In-Hospital Acute Stress Symptoms Are Associated with Impairment in Cognition 1 Year after Intensive Care Unit Admission

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Abstract

Rationale: Prior studies have found that cognitive dysfunction is common in intensive care unit (ICU) survivors. Yet, relatively little is known about potentially modifiable risk factors for longer-term post-ICU cognitive impairment.

Objectives: To determine if in-hospital acute stress symptoms were associated with impaired 12-month cognitive functioning among ICU survivors.

Methods: We prospectively enrolled 150 nontrauma patients without cognitive impairment or a dementia diagnosis who were admitted to an ICU for more than 24 hours. Patients were interviewed before hospital discharge and again via telephone at 12 months post-ICU.

Measurements and Main Results: Demographics and clinical information were obtained through medical record reviews and in-person interviews. In-hospital acute stress symptoms were assessed with the Posttraumatic Stress Disorder Checklist-Civilian Version. Twelve-month post-ICU cognition was assessed with the modified Telephone Interview for Cognitive Status. Follow-up interviews were completed with 120 (80%) patients. Patients' mean age at hospitalization was 48.2 years (SD, 13.7). In unadjusted analyses, a greater number of in-hospital acute stress symptoms was associated with significantly greater impairment in 12-month cognitive functioning (β, −0.1; 95% confidence interval, −0.2 to −0.004; $P = 0.04$). After adjusting for patient and clinical factors, in-hospital acute stress symptoms were independently associated with greater impairment in 12-month cognitive functioning (β, −0.1; 95% CI, −0.2 to −0.01; $P = 0.03$).

Conclusions: In-hospital acute stress symptoms may be a potentially modifiable risk factor for greater impairment in cognitive functioning post-ICU. Early interventions for at-risk ICU survivors may improve longer-term outcomes.

Keywords: critical care; acute stress symptoms; cognitive impairment

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Quality of survivorship is becoming increasingly important for the millions of Americans surviving hospitalizations in intensive care units (ICUs) for the treatment of critical illnesses annually (1). Critical illnesses are life-threatening experiences that expose patients to enormous physiological and psychological stressors, including hypoxia, extreme pain, release of inflammatory cytokines, and delirium (2). More than one-fourth of ICU survivors have clinically meaningful posttraumatic stress disorder (PTSD) and depressive symptoms (2–5), and considerable physical impairments over the course of recovery are common (5–7).

A growing body of literature has identified that ICU survivors are at increased risk for incident cognitive impairment and overall cognitive decline (8, 9). Yet, there is limited understanding of potential risk factors for this adverse outcome. Prior studies have identified that preexisting depression as well as

ICU-related exposures, such as hypoxia, delirium, and conservative fluid management, were associated with risk of post-ICU cognitive impairment (10–13). In addition, anxiety and depressive symptoms have been found to be correlated with post-ICU cognitive impairment (13, 14).

Recently, PTSD has been found to be associated with greater risk of dementia in later life (15, 16). This literature is of particular interest in the context of critical illness survival, because ICU survivors have high rates of both long-term cognitive dysfunction and PTSD (2, 8, 9). An important risk factor for the development of longer-term PTSD after a traumatic stressor is the presence of acute stress symptoms (17), which are PTSD symptoms that develop less than 1 month after the occurrence of the traumatic stressor. However, no studies have examined if post-ICU acute stress symptoms are prospectively associated with longer-term cognitive impairment. Determining if such an association is present is crucial, because cognitive impairment is an important contributor to preventable hospitalizations, rising healthcare costs, caregiver burden, and mortality (8, 18). Importantly, in-hospital acute stress symptoms in critical illness survivors are potentially modifiable if identified.

The present study is a prospective cohort investigation of potentially modifiable in-hospital risk factors for impaired cognition 12 months after medical-surgical ICU admission. We hypothesized that a greater number of in-hospital acute stress symptoms would be associated with impaired cognitive functioning post-ICU even after adjusting for baseline patient characteristics and other in-hospital clinical factors.

