**Supplemental Data**

This appendix has been provided by the authors to give readers additional information about their work.

**Supplemental Data to:**

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

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16. 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.

1. Exclusion Criteria

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

(1) 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.

(2) 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.

(3) ICU admission post cardiopulmonary resuscitation with suspected anoxic injury.

(4) 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.

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

(6) Moribund and not expected to survive for an additional 24 hours and / or withdrawing life support to focus on comfort measures only.

(7) Prisoners.

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

(9) 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.

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

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

1. **Summary of the BRAIN-ICU and MIND-ICU study protocols**

The (BRAIN-ICU) 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.

1. **Details of the Repeatable Battery for the Assessment of Neuropsychological Status, Katz Activities of Daily Living Index, and Beck Depression Inventory-II** 
   1. Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (1)

The RBANS assesses global cognition, including individual domains of immediate and delayed memory, attention, visuospatial construction, and language. 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)

* 1. Katz Activities of Daily Living Index (Katz ADL)

The Katz ADL measures 6 basic activities of daily living: bathing, dressing, toileting, transferring, continence, and feeding. Each question is scored from 0 (independent) to 2 (disabled). Thus, scores range from 0 to 12; scores other than 0 indicate disability in basic ADLs. We defined disability as a score of greater than or equal to 1.

* 1. Beck Depression Inventory Second Edition (BDI-II)

The BDI-II is a 21-item self-report questionnaire that assesses the presence and severity of depression symptoms. Each question has 4 possible responses that range in intensity from 0 to 3. Thus, 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 (2). We defined depression as a BDI-II score of >13.

1. **Definitions of Selected Predictors and Rationale**
   1. 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) (3).

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.

* 1. 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(4).

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.*

* 1. 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].
  2. Sequential Organ Failure Assessment (SOFA) score is an organ dysfunction scoring system and is a validated marker of severity of illness over time(5). 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.
  3. 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) (6, 7) was positive.
  4. 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) (8, 9).
  5. Duration of mechanical ventilation was calculated as the number of days (or portion thereof) where the patient was treated with mechanical ventilation.

**B. Results**

**Table S1: Scores for RBANS, Katz ADL, and BDI of the cohort at 3 and 12 months follow-up**

|  |  |  |
| --- | --- | --- |
|  | 3 months | 12 months |
| RBANS global Scorea | 81 (72 to 89) | 83 (73 to 91) |
| Katz ADL Scoreb | 0.0 (0 to 1) | 0.0 (0 to 0) |
| BDI-II Scorec | 10 (5 to 16) | 9.0 (5 to 16) |

Abbreviations: 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.

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

bKatz 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.

cBDI-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 S2: 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 Impairmenta, n (%) | 0 (0%) | 124 (59%) |
| RBANS global score | 88 (81-95) | 75 (68-83) |
| ADL Disabilityb, n (%) | 0 (0%) | 78 (37%) |
| Katz ADL Score | 0 (0-0) | 0 (0-1) |
| Depressionc, n (%) | 0 (0%) | 109 (52%) |
| BDI-II score | 6 (3-9) | 14 (8-20) |

Abbreviations: 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

aCognitive 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 S3:  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 Impairment1, n (%) | 0 (0%) | 93 (58%) |
| RBANS global score | 89 (83-94) | 75 (68-83) |
| ADL Disability2, n (%) | 0 (0%) | 50 (31%) |
| Katz ADL Score | 0 (0-0) | 0 (0-1) |
| Depression3, n (%) | 0 (0%) | 88 (55%) |
| BDI-II score | 5 (3-9) | 14 (8-23) |

Abbreviations: 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

aCognitive 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 S4: Association between baseline and clinical factors with the odds of being PICS-free (sensitivity analysis excluding in patients without a known history of depression)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| N=260 | Comparison (75th vs 25th percentile) | Odds Ratio  (95% CI)  at 3 months | P | Odds Ratio  (95% CI)  at 12 months | P |
| Age | 70 vs 51 years | 1.1 (0.7 to 1.6) | 0.71 | 1.0 (0.7 to 1.5) | 0.06 |
| Years of education | 14 vs 12 years | 1.6 (1.2 to 2.1) | <0.001 | 1.4 (1.1 to 1.8) | 0.005 |
| Clinical frailty score | 4 vs 2 | 0.6 (0.4 to 1.0) | 0.05 | 0.7 (0.4 to 1.2) | 0.21 |
| Duration of mechanical ventilation | 5 vs 1 day | 1.0 (0.7 to 1.3) | 0.87 | 0.9 (0.4 to 2.3) | 0.53 |
| Duration of delirium | 5 vs 0 days | 0.7 (0.4 to 1.1) | 0.17 | 0.6 (0.2 to 1.5) | 0.50 |
| Duration of severe sepsis | 6 vs 0 days | 0.7 (0.4 to 1.1) | 0.30 | 0.8 (0.3 to 2.1) | 0.56 |

