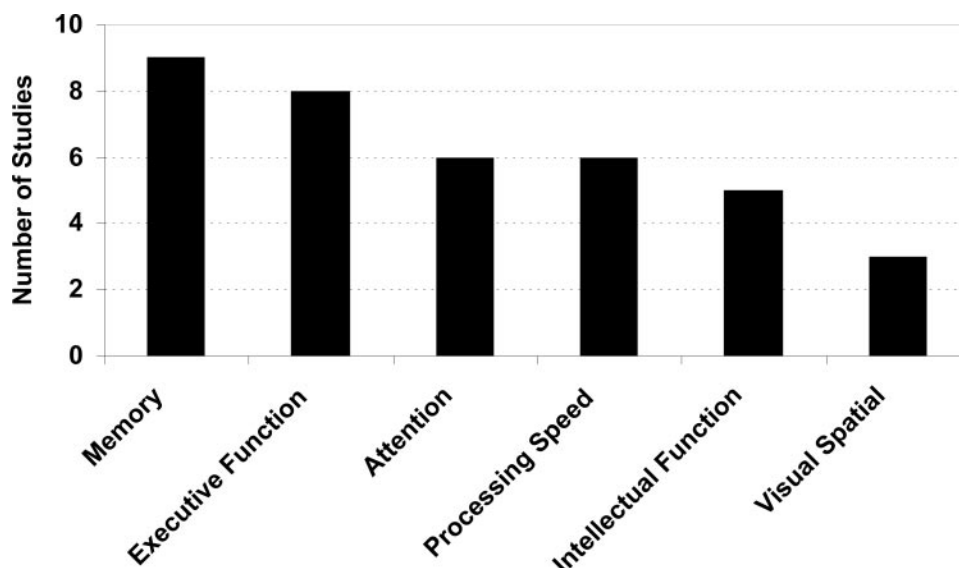A more complete understanding of the neurocognitive impairments following critical illness will re-

FIGURE 2. The number of studies that report neurocognitive impairments listed by neurocognitive domain.

quire larger samples. Such studies may be hampered by the difficulties of performing in-person neurocognitive assessments in large multicenter studies or where face-to-face neurocognitive testing is impossible or impractical (such as in centers with a large geographic referral area). A 2004 study[26] assessed neurocognitive function in ARDS survivors using questionnaires and tests administered over the telephone. One caveat concerning telephone-based testing is its ability to administer only verbal tests, reducing the neurocognitive functions that can be assessed. Two groups of ARDS patients were administered neurocognitive tests over the telephone.[26] Of the ARDS survivors, 24% had impaired memory and 29% had executive dysfunction. The detection of neurocognitive abnormalities in ARDS survivors using a telephone-administered test battery derived from standard neuropsychological tests was feasible and valid. This battery may be useful as a research tool for future multicenter studies.[26]

No Evidence for Association With Neurocognitive Impairments

Clinical Variables

A consistent finding across investigations is that no associations were found between some indicators of illness severity and the development of neurocognitive impairment or unfavorable neurocognitive outcomes. ICU length of stay, acute physiology and chronic health evaluation (APACHE) II scores, duration of mechanical ventilation, tidal volume, or number of days receiving sedative, narcotic, or paralytic medications were not associated with neurocognitive impairments in critically ill patients.[24,28] This finding suggests that the neuropsychological dysfunction experienced by ICU survivors cannot be explained simply in terms of the degree of acute illness severity, as one might intuitively conclude. Alternatively, Jones and colleagues[17] found that impaired executive function measured during ICU treatment was associated with ICU and hospital length of stay, and that impaired memory measured during ICU and hospital treatment were associated with hospital admission APACHE II scores. However, consistent with the studies cited above, Jones et al[17] found no correlations between any neurocognitive test score and ICU or hospital length of stay or APACHE II scores at the 2-month follow-up. One limitation of the current data was the small sample sizes, which can result in insufficient power to detect real differences when they may actually exist. Thus, neurocognitive outcome studies in larger samples may find relationships between neurocognitive impairments and indicators of illness severity.

