The Evolution of Post Intensive Care Syndrome

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In September of 2010, a stakeholders' conference was convened with a daunting, yet vital, overarching goal for the field of Critical Care Medicine: improve the long-term outcomes of patients and their family members after discharge from intensive care (1). With the end in mind, the stakeholders began with a more proximal goal: "understand the long-term outcomes of intensive care patients and their families." To facilitate this goal, and simultaneously raise awareness, the term "post intensive care syndrome" (PICS) was born. The term, which was designed to be applied to survivors and family members (mental health problems and sleep disturbances that continue to impact family members of those who were recently critically ill [PICS-F]), encompasses the detrimental changes in cognition, mental health, and physical function, which individuals face following critical care (1).

In the interim, the medical community has become more aware of PICS, and our understanding has evolved. It is now well established that PICS and PICS-F are common (2, 3), have a profound and lasting impact on patients, families, and society (2–6), and that sepsis plays a pivotal role in the relationship between critical illness and PICS (7). And yet, fundamental epidemiologic questions remain unanswered conclusively. For example, what proportion of survivors experience PICS at 3 and 12 months? Can we predict who will develop PICS? And, among those who develop PICS, is co-occurrence across the physical and mental health domains the norm or the exception?

In this issue of *Critical Care Medicine*, Marra et al (8) provide the results from the largest epidemiologic study of PICS conducted to date. In a prospective cohort study, the investigators examined the frequency and determinants of physical disability, depression, and cognition in critically ill survivors from five hospitals. In-person assessments were conducted at 3 and 12 months post discharge. Cognition, depression, and disability were measured using the Repeatable Battery for the Assessment of Neuropsychologic Status, Beck Depression Inventory Second Edition, and Katz Activities of Daily Living (ADL), respectively. With a PICS focus on what is "new," rather than what is "worse," patients with preexisting cognitive impairment and disability were excluded from participation.

By design, therefore, of 781 survivors, 250 (32%) were excluded due to preexisting mild cognitive impairment and/or functional disability, and an additional 589 were excluded upstream given preexisting severe cognitive impairment. Collectively, these details reveal the frequency with which significant impairments predate critical illness. Further, providing a more comprehensive view of "survivorship," among 531 eligible survivors, 66 died before 3 months, and an additional 46 died between the 3- and 12-month assessments.

Armed with excellent cohort retention, the investigators confirmed estimates that the majority of survivors of critical illness incur PICS. Specifically, new PICS was present in 64% and 56% of survivors at 3 and 12 months, respectively. When new impairment was identified, it was most frequently confined to one domain, as only 19% and 6% of survivors had two or three problems, respectively, at 3 months. Notably, the infrequent nature of co-occurrence observed by Marra et al (8) contrasts with a small study conducted at two hospitals by Maley et al (9). In the latter study, which was not limited to "new" PICS, 56% of survivors self-reported impairment in at least two PICS domains and one of three reported impairment in all PICS domains (9). As 54% of survivors in the study by Maley et al (9) self-reported that function was worse in one or more domains, the collective data reveal that the vast majority of survivors of critical illness have neuropsychologic or functional impairment, and many of these impairments are new or worse.

In the study by Marra et al (8), the most common new impairment at 3 and 12 months was cognitive impairment (38% and 33%, respectively). Depression was present in approximately one third of survivors at 3 and 12 months, whereas disability was present in 26% of survivors at 3 months and 21% at 12 months. In general, new impairment present at 3 months persisted (i.e., only 21% transitioned to being PICS free), and those free of impairment at 3 months largely remained free of impairment at 12 months. Interestingly, Marra et al (8) found that two noncritical illness markers were associated with long-term outcomes; severe frailty was associated with lower odds of being PICS free,

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*See also p. 1393.

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and more years of education was associated with a greater odds of being PICS free at both 3 and 12 months.

Major strengths of the study by Marra et al (8) include the adoption of an ADL outcome measure, in contrast to traditional physical outcome measures such as muscle strength, endurance measurements, or a pulmonary function test. There is emerging evidence demonstrating that this type of approach to outcome measurement is more meaningful to survivors than standard physiologic measures and that daily functional measures should be the focus of all long-term trials within the critical care field (10). The large number of participants involved and retention rate achieved are additional key strengths of the presented work (8). The challenges with sustaining retention in long-term studies are well documented, and the authors should be congratulated for this.

An additional strength, worthy of our attention given its ability to illuminate a new path forward in survivorship, is the focus on social determinants of health. The identified relationship between greater degree of educational attainment and socioeconomic status and the ability to remain PICS free is a novel path forward for survivorship. Evidence from across social science has demonstrated that strong educational foundations can help shape health outcomes. For example, education can foster supportive social connections, facilitate access to greater employment opportunities, help develop lifelong learning and problem solving, and assist the individual to feel empowered and valued (11). These are important social determinants of health and well-being and attributes that seem well aligned with optimal recovery from critical illness. Indeed, if we are to create a culture of resilience and posttraumatic growth in this population, these would appear to be important components of any rehabilitation program.

Unfortunately, the educational background of our patient population is not something a clinician can modify. Nevertheless, understanding how these important social determinants of health and well-being interact with recovery from critical care is crucial. As well as preexisting social issues, new onset issues such as social isolation and financial problems may surface after a critical care stay. Further work around how we support individuals in each of these dimensions will be an important step in creating safe and effective interventions in the future.

