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Co-occurrence of Problems in the Post-Intensive Care Syndrome among 406 Survivors of Critical Illness

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Table of Contents

INTRODUCTION

New or worsened cognitive impairment, disabilities in activities of daily living (ADLs), and mental health impairment that arise after critical illness and persist beyond acute care hospitalization is referred to as Post-Intensive Care Syndrome (PICS) (1, 2). Despite growing awareness of PICS, effective interventions to reduce this component of suffering after critical illness remain elusive (3-5). The lack of effective interventions may relate, in part, to an incomplete understanding of both the potential subtypes of PICS and of the associated factors that may predispose patients to, or protect them from, the development of PICS.

Several large cohort studies of survivors of the Acute Respiratory Distress Syndrome (ARDS) and sepsis report problems in cognition, disability, and/or mental health among survivors of critical illness (6-11). Nevertheless, the co-occurrence of these problems (i.e., the frequency with which 1, 2, or 3 problems are present) in individual patients remains unclear.

Moreover, despite the high prevalence of PICS reported in prior studies, some patients will survive a critical illness without problems. To date, however, studies have focused on factors associated with the development of PICS. Little is known about factors that may predict survival from critical illness without PICS.

Therefore, to address these gaps in knowledge, we measured the co-occurrence of cognitive impairment, disability in activities of daily living, and depression among survivors of critical illness. We also evaluated potential predictors of being PICS-free (i.e., no problems in any of the three PICS domains). We hypothesized that subtypes of PICS could be identified according to patterns of co-occurring problems. We also

hypothesized that factors present before and during critical illness would be associated with being PICS-free.

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) and Delirium and Dementia in Veterans Surviving ICU Care (MIND-ICU) studies (NCT00392795 and NCT00400062, respectively). 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

a) Inclusion Criteria

We enrolled adult patients in a medical or surgical intensive care unit (ICU) receiving treatment for respiratory failure or shock (cardiogenic or septic).

We considered a patient to be in respiratory failure if, at the time of enrollment, they were receiving any of the following treatments: invasive mechanical ventilation, noninvasive positive pressure ventilation, continuous positive airway pressure, supplemental oxygen via a nonrebreather mask, or nasal cannula delivering heated high-flow oxygen.

Patient were considered to be in cardiogenic shock if they were being treated at the time of enrollment with an intra-aortic balloon pump or any of the following medications administered for acute cardiac dysfunction: dopamine ≥ 7.5mcg/kg/min, dobutamine ≥ 5 mcg/kg/min, norepinephrine ≥ 5 mcg/min, phenylephrine ≥ 75 mcg/min,

epinephrine at any dose, milrinone at any dose (if used with another vasopressor), or vasopressin ≥ 0.03 units/min (if used with another vasopressor).

We considered a patient in septic shock when suspected or proven infection was documented in the setting of hypotension being treated with any of the previously listed medications. Patients who were on long-term ventilatory support prior to the acute illness that resulted in the hospitalization, qualified for enrollment in this study if they met criteria for shock (as defined above) or they had a new onset of respiratory failure, defined as either an increase of pressure support of 5 cmH2O or positive end expiratory pressure of 2 cmH2O from baseline ventilatory settings.

b) Exclusion Criteria

Patients who meet the inclusion criteria will be excluded if they meet any of the following criteria:

- Cumulative ICU time > 5 days in the past 30 days, not including the current ICU stay, as this might create a state of flux regarding patients' cognitive baseline.

- Severe cognitive or neurodegenerative diseases that prevent a patient from living independently at baseline, including mental illness requiring institutionalization, acquired or congenital mental retardation, known brain lesions, traumatic brain injury, cerebrovascular accidents with resultant moderate to severe cognitive deficits or ADL disability, Parkinson's disease, Huntington's disease, severe Alzheimer's disease or dementia of any etiology.

- ICU admission post cardiopulmonary resuscitation with suspected anoxic injury.

- An active substance abuse or psychotic disorder, or a recent (within the past 6 months) serious suicidal gesture necessitating hospitalization. This exclusion will enrich follow-up rates by avoiding patients with whom it is particularly challenging to maintain long-term contact.

- Blind, deaf, or unable to speak English, as these conditions would preclude our ability to perform the follow-up evaluation interviews.

- Overly moribund and not expected to survive for an additional 24 hours and / or withdrawing life support to focus on comfort measures only.

- Prisoners.

- Patients who live further than 200 miles from Nashville and who do not regularly visit the Nashville area.

- Patients who are homeless and have no secondary contact person available. This exclusion will enrich follow-up rates by avoiding patients with whom it is particularly challenging to maintain long-term contact.

- The onset of the current episode of respiratory failure, cardiogenic shock, or septic shock was > 72 hours ago.

- Patients who have had cardiac bypass surgery within the past 3 months (including the current hospitalization).

- Because we sought to describe the co-occurrence, defined as the presence of problems in 2 or more PICS domains, that arose after critical illness (i.e., did not reflect worsening of preexisting symptoms), we excluded those who had cognitive impairment

or disability in ADLs at enrollment from the present analyses. We defined preexisting cognitive impairment as a score of ≥3.6 on the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (14), a proxy measure of pre-illness cognition. We defined preexisting disability in ADLs as a score of ≥1 on the Katz ADL (15), the proxy measure of pre-illness disability. No reliable measure for preexisting depression was available in the BRAIN-ICU and MIND-ICU studies; therefore, we did not include depression among our exclusions for our primary analyses. Patients or their proxies provided informed consent. The institutional review boards at each center approved the study protocol.