Age

The majority of the patients in the 10 cohorts studied to date were young or middle-aged adults, with a mean (± SD) age of 54 ± 11 years. The mean ages by study are shown in Figure 3. Age was not related to chronic neurocognitive impairments.[16,24,25] Age was related to impaired executive function measured during ICU treatment but not at the 2-month follow-up.[17] Several studies[16,19,28,34] used demographically corrected scores that accounted for age, gender, and education. Jackson and colleagues[24] used a multivariable analysis adjusted for age and found that age did not account for the neurocognitive impairments. However, geriatric patients (ie, patients > 60 years of age) were significantly more likely than their nongeriatric counterparts to have impairment of global mental status, visuospatial construction, and visual memory.[24] Elderly patients (ie, patients > 65 years of age) were included in all of the studies[16,18–26,28]; however, only the study by Sukantarat et al[21] included a predominantly older population with a median age of 60 years (age range, 26 to 82 years). Elderly patients (ie, patients > 65 years of age) account for almost half of critical care admissions[35] and for over half of all ICU days.[5] The elderly are more likely to have premorbid disorders, such as cardiovascular disease and dementia, that are associated with neurocognitive impairments.[36] The prevalence of preexisting cognitive impairment in elderly medical ICU patients is 37%.[37] The majority of the neurocognitive studies[16,18–23,25,26,28] excluded patients with preexisting neurocognitive impairments or disorders with known neurocognitive effects. Jackson et al[13] identified 17% of patients (7 of 41 patients) with preexisting neurocognitive impairments determined by surrogate assessment, who were subsequently excluded from the data analysis. Data from the existing studies indicate that age was not related to neurocognitive outcome, which was likely due to the restricted age range. Additional studies in larger and older ICU cohorts are needed to confirm this finding. While critical illness may affect an individual's neurocognitive functioning regardless of age, subjects of an advanced age may be more vulnerable to the development of neurocognitive impairment due to preexisting age-related vulnerabilities.

Lack of Recognition of Cognitive Impairments

A recent study[28] found that 42% of ARDS survivors underwent rehabilitation therapy, but most
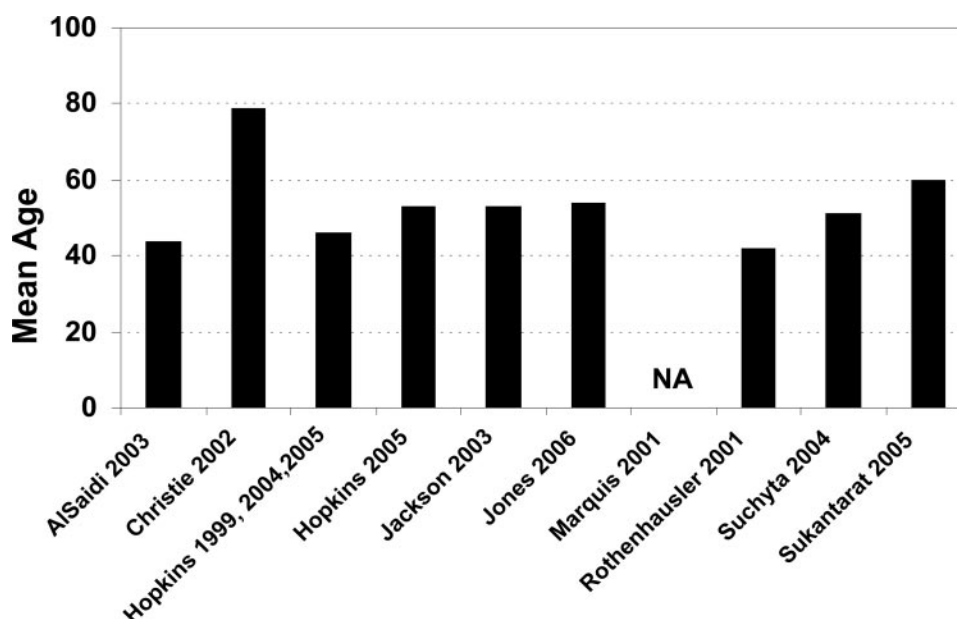
FIGURE 3. The mean age of the critically ill patients listed by study in alphabetical order by first author. NA = not available.

were not evaluated for neurocognitive impairments, with only 12% identified as having neurocognitive impairments by the clinical rehabilitation team. Neurocognitive impairments appear to be underrecognized by both ICU and rehabilitation providers. Studies have suggested that in non-ICU clinical settings many physicians fail to recognize (or assess) neurocognitive impairment in 35 to 90% of patients.[38] Neurocognitive impairments are rarely evaluated in critically ill patients[13] and may be overlooked in one of every two cases.[39] This may partly be because the manifestations of neurocognitive impairments are often subtle, and patients may experience impairment in select domains even if they are alert, oriented, and generally cognitively intact. The education of clinical care providers regarding clinical manifestations of neurocognitive impairments in patients prior to ICU discharge may help to increase the identification rates.[40] the increased identification of neurocognitive impairment in ICU survivors may benefit patients by raising physician awareness, potentially leading to increased referrals to rehabilitation specialists, neuropsychologists, speech and language therapists, and other health-care providers who can provide interventions such as cognitive remediation. It should be noted that there is a paucity of data regarding interventions for neurocognitive impairments, or about the potential benefit of such interventions in critically ill patients.