Although the study by Marra et al (8) advances our understanding of PICS greatly, lingering questions remain. First, as mental health issues frequently coexist, and posttraumatic stress disorder and anxiety were not assessed, mental health problems were likely underestimated in the study by Marra et al (8). Future research is needed to unravel the complex interplay between mental and physical health, both as a risk factor for developing critical illness and recovering from critical illness. Second, although the results support the hypothesis that heterogeneous subtypes of PICS exist, it is unclear whether this applies to the population of survivors with preexisting impairments. Third, given the potential salience of social determinants of health, future work designed to examine the bidirectional relationship between physical and neuropsychologic impairments and loneliness and isolation is needed (12).

In conclusion, PICS was a concept which was created almost a decade ago. Since then, our understanding about the challenges patients face and how frequently they face them has matured. The article by Marra et al (8) confirms that PICS is the norm and also lays down a foundation for a new direction to anticipate, and rehabilitate, PICS. The highly relevant study by Marra et al (8) helps us comprehend how some of the different components of PICS interact and which patients are most at risk for developing long-term problems following critical care discharge. The field is more equipped than ever to look beyond recording and documenting the problems which patients face and test and implement strategies to mitigate and rehabilitate PICS. A novel direction to achieve these goals will require a firm grasp of how the social determinants of health, including issues such as social networks, health literacy, and education, interact with recovery from critical illness (13). Furthermore, there must be a focus on how these issues affect the entire critical care journey; this includes the contextual factors which bring some patients to the ICU in the first place. It is only with this focus that we will truly start to realize the improvements in patients' quality of life, which we are all so desperate to see.

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Co-Occurrence of Post-Intensive Care Syndrome Problems Among 406 Survivors of Critical Illness*

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***See also p. 1551.**

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Drs. Marra and Brummel had full access to all study data, take responsibility for the integrity of the data and the accuracy of the data analysis. Drs. Marra, Pandharipande, Girard, Ely, and Brummel designed and conducted the study. Drs. Thompson and Chandrasekhar contributed to statistical analysis. Drs. Marra and Brummel drafted the article. Drs. Pandharipande, Girard, Ely, and Brummel obtained funding. All authors contributed to data acquisition, analysis, and interpretation of the data; critical revision of the article for important intellectual content; and final approval of the article.

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Objectives: To describe the frequency of co-occurring newly acquired cognitive impairment, disability in activities of daily livings, and depression among survivors of a critical illness and to evaluate predictors of being free of post-intensive care syndrome problems.

Design: Prospective cohort study.

Setting: Medical and surgical ICUs from five U.S. centers.

Patients: Patients with respiratory failure or shock, excluding those with preexisting cognitive impairment or disability in activities of daily livings.

Interventions: None.

Measurements and Main Results: At 3 and 12 months after hospital discharge, we assessed patients for cognitive impairment, disability, and depression. We categorized patients into eight groups reflecting combinations of cognitive, disability, and mental health problems. Using multivariable logistic regression, we modeled the association between age, education, frailty, durations of mechanical ventilation, delirium, and severe sepsis with the odds of being post-intensive care syndrome free. We analyzed 406 patients with a median age of 61 years and an Acute Physiology and Chronic Health Evaluation II of 23. At 3 and 12 months, one or more post-intensive care syndrome problems were present in 64% and 56%, respectively. Nevertheless, co-occurring post-intensive care syndrome problems (i.e., in two or more domains) were present in 25% at 3 months and 21% at 12 months. Post-intensive care syndrome problems in all three domains were present in only 6% at 3 months and 4% at 12 months. More years of education was associated with greater odds of being post-intensive care syndrome free ($p < 0.001$ at 3 and 12 mo). More severe frailty was associated with lower odds of being post-intensive care syndrome free ($p = 0.005$ at 3 mo and $p = 0.048$ at 12 mo).

Conclusions: In this multicenter cohort study, one or more post-intensive care syndrome problems were present in the majority of survivors, but co-occurring problems were present in only one out of four. Education was protective from post-intensive care syndrome problems and frailty predictive of the development of post-intensive care syndrome problems. Future studies are needed to understand better the heterogeneous subtypes of post-intensive care syndrome and to identify modifiable risk factors. (*Crit Care Med* 2018; 46:1393–1401)

Key Words: activities of daily living; cognitive dysfunction; critical illness; depression; post-intensive care syndrome; survivors

New or worsened cognitive impairment, disabilities in activities of daily livings (ADLs), and mental health impairment arising after critical illness and persisting beyond acute care hospitalization are referred to as "Post-Intensive Care Syndrome" (PICS) (1, 2). Despite growing awareness of PICS, effective interventions remain elusive (3–5). This may relate, in part, to an incomplete understanding of the potential subtypes of PICS and of the associated factors that may predispose patients to, or protect them from, the development of PICS.

Cohort studies of survivors of the acute respiratory distress syndrome and sepsis report problems in cognition, disability, and/or mental health (6–11). Nevertheless, the co-occurrence of these problems (i.e., how often one, two, or all three are present) in individual patients remains unclear. Furthermore, despite the high prevalence of PICS reported in prior studies, some patients survive critical illness without problems. Little is known about factors that may predict survival from critical illness without PICS problems.

To address these gaps in knowledge, we measured the co-occurrence of cognitive impairment, disability in ADL, and depression among survivors of critical illness who did not have cognitive impairment or disability in ADLs prior to the index illness. We also evaluated potential predictors of being PICS free (i.e., without clinically significant problems in any of the three PICS domains). We hypothesized that different subtypes of PICS would be present. We also hypothesized that factors present before and during critical illness would be associated with being PICS free.