Summary of the BRAIN-ICU and MIND-ICU study protocols

The (BRAIN-ICU)(12) study was conducted at Vanderbilt University Medical Center and Saint Thomas Hospital (both Nashville, TN, USA) and the MIND-ICU Study was conducted at the Tennessee Valley Healthcare System (Nashville, TN, USA), George E. Wahlen Department of VA Medical Center in VA Salt Lake City Health Care System (Salt Lake City, UT, USA), and Seattle Division of the VA Puget Sound Health Care System (Seattle, WA, USA).

Each day, study personnel screened the census of the medical and surgical ICUs at each enrolling site. At enrollment, study personnel collected baseline information including sociodemographic, comorbid medical conditions, disability in basic and instrumental activities of daily living, baseline cognitive function, and baseline. Enrolled patients were followed daily in the hospital until they were discharged (or for up to 30 days). Each day, study personnel collected detailed physiologic and pharmacologic data used to calculate the covariates described below, including daily severity of illness

scores, duration of delirium, duration of coma, duration of severe sepsis, duration of mechanical ventilation and mean daily doses of sedatives and opiates. Patients then underwent in-person follow-up assessments 3 and 12 months after discharge.

Determining Co-occurrence of Problems in the Post-Intensive Care Syndrome

At 3 and 12 months after hospital discharge, study personnel who were masked to all data regarding ICU hospitalization, assessed patients for problems in the PICS domains of cognition, disability in activities of daily living, and mental health. We measured cognition using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (16). The RBANS assesses global cognition, including individual domains of immediate and delayed memory, attention, visuospatial construction, and language. We measured disabilities in activities of daily living using the Katz ADL (17). The Katz ADL measures the ability to complete basic activities of daily living such as bathing, dressing, eating and toileting. Finally, we measured mental health problems using the Beck Depression Inventory-II (BDI-II) (18). We chose depression as a representative measure of mental health problems based on previous work in survivors of critical illness showing that depression is five times more common than post-traumatic stress disorder (PTSD) (19) and because other mental health symptoms such as anxiety and PTSD frequently co-occur with depression (10).

We defined problems in PICS using accepted limits to determine the presence of cognitive impairment, disability in ADLs, and depression. The age-adjusted mean score on the RBANS is 100, with a standard deviation of 15; lower scores indicate worse

cognition. We defined cognitive impairment as an RBANS score 78 or less (i.e., a conservative definition representing 1.5 standard deviations below the age-adjusted mean)(16). Katz ADL scores range from 0 to 12; scores other than 0 indicate disability in basic ADLs (15). Scores on the BDI-II range from 0 to 63; a score of >13 represents the presence of mild depression, with higher scores indicating increasing severity of depression (18). We defined depression as a BDI-II score of >13.

Predictors of Being Post-Intensive Care Syndrome-Free

Using prior research and clinical experience, 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 (CSHA) Clinical Frailty Scale score (20), and durations of severe sepsis, delirium (21), and mechanical ventilation.

Definitions of Selected Predictors and Rationale

- Frailty

We used the Canadian Study of Health and Aging (CSHA) Clinical Frailty Scale to measure frailty. CSHA scores range from 1 (very fit) to 7 (severely frail) (20).

1: Very fit — robust, active, energetic, well-motivated and fit; these people commonly exercise regularly and are in the most fit group for their age;

2: Well — without active disease, but less fit than people in category 1;

3: Well, with treated comorbid disease — disease symptoms are well controlled compared with those in category 4;

4: Apparently vulnerable — although not frankly dependent, these people commonly complain of being “slowed up” or have disease symptoms;

5: Mildly frail — with limited dependence on others for instrumental activities of daily living

6: Moderately frail — help is needed with both instrumental and non-instrumental activities of daily living;

7: Severely frail — completely dependent on others for the activities of daily living, or terminally ill.

- Charlson comorbidity index provides a marker for chronic disease burden and can predicts the ten-year mortality for a patient who may have a range of comorbid conditions(22).

  Clinical conditions and associated scores are as follows:

  1 point each for: myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic lung disease, connective tissue disease, ulcer, chronic liver disease and diabetes;

  2 points each for: hemiplegia, moderate or severe kidney disease, diabetes with complication, tumor, leukemia, lymphoma;

  3 points for: moderate or severe liver disease;

  6 points each for: malignant tumor, metastasis, AIDS.

  Scores are summed to provide a total score that ranges from 0 to 33.

- Duration of severe sepsis was calculated as the number of days where severe sepsis was present. Severe sepsis was defined as sepsis plus any of the following signs of organ dysfunction (mechanical ventilation, cardiovascular or renal, Sequential Organ Failure Assessment (SOFA) score (SOFA) > 2, or neurological organ dysfunction, defined as delirium or coma). The presence of sepsis was determined using prospectively collected data that was adjudicated following the ICU stay by a panel of 3 intensivists [PPP, TDG and EWE].

- Sequential Organ Failure Assessment (SOFA) score is an organ dysfunction scoring system and is a validated marker of severity of illness over time(23). The score is based on six different scores, one each for the respiratory, cardiovascular, hepatic, coagulation, renal, and neurological system from 0 for no dysfunction to 4 for organ system failure. The score range from 0 to 24, with higher scores denoting worse organ dysfunction. We used a modified SOFA score in our regression models, which excluded the neurological components of the SOFA score, since we accounted for coma separately in all our regression models.
- Duration of delirium was calculated as the number of days where the Richmond Agitation-Sedation Scale (RASS) was > -4 and the Confusion Assessment Method for the ICU (CAM-ICU) (21, 24) was positive.
- Duration of coma was calculated as the number of days where the patient's level of consciousness was a -4 or -5 on the Richmond Agitation-Sedation Scale (RASS) (25, 26).