Consequences of Chronic Neurocognitive Impairments

The consequences of chronic neurocognitive impairments are far-reaching and typically contribute to a decreased ability to perform activities of daily living, decreased quality of life, increased medical costs, and the inability to return to work. Two years after hospital discharge, 34% of ARDS survivors were working or were full-time students, 34% were receiving disability payments that started after hospital discharge for ARDS, and 32% patients (20 of 62 patients) were not working or were retired.[28] An investigation[12] that focused on 1-year outcomes, reported that 51% of ARDS survivors were not working. Although a significant number of the patients had not reentered the workforce, most of these individuals reported physical as opposed to neuro-cognitive-related reasons for the failure to return to work.

Decreased quality of life was not associated with neurocognitive impairments in ARDS survivors[19] or with executive dysfunction in a critically ill medical population.[21] In contrast, ARDS patients with neurocognitive impairments had lower quality of life compared to patients with no impairments.[26] Similarly, survivors of acute lung injury with neurocognitive impairments had worse quality of life compared to those without neurocognitive impairments, and both groups had lower quality of life compared to age-matched and gender-matched healthy control

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subjects.[25] Decreased quality of life is associated with neurocognitive impairments following stroke,[41] among ICU survivors with multiple trauma,[42] and following carbon monoxide poisoning.[43] Neurocognitive impairments are a major determinant of the ability to return to work, work productivity, and life satisfaction following ARDS.[25] Relatively little is known about the specific impact of neurocognitive impairments secondary to critical illness, on important daily activities such as balancing a checkbook, on following written directions, and on complying with complex medication regimes, among other tasks. However, research on other populations[44,45] has suggested that even mild neurocognitive impairments can lead to significant deficits in the completion of instrumental activities of daily living such as driving and money management.

The financial impact of critical illness on patients and their families has not been adequately studied but is almost certainly substantial. The Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment[46] found that 20% of patients reported a family member had to quit work, 29% lost a major source of income, and 31% lost the majority of the family savings. The underlying contributors of these financial costs were unclear, and the costs of chronic neurocognitive impairments were not assessed. The potential financial implications of a growing population of critically ill survivors with neurocognitive impairments are high. Neurocognitive decline in a previously high-functioning older person predicts institutionalization.[47] Nine of 10 seriously ill patients indicated that they would rather die than survive with severe neurocognitive impairments.[48] The annual "per-patient societal cost burden" has been estimated to be $15,022 for mild neurocognitive impairments to $34,515 for more severe impairments.[49] A significant number of critically ill survivors require caregiver support at 1 year, with an associated $18 billion annual financial burden.[50]

Potential Mechanisms of Neurocognitive Impairments

There is probably not a single uniform cause of neurocognitive impairments, but rather a number of more or less significant factors that interact dynamically with premorbid variables and result in adverse outcomes (Fig 4). Data regarding the potential mechanisms of neurocognitive impairments are limited, but possible mechanisms may include hypoxemia,[16] the use of sedatives or analgesics,[51] hypotension,[19] delirium,[52] and hyperglycemia.[18] The degree and duration of hypoxemia were modestly associated with attention, verbal memory, and executive function at hospital discharge.[28] The correlations between the duration of hypoxemia and neuropsychological outcome were less robust than previously reported.[16] The duration of hypotension was modestly associated with impaired memory at hospital discharge and at 1 year, but not at 2 years.[28] Others have reported that the cumulative dose of some sedatives[53] and delirium[52] may contribute to neurocognitive and affective sequelae in critically ill patients. The etiology of the neurocognitive impairments is undoubtedly multifactorial, and is the subject of ongoing discussion and research.