MATERIALS AND METHODS

We tested these hypotheses in a prospective cohort study nested within the identical Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors (BRAIN-ICU) (NCT00392795) and Delirium and Dementia in Veterans Surviving ICU Care (MIND-ICU) (NCT00400062) studies. We included participants who survived the index hospitalization and completed long-term follow-up (12). These original data have been presented in abstract form (13).

Setting and Study Participants

The study protocol and the eligibility criteria have been published and are presented in the **supplemental data** (Supplemental Digital Content 1, http://links.lww.com/CCM/D594) (12). We included adult patients age 18 years old or older treated for respiratory failure or shock in medical and surgical ICUs from five U.S. centers (supplemental data, Supplemental Digital Content 1, http://links.lww.com/CCM/D594). The primary aim of the parent study was to prospectively evaluate the effects of acute critical illness on cognitive function, disability, and mental health outcomes in survivors of critical illness. We therefore excluded those at high risk for preexisting cognitive impairment (i.e., severe dementia, suspected anoxic brain injury, neurodegenerative disease, or recent cardiac surgery), and, to enhance prospective data collection about the present episode of critical illness, those with a previous episode of critical illness in the last 30 days and those with greater than 72 hours of organ dysfunction prior to enrollment in the study. To facilitate follow-up, we also excluded those who were moribund, those with blindness, deafness, inability to speak English, active substance abuse, psychotic disorders, homelessness, or who lived greater than 200 miles from an enrolling center. Further, because we sought to describe the co-occurrence of PICS problems, defined as the presence of new problems in two or more PICS domains, we also excluded those with less overt cognitive impairment (i.e., an Informant Questionnaire on Cognitive Decline in the Elderly score of ≥ 3.6) (14), and preexisting disability (i.e., score of ≥ 1 on the Katz ADL) (15). Because no objective measure for preexisting depression or its severity was available in the original studies, we did not exclude those with preexisting depression from our primary analyses. Patients or their proxies provided informed consent. The institutional review boards at each center approved the study protocol.

Determining the Co-Occurrence of PICS Problems

At 3 and 12 months after hospital discharge, study personnel who were masked to the events of the index critical illness performed in-person assessment for cognitive impairment, disability in ADL, and mental health problems using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (16), the Katz ADL (15), and the Beck Depression Inventory Second Edition (BDI-II) (17), respectively (for detailed descriptions of these instruments, see supplemental data, Supplemental Digital Content 1, http://links.lww.com/CCM/D594). We chose depression as a representative measure of mental health problems because we wanted to study newly acquired problems, based on previous work in showing that depression is five times more common than posttraumatic stress disorder (PTSD) in survivors of critical illness (18), and because other mental health symptoms such as anxiety and PTSD frequently co-occur with depression (10).

We defined PICS problems using accepted limits to determine the presence of clinically significant cognitive impairment, disability in ADLs, and depression. We defined cognitive impairment as an RBANS score of 78 or less, disability as a Katz ADL score greater than or equal to 1, and depression as a BDI-II score greater than 13.

Predictors of Being Post-Intensive Care Syndrome Free

We selected a priori potential predictors for being PICS free at follow-up. We included age, years of education, Canadian Study of Health and Aging Clinical Frailty Scale score (19), and durations of severe sepsis, delirium (20), and mechanical ventilation (for complete descriptions, see supplemental data, Supplemental Digital Content 1, http://links.lww.com/CCM/D594).

Missing Data

We used predictive mean matching multiple imputation at the time of regression modeling to account for incomplete predictor and outcome data among patients who participated in follow-up testing at each time point (21).

Statistical Analysis

We used the cutoffs defined above and descriptive statistics to determine the co-occurrence of PICS problems. We categorized patients into eight groups ranging from having no problems to problems in all three PICS domains: 1) no problems, 2) cognitive impairment only, 3) disability in ADLs only, 4) depression only, 5) cognitive impairment and disability in ADLs, 6) cognitive impairment and depression, 7) disability in ADLs and depression, and 8) cognitive impairment, disability in ADLs, and depression. Data are reported as median and interquartile ranges (IQRs).

We used multivariable logistic regression to determine the association and the odds of being PICS free at 3 and 12 months, adjusting for covariates. We conducted two sensitivity analyses: 1) excluding patients with proxy reported history of depression and 2) substitution of Agency for Healthcare Research Quality (AHRQ) Index of Socioeconomic Status for years of education (22).

Associations with continuous covariates were allowed to be nonlinear using restricted cubic splines. Nonlinear terms were forced to be linear if the p value of the global test for nonlinearity was greater than 0.20. We used R (Version 3.1.2; R Project for Statistical Computing, Vienna, Austria) for all analyses. p values less than 0.05 were considered significant.

RESULTS

Characteristics of the Patients

Between January 2007 and December 2010, we enrolled 1,047 patients (**Fig. 1**). During the hospitalization, seven patients withdrew consent and requested their data be destroyed. Of the remaining 1,040 patients, 214 died and 45 withdrew from further participation during hospitalization. Of the 781 hospital survivors, we excluded 250 who had preexisting cognitive impairment and/or preexisting disability in ADLs, leaving 531 patients eligible for this long-term follow-up study. We assessed 384 of 465 survivors (83%) at 3 months and 334 of 419 survivors (80%) at 12 months.