- Duration of mechanical ventilation was calculated as the number of days (or portion thereof) where the patient was treated with mechanical ventilation

Missing Data

We used predictive mean matching multiple imputations 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 (27).

Statistical Analysis

We used the cutoffs described above and descriptive statistics to determine the co-occurrence of problems in PICS. We categorized patients who completed all cognitive, disability, and depression assessments into 8 groups ranging from having no problems to problems in all 3 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 (IQR).

We used multivariable logistic regression to determine the independent association between baseline factors and those present during critical illness with the odds of being PICS-free at 3 and 12 months. We conducted two sensitivity analyses: one that excluded patients with a proxy reported a preexisting history of depression and a second that substituted Agency for Healthcare Research Quality Index of Socioeconomic Status for years of education (28).

Associations with continuous predictors were allowed to be nonlinear using restricted cubic splines. For the sake of parsimony in our models, nonlinear terms were forced to be linear if the P-value of the global test for nonlinearity was >0.20. We used R (version 3.1.2) for all analyses. P-values <0.05 were considered significant.

RESULTS

Characteristics of the patients

Between January 2007 and December 2010, we enrolled 1047 patients. During the hospitalization, 7 patients withdrew consent and requested their data be destroyed. Of the remaining 1040 patients, 214 patients died and 45 withdrew from further participation while in the hospital. Thus, 781 patients survived the index hospitalization. Of these, we excluded 13 patients who had preexisting mild cognitive impairment, 202 who had preexisting disability in ADLs, and 35 who had both, leaving 531 patients eligible to participate in this long-term follow-up study. We assessed 384/465 (83%) of survivors at 3 months and 334/419 (80%) of survivors at 12 months (**Figure 1**).

Overall, 406 unique patients, who were a median age of 61 (IQR: 51-70) years old and who had a high severity of illness (APACHE II score of 23 [IQR: 16-29]) at admission, contributed data to these analyses (**Table 1**).

Prevalence and Co-occurrence of Problems of the Post-Intensive Care Syndrome

Among patients who participated in 3-month follow-up, 128/337 (38%) had cognitive impairment, 100/383 (26%) had disability in ADLs and 121/363 (33%) had depression. At 12 months, 97/292 (33%) had cognitive impairment, 69/332 (21%) had disability in ADLs, and 97/313 (31%) had depression. The median scores and IQR on the each of the follow-up assessment measures may be found in **Table 2**.

There were 330 patients (86% of those who participated in follow-up) who completed all three assessments at 3 months, and 285 (85% of those who participated in follow-up) who completed all three assessments at 12 months. Approximately 6 out of every 10 patients had one or more problems of PICS (211/330 [64%] at 3 months and 160/285 [56%] at 12 months) (**Figure 2**). The majority of these patients (130/211 [62%] at 3 months and 101/160 [63%] at 12 months) had only a single problem. Co-occurring problems among those with PICS were present in 81/211 (38%) at 3 months and 59/160 (37%) at 12 months. Nevertheless, only 19/211 (9%) and 12/160 (8%), had problems in all three domains. Though the proportion of patients who were PICS-free during follow-up increased from 36% (119/330) at 3 months to 44% (125/285) at 12 months, the total number of patients without any problems was similar (**Figure 2**).

Predictors Being PICS-Free at Follow-up

Survivors who were PICS free tended to be younger, more educated, had fewer coexisting illnesses, and were more fit than those who developed symptoms of PICS during follow-up (**Tables 3 and 4**). Although severity of illness scores were similar at ICU admission, fewer patients who were PICS-free required mechanical ventilation, had sepsis, delirium, or coma during their critical illness. Moreover, the duration of each of these conditions was shorter among these patients (**Tables 3 and 4**).

After adjusting for covariates, more years of education were an independent predictor of greater odds of being PICS-free at follow-up (P<0.001 at 3 and 12 months **Table 5 and Figure 3A and 3B)**. Conversely, higher Clinical Frailty Scale score at ICU admission was an independent predictor of lower odds being symptom-free at 3 months (P=0.005 **Table 5 and Figure 3C**). At 12 months, however, the association was of

marginal significance (P=0.06; **Table 5 and Figure 3D**). Longer duration of severe sepsis was associated with lower odds of being PICS-free at 3 months (P=0.048; **Table 5 and Figure 3E**), but not at 12 months (P=0.28; **Table 5 and Figure 3F**). Age, duration of delirium, and duration of mechanical ventilation were not significantly associated with symptoms at follow-up (**Table 5**).

In the sensitivity analysis that excluded an additional 53 patients who had a proxy-reported history of preexisting depression, more years of education remained a significant predictor of being PICS-free at follow-up ($p<0.001$ at 3 months and $p=0.01$ at 12 months, **Table 6**), but the association with the Clinical Frailty Scale score was no longer significant. The AHRQ Socioeconomic Index score did not predict being PICS-free at follow-up ($p=0.62$ at 3 months and $p=0.17$ at 12 months, **Table 7).**

DISCUSSION

In this multicenter cohort study of over 400 survivors of critical illness, we found that 6 out of 10 patients who had no overt cognitive impairment or disability in activities of daily living prior to their illness developed one or more problems of the Post-Intensive Care Syndrome. Most patients with PICS had problems in a single domain, with cognitive impairment being most common, but disability in ADLs and depression also occurring frequently. Co-occurring problems (i.e., problems in 2 or more PICS domains) were present in 2 out of 10 patients. These data highlight the heterogeneous patterns of PICS and suggest that cognitive impairment, disability, and depression may be distinct sequelae of critical illness rather than part of a unifying syndrome with a single etiology.