Methods

Study Setting, Participants, and Procedures

The present investigation took place at Harborview Medical Center (HMC) in Seattle, Washington. HMC is an urban, public medical center operated by the University of Washington (UW). The cohort has been previously described (19). In summary, between September 2010 and August 2011, we prospectively recruited 150 patients admitted to any of the ICUs at HMC. Key exclusion criteria for the study were: (*1*) initial admission diagnosis of traumatic injury, (*2*) preexisting cognitive impairment or dementia diagnosis noted in the medical record, (*3*) non-English speaking, (*4*) ICU length of stay less than or equal to 24 hours, (*5*) preexisting medical illness with life expectancy of less than 12 months noted in the medical record (e.g., terminal cancer, terminal HIV disease), and (*6*) admission for a suicide attempt. The study protocol was approved by the UW Institutional Review Board, and all participants provided informed consent before enrollment.

Study research assistants identified eligible subjects through review of HMC's electronic admission records. Eligible subjects were approached for study consent before transfer from the ICU to the general medical-surgical ward. Because the UW Institutional Review Board did not allow surrogate consent for study participation, if the patient was unable to provide consent, typically due to ongoing delirium and/or cognitive impairment, consent was not obtained, and they were approached again once their delirium and/or cognitive impairment had resolved. Cognitive impairment was assessed using a cutoff score of three or more errors on the Six-Item Cognitive Screen (20). The area under the receiver operating characteristic curve for the Six-Item Cognitive Screen was 0.86 for a community-based sample compared with the Community Screening Instrument for Dementia and 0.91 for a clinical sample based on a battery including the Mini-Mental State Examination and the Consortium for Establishment of Registry for Alzheimer Disease battery (20).

Enrolled patients were administered an in-person interview before hospital discharge and were reinterviewed via telephone at 12 months post-ICU.

Primary Independent Variable

The primary independent variable of interest in our analyses was the presence of in-hospital acute stress symptoms as ascertained by the PTSD Checklist-civilian version (PCL-C) administered in-person before hospital discharge. The 17-item PCL-C includes questions regarding five symptoms in the intrusive symptom cluster (e.g., intrusive thoughts, nightmares), seven symptoms in the avoidant symptom cluster (e.g., avoidance of thoughts or activities that remind the patient of the stressor, emotional numbing), and five symptoms in the arousal symptom cluster (e.g., impaired sleep, hypervigilance), and symptom severity is rated on a 5-point Likert scale (21). Scores range from 0 to a maximum of 85, with higher scores indicating greater severity of symptoms. Substantial acute stress symptoms, defined as PTSD symptoms present within 1 month of a traumatic stressor that are suggestive of a diagnosis of acute stress disorder, can be ascertained with the PCL-C in one of two ways: (*1*) following an algorithm that considers a score of 3 or more on at least one intrusive symptom, three avoidant symptoms, and two arousal symptoms as consistent with Diagnostic and Statistical Manual of Mental Disorders-IV diagnostic criteria; or (*2*) a total PCL-C score greater than or equal to 45 (21).

Covariates of Interest

Covariates of interest included baseline patient characteristics and ICU clinical factors, which were obtained through medical record review and in-person interview with the patient. Medical record–obtained covariates included demographics (e.g., age, sex, race); ICU admission diagnosis; baseline medical comorbidity information to compute a Charlson Comorbidity Score (22); illness severity measures at ICU admission to compute a Simplified Acute Physiology Score II (SAPS II) (23); ICU length of stay; requirements for mechanical ventilation, major surgery, or blood product transfusion; days of exposure (both in the ICU and on the medical-surgical ward) to benzodiazepine, opioid, antipsychotic, and antidepressant medications; presence of delirium in the ICU per nursing-documented assessment using the Confusion Assessment Method-ICU (CAM-ICU) (24); and presence of confusion/disorientation/difficulty following commands in nursing documentation. We defined probable delirium as a documented positive CAM-ICU assessment in the ICU- or nursing-documented presence of confusion/disorientation/difficulty following commands at any point during the hospitalization.