Conclusions

The investigation of neurocognitive function after critical illness is in its infancy, with a small number of investigations in existence documenting both the presence of *de novo* neurocognitive impairment in a significant percentage of ICU survivors without pre-existing deficits and the worsening of neurocognitive impairment in individuals who were previously impaired. It has been widely recognized that the physical consequences of critical illness are far-reaching and sometimes permanent, leading to the development of chronic health-related conditions. Until recently, little attention has been paid to the idea that neurologic functioning after a critical illness might be affected similarly to that of other organ systems and may contribute to the morbidity experienced by ICU survivors secondary to the development of neurocognitive deficits. Today, it is recognized that neurocognitive sequelae following critical illness occur, are long-lasting, and may be permanent, although substantial research needs to be done to fully understand the prevalence, nature, risk factors, and nuances of neurocognitive impairments in ICU survivors.

Current data suggest that neurocognitive impairments following critical illness are common and may persist up to 6 years after ICU discharge. Some improvement in neurocognitive function occurs during the course of the first 6 months to 1 year post-ICU discharge. While the study of neurocognitive impairments following critical illness is in its infancy, this knowledge can benefit critical care providers, patients, and their families. Referrals to colleagues in rehabilitation medicine, psychiatric, neurology, or psychology would facilitate the evaluation of potential areas of concern. Attention to proximal determinants and possible interventions to prevent neurocognitive morbidity are warranted and
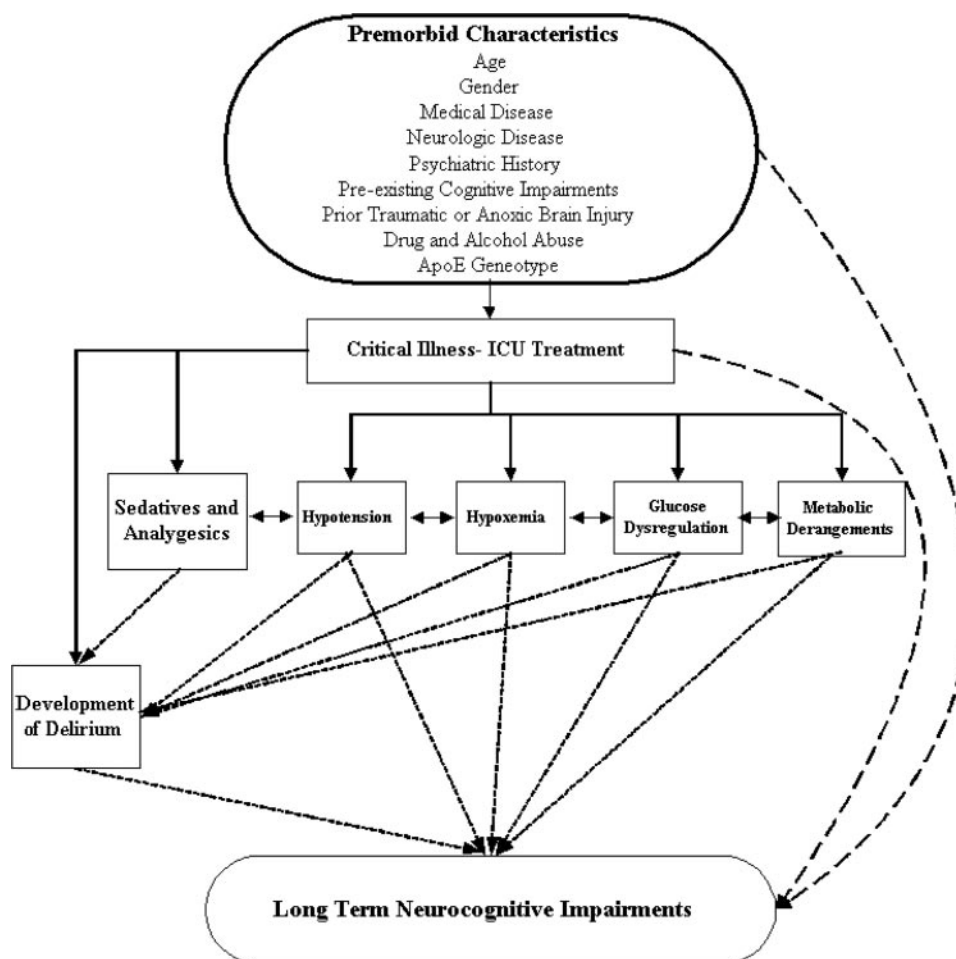
FIGURE 4. A possible explanatory model of neurocognitive impairments among ICU survivors. ApoE = apolipoprotein E.

should be an emphasis in critical care outcomes research. Such research will likely yield valuable insights into the identification, natural history, prognosis, and potential mechanisms of neurocognitive deficits in survivors of critical illness, and should guide the development, implementation, and fine-tuning of intervention programs.

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