Over the last decade and a half, investigators have conducted careful assessment of the cognitive, physical, and mental health function among survivors of critical illness and have reported that significant proportions of these patients suffer from new or worsened impairments and disabilities, giving rise to the concept of Post-Intensive Care Syndrome (1, 6-9, 12, 19, 29). To our knowledge, only one small cohort study has reported the co-occurrence of problems in PICS. Using a telephone battery, Maley et al., used patient-reported assessment of cognitive, physical, and mental health function among 43 survivors a median of 8 months after critical illness (30). At least one problem of PICS was present in 84% (36/43) of patients. When this analysis was 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. Maley and colleagues also reported that 2 or more problems of PICS were present in 56% (24/43) of patients, but did not report the

co-occurrence of problems that were worse after critical illness. In contrast, we report that 2 or more new problems of PICS were present in 20%. Thus, the difference in the prevalence of co-occurring problems of PICS between these studies may be because we considered only new problems of PICS after critical illness, whereas the prior study did not make this distinction.

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 (31-35). The exact mechanisms by which education may be protective from these problems are unclear though a number of hypotheses have been proposed. Education is associated with occupational attainment, greater income, better cognitive and critical thinking skills, and larger social/support networks (36). Thus, it could be the case that those who did not develop problems of PICS may have had more resources at their disposal to facilitate recovery. To explore this hypothesis, we conducted a sensitivity analysis where socioeconomic status was substituted for education but found no association between socioeconomic status and freedom from PICS problems at follow-up. The association between education and good outcomes after critical illness could be related to unmeasured non-economic factors. For example, healthy behaviors (e.g., avoidance of cigarettes and heavy alcohol use, exercise, control of chronic disease) may be present among those with more years of education (36) and may facilitate recovery from critical illness. More years of education could also represent better health literacy and/or greater access to the health care system that could enhance recovery from symptoms of PICS. Alternatively, because the RBANS is age, 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 (37). 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 heightened vulnerability characterized by diminished physiological reserve across multiple domains that results in the reduced ability to maintain and restore homeostasis in the setting of acute stress (38). In patients with critical illness, frailty is associated with greater mortality and subsequent disability (39-41). Although worse pre-existing cognition and ability to carry out self-care activities could explain these findings, because we excluded those with cognitive impairment and disability in ADLs from this analysis and adjusted for pre-illness cognition and disability status in our models, this is less likely. Thus, the association between greater clinical 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 higher Clinical Frailty Scale scores 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.

A major strength of this investigation was enrollment of a large and geographically diverse cohort of medical and surgical critical illness survivors from academic, community, and Veterans Affairs hospitals; our cohort of survivors was 10-fold larger than the only other study to examine patterns of PICS. We used a thorough 3-step process to exclude patients from enrollment who had preexisting moderate or severe cognitive impairment, and we assessed participants for mild pre-illness cognition and disabilities using well-validated surrogate measures. We also prospectively collected a range of detailed clinical, physiologic, and pharmacologic parameters daily throughout the hospitalization. Finally, we achieved excellent long-term in-person follow-up performed by study staff who were blinded to the details of the ICU course.

Our findings should be interpreted in the context of several limitations. First, given the emergent nature of critical illness, we were unable to directly assess participants' cognitive function, disability, and mental health prior to critical illness. Nevertheless, we used well-validated surrogate measures to determine the pre-illness cognitive function, disability, and depression at study enrollment. Second, though we chose previously published definitions of clinically significant cognitive impairment, disability and depression, these definitions are conservative and may underestimate problems of PICS that are less overt yet still clinically important (12). Third, we did not assess physical function directly but relied on disability in activities of daily living to evaluate this domain of PICS. While function and disability are separate constructs, the ability to carry out activities of daily living is dependent on physical function and therefore represents significant physical impairment (17). Fourth, 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. Finally, although we excluded from this study patients who had evidence of mild cognitive impairment and disability prior to their critical illness, we were unable to determine patients' pre-illness trajectories of cognition, disability and mental health, an issue present in all inception cohort studies.

CONCLUSION:

We found 6 out of 10 survivors of critical illness had one or more problems of PICS up to a year after ICU admission. Co-occurring problems of PICS were present in 2 out of 10. More years of education was associated with 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 then be used to facilitate the evaluation of interventions directed to improve outcomes for survivors of critical illness.

TABLES

Table 1. Demographic and Clinical Characteristics of Patients

	N = 406
Age (years)	61 (51-70)
Male Sex, n (%)	256 (63%)
Education (years)	12 (12-14)
Katz ADL score[a]	0 (0-0)
IQCODE score[b]	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]	2 (1-3)
APACHE II Score at admission[d]	23 (16-29)
Mean Daily SOFA Score[e]	7 (5-8)
Diagnoses at Admission, n (%)	
Sepsis, ARDS due to infection or septic shock	118 (29%)
Acute Respiratory Failure[f]	42 (10%)
Cardiogenic shock, CHF, 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	3 (1-7)

mechanically ventilated, days	
Severe Sepsis	
Patients, n (%)	259 (64)
Duration of severe sepsis among those who were ever septic, days	4 (2-8)
Delirium	
Patients, n (%)	289 (71)
Duration of delirium among those who were ever delirious, days	3 (2-7)
Coma	
Patients, n (%)	221 (54)
Duration of coma among those who were ever comatose, days	2 (1-5)

Data are median (interquartile range) unless otherwise indicated. APACHE II, Acute Physiology And Chronic Health Evaluation, version II; ARDS, Acute Respiratory Distress Syndrome; CHF, Congestive Heart Failure; IQCODE, Short Informant Questionnaire on Cognitive Decline in the Elderly, assessment of pre-illness cognition; Katz ADL, Assessment of basic activities of daily living; SOFA, Sequential Organ Failure Assessment

[a]Katz ADL scores range from 0 to 12, where higher scores indicate more severe disability in activities of daily living. A score of 0 indicates no disability.