Additional covariates of interest obtained from the baseline interviews included demographics not obtained from medical records (e.g., marital/partnered status, education); assessment of prior trauma exposure with the National

Comorbidity Survey-Replication Trauma History Screen (25); lifetime history of major depression with the Mini International Neuropsychiatric Interview major depression module (26); alcohol use in the previous year with the Alcohol Use Disorders Identification Test, with baseline problem drinking defined as a score greater than or equal to 8 (27); and drug use in the previous year with the Drug Abuse Screening Test-10, with baseline problem drug use defined as a score greater than or equal to 3 (28).

As part of the 12-month telephone follow-up interview, post-ICU PTSD symptoms were assessed with the PCL-C, and post-ICU depressive symptoms were assessed with the Patient Health Questionnaire-9 (29).

Outcome of Interest

Our outcome of interest was post-ICU cognitive functioning as assessed with the modified Telephone Interview for Cognitive Status (TICSm) at the 12-month telephone follow-up interview. The TICSm is a 13-item validated measure of cognition that is composed of four domains: (*1*) orientation; (*2*) registration, free recall, and delayed recall; (*3*) attention/calculation; and (*4*) semantic memory, comprehension, and repetition (30). The maximum score possible is 39, with higher scores indicating better cognitive functioning (30).

Statistical Analysis

We present descriptive data as means and SDs, medians and interquartile ranges (IQRs), or proportions.

We used multiple linear regression analyses to examine potential risk factors for worse cognitive functioning at 12 months post-ICU. The dependent variable for these analyses was the continuous TICSm score. Initially, we tested the association of in-hospital acute stress symptoms, defined by the continuous PCL-C score, with post-ICU TICSm score without adjustment. We then added two groups of potential confounding variables to the regression models all chosen *a priori* because they have been found to be important in critical illness-related research (2–4, 10, 12, 13): (*1*) demographics and baseline clinical characteristics (age, sex, race, education, marital/partnered status, lifetime history of major depression, number of prior traumatic event exposures, presence of unhealthy alcohol use during the year pre-ICU, problem drug use during the year pre-ICU, and Charlson score); and (*2*) clinical characteristics of the ICU admission (SAPS II score, presence of probable delirium during the hospitalization, and requirements for mechanical ventilation, major surgery, blood product transfusion, as well as receipt of benzodiazepines, opioids, antipsychotics, and antidepressants). Finally, in sequential models we adjusted for 12-month Patient Health Questionnaire-9 scores, 12-month PCL-C scores, and both, to determine if any association between in-hospital acute stress symptoms might be mediated by post-ICU depressive and/or PTSD symptoms.

We used Student *t* tests to examine associations between in-hospital acute stress symptoms and individual 12-month TICSm domains.

To examine the extent to which our results might be biased by nonresponse, we conducted a series of sensitivity analyses in which we repeated the regressions with assignment of the lowest observed TICSm score, the mean observed TICSm score, and the highest observed TICSm score, to patients who were missing 12-month follow-up.

We used two-sided significance tests for all analyses with statistical significance set at a *P* value of 0.05. Analyses were performed with appropriate components of the IBM SPSS Statistics 18 (SPSS Inc., Chicago, IL) and STATA 11.2 (Stata Corporation, College Station, TX) statistical software programs.

Results

Nearly 1,200 patients were eligible for study participation (Figure 1). Of the 150 patients originally enrolled in the study, 10 were deceased and 3 were incarcerated at 12 months post-ICU, leaving 137 patients eligible to complete follow-up. One hundred twenty patients (88% of those eligible to complete follow-up, 80% of the original cohort) completed a 12-month telephone follow-up interview. Among the entire cohort, patients' mean age at hospitalization was 48.2 years (SD, 13.7), their median Charlson Comorbidity score was 1.0 (IQR, 0.0–2.0), and 129 (86%) had graduated from high school. Their median ICU length of stay was 5.0 days (IQR, 3.0–9.0), and their median SAPS II score on admission was 23.0 (IQR, 13.0–37.0). Nearly one-half required mechanical ventilation during their ICU admission, with a median duration of 2.0 days (IQR, 1.0–4.0). The prevalence of probable delirium during the course of hospitalization was 51%.