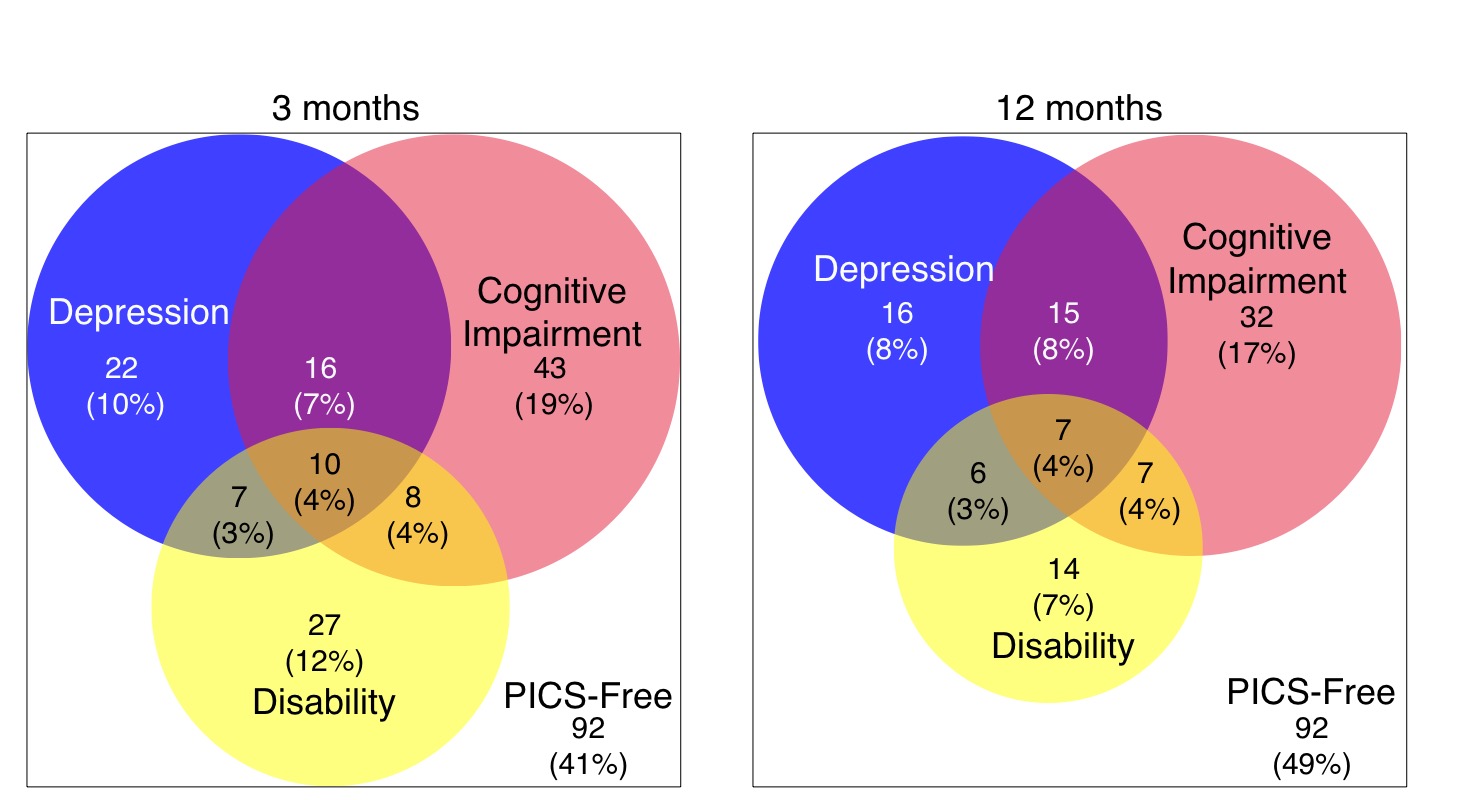
Each odds ratio represents the odds being symptom-free at follow-up in a comparison of patients who have values of the exposure of interest at 75th percentile with patients who have values at the 25th percentile. Because the P-values consider all beta coefficients together, in cases where the 95% confidence interval includes 1, but the P-value is <0.05, the P-value is correct. Interpretive example, at 3-month follow-up 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 PICS-free compared to a patient with 12 years of education.

Table S5: 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) | Odds Ratio  (95% CI)  at 3 months | P | Odds Ratio  (95% CI)  at 12 months | P |
| Age | 70 vs 51 years | 1.1 (0.8 to 1.6) | 0.41 | 1.0 (0.7 to1.4) | 0.05 |
| AHRQ Socioeconomic score | 53 vs 48 | 0.1 (0.7 to 1.2) | 0.62 | 1.3 (0.9 to 1.7) | 0.17 |
| Clinical frailty score | 4 vs 2 | 0.5 (0.4 to 0.8) | 0.003 | 0.5 (0.3 to 0.9) | 0.01 |
| Duration of mechanical ventilation | 5 vs 1 day | 1.2 (0.9 to 1.7) | 0.17 | 0.9 (0.6 to 1.2) | 0.31 |
| Duration of delirium | 5 vs 0 days | 0.7 (0.4 to 1.1) | 0.12 | 0.6 (0.3 to 1.2) | 0.27 |
| Duration of severe sepsis | 6 vs 0 days | 0.6 (0.4 to 1.0) | 0.04 | 0.9 (0.5 to 1.9) | 0.34 |

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, at 3-month follow-up 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 a Clinical Frailty Scale score of 4 would have, on average, 50% lower odds of being PICS-free compared to a patient with a Clinical Frailty Scale score of 4.

Figure S1. Co-Occurring Post-Intensive Care Syndrome Problems at 3- and 12-Month Follow-Up, sensitivity analysis excluding those with pre-existing depression.



This diagram illustrates the co-occurrence of PICS problems at 3 and 12 months in the sensitivity analysis cohort that excluded patients with a proxy report of pre-existing depression. 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. In a sensitivity analysis that excluded patients with a proxy report of pre-existing depression, the proportion of patients who were considered to have PICS decreased by 5% at both 3 months and 12 months. 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.

**C.** **References**

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