[b]IQCODE scores range from 1 to 5, with a score of 3 indicating no change in cognition over the past 10 years. 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]APACHEII scores range from 0 to 71, with higher scores indicating more severe critical illness.

[e]SOFA scores range from 0 to 24, with higher scores indicating more severe organ dysfunction.

[f]Acute respiratory failure includes ARDS, 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.

Table 2: Scores for RBANS, Katz ADL, and BDI of the cohort at 3 and 12 months follow-up

	3 months	12 months
RBANS global Score[a]	81 (72 to 89)	83 (73 to 91)
Katz ADL Score[b]	0.0 (0 to 1)	0.0 (0 to 0)
BDI-II Score[c]	10 (5 to 16)	9.0 (5 to 16)

RBANS, Repeatable Battery for the Assessment of Neuropsychological Status Update; Katz ADL, Assessment of basic activities of daily living; BDI-II, Beck Depression Inventory II; PICS, Post-intensive care syndrome. Data represent the median (interquartile range) of scores for all patients assessed.

[a]Age-adjusted mean scores for the RBANS global cognition test are 100 with a standard deviation of 15. Lower scores represent worse cognitive function.

[b]Katz ADL scores range from 0 to 12, with higher scores indicating more severe disability in activities of daily living. A score of 0 indicates no disability.

[c]BDI-II scores range from 0 to 63, with higher scores indicating more severe depression. A score of 13 indicates the presence of mild depression.

Table 3: Clinical characteristics and outcomes of patients according to PICS status at 3-month follow-up

	PICS-free (N=119)	PICS (N=211)
Age at enrollment	60 (50-70)	62 (51-69)
Years of education	13 (12-16)	12 (12-14)
Clinical Frailty Scale Score, n (%)		
1. Very fit	9 (8%)	8 (4%)
2. Well	31 (26%)	40 (19%)
3. Well with treated comorbid disease	52 (44%)	85 (40%)
4. Apparently vulnerable	19 (16%)	47 (22%)
5. Mildly frail	4 (3%)	20 (9%)
6. Moderately frail	2 (2%)	11 (5%)
7. Severely frail	2 (2%)	0 (0%)
Charlson Comorbidity Index Score	1 (0-3)	2 (1-3)
APACHE II Score at admission	23 (16- 28)	23 (17-29)
Mean Daily SOFA Score	7 (5-9)	6.5 (5-8)
Mechanical ventilation		
Patients, n (%)	104 (87%)	187 (89%)
Duration of mechanical ventilation among those who were ever mechanically ventilated, days	2 (1-5)	3 (1-8)
Severe Sepsis		
Patients, n (%)	63 (53%)	142 (68%)
Duration of severe sepsis among those who were ever septic, days	3 (2-6)	5 (2-9)
Delirium		
Patients, n (%)	70 (59%)	158 (75%)
Duration of delirium among those who were ever delirious, days	3 (1-6)	4 (2-7)
Coma		
Patients, n (%)	58 (49%)	124 (59%)
Duration of coma among those who were ever comatose, days	2.5 (1-4)	2 (1-5)

Cognitive Impairment[a], n (%)	0 (0%)	124 (59%)
RBANS global score	88 (81-95)	75 (68-83)
ADL Disability[b], n (%)	0 (0%)	78 (37%)
Katz ADL Score	0 (0-0)	0 (0-1)
Depression[c], n (%)	0 (0%)	109 (52%)
BDI-II score	6 (3-9)	14 (8-20)

RBANS, Repeatable Battery for the Assessment of Neuropsychological Status Update; Katz ADL, Assessment of basic activities of daily living; BDI-II, Beck Depression Inventory II; PICS, Post-intensive care syndrome

[a]Cognitive impairment was defined as an RBANS score 78 or less.

[b] Disability in ADLs was defined score of ≥ 1.

[c] Depression was defined as a BDI-II score of >1

Table 4: Clinical characteristics and outcomes of patients according to PICS status at 12-month follow-up

	PICS-Free (N=125)	PICS (N=160)
Age at enrollment	60 (52-69)	61 (50-69)
Years of education	13 (12-14)	12 (11-14)
Clinical Frailty Scale Score, n (%)		
1. Very fit	7 (6%)	10 (6%)
2. Well	32 (26%)	34 (21%)
3. Well with treated comorbid disease	56 (45%)	58 (36%)
4. Apparently vulnerable	21 (17%)	37 (23%)
5. Mildly frail	6 (5%)	11 (7)
6. Moderately frail	3 (2%)	9 (6%)
7. Severely frail	0 (0%)	1 (1%)
Charlson Comorbidity Index Score	1 (0-3)	2 (1-3)
APACHE II Score at admission	22 (15-29)	23 (17-29)
Mean Daily SOFA Score	6 (5-8)	7 (5-9)
Mechanical ventilation		
Patients, n (%)	111 (89%)	145 (91%)
Duration of mechanical ventilation among those who were ever mechanically ventilated, days	2 (1-5)	3 (1-9)
Severe Sepsis		

Patients, n (%)	73 (58%)	111 (70%)
Duration of severe sepsis among those who were ever septic, days	3 (2-6)	5 (2-9)
Delirium		
Patients, n (%)	77 (62%)	124 (78%)
Duration of delirium among those who were ever delirious, days	3 (1-6)	4 (2-8)
Coma		
Patients, n (%)	64 (51%)	96 (60%)
Duration of coma among those who were ever comatose, days	2 (1-4)	3 (1-5)
Cognitive Impairment[1], n (%)	0 (0%)	93 (58%)
RBANS global score	89 (83-94)	75 (68-83)
ADL Disability[2], n (%)	0 (0%)	50 (31%)
Katz ADL Score	0 (0-0)	0 (0-1)
Depression[3], n (%)	0 (0%)	88 (55%)
BDI-II score	5 (3-9)	14 (8-23)

RBANS, Repeatable Battery for the Assessment of Neuropsychological Status Update; Katz ADL, Assessment of basic activities of daily living; BDI-II, Beck Depression Inventory II; PICS, Post-intensive care syndrome

[a]Cognitive impairment was defined as an RBANS score 78 or less.