Baseline interviews were completed at a mean of 11.1 days after hospital admission (SD, 9.5). At baseline, patients' mean PCL-C score was 30.8 (SD, 12.3), 15% had substantial acute stress symptoms based on the PCL-C algorithm, and 29% met criteria for lifetime history of major depression based on the Mini International Neuropsychiatric Interview.

Table 1 presents the baseline and hospitalization-related clinical characteristics of patients who completed 12-month follow-up.

At 12 months post-ICU (mean, 356.4 d; SD, 29.2), patients had a mean total TICSm score of 23.9 (SD, 4.7; range, 12–39). Patients with in-hospital substantial acute stress symptoms had a mean total TICSm score of 22.2 (SD, 4.8; range, 12–29) compared with 24.2 (SD, 4.6; range, 12–39) among those without in-hospital substantial acute stress symptoms.

In unadjusted analyses, an additional point on the in-hospital PCL-C was associated with a significantly lower 12-month TICSm score (β, −0.1; 95% confidence interval (CI), −0.2 to 0.004; $P = 0.04$). After adjusting for patient baseline characteristics, in-hospital PCL-C remained associated with a significantly lower 12-month TICSm score (β,−0.1; 95% CI, −0.2 to −0.01; $P = 0.04$) (Table 2). Patient characteristics associated with a lower 12-month TICSm score included less than high school education (β, −4.0; 95% CI, −6.4 to −1.5; $P = 0.002$) and greater medical comorbidity (β, −0.5; 95% CI, −0.9 to −0.04; $P = 0.03$). When we adjusted for both patient and in-hospital clinical characteristics of the ICU admission, in-hospital PCL-C score was independently associated with a lower 12-month TICSm score (β, −0.1; 95% CI, −0.2 to −0.01; $P = 0.03$). No other hospitalization-related factors were independently associated with 12-month TICSm scores. Less than high school education (β, −4.2; 95% CI, −6.8 to −1.6; $P = 0.002$) and greater medical comorbidity (β, −0.6; 95% CI, −1.1 to −0.1; $P = 0.03$) were also independently associated with a lower 12-month TICSm score.

After we adjusted for 12-month depressive symptoms, in-hospital PCL-C

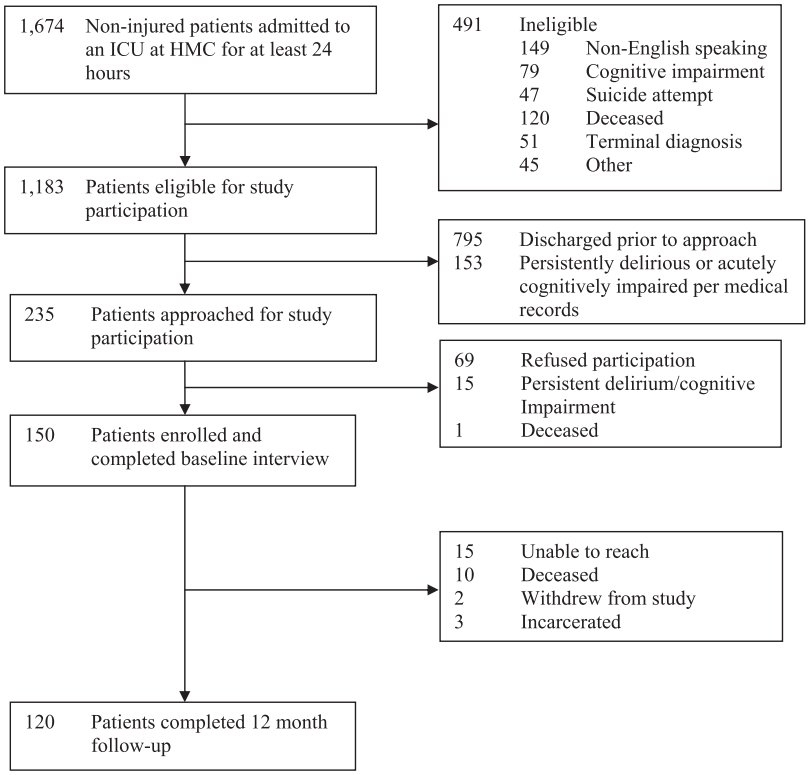

Figure 1. Study flow diagram. HMC = Harborview Medical Center; ICU = intensive care unit.