Overall, 406 unique patients, who were at a median age of 61 years old (IQR, 51–70 yr old) with high severity of illness (median Acute Physiology and Chronic Health Evaluation II score of 23 [IQR, 16–29]) at admission, and the majority of whom were not frail (median Clinical Frailty Scale score of 3 [IQR, 2–4]) contributed data to these analyses (**Table 1**).

Co-Occurrence of PICS Problems

Among patients who participated in 3-month follow-up, we assessed 337 for cognitive impairment (88%), 383 for disability (99%), and 363 patients (95%) for depression. Of patients assessed, 128 (38%) had cognitive impairment, 100 (26%) had disability, and 121 (33%) had depression. At 12 months, we assessed 292 patients for cognitive impairment (87%), 332 for disability (99%), and 313 for depression (94%). Of these, 97 (33%) had cognitive impairment, 69 (21%) had disability, and 97 (31%) had depression. The median scores on the each of the follow-up assessments are reported in **Table S1** (Supplemental Digital Content 1, http://links.lww.com/CCM/D594).

There were 330 patients (86% of survivors) and 285 (85% of survivors) who completed all three assessments at 3 and 12 months, respectively. A single PICS problem was present in 130 (39%) at 3 months and 101 (35%) at 12 months (**Fig. 2**). Two problems were present in 62 patients (19%) at 3 months and 47 patients (16%) at 12 months. Only 19 patients (6%) and 12 patients (4%) had problems in all three domains at 3 and 12 months, respectively. Among those patients with any PICS problems, the proportion with one, two, or three problems was 62%, 29%, and 9%, respectively at 3 months, and 63%, 29%, and 9%, respectively at 12 months. Approximately four out of every 10 patients were PICS free (119/330 [36%] at 3 mo and 125/285 [44%] at 12 mo) (Fig. 2). Although the proportion of patients who were PICS free during follow-up increased from 3 to 12 months, the total number of patients without any problems was similar (Fig. 2).

In a sensitivity analysis that excluded patients with a proxy report of preexisting depression, the proportion of patients who had one or more PICS problems decreased by 5% at 3 months and 12 months (**Fig. S1**, Supplemental Digital Content 1, http://links.lww.com/CCM/D594). This decrease was due, in large part, to fewer patients having PICS related to depression either as a single problem or co-occurring with disability or cognitive impairment.

Among the 211 patients with at least one PICS problem at 3 months, 44 patients (21%) no longer had any PICS problems at 12 months, 115 patients (55%) still had at least one PICS problem, 19 patients (9%) died, and 33 patients (16%) withdrew or were lost to follow-up. Of the 119 patients who had no PICS problems at 3 months, 76 patients (64%) remained without PICS problems at 12 months, 19 patients (16%) developed at least one PICS problem, 8 patients (7%) died, and 16 patients (13%) withdrew or were lost to follow-up.

Predictors Being PICS Free at Follow-Up

Survivors who were PICS free tended to be younger, more educated, less frail, and had fewer comorbidities than

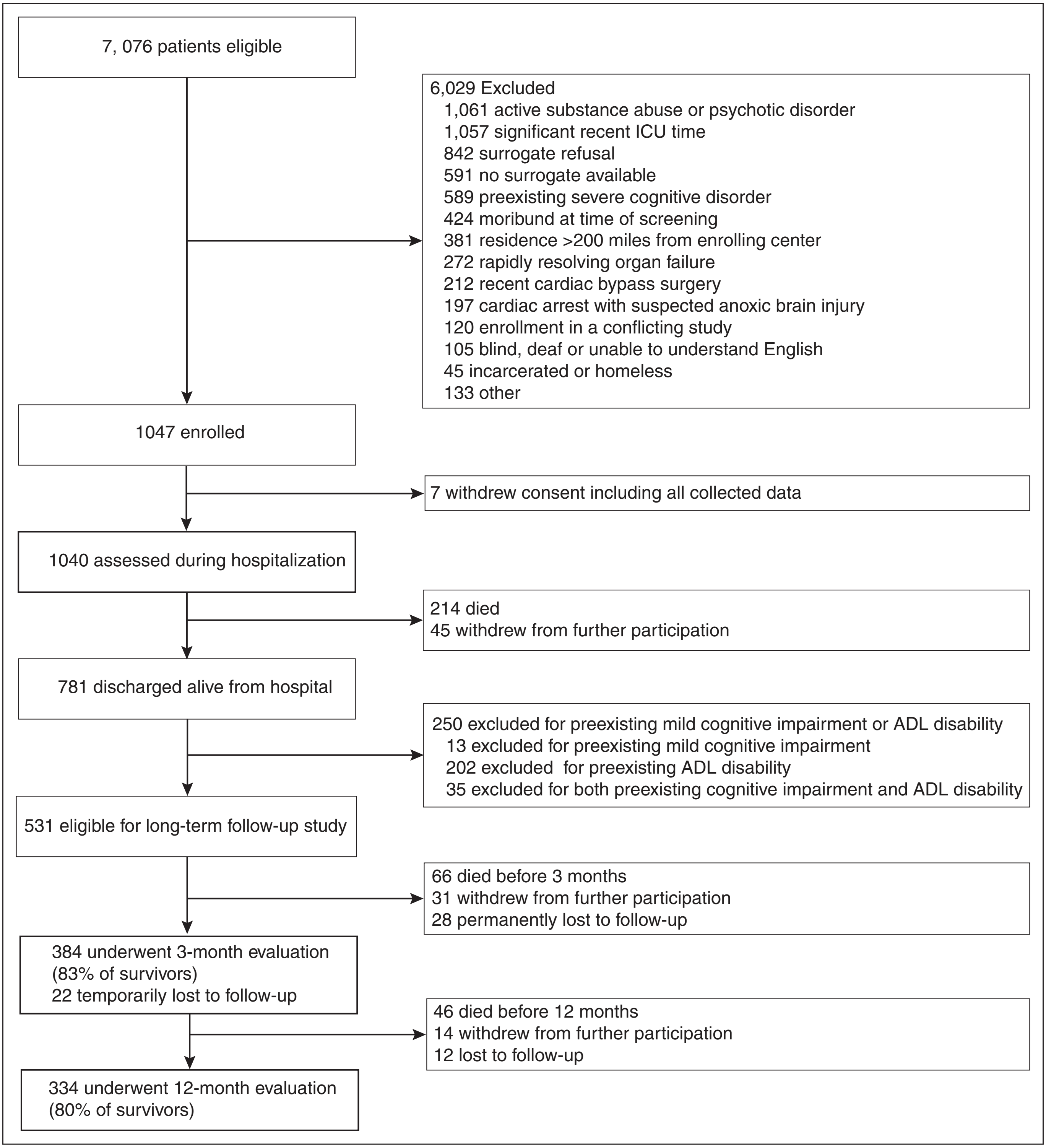

Figure 1. Enrollment and follow-up. ADL = activities of daily living.

those with PICS (**Tables S2** and **S3**, Supplemental Digital Content 1, http://links.lww.com/CCM/D594). Although severity of illness scores at ICU admission were similar between those who developed PICS and those who were PICS free, the proportion of patients who were mechanically ventilated, were septic, delirious, or comatose during their ICU stay was lower among those who were PICS free. Furthermore, the duration of each of these conditions was shorter in those who were PICS free (Tables S2 and S3, Supplemental Digital Content 1, http://links.lww.com/CCM/D594).

After adjusting for covariates, more years of education independently predicted greater odds of being PICS free at 3 and 12 months ($p < 0.001$ at both time points)

TABLE 1. Demographic and Clinical Characteristics of Patients

Characteristics	*n* = 406
Age (yr), median (IQR)	61 (51–70)
Male sex, *n* (%)	256 (63)
Education (yr), median (IQR)	12 (12–14)
Katz Assessment of Basic Activities of Daily Living score[a], median (IQR)	0 (0–0)
Short Informant Questionnaire on Cognitive Decline in the Elderly, assessment of preillness cognition score[b], median (IQR)	3 (3–3)
Clinical Frailty Scale score, *n* (%)	
1 (very fit)	21 (5)
2 (well)	87 (21)
3 (well, with treated comorbidities)	164 (40)
4 (apparently vulnerable)	86 (21)
5 (mildly frail)	28 (7)
6 (moderately frail)	17 (4)
7 (severely frail)	3 (1)
Charlson Comorbidity Index score[c], median (IQR)	2 (1–3)
Acute Physiology and Chronic Health Evaluation II score at admission[d], median (IQR)	23 (16–29)
Mean daily Sequential Organ Failure Assessment score[e], median (IQR)	7 (5–8)
Diagnoses at admission, *n* (%)	
Sepsis, acute respiratory distress syndrome due to infection or septic shock	118 (29)
Acute respiratory failure[f]	42 (10)
Cardiogenic shock, congestive heart failure, myocardial infarction, or arrhythmia	79 (19)
Upper airway obstruction[g]	40 (10)
Gastric or colonic surgery	26 (6)
Neurologic disease or seizure	5 (1)
Other surgical procedure[h]	58 (14)
Other diagnoses[i]	38 (9)
Mechanical ventilation	
Patients, *n* (%)	360 (89)
Duration of mechanical ventilation among those who were ever mechanically ventilated, d, median (IQR)	3 (1–7)
Severe sepsis	
Patients, *n* (%)	259 (64)
Duration of severe sepsis among those who were ever septic, d, median (IQR)	4 (2–8)
Delirium	
Patients, *n* (%)	289 (71)
Duration of delirium among those who were ever delirious, d, median (IQR)	3 (2–7)
Coma	
Patients, *n* (%)	221 (54)
Duration of coma among those who were ever comatose, d, median (IQR)	2 (1–5)

IQR = interquartile range.

[a] Katz Activities of Daily Living (ADL) scores range from 0 to 12, where higher scores indicate more severe disability in ADL. A score of 0 indicates no disability.

[b] Informant Questionnaire on Cognitive Decline in the Elderly scores range from 1 to 5, with a score of 3 indicating no change in cognition over the past 10 yr. Scores lower than 3 indicate improvement, whereas scores greater than 3 indicate decline.

[c] Charlson Comorbidity scores range from 0 to 33, with higher scores indicating a greater burden of chronic illness.

[d] Acute Physiology and Chronic Health Evaluation II scores range from 0 to 71, with higher scores indicating more severe critical illness.

[e] Sequential Organ Failure Assessment scores range from 0 to 24, with higher scores indicating more severe organ dysfunction.

[f] Acute respiratory failure includes acute respiratory distress syndrome, acute exacerbations of chronic obstructive pulmonary disease or asthma, pulmonary edema, pulmonary embolism, and pulmonary fibrosis.

[g] Upper airway obstruction also includes patients intubated for airway protection.

[h] Other surgical procedures includes vascular, urologic, orthopedic, obstetric/gynecologic, hepatobiliary, otolaryngologic, and liver transplant surgery.