[b] Disability in ADLs was defined score of ≥ 1.

[c]Depression was defined as a BDI-II score of >13.

Table 5: Association between Baseline and Clinical Factors and the Odds of Being PICS-Free at Follow-up.

	Comparison (75th vs 25th percentile)	Odds Ratio (95% CI) at 3 months	P	Odds Ratio (95% CI) at 12 months	P
Years of education	14 vs 12 years	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	0.7 (0.4-1.0)	0.06
Duration of Severe Sepsis	6 vs 0 days	0.7 (0.4-1.1)	0.048	0.9 (0.5-2.0)	0.28
Age	70 vs 51 years	1.2 (0.9-1.6)	0.33	1.1 (0.8-1.6)	0.07
Duration of Delirium	5 vs 0 days	0.7 (0.5-1.0)	0.09	0.6 (0.3-1.3)	0.27
Duration of Mechanical Ventilation	5 vs 1 day	1.1 (0.9-1.5)	0.34	0.9 (0.7-1.2)	0.33

Each odds ratio represents the odds being symptom-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% confidence interval includes 1, but the P-value is <0.05, the P-value is correct. Interpretive example, in a comparison of two patients alike in all other ways (that is, all covariates adjusted to their respective median or mode value) the patient with 14 years of education would have, on average, 60% greater odds of being symptom-free compared to a patient with 12 years of education.

Table 6: Association between baseline and clinical factors with the odds of being PICS-free (sensitivity analysis excluding in patients without a known history of depression)

	Comparison (75th vs 25th percentile)	3-month follow-up OR (95% CI)	P	12-month follow-up OR (95% CI)	P
Age	70 vs 51 years	1.10 (0.76 to 1.58)	0.63	1.22 (0.83 to 1.77)	0.31
Years of education	14 vs 12 years	1.64 (1.2 to 2.12)	<0.001	1.40 (1.07 to 1.82)	0.01
Clinical frailty score	4 vs 2	0.62 (0.38 to 1.03)	0.07	0.73 (0.42 to 1.29)	0.28
Duration of mechanical ventilation	5 vs 1 day	1.17 (0.85 to 1.62)	0.34	0.81 (0.58 to 1.12)	0.20
Duration of delirium	5 vs 0 days	0.68 (0.41 to 1.12)	0.13	0.82 (0.54 to 1.26)	0.38
Duration of severe sepsis	6 vs 0 days	0.66 (0.37 to 1.16)	0.15	0.94 (0.58 to 1.53)	0.80

Table 7: Association between baseline and clinical factors with the odds of being PICS-free (sensitivity analysis adjusting for AHRQ Socioeconomic Status in lieu of years of education)

	Comparison (75th vs 25th percentile)	3-month follow-up OR (95% CI)	P	12-month follow-up OR (95% CI)	P
Age	70 vs 51 years	1.14 (0.83 to 1.57)	0.41	0.99 (0.69 to1.42)	0.05
AHRQ Socioeconomic score	53 vs 48	0.94 (0.73 to 1.21)	0.62	1.27 (0.93 to 1.74)	0.17
Clinical frailty score	4 vs 2	0.53 (0.35 to 0.81)	0.003	0.53 (0.32 to 0.86)	0.01
Duration of mechanical ventilation	5 vs 1 day	1.23 (0.92 to 1.65)	0.17	0.86 (0.64 to 1.15)	0.31
Duration of delirium	5 vs 0 days	0.70 (0.44 to 1.09	0.12	0.59 (0.29 to 1.20)	0.27
Duration of severe sepsis	6 vs 0 days	0.62 (0.39 to 0.98)	0.04	0.93 (0.45 to 1.90)	0.34

FIGURE LEGENDS

Figure 1: Enrollment and Follow-up

Figure 2: Co-Occurring Problems in the Post-Intensive Care Syndrome at 3- and 12-Month Follow-Up

This diagram illustrates the co-occurring problems in PICS. The proportion of patients with problems in each PICS domain at 3 months is presented in the left panel and at 12 months in the right panel. 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 2 or 3 problems. Overall, 6 out of 10 patients had PICS. The most common pattern at both 3 and 12 months was problems in a single domain and was present in 4 out of 10 patients. Co-occurring problems (i.e., in 2 or 3 domains) were present in 2 out of 10 patients.

Figure 3: Associations between Baseline and Clinical Factors and the Adjusted Probability of being PICS-Free at Follow-up.

These figures display the association between baseline and clinical factors with the adjusted probability of being PICS-free at 3 months (left column) and 12 months (right column). For panels A, B, E, and F, the blue lines represent the association and blue shading represents the 95% confidence interval. For panels C and D, dots represent the point estimate and error bars the 95% confidence interval. 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 ($P<0.001$ at 3 months, Panel A, and $P<0.001$ at 12 months, Panel B). Higher Clinical Frailty Scale scores were

associated with a lower probability of being PICS-free at 3 months (P=0.005, Panel C) and had a marginal association at 12 months (P=0.06, Panel D). Longer duration of severe sepsis was associated with lower probability of being PICS-free at 3 months (P=0.048, Panel E), but not at 12 months (P=0.2, Panel F).