score remained independently associated with a lower 12-month TICSm score (β, −0.1; 95% CI, −0.2 to −0.01; P = 0.03). Adjustment for 12-month PTSD symptoms appeared to attenuate the association of in-hospital acute stress symptoms with 12-month TICSm score slightly (β, −0.1; 95% CI, −0.2, 0.01; P = 0.11). In the final model, which adjusted for both 12-month depressive and PTSD symptoms, the magnitude of the association between in-hospital acute stress symptoms per PCL-C with lower 12-month TICSm score remained similar (β,−0.1; 95% CI, −0.2 to 0.03; P = 0.13).

Of the individual 12-month TICSm domains, higher in-hospital PCL-C scores were associated with worse performance in attention/calculation (t = −2.81, P = 0.006) and delayed recall (t = −2.1, P = 0.04), but not with any other TICSm domain.

In our sensitivity analysis in which we replaced missing 12-month TICSm scores with the lowest observed TICSm score, an additional point on the in-hospital PCL-C remained independently associated with a significantly lower 12-month TICSm score (β, −0.1; 95% CI, −0.2 to −0.04; P = 0.005). When we reran our fully adjusted linear regression model after replacing missing 12-month TICSm scores with the mean observed TICSm score, the point estimates suggested a similar magnitude of association but were less precise (β, −0.1; 95% CI, −0.1 to 0.001; P = 0.05). When we replaced missing 12-month TICSm scores with the highest observed TICSm score, there was no longer an independent association between the in-hospital PCL-C score and 12-month TICSm score (β, 0.03; 95% CI, −0.1 to 0.1; P = 0.62).

Discussion

In this prospective investigation of cognitive functioning in medical-surgical ICU survivors, we highlight a potentially modifiable risk factor for post-ICU cognitive dysfunction. We found that developing a greater number of acute stress symptoms before hospital discharge was independently associated with greater impairment in 12-month cognitive functioning, even after adjusting for patient characteristics and other ICU and hospital-related exposures. This finding builds on our prior work identifying in-hospital acute stress symptoms as independently associated with both longer-term post-ICU PTSD and depressive symptoms as well as increased alcohol use (19, 31). Furthermore, the association we found between in-hospital acute stress symptoms and greater impairment in 12-month cognitive functioning was independent of post-ICU depressive symptoms. Our results suggest that the association between in-hospital acute stress symptoms and greater risk of post-ICU cognitive impairment could be partially mediated by post-ICU PTSD; however, it is possible that we simply lacked sufficient statistical power, because the point estimates after controlling for 12-month PTSD symptoms were quite similar.

Our study adds to the growing body of literature identifying an association between PTSD symptoms and potential risk of cognitive impairment. Two large prospective cohort studies of combat veterans found significant associations between PTSD diagnosis and increased risk of later dementia diagnosis (15, 16). A third national multisite investigation of outcomes after traumatic injuries found that PTSD symptoms at 12 months postinjury were independently associated with worse 12-month cognitive functioning for patients with mild, moderate, or severe traumatic brain injury (32). Incorporating our findings into this larger context, PTSD symptoms appear to be an important risk factor for cognitive impairment across a diverse group of patient populations.

We found that in-hospital acute stress symptoms were associated with greater impairment in 12-month performance in the attention/calculation and delayed recall domains of the TICSm. These results are in line with prior studies, which have found associations between PTSD and impairments in sustaining attention, learning, and verbal memory (33–35). However, unlike these studies, we show that PTSD symptoms in the acute aftermath of a medical traumatic stressor are associated with poorer cognitive functioning 12 months later. If our findings are replicated in larger cohorts of critical illness survivors, then this distinction has important clinical implications, because these patients