[i] Other diagnoses include acute renal failure, acid/base disturbance, endocrinologic, hemorrhagic shock, gastrointestinal bleeding, coagulopathy, cirrhosis, and acute liver failure.

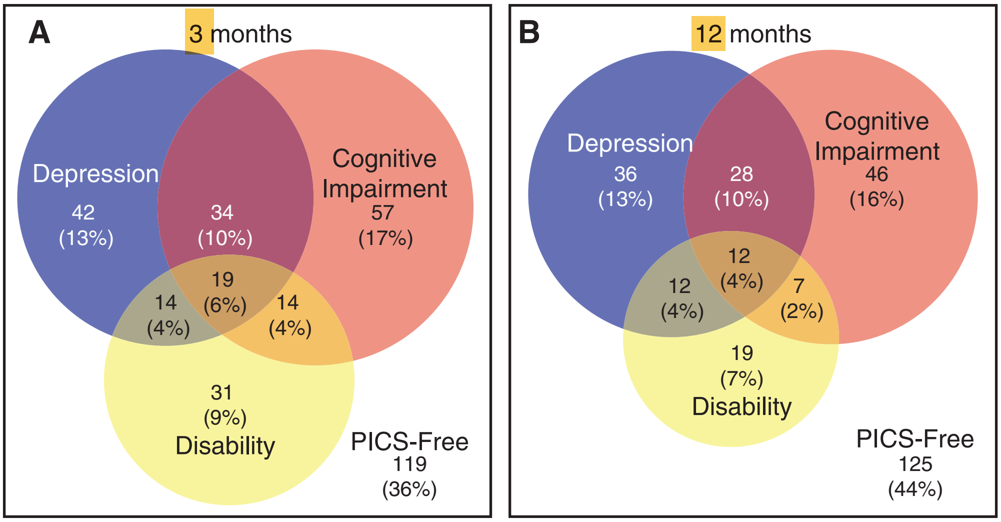

Figure 2. Co-occurring post-intensive care syndrome (PICS) problems at 3- and 12-mo follow-up. This diagram illustrates the co-occurrence of PICS problems at 3 and 12 mo. The proportion of patients with PICS problems in each domain at 3 mo is presented in (**A**) and at 12 mo in (**B**). Cognitive impairment is represented by the *red circle*. Disability in activities of daily living by the *yellow circle*. Depression by the *blue circle*. The overlap between the *circles* represents the co-occurrence of two or three problems. Overall, six out of 10 patients had PICS. The most common pattern at both 3 and 12 mo was problems in a single domain and was present in four out of 10 patients. Co-occurring problems (i.e., in two or three domains) were present in two out of 10 patients.

(**Table 2** and **Fig. 3**, ***A*** and ***B***). Conversely, higher Clinical Frailty Scale scores at ICU admission independently predicted lower odds of being PICS free ($p = 0.005$ at 3 mo and $p = 0.048$ at 12 mo) (Table 2 and **Fig. 3**, ***C*** and ***D***). Age, duration of delirium, duration of severe sepsis, and duration of mechanical ventilation were not associated with being PICS free (Table 2).

In the sensitivity analysis excluding 53 patients with a history of depression, education remained a significant predictor of being PICS free, but the association with frailty was no longer statistically significant (**Table S4**, Supplemental Digital Content 1, http://links.lww.com/CCM/D594). The AHRQ Index of Socioeconomic Status score was not associated with being PICS free (**Table S5**, Supplemental Digital Content 1, http://links.lww.com/CCM/D594).

DISCUSSION

In this multicenter cohort study of survivors of critical illness, we found that six out of 10 patients without preexisting cognitive impairment or disability developed one or more PICS problems. Most patients with PICS had problems in a single domain, with cognitive impairment being most common, but disability in ADLs and depression also occurred frequently. Co-occurring PICS problems (i.e., problems in two or three domains) were present in two out of 10 patients. These data highlight the heterogeneous subtypes of PICS. Because the majority of patients included in this study were affected in only a single domain, our findings suggest that cognitive impairment, disability, and depression may be distinct sequelae of critical illness rather than part of a single unifying syndrome.

Over the last 15 years, investigators have studied cognitive, physical, and mental health function among survivors of critical illness, reporting significant proportions of these patients suffer from new or worsened impairments and disabilities, giving rise to the concept of PICS (1, 2, 6–9, 12, 18). To our knowledge, only one small cohort study has reported the co-occurrence of PICS problems. Maley et al (23) used a phone-based, patient-reported assessment of cognitive, physical, and mental health function among 43 survivors a median of 8 months after critical illness. At least one PICS problem was present in 84% of patients (36/43). When this analysis was

TABLE 2. Association Between Baseline and Clinical Factors and the Odds of Being Post Intensive Care Syndrome Free at Follow-up

Baseline or Clinical Factor	Comparison (75 vs 25th Percentile)	OR (95% CI) at 3 mo	*p*	OR (95% CI) at 12 mo	*p*
Years of education	14 vs 12 yr	1.6 (1.3–2.0)	< 0.001	1.6 (1.3–2.0)	< 0.001
Clinical Frailty Scale score	4 vs 2	0.5 (0.3–0.8)	0.005	0.6 (0.3–1.0)	0.048
Duration of severe sepsis	6 vs 0 d	0.7 (0.4–1.1)	0.09	0.6 (0.3–1.3)	0.42
Age	70 vs 51 yr	1.2 (0.9–1.7)	0.30	1.1 (0.7–1.5)	0.09
Duration of delirium	5 vs 0 d	0.8 (0.5–1.2)	0.35	0.5 (0.2–1.1)	0.20
Duration of mechanical ventilation	5 vs 1 d	1.0 (0.8–1.3)	0.97	1.2 (0.6–2.5)	0.80

OR = odds ratio.

Each OR represents the odds being problem-free at follow-up in a comparison of patients who have values of the exposure of interest at 75th percentile with patients who have values at the 25th percentile. Because the *p* values consider all beta coefficients together, in cases where the 95% CI includes 1, but $p < 0.05$, the p value is correct. Interpretive example, in a comparison of two patients alike in all other ways (i.e., all covariates adjusted to their respective median or mode value) the patient with 14 yr of education would have, on average, 60% greater odds of being post-intensive care syndrome free compared with a patient with 12 yr of education.

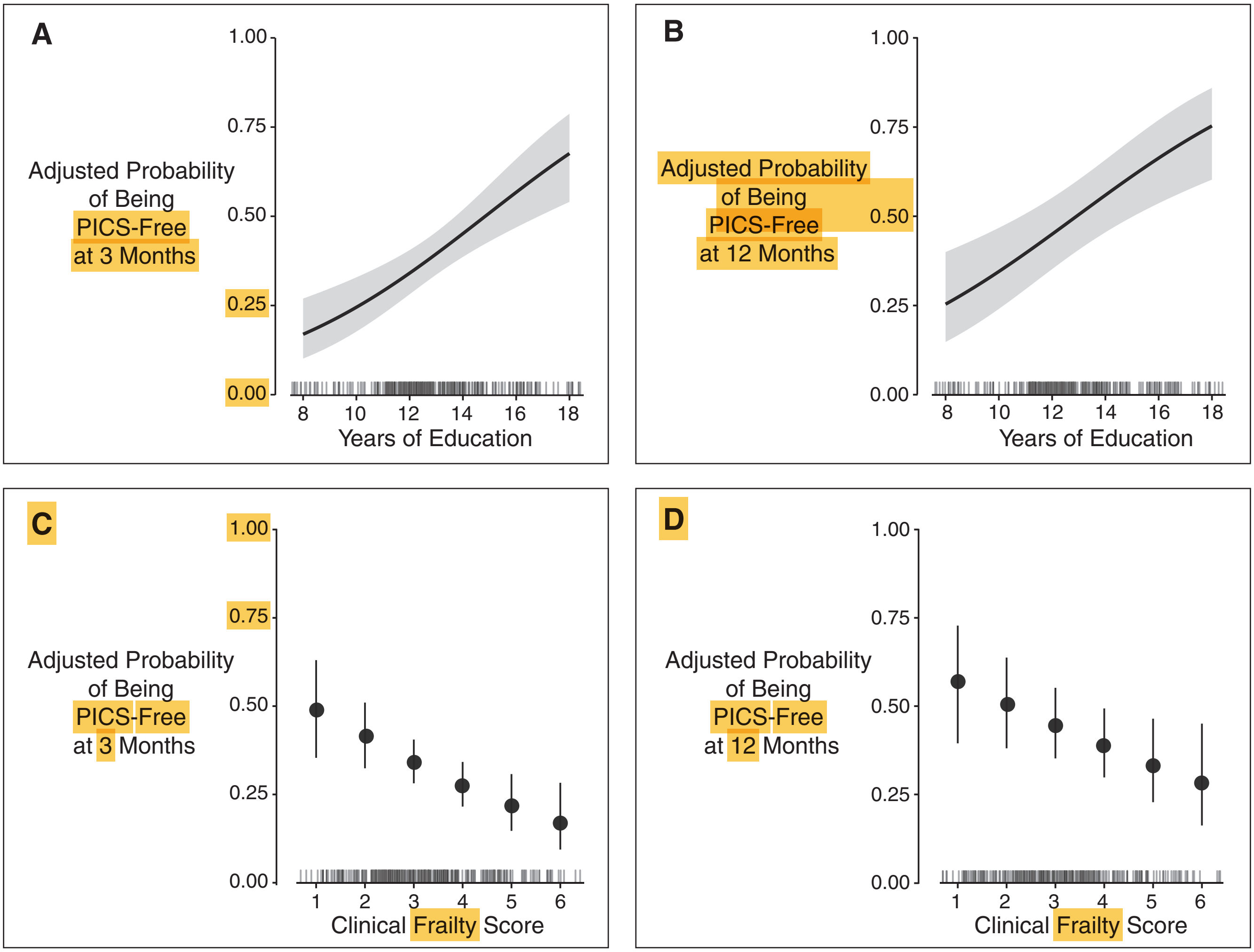

Figure 3. Associations between years of education and Clinical Frailty Scale score with the adjusted probability of being post-intensive care syndrome (PICS) free at follow-up. These figures display the association between years of education and Clinical Frailty Scale score with the adjusted probability of being PICS free at 3 mo (*left column*) and 12 mo (*right column*). For (**A**) and (**B**), the *blue lines* represent the association, and *blue shading* represents the 95% CI. For (**C**) and (**D**), *dots* represent the point estimate, and *error bars* the 95% CI. The rug plot (just above the *x*-axes) shows the distribution of the exposure of interest. More years of education were associated with greater probability of being PICS free at 3 mo ($p < 0.001$) (**A**) and at 12 mo ($p < 0.001$) (**B**). Higher Clinical Frailty Scale scores, conversely, were associated with a lower probability of being PICS free at 3 mo ($p = 0.005$) (**C**) and at 12 mo ($p = 0.048$) (**D**).

restricted to only patients who reported problems that were worse after critical illness, however, the overall prevalence of PICS decreased to 54%, nearly identical to the prevalence of PICS in the present study. They also reported that two or more PICS problems were present in 56% of patients (24/43) but did not report the co-occurrence of problems that were worse after critical illness. In contrast, we report that two or more new PICS problems were present in 20% of our cohort. Thus, the different prevalence of co-occurring PICS problems between these studies may be because we considered only new PICS problems after critical illness.

We report that more years of education were associated with greater odds of being PICS free. In studies of community-dwelling adults, those with more years of education have lower rates of dementia, disability, and depression (24–28). The exact mechanisms by which education may be protective from these problems are unclear. Education is associated with occupational attainment, greater income, better cognitive and critical thinking skills, and larger social/support networks that could represent greater resources to facilitate recovery (29). Our sensitivity analysis showing no association between socioeconomic status and freedom from PICS, however, suggests good outcomes after critical illness could be related to unmeasured education-related noneconomic factors such as health behaviors (e.g., avoidance of cigarettes and heavy alcohol use, exercise, and control of chronic disease), health literacy, or greater access to the healthcare system (28). Alternatively, because the RBANS is age adjusted, but not education adjusted, this finding could represent that those with greater years of education scored higher on the RBANS and therefore did meet our conservative definition of cognitive impairment. Finally, personality traits, such as the ability to persevere toward long-term goals (i.e., grit) that are associated with more years of education, may allow the those with more education to endure the road to recovery (30). These hypotheses should be evaluated in future long-term follow-up studies.

We also found that higher Clinical Frailty Scale scores were associated with lower odds of being PICS free. Frailty is a state of increased vulnerability characterized by diminished physiologic reserve across multiple domains that results in the reduced ability to maintain and restore homeostasis in the setting of acute stress (31). In patients with critical illness, frailty is associated with greater mortality and subsequent disability (32–34). The association between greater frailty and lower odds of being PICS free could reflect greater declines in cognitive, physical, and/or mental health by those with higher Clinical Frailty Scale scores during critical illness. Alternatively, if the declines in these domains were similar among patients across the fitness to frailty continuum, those with more severe frailty may possess reduced abilities to recover to their pre-illness status. These hypotheses need to be evaluated in future trials where trajectories of decline and recovery in each of the three PICS domains are measured using more frequent assessment than was available in the current study.

Although we evaluated several modifiable risk factors for PICS (i.e., durations of sepsis, delirium, and mechanical ventilation), none were associated with being PICS free at follow-up. Since collection of these data, however, interventions to reduce the modifiable risk factors of sedation and immobility have been shown effective. Nevertheless, future studies are needed to determine the association between sedation, immobility, and PICS problems and whether reducing these modifiable ICU-related risk factors for translates into improved outcomes for survivors.

Strengths of this investigation include enrollment of a geographically diverse cohort of medical and surgical critical illness survivors, that our cohort was 10-fold larger than the only other study to examine patterns of PICS problems, and that we achieved excellent long-term in-person follow-up. Moreover, we used a thorough three-step process to exclude patients from enrollment who had preexisting moderate or severe cognitive impairment, and we assessed participants for mild preillness cognition and disabilities using well-validated surrogate measures. We also prospectively collected a range of detailed clinical, physiologic, and pharmacologic variables daily throughout the hospitalization.

Several limitations need to be acknowledged. First, given the emergent nature of critical illness, we were unable to directly assess participants' cognitive function, disability in ADLs, and mental health prior to critical illness. Second, although we chose previously published definitions of clinically significant cognitive impairment, disability, and depression, these definitions are conservative and may underestimate PICS problems that are less overt yet still clinically important (12). Third, we did not assess for preexisting anxiety or PTSD and therefore did not include these mental health problems in our analyses that were focused on newly acquired PICS problems. Given that precritical illness mental health symptoms are strong risk factors for post-critical illness mental health symptoms (35, 36), future studies that account for preexisting symptoms of anxiety and PTSD are needed to determine the effects of critical illness on these important mental health problems. Fourth, since it is unlikely that death and/or loss to follow-up occurred at random in this study, analyzing data only from survivors who were not lost to follow-up could have resulted in survivor bias. Nevertheless, whether this bias represents unhealthy survivor bias (e.g., those with severe PICS problems could have been more likely to die or to be unable to participate in follow-up) or healthy survivor bias (e.g., those with no PICS problems resumed normal work and family activities and were therefore too busy to participate in follow-up) is unknown. Further study of the effects of survivorship bias on outcomes after critical illness is needed. Finally, as with any observational study, the possibility of residual confounding cannot be excluded. Nevertheless, we adjusted for a number of potential confounders in our multivariable analysis.

CONCLUSIONS

We found six out of 10 survivors of a critical illness had one or more PICS problems up to a year after ICU admission. Co-occurring PICS problems were present in two out of 10. More years of education was associated with being PICS free and more severe frailty with lower odds of being PICS free. Future work is needed to define better the specific subtypes of PICS, to identify the risk factors for co-occurring patterns of PICS, and to understand better the clinical, biological, and social factors related to the ability to withstand and recover successfully from critical illness. This understanding could facilitate the evaluation of interventions directed to improve outcomes for survivors of critical illness.

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