Figure 1: Enrollment and Follow-up

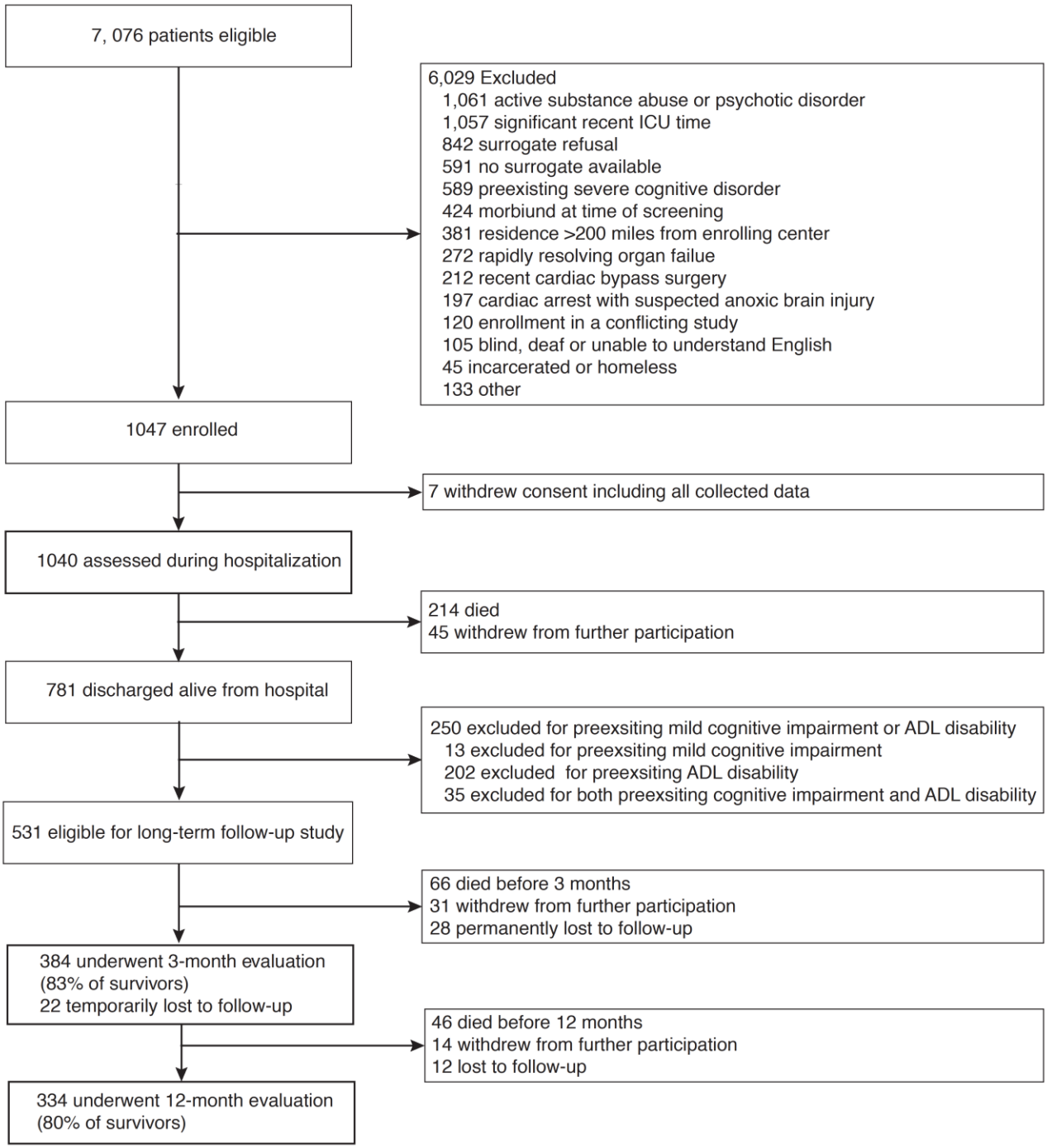


Figure 2: Co-Occurring Problems in the Post-Intensive Care Syndrome at 3- and 12-Month Follow-Up