Table 1. Characteristics of participants who completed 12-month follow-up

Variables	N = 120
Patient baseline characteristics	
Age	49.0 ± 14.6
Female	51 (42.5)
Nonwhite	30 (25.2)
< High school graduate	15 (12.6)
Married/partnered	63 (52.5)
Lifetime major depression	32 (26.9)
Lifetime traumatic event exposures	4.1 ± 2.8
Problem drinking (AUDIT ⩾ 8)	14 (11.7)
Problem drug use (DAST-10 ⩾ 3)	14 (11.7)
Charlson Comorbidity score	1.0 (0–2.0)
Admission clinical characteristics	
ICU LOS, d	5.0 (3.0–9.0)
SAPS II	22.0 (13.0–36.8)
Admission diagnosis	
Cardiovascular	11 (9.2)
Pulmonary	18 (15.0)
Infectious disease	31 (25.8)
Neurologic	33 (27.5)
Vascular surgery	19 (15.8)
Gastrointestinal	14 (11.7)
Endocrine/renal	5 (4.2)
Orthopedic	10 (8.3)
Oncologic	3 (2.5)
Other	3 (2.5)
Mechanically ventilated	56 (46.7)
Had major surgery	56 (46.7)
Received blood product transfusion	29 (24.2)
Probable delirium	63 (52.5)
Days of benzodiazepines	2.0 (0.3–4.8)
Days of opioids	10.0 (5.0–19.0)
Days of antipsychotics	0 (0–0)
Days of antidepressants	0 (0–0)
PCL-C score at baseline interview	29.8 ± 11.7

Definition of abbreviations: AUDIT = Alcohol Use Disorders Identification Test; DAST-10 = Drug Abuse Screening Test-10; ICU = intensive care unit; LOS = length of stay; MV = mechanical ventilation; PCL-C = Posttraumatic Stress Disorder Checklist-civilian version; SAPS II = Simplified Acute Physiology Score II.
All values are mean ± SD, median (IQR) or N (%) unless otherwise indicated.

could be identified before hospital discharge to facilitate receipt of evidence-based treatments with the aim of preventing the development of PTSD (36, 37). Additional research is warranted to determine if implementing such interventions for medical-surgical ICU survivors could also prevent post-ICU cognitive impairment.

For clinicians working with critical illness survivors in the early aftermath of the ICU, our findings suggest that patients exhibiting symptoms such as insomnia with accompanying nightmares, anxiety with hyperarousal, and/or intrusive recollections of the ICU experience, whether of real events or of psychotic experiences (i.e., "delusional memories"), are at risk for the development of PTSD and possibly longer-term cognitive impairment. These patients warrant referral for careful evaluation for acute stress disorder by a specialist to receive evidence-based treatments if needed.

Although observational studies such as this one cannot prove causation, credible biological pathways exist that reduce the concern that the association presented here between in-hospital acute stress symptoms and impairment in 12-month post-ICU cognitive functioning is due to residual confounding or a chance finding. Exposure to profound stress has been associated with damage to the hippocampus, as evidenced by decreased levels of the hippocampal neuronal marker, *N*-acetyl aspartate (38). Furthermore, neuroimaging studies have found that adults exposed to trauma may have smaller hippocampal volumes (39, 40). In addition, critical illnesses and PTSD symptoms have been found to be associated with increased release of proinflammatory cytokines (41, 42), which has been hypothesized to lead to neurodegenerative changes (43).

In addition to in-hospital acute stress symptoms, we also found that less than a high school level of education and greater medical comorbidity were also associated with greater impairment in cognitive functioning at 1 year post-ICU. These findings are consistent with previous studies identifying lower education and chronic medical conditions as potential risk factors for cognitive decline and dementia (44–46). Importantly, improved management of chronic medical conditions could prevent ICU admissions and subsequent post–critical illness cognitive decline.

Our study has several potential limitations. Because we were unable to obtain surrogate consent from patients who were persistently delirious and therefore could not include them in our study, we could not effectively evaluate whether prolonged delirium was associated with post-ICU cognitive dysfunction. However, requiring patients to pass a validated cognitive screen before providing consent for study participation likely minimized the possibility that our assessment of in-hospital acute stress symptoms was confounded by residual hyperactive delirium, reduced the chance that patients with undiagnosed substantial cognitive impairment were recruited into the study, and decreased the likelihood that the acute stress symptoms seen were a response to acute cognitive deficits. Although we cannot definitively rule out the possibility that in-hospital acute stress symptoms in our cohort are a marker for pre-ICU cognitive impairment, this possibility is minimized by the procedures we used to enroll patients. Furthermore, a recent study found that in-hospital cognitive testing results did not predict longer-term cognitive dysfunction in critical illness survivors (47), suggesting that in-hospital acute stress symptoms could be a unique early predictor of later cognitive impairment in this patient population.

Although we cannot completely rule out that our findings are biased by nonresponse, we conducted multiple sensitivity analyses to quantify the potential effects of such bias and found that our

Table 2. Adjusted associations of in-hospital acute stress symptoms and cognitive performance at 12 months after medical-surgical intensive care unit admission

Variables	Adjusted for Patient Characteristics	Adjusted for Hospitalization Characteristics	Adjusted for 12-Month Post-ICU Depressive Symptoms	Adjusted for 12-Month Post-ICU PTSD Symptoms	Adjusted for 12-Month Post-ICU Depressive and PTSD Symptoms
In-hospital acute stress symptoms (PCL-C)	−0.1 (−0.2 to −0.01)*	−0.1 (−0.2 to −0.01)*	−0.1 (−0.2 to −0.01)*	−0.1 (−0.2 to 0.01)	−0.1 (−0.2 to 0.03)
Age	−0.01 (−0.1 to 0.1)	−0.03 (−0.1 to 0.1)	−0.02 (−0.1 to 0.1)	−0.03 (−0.1 to 0.1)	−0.02 (−0.1 to 0.1)
Male	0.1 (−1.6 to 1.8)	−0.02 (−1.8 to 1.8)	−0.01 (−1.8 to 1.8)	−0.03 (−1.8 to 1.8)	−0.03 (−1.8 to 1.8)
Nonwhite	0.5 (−1.4 to 2.5)	0.6 (−1.6 to 2.6)	0.5 (−1.6 to 2.6)	0.5 (−1.6 to 2.6)	0.5 (−1.6 to 2.6)
Education less than high school	−4.0 (−6.4 to −1.5)†	−4.2 (−6.8 to −1.6)†	−4.2 (−6.8 to −1.5)†	−4.2 (−6.8 to −1.6)†	−4.2 (−6.8 to −1.5)†
Married	0.3 (−1.4 to 2.0)	0.1 (−1.6 to 1.9)	0.1 (−1.8 to 1.9)	0.2 (−1.6 to 2.0)	0.1 (−1.8 to 1.9)
Lifetime major depression	0.6 (−1.3 to 2.5)	0.4 (−1.7 to 2.5)	0.3 (−1.8 to 2.4)	0.4 (−1.7 to 2.5)	0.4 (−1.8 to 2.5)
Problem drinking	0.6 (−2.1 to 3.2)	0.2 (−2.8 to 3.1)	0.2 (−2.8 to 3.1)	0.1 (−2.8 to 3.1)	0.2 (−2.8 to 3.1)
Problem drug use	−1.1 (−3.8 to 1.7)	−1.2 (−4.2 to 1.7)	−1.2 (−4.2 to 1.7)	−1.2 (−4.2 to 1.7)	−1.2 (−4.2 to 1.8)
Number of prior traumatic event exposures	0.1 (−0.2 to 0.4)	0.1 (−0.2 to 0.5)	0.1 (−0.2 to 0.5)	0.1 (−0.2 to 0.5)	0.1 (−0.2 to 0.5)
Charlson Comorbidity Score	−0.5 (−0.9 to −0.04)*	−0.6 (−1.1 to −0.1)*	−0.6 (−1.1 to −0.1)*	−0.6 (−1.1 to−-0.1)*	−0.6 (−1.1 to −0.1)*
SAPS II		0.01 (−0.03 to 0.1)	0.1 (−0.04 to 0.1)	0.1 (−0.04 to 0.1)	0.1 (−0.04 to 0.1)
Mechanical ventilated		−0.3 (−2.9 to 2.3)	−0.3 (−2.9 to 2.4)	−0.3 (−2.9 to 2.3)	−0.3 (−2.9 to 2.4)
Required major surgery		−0.3 (−2.2 to 1.6)	−0.3 (−2.2 to 1.6)	−0.3 (−2.2 to 1.6)	−0.3 (−2.2 to 1.6)
Required blood product transfusion		0.3 (−1.9 to 2.5)	0.4 (−1.9 to 2.6)	0.5 (−1.9 to 2.5)	0.4 (−1.9 to 2.6)
Probable delirium		−0.3 (−2.6 to 2.0)	−0.3 (−2.6 to 2.0)	−0.3 (−2.6 to 2.1)	−0.2 (−2.6 to 2.2)
Received benzodiazepines		−0.2 (−2.4 to 2.0)	−0.2 (−2.4 to 2.0)	−0.2 (−2.4 to 2.0)	−0.2 (−2.4 to 2.0)
Received opioids		−5.2 (−14.5 to 4.2)	−5.2 (−14.7 to 4.2)	−5.0 (−14.5 to 4.4)	−5.1 (−14.6 to 4.5)
Received antipsychotics		−0.3 (−2.9 to 2.3)	−0.3 (−3.0 to 2.3)	−0.3 (−2.9 to 2.4)	−0.3 (−3.0 to 2.3)
Received antidepressants		−0.4 (−2.6 to 1.8)	−0.4 (−2.6 to 1.9)	−0.4 (−2.7 to 1.8)	−0.4 (−2.6 to 1.9)
12-mo PHQ-9 Scores			0.02 (−0.2 to 0.2)		0.1 (−0.2 to 0.3)
12-mo PCL-C Scores				−0.01 (−0.1 to 0.1)	−0.03 (−0.1 to 0.1)

Definition of abbreviations: PCL-C = Posttraumatic Stress Disorder Checklist-civilian version; PHQ-9 = Patient Health Questionniare-9; PTSD = posttraumatic stress disorder; SAPS II = Simplified Acute Physiology Score II.
Data are presented as β coefficient (95% confidence interval).
*$P < 0.05$.
†$P < 0.01$.

results were only substantively affected by the extreme situation in which all participants missing 12-month follow-up had perfect cognitive functioning. Also, in our prior examinations of predictors of greater severity of post-ICU PTSD and depressive symptoms as well as increased alcohol use in this cohort, we found that patients with in-hospital substantial acute stress symptoms were more likely to be lost to follow-up (19, 31), suggesting the possibility that the magnitude of the association we describe here between in-hospital acute stress symptoms and impairment in post-ICU cognition may be underestimated. Information on prior traumatic event exposure, lifetime major depression, and pre-ICU substance use may be subject to recall bias, as these data were obtained from patients while they were still in the hospital and is therefore retrospective in nature. Also, although the TICSm has not been specifically validated as an assessment of cognitive functioning in medical-surgical ICU survivors or among patients under the age of 50, it has been used previously in similar populations (8, 48) and has been validated against neuropsychiatric interview (49). Moreover, our study was conducted in a single center serving a safety net population, and a majority of patients potentially eligible for our study were discharged before approach. Because we only have data from patients who consented to participate in our study, we cannot characterize potential differences between our cohort and all eligible ICU survivors from our institution. Therefore, these factors limit the generalizability of our results to the entire population of medical-surgical ICU survivors. Because our sample size was relatively small, our findings warrant replication in larger prospective cohort studies. Finally, the possibility of residual confounding remains, as in any observational study.

In conclusion, we identified that in-hospital acute stress symptoms are independently associated with greater impairment in cognitive functioning 12 months after a medical-surgical ICU admission. Efforts to incorporate screening of medical-surgical ICU survivors for acute stress symptoms into routine care after critical illnesses, as well as additional research into the mechanisms linking PTSD symptoms, critical illnesses, and cognitive impairment, are crucial in light of the enormous toll that critical illnesses, PTSD, and cognitive dysfunction take on patients, their families, and society. ■

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