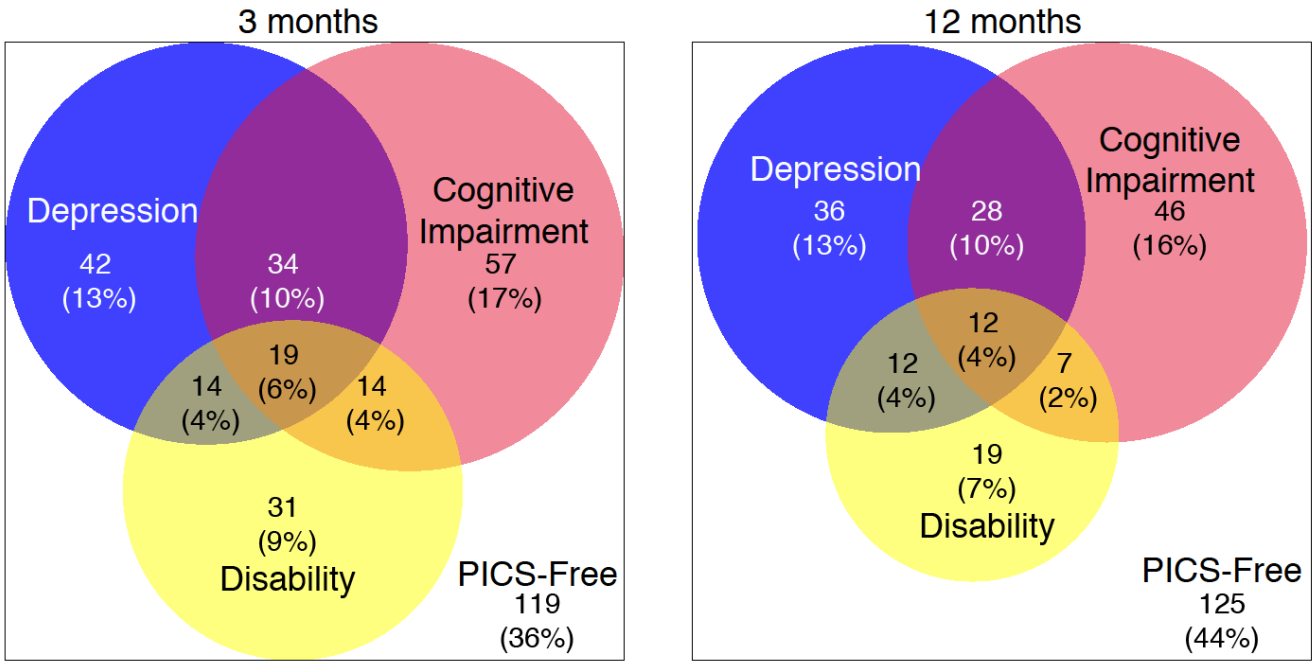
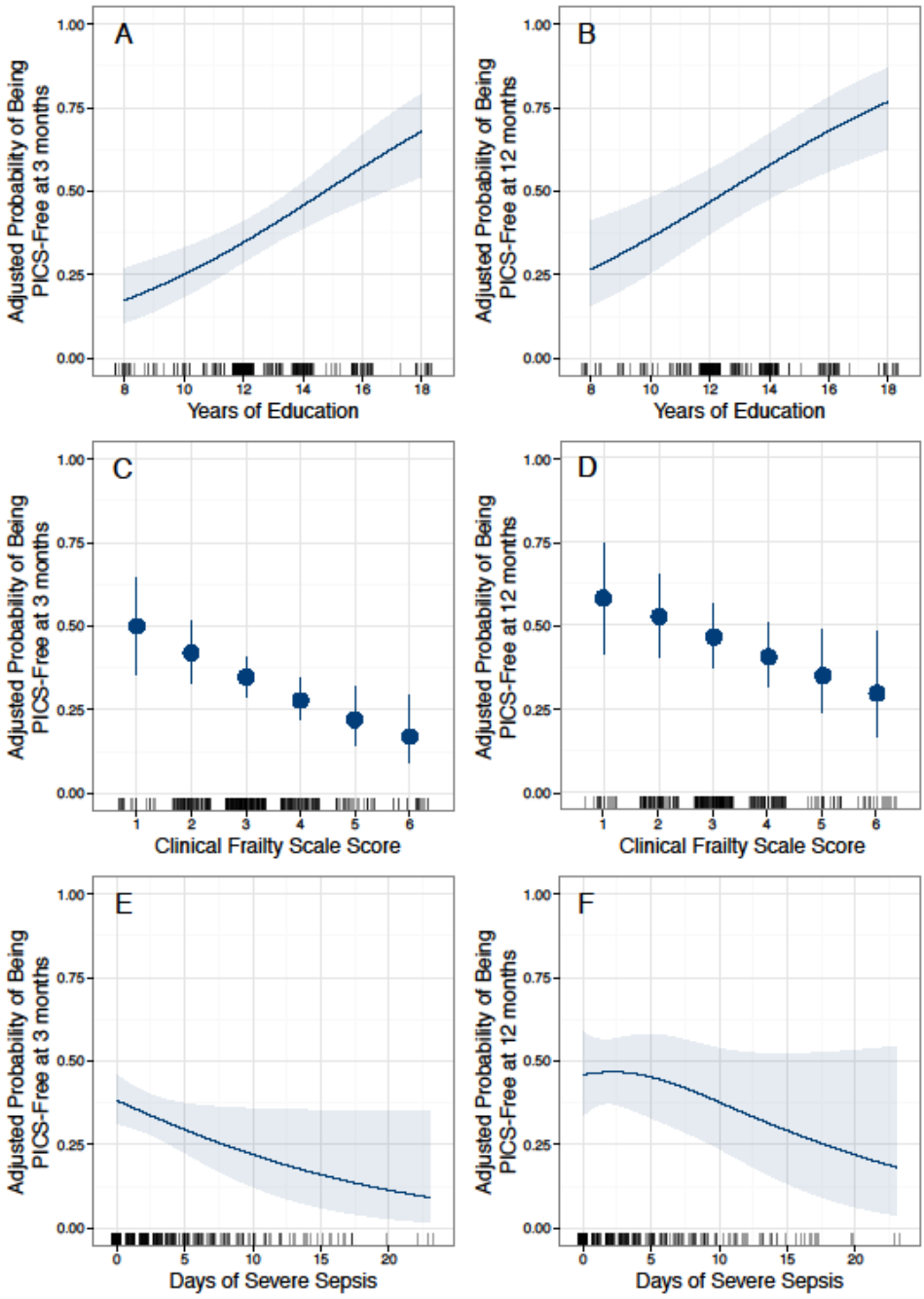


Figure 3: Associations between Baseline and Clinical Factors and the Adjusted Probability of being PICS-Free at Follow